The post-thrombotic syndrome

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The post-thrombotic syndrome (PTS) is a frequent, sometimes disabling complication of deep vein thrombosis (DVT) that reduces quality of life and is costly. This article discusses risk factors for PTS after DVT and available means to prevent and treat PTS, with a focus on new information in the field. After DVT, PTS will develop in 20% to 50% of patients, and severe PTS, including venous ulcers, will develop in 5% to 10%. The principal risk factors for PTS are anatomically extensive DVT, recurrent ipsilateral DVT, persistent leg symptoms 1 month after acute DVT, obesity, and older age. By preventing the initial DVT and ipsilateral DVT recurrence, primary and secondary prophylaxes of DVT will prevent cases of PTS. Based on recent evidence from a large multicenter trial, routine use of elastic compression stockings (ECS) after DVT to prevent PTS is not advocated, but in patients with DVT-related leg swelling that is bothersome, a trial of ECS is reasonable. Selecting DVT patients for catheter-directed thrombolytic treatment as a means of preventing PTS should be done on a case-by-case basis, with a focus on patients with extensive thrombosis, recent symptoms onset, and low bleeding risk. For patients with established PTS, daily use of ECS may help to relieve symptoms and edema. Intermittent compression devices can be tried in patients with moderate-to-severe PTS whose symptoms are inadequately controlled with ECS alone. A supervised exercise training program may improve PTS symptoms. Management of post-thrombotic ulcers should ideally involve a multidisciplinary approach. Important areas for future research are summarized.

Learning Objectives

- To gain understanding of current knowledge on risk factors for the post-thrombotic syndrome
- To review up-to-date approaches to preventing and treating the post-thrombotic syndrome

Introduction

The post-thrombotic syndrome (PTS), an important chronic consequence of deep venous thrombosis (DVT), is a burdensome and potentially debilitating condition for which patients frequently seek medical advice. PTS develops in 20% to 50% of patients with DVT, even when appropriate anticoagulant therapy is used to treat the DVT. Manifestations of PTS vary from mild clinical symptoms or signs to more severe manifestations such as chronic leg pain that limits activity and the ability to work, intractable edema, and leg ulcers.[1] PTS adversely affects quality of life and productivity and is costly as measured by health resource utilization, direct costs, and indirect costs.[2]

The present review focuses on risk factors for PTS after DVT and the available means to prevent and treat PTS, highlighting new information and concepts in the field. In addition, gaps in our understanding of PTS that merit further research are noted. Readers are also encouraged to consult a recently published scientific statement[1] and clinical guidance document[3] that focus on PTS. Readers with an interest in PTS in children are referred to recent reviews of this topic.[4,5]

What are the clinical manifestations of PTS?

The clinical manifestations of PTS are similar to those of primary venous insufficiency and comprise a constellation of symptoms and signs that vary from patient to patient.[1] Typical PTS symptoms include leg pain; sensations of leg heaviness, pulling, or fatigue; and limb swelling. Symptoms can be present in various combinations, may be persistent or intermittent, and are usually aggravated by standing or walking and tend to improve with rest and leg elevation. Typical signs may include leg edema, redness, dusky cyanosis when the leg is in a dependent position, perimalleolar or more extensive telangiectasiae, new varicose veins, stasis hyperpigmentation, thickening of the skin and subcutaneous tissues of the lower limb known as lipodermatosclerosis, and in severe cases, leg ulcers, which may be precipitated by minor trauma. These are characteristically chronic, painful, and slow to heal; require close medical attention; and often recur. The intensity of symptoms and signs of PTS tends to increase over the course of the day. Their severity ranges from minimal discomfort and cosmetic concerns to severe clinical manifestations such as chronic pain, intractable edema, and leg ulceration.

What is the underlying pathophysiology of PTS?

PTS is thought to develop after DVT as a result of venous hypertension (ie, increased venous pressures). Venous hypertension reduces calf muscle perfusion, increases tissue permeability, and promotes the associated clinical manifestations of PTS. Two pathologic mechanisms contribute to venous hypertension: persistent (acute, then residual) venous obstruction and valvular reflux caused by damage to vein valves.[6] Standard anticoagulant treatment of

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DVT prevents thrombus extension and embolization to the pulmonary arteries but does not directly lyse the acute thrombus, and in many cases only partial clearance of thrombus occurs. Inflammation may play a role in promoting the development of PTS by delaying thrombus resolution and by inducing vein wall fibrosis, which promotes valvular reflux.[7,8] There may also be a genetic predisposition to PTS from gene polymorphisms associated with vein wall remodeling.[9]

How is PTS diagnosed?

There exists no gold standard biomarker, imaging, or physiologic test that establishes the diagnosis of PTS. PTS is primarily diagnosed on clinical grounds, based on the presence of typical symptoms and signs in a patient with previous DVT. In some patients, it can take a few 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 (ie, 3-6 months) has passed.[10] Symptoms of PTS usually manifest within 3 to 6 months after DVT, but can occur up to 2 years or longer after DVT.[11]

The Villalta scale (sometimes called the Villalta-Prandoni scale)[12] has been adopted by the International Society on Thrombosis and Haemostasis as a standard to diagnose and grade the severity of PTS in clinical studies.[10] The scale's components (5 patient-reported symptoms and 6 clinician-assessed signs) are each rated on a 4-point severity scale (from 0 to 3), and the points are summed to produce a total score; a score >4 or the presence of an ulcer denotes PTS (Table 1). The scale has been shown to be valid, reproducible, and responsive to clinical change and is easy to administer. The Villalta scale has been used to diagnose PTS in a number of recent multicenter randomized trials of interventions to prevent and treat PTS.[13-17]

Recently, a fully patient-reported version of the Villalta scale was developed and validated.[18] In this version, the patient completes all questions on symptoms and signs, using a visual guide for assistance with ratings of clinical signs severity. By reducing the need for in-person study visits, use of this tool may increase the efficiency and reduce resource needs in future clinical studies of PTS.

Additional diagnostic or classification scales have been used to assess PTS, including the CEAP classification, Ginsberg measure, and Venous Clinical Severity Score (VCSS).[1]

Incidence and risk factors for PTS after DVT

PTS is a frequent complication of DVT. It develops in ~20% to 50% of patients within 2 years of DVT diagnosis and is severe in 5% to 10% of cases.[1] Hence on average, about 6 of 10 patients can expect to recover from DVT without any residual symptoms, 3 of 10 will have some degree of PTS, and 1 in 10 to 1 in 20 will have severe PTS, which can include leg ulcers.

Risk factors for PTS

Although it is not yet possible to precisely predict the absolute risk of PTS in an individual patient with DVT, research done over the last 5 to 10 years has provided new information on various risk factors for PTS, which has been detailed in 2 recent reviews.[19,20] This information is summarized next, grouped according to the time points at which patients with DVT are assessed in clinical practice.

Risk factors apparent at time of DVT diagnosis.

- DVT location: Risk of PTS is higher (two- to threefold) after proximal (especially with involvement of the iliac or common femoral vein) than distal (calf) DVT.

Table 1. Villalta PTS scale

Assessment of:	
• 5 symptoms (pain, cramps, heaviness, pruritus, paresthesia) by patient self-report	
• 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) by clinician assessment	
Severity of each symptom and sign is rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). In addition, ulcer is noted as present or absent.	
Points are summed to yield the total Villalta score:	
0-4:	No PTS
5-9:	Mild PTS
10-14:	Moderate PTS
≥15, or presence of ulcer	Severe PTS

- Previous ipsilateral DVT.
- Preexisting primary venous insufficiency: up to twofold increased risk of PTS.
- Elevated body mass index (BMI): obesity (BMI >30) more than doubles the risk of PTS.
- Older age increases the risk of PTS; reported increased risk from 30% to threefold.

The following factors appear to have little or no effect on the risk of developing PTS: sex, whether DVT was provoked vs unprovoked, and biological thrombophilia.

Risk factors related to treatment of acute DVT.

- Quality of oral anticoagulation: PTS risk increases twofold if the level of anticoagulation is inadequate (eg, subtherapeutic international normalized ratio [INR] >50% time) during the first 3 months of treatment with vitamin K antagonists.
- Choice of anticoagulant to treat DVT: It is not known whether use of the new direct oral anticoagulants to treat DVT influences the risk of PTS, compared with treatment with low-molecular-weight heparin (LMWH) or vitamin K antagonists. A meta-analysis of available data suggested that use of LMWH monotherapy to treat DVT may lead to lower rates of PTS than treatment with LMWH for 5 to 7 days followed by vitamin K antagonists.[21] Large multicenter trials that use validated criteria to diagnose PTS are needed to confirm the effectiveness of extended LMWH in patients at high risk for PTS, and also to assess the effectiveness of new direct oral anticoagulants in preventing PTS.
- The potential role of thrombolysis in reducing the risk of PTS is discussed in the next section.

Risk factors apparent during follow-up after DVT.

- Ipsilateral DVT recurrence: Increases risk of PTS four- to sixfold, presumably by damaging compromised venous valves or aggravating venous outflow obstruction.
- Persistent venous symptoms and signs 1 month after acute DVT: Increases risk of subsequent PTS.[22,23]
- Residual thrombosis on ultrasound (eg, 3-6 months after acute DVT): Modest (1.5- to twofold) increased risk of PTS.
- Persistent elevation of D-dimer: Elevated levels of D-dimer in the weeks to months after DVT may be a modest risk factor for PTS.[24]

Can PTS be prevented?

Preventing first and recurrent DVT

Preventing the first occurrence of DVT by improving the systematic use of thromboprophylaxis in high-risk hospitalized patients as recommended in evidence-based consensus guidelines will prevent

some cases of PTS.[25-27] Because ipsilateral DVT recurrence is a strong risk factor for PTS, reducing the risk of recurrent DVT by providing optimal anticoagulation of appropriate intensity and duration to treat the initial DVT is an important clinical goal.[28] In patients treated with vitamin K antagonists, frequent, regular INR monitoring to avoid subtherapeutic INRs in the first months after DVT may also reduce the risk of PTS.[29,30] Data are insufficient to make specific recommendations regarding choice of anticoagulant to treat DVT, namely a vitamin K antagonist vs a direct, target-specific oral anticoagulant vs LMWH monotherapy, on the outcome of developing PTS.

Use of elastic compression stockings

Elastic compression stockings (ECS), by reducing leg swelling and venous hypertension, could plausibly play a role in preventing PTS. However, there are conflicting data on the long-term effectiveness of ECS to prevent PTS. In the past, evidence-based consensus guidelines recommended the use of ECS for at least 2 years after DVT to prevent PTS, based on results of 2 previous small open-label trials that reported that wearing 30- to 40-mm Hg knee-high ECS for at least 2 years after proximal DVT was effective in preventing PTS.[31] However, a recent multicenter, randomized, placebo-controlled trial in 803 patients with proximal DVT (SOX Trial) showed no evidence of benefit of active compression stockings, worn for 2 years, to prevent PTS, to reduce the risk of recurrent venous thromboembolism, or to improve quality of life.[14] A recent meta-analysis that incorporated data from the SOX Trial reported a pooled hazard ratio for PTS with ECS of 0.69 (95% confidence interval [CI], 0.47-1.02). However, the authors caution that there is very low confidence in this pooled estimate because of heterogeneity and inclusion of unblinded studies at high risk of bias, and that the recent, highest-quality evidence available suggests no effect of ECS on PTS.[32] Based on these new data, the latest guideline statements do not advocate the routine use of ECS to prevent PTS.[1,28]

Although ECS are unlikely to cause harm, they can be difficult to apply, uncomfortable, expensive, and require replacement every few months. In light of the current state of evidence, I do not routinely prescribe ECS to all my patients with DVT. My clinical approach is to prescribe a trial of 20- to 30-mm Hg or 30- to 40-mm Hg below-knee ECS to patients with residual leg swelling or discomfort after proximal or distal DVT, and to continue wearing them for as long as the patient derives symptomatic benefit or is able to tolerate them.

Thrombolysis of acute DVT to prevent PTS

Up-front thrombolytic therapy in conjunction with heparin to treat acute DVT leads to higher rates of vein patency and better preservation of valve function than the use of heparin alone.[6] Catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (catheter-directed thrombolysis plus mechanical disruption of thrombus) are likely to be safer and more effective than systemic thrombolytic therapy and could prove to be promising techniques as a means of preventing PTS, primarily after proximal DVT.[33] In a recent multicenter randomized controlled trial of modest size (n = 189), the use of additional CDT in anticoagulated patients with acute DVT involving the iliac and/or upper femoral vein was associated with a statistically significant ($P = .047$) 26% relative reduction in risk of PTS at 2 years, at the cost of an additional 3% rate of major bleeding.[13] However, PTS still developed in 41% of CDT patients, indicating that CDT does not eliminate the risk of PTS, and CDT did not result in improved quality of life at 2 years'[34] or 5 years' follow-up,[35] suggesting that additional endovascular thrombolytic approaches should be investigated. Larger multicenter trials of pharmacomechanical CDT plus standard anticoagulation vs standard anticoagulation alone to prevent PTS are ongoing,[15,36] with results expected within 1 to 2 years. In my own practice, consistent with recently published guidelines,[1,28] I carefully consider patients for these techniques on a case-by-case basis: namely, those with extensive (eg, iliofemoral) thrombosis with recent onset (ie, ≤14 days) of symptoms, a low risk of bleeding, and a life expectancy of at least 1 year, who are seen at hospital centers experienced in performing these techniques.

Current approaches to treating PTS

Compression therapy

Compression-based therapies, usually ECS, are the cornerstones of managing established PTS. Their use is intended to reduce PTS symptoms (especially leg swelling, sensation of heaviness, and discomfort) and improve daily functioning. Patients should be educated on how to apply and use ECS and on the importance of compliance to maximize their benefit. Because few controlled studies of their effectiveness in PTS have been performed, their use in clinical practice is based primarily on extrapolation from patients with primary venous insufficiency, the low risk of harm, and the possibility of benefit to at least some patients with PTS. The principal contraindication to using ECS is symptomatic peripheral arterial disease, because claudication can worsen when stockings are worn. My approach is to prescribe the daily use of 20- to 30-mm Hg ECS to patients with PTS-related leg heaviness or swelling, and advise the patient to apply their stockings in the morning and to remove them at bedtime or in the early evening. I prescribe knee-length ECS, which have similar physiologic effects to thigh-length ECS and are easier to apply, more comfortable, and less costly.[37] If 20- to 30-mm Hg ECS does not adequately control PTS symptoms, a stronger pressure stocking (30-40 mm Hg; or 40-50 mm Hg) can be tried.

In patients with moderate to severe PTS whose symptoms are not adequately controlled with ECS alone, the portable, battery-powered Venowave intermittent compression device can be tried. In a randomized crossover trial in 32 patients with severe PTS, wearing the device on the affected leg alone or in combination with ECS was associated with improvement in quality of life and reduced severity of PTS.[16] For patients with severe, intractable PTS symptoms or severe edema, intermittent pneumatic compression sleeve units (eg, used for 20-30 minutes at a time, 2-3 times per day) can be used to provide symptom relief[38]; however, patients may find these units to be cumbersome and expensive.

Medications

As summarized in a recent systematic review and meta-analysis,[39] 4 randomized trials have evaluated the effectiveness of "venoactive" drugs for PTS: 3 parallel trials and 1 crossover study. The drugs evaluated were rutosides (thought to reduce capillary filtration and microvascular permeability), defibrotide (downregulates plasminogen activator inhibitor-1 release and upregulates prostacyclin, prostaglandin E2, and thrombomodulin), and hidrosmin (mechanism of action unknown). Overall, there is low-quality evidence to support the use of venoactive drugs to treat PTS because studies were limited by a high degree of inconsistency and imprecision. Also, drug treatment was usually of short duration (eg, 8 weeks to a few months), and potential long-term side effects are unknown. More rigorous studies using validated measures of clinically important outcomes, including quality of life, are needed to assess the safety, effectiveness, and sustainability of pharmacologic treatments for PTS. At present, I do not suggest the use of venoactive drugs to treat PTS. Further, there is no evidence that use of diuretics is effective for the treatment of PTS-related edema.

Table 2. Suggested approaches to prevent and treat PTS

Prevention
Prevent the occurrence of 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.
In patients whose DVT is treated with a vitamin K antagonist, frequent, regular INR monitoring should be performed to avoid subtherapeutic INRs, especially in the first 3 months of treatment.
Do not routinely prescribe elastic compression stockings (ECS) for 2 years to all DVT patients. However, it is reasonable to prescribe a trial of 20-30–mm Hg or 30-40–mm Hg below-knee ECS to patients who have residual leg swelling or discomfort after DVT, and to continue wearing them for as long as the patient derives symptomatic benefit or is able to tolerate them.
The role of thrombolysis for the prevention of PTS is not yet established. Pharmacomechanical catheter-directed thrombolysis is currently undergoing evaluation in large, well-designed trials. At present, selection of patients for these techniques should be done on an individual patient basis, and mainly considered for those with extensive thrombosis, recent symptom onset, low risk of bleeding, and long life expectancy, seen at experienced centers.
Treatment
Use ECS to reduce edema and improve PTS symptoms such as leg pain and heaviness. If 20-30–mm Hg stockings do not adequately control PTS symptoms, a stronger pressure stocking (30-40 mm Hg; or 40-50 mm Hg) can be tried.
Consider a trial of intermittent pneumatic compression units in patients with moderate to severe PTS.
Consider prescribing a supervised exercise training program with leg strengthening and aerobic components for ≥6 months to patients with PTS who can tolerate it.
Until more safety and effectiveness data are available, do not use venoactive drugs to treat PTS.
A multidisciplinary approach should be used for venous ulcer management, which typically consists of compression therapy, skin care, and topical dressings.
In patients with symptoms of upper extremity PTS, a 20-30–mm Hg or 30-40–mm Hg compression sleeve should be tried.
Providing patient support and ongoing follow-up is an important component of PTS management.

Exercise and lifestyle considerations

Two small trials have assessed the effectiveness of exercise to treat PTS. In a study of 30 patients with chronic venous insufficiency (half had prior DVT), a 6-month leg-strengthening exercise program led to improved calf muscle function and calf muscle strength.[40] In a 2-center Canadian pilot study, a 6-month exercise training program designed to increase leg strength, leg flexibility, and overall cardiovascular fitness improved PTS severity and quality of life, with no adverse events.[17] Although not definitive, the available data suggest that exercise may benefit patients with PTS. I recommend my patients with PTS to undertake a supervised (at least initially) exercise training program consisting of leg strengthening and aerobic activity for 6 months or more, if they can tolerate it.

Additional common sense lifestyle advice that is relevant to all patients with chronic venous insufficiency includes reducing venous stasis by keeping active and avoiding a sedentary lifestyle; raising the legs on a footrest when seated or elevating the legs on a firm pillow when lying down; avoiding prolonged exposure to heat, which can aggravate symptoms of leg heaviness and swelling; maintaining a healthy, nonobese body weight; and using a moisturizing lotion to avoid skin dryness and breakdown.

Venous ulcer management

DVT in 5% to 10% of patients will progress to severe PTS, which can include venous leg ulcers. Patients with post-thrombotic ulcers should be treated using a multidisciplinary team approach that ideally includes an internist, dermatologist, vascular surgeon, and wound care nurse. Post-thrombotic venous ulcers are treated with compression therapy, including multicomponent compression bandages, leg elevation, topical dressings, and sometimes hemorheologic agents like pentoxifylline, and may require weeks to months to heal. Ulcers can be refractory to therapy, and they often recur. Surgery or endovascular procedures to treat a major refluxing vein may be advocated in select patients when conservative treatment fails. For more detailed discussion of venous ulcer management, please refer to recent published reviews and consensus guidelines.[1,41]

Surgical or endovascular treatment of PTS

Surgical or endovascular procedures such as venous valve repair, venous bypass, and venous stents to treat appropriately selected patients with PTS may have potential to decrease post-thrombotic manifestations that are attributable to deep vein obstruction or valvular reflux. However, well-designed studies have not been performed to date, experience with these procedures varies significantly among practitioners, and complications and failure rates are uncertain. Hence, these interventions should not be routinely used in unselected PTS populations. However, for selected patients with moderate-to-severe PTS who have substantial disability and daily

Table 3. Research needs in PTS

Mechanistic studies to improve understanding of the pathophysiology of PTS and to suggest future therapeutic targets.
Development and validation of risk prediction indices to predict risk of PTS.
Studies of risk factor or lifestyle modification (eg, weight reduction, exercise) to prevent and treat PTS.
Studies of the relative effects and cost-effectiveness of extended LMWH and direct, target-specific oral anticoagulants on the risk of PTS
Studies of the effectiveness of ECS to prevent PTS in high-risk subgroups.
Studies of the effectiveness, safety, and cost-effectiveness of pharmacomechanical catheter-directed lysis to treat DVT as a means to prevent PTS.
Studies of the effectiveness of ECS and other compression modalities to treat PTS.
Studies of the effectiveness and safety of venoactive drugs to treat PTS.
Rigorous evaluation of the safety and long-term effectiveness of endovascular and surgical procedures to treat severe PTS.

life limitations, it may be appropriate to consult with an endovascular specialist who has experience with assessing and managing complex venous disease. For more detailed discussion of surgical and endovascular treatments for PTS, please refer to a recently published AHA consensus guideline[1] and a White Paper on endovascular therapy for PTS management.[42]

Table 2 summarizes available strategies to prevent and treat PTS.

Upper extremity PTS

After upper extremity DVT, PTS will develop in 15% to 25% of patients.[43] Upper extremity PTS can reduce quality of life and limb function.[44] Symptoms include arm swelling, heaviness, and exertional fatigue. Dilation of the superficial veins of the upper arm and chest wall and dependent cyanosis of the arm may be noted. Not surprisingly, dominant-arm PTS is associated with worse quality of life and disability than non–dominant-arm PTS.[45] Data to guide the management of upper extremity PTS are lacking. There have been no trials of compression sleeves or bandages to prevent or treat upper extremity PTS, and it is not known whether endovascular or surgical treatment of upper extremity DVT leads to lower rates of PTS than standard anticoagulation alone. Anecdotal experience suggests that patients with persistent arm swelling and pain after upper extremity DVT may derive symptomatic relief from elastic bandages or compression sleeves. Because of the potential for benefit and low potential for harm, I prescribe a trial of a 20- to 30-mm Hg or 30- to 40-mm Hg compression sleeve in patients with symptoms of upper extremity PTS.

Research needs

PTS-related research needs are substantial. Important subjects for future research are summarized in Table 3.

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