

# Medical Treatment for Postthrombotic Syndrome

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## Abstract

Deep vein thrombosis (DVT) is a prevalent disease. About 20 to 30% of patients with DVT will develop postthrombotic syndrome (PTS) within months after the initial diagnosis of DVT. There is no gold standard for diagnosis of PTS, but clinical signs include pitting edema, hyperpigmentation, phlebectatic crown, venous eczema, and varicose veins. Several scoring systems have been developed for diagnostic evaluation. Conservative treatment includes compression therapy, medications, lifestyle modification, and exercise. Compression therapy, the mainstay and most proven noninvasive therapy for patients with PTS, can be prescribed as compression stockings, bandaging, adjustable compression wrap devices, and intermittent pneumatic compression. Medications may be used to both prevent and treat PTS and include anticoagulation, anti-inflammatories, vasoactive drugs, antibiotics, and diuretics. Exercise, weight loss, smoking cessation, and leg elevation are also recommended. Areas of further research include the duration, compliance, and strength of compression stockings in the prevention of PTS after DVT; the use of intermittent compression devices; the optimal medical anticoagulant regimen after endovascular therapy; and the role of newer anticoagulants as anti-inflammatory agents.

## Keywords

- ▶ postthrombotic syndrome
- ▶ deep vein thrombosis
- ▶ chronic venous insufficiency

**Objectives:** Upon completion of this article, the reader will be able to describe the noninvasive therapeutic options (compression, medications, and lifestyle changes) for treatment and prevention of postthrombotic syndrome.

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Deep vein thrombosis (DVT) affects 1.3 per 1,000 patients in the United States annually.<sup>1</sup> Postthrombotic syndrome (PTS) develops in 20 to 50% of patients with DVT within the first months to years from the index event.<sup>2</sup>

Signs of PTS include phlebectatic crown, pitting edema, brownish hyperpigmentation of the skin, venous eczema, and secondary varicose veins, as well as manifestations of more severe PTS such as atrophie blanche, lipodermatosclerosis, and leg ulceration.

There are no standard criteria to diagnose PTS, although several clinical scores exist that define the presence and severity of the disease. The lack of a gold standard definition poses a challenge in evaluating the incidence and prevalence of PTS, as well as the efficacy of different treatment strategies. The most common scoring systems are briefly described later.

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## Scoring Systems

The most commonly used clinical scores are the Villalta score, the Ginsberg score, the Brandjes scale, CEAP scale (clinical, etiology, anatomy, pathophysiology), the VCSS (venous clinical severity score), and the Widmer classification.

The Villalta score measures five subjective patient-reported elements (heaviness, cramps, paresthesia, pruritus, and pain) and six objective provider-reported findings (redness, venous ectasia, pretibial edema, skin induration, pain on calf compression, and hyperpigmentation) and correlates with disease-specific and generic quality-of-life scores. It reflects severity and has been deemed the most reliable scale to diagnose and rate the severity of PTS by the International Society of Thrombosis and Hemostasis.<sup>3</sup>

The Ginsberg score relies on patient report of symptoms and deems the presence of PTS in patients who report that they have daily pain that worsens with ambulation and is relieved by elevation or rest, and that is present after 6 months of the index DVT event. There is no rating of severity, but there is a good correlation with quality of life<sup>4</sup>; a shortcoming from this score is the nonspecificity of the symptoms that might be related to nonvenous conditions.<sup>4</sup>

The Brandjes scale uses subjective (pain, edema, "heaviness," impairment of daily activities) and objective criteria (calf and ankle circumference increase, skin pigmentation, presence of varicose veins, presence of ulcers), measured in two separate visits 3 months apart. It classifies patients as having no PTS, mild to moderate PTS, and severe PTS.<sup>5</sup>

The Widmer classification was originally developed to classify chronic venous insufficiency (CVI) according to clinical signs (edema, lipodermatosclerosis/skin atrophy, and presence of ulcers), but has been used to diagnose PTS and assess effectiveness of compression therapy.<sup>6</sup>

The CEAP classification is used to diagnose CVI and it is useful in comparing effectiveness of treatments for venous disorders, combining clinical presentation as well as description of etiology and pathology. It has been used to diagnose and descriptively classify PTS, but does not differentiate severity nor respond to clinical change.<sup>7</sup>

The VCSS score incorporates one symptom (pain), physical elements from CEAP, presence of ulcers, and use of compression. It was developed as an evaluative instrument that would be responsive to changes in disease severity over time and in response to treatment.<sup>7</sup>

When comparing PTS scoring systems, there is poor to moderate agreement between the Villalta scale and CEAP, and VCSS shows poor correlation with other systems.<sup>8</sup> Patients might be classified as having PTS by Villalta scoring up to five times more than if assessed by the Ginsberg measure.<sup>9</sup> A comparison between the Villalta score and VCSS showed good correlation for mild to moderate PTS; however, VCSS was more sensitive for severe disease.<sup>10</sup>

While scoring systems have been commonly used for diagnostic classification and treatment effect in evaluation of compression and endovascular therapies, they are used less frequently to describe improvements with medical therapies. However, noninterventional therapy for PTS should be con-

sidered first-line therapy and includes compression therapy, medications, lifestyle modification, and exercise.

## Compression

Compression has been used to manage venous disease since 400 BC in Ancient Greece.<sup>11</sup> As the ankle venous pressure can rise up to 80 to 100 mm Hg with standing, compression therapy is effective by increasing venous return and reducing ambulatory pressure.<sup>12</sup> Compression therapy also reduces levels of vascular endothelial growth factor and tumor necrosis factor- $\alpha$  in patients with venous ulcers, which correlates with ulcer healing.<sup>13</sup>

Several classifications for strength of compression exist. An international recommendation for standard compression strength has been published establishing mild (15–20 mm Hg), moderate (20–40 mm Hg), strong (40–60 mm Hg), and very strong (>60 mm Hg).<sup>14</sup> In the United States, compression strength is classified as light (<20 mm Hg), Class I or moderate (21–30 mm Hg), Class II or high (31–40 mm Hg), and Class III or very high (>40 mm Hg).<sup>11</sup>

Compression modalities include bandaging (single or multilayer), elastic compression stockings (ECS) of different lengths and strengths, and intermittent pneumatic compression (IPC).

## Bandaging

Inelastic short-stretch bandages reinforce calf pump function during ambulation aiding venous return. Short-stretch bandages are more effective in resisting changes in venous pressure than long-stretch bandages (e.g., ACE, BP Medical Supplies). Long-stretch bandages may lose compression strength quickly, especially with ambulation, requiring frequent changes. Short-stretch bandages are the appropriate initial treatment of moderate to severe edema before fitting for maintenance ECS, or for patients who cannot tolerate ECS. Bandages are usually applied in a 50% overlapping manner from foot to the proximal end of the edema. Patients should be educated that edema may accumulate above the proximal portion of the wrap. Multilayer bandages that usually include a cotton lining, short-stretch layer held in place by a more rigid self-adherent support wrap layer (e.g., Coban, 3M) are appropriate for patients with ulcerations or edema with drainage, such as shown in **►Fig. 1**.<sup>15</sup>

Venous ulcers are a complication of PTS that may be initially managed by compression therapy. A meta-analysis of 12 studies comparing compression stockings (650 patients) with compression bandages (668 patients) revealed no overall difference in venous ulcer healing outcomes. Significantly more ulcers recurred in the stocking group compared with the four-layer bandaging group (hazard ratio of 0.56; 95% confidence interval [CI]: 0.33–0.94;  $p = 0.03$ ). Four-layer bandaging was also found to be no better for ulcer healing compared with fewer layers. Fifteen trials were identified comparing short-stretch bandages (910 limbs) with long-stretch bandages (909 limbs) and revealed no difference in wound healing between the groups. When only the three most high-quality studies were included, a nonsignificant



**Fig. 1** A CVI patient's leg before and after multilayer compression.

trend toward superior ulcer healing in the long-stretch group at 12 months was found. No significant difference in ulcer recurrence between long-stretch bandaging and short-stretch bandaging was found, based on two studies with 365 patients who were followed up for 30 months. Based on these results, the authors supported compression over no compression, multicomponent systems over single component systems, and bandaging with an elastic component over those without.<sup>16</sup> These recommendations were incorporated in the most recent clinical practice guidelines for venous ulcer management from the Society for Vascular Surgery and the American Venous Forum.<sup>17</sup>

### Elastic Compression Stockings

Several trials have evaluated the prevention of PTS using ECS. An open label trial randomized 194 patients with symptomatic proximal DVT to a custom-made, knee-high 40 mm Hg ECS versus no socks; patients wore ECS for at least 2 years and were assessed every 3 months, and later followed up every 6 months for 5 years. This trial showed that the use of stockings reduced the incidence of mild to moderate PTS from 47 to 20% and severe PTS from 23 to 11%, using the Brandjes scale.<sup>5</sup>

A recent large multicenter double-blinded placebo-controlled trial (Sox trial) randomized 806 patients with first symptomatic proximal DVT to either a 30 to 40 mm Hg graduated knee length ECS or a placebo stocking with no more than 5 mm Hg compression. Patients were followed up every 6 months for 2 years. There was no significant difference in the incidence of PTS, evaluated by either Ginsberg criteria or the Villalta score. This led the authors to conclude that ECS did not affect the incidence of PTS at 2 years. Other findings showed that ESC did not decrease the occurrence of

venous ulcers, rate of recurrent DVT, prevalence of venous valvular reflux at 12 months, or improve generic or venous disease-specific quality of life.<sup>18</sup> The American College of Chest Physician recently updated their 2016 guidelines to recommend against the use of ECS for the prevention of PTS, suggesting it only for edema control.<sup>19</sup> The results of this large trial, however, were controversial because patients received the designation of frequent compression users if they used their ECS three times a week or more. Compliance after 2 years was low, with only 55.6% of patients reporting themselves as "frequent compression" users. Previous trials suggesting benefit of ECS reported compliance rates of 90%.<sup>5</sup>

Compliance is considered a major determinant of the effectiveness of ECS therapy. A questionnaire of patients receiving ECS for prevention of PTS concluded that providers should spend more time educating patients about ECS and PTS and should support the ability of patients to don and remove ECS independently.<sup>20</sup>

Two meta-analyses published in the same month in 2016 reached opposite conclusions regarding ECS effectiveness for preventing PTS. An analysis of five eligible randomized controlled trials (RCTs) with a total of 1,393 patients (sample sizes ranged from 47 to 803 patients) concluded that it was not justifiable to entirely abandon the recommendations of using compression stockings to prevent PTS in patients with DVT.<sup>21</sup> The other study included five RCTs ( $n = 1,418$ ) and concluded that highest-quality evidence available suggests no effect of ECS on incidence of PTS.<sup>22</sup>

In an effort to shed some light in this controversy, another multicenter, single-blinded, allocation concealed, randomized, noninferiority trial is underway. The IDEAL DVT study randomizes 864 patients with acute DVT to an experimental arm and an active comparator arm of the same ECS strength (class III, 40 mm Hg ankle pressure). The intervention arm will have a tailored duration of ECS therapy, based on signs and symptoms according to the Villalta scale, following an initial therapeutic period of 6 months. The active comparator arm will have ECS with a standard duration of 24 months. The primary outcome is the incidence of PTS at 24 months after acute DVT. Enrollment is complete and results expected in July 2017 (NCT01429714).

### Adjustable Compression Wrap Devices

Due to challenges that remain in achieving acceptable, safe, effective, and cost-efficient compression therapy, adjustable compression wrap devices using hook and loop fasteners, commonly called Velcro brand fasteners, present new opportunities for improving treatment outcomes, and supporting patient independence and self-management.<sup>23</sup> A recent trial randomized 40 legs of 36 patients with untreated venous edema to adjustable wraps<sup>20</sup> or inelastic bandages,<sup>20</sup> wore day and night, with the inelastic bandages renewed after 1 day and the adjustable wraps adjusted by the patients whenever they felt loose. Leg volumes were measured at baseline, day 1, and day 7. Inelastic bandages achieved higher mean pressures than adjustable wraps (63 vs. 43 mm Hg), but bandage pressure decreased over time, whereas the adjustable wrap maintained pressure due to patient adjustment.

Volume reduction was higher in the adjustable wraps group than in the bandage group (26 vs. 19%,  $p < 0.001$ ).

### Intermittent Pneumatic Compression

IPC for venous disease uses an air pump and inflatable auxiliary sleeves, gloves, or boots in a system designed to improve venous circulation in the limbs by compressing the limb sequentially with varying cycles (usually 30-second inflation time, followed by 45-second deflation time) exerting a pressure of 40 to 60 mm Hg. It improves venous return by mimicking calf pump function. These devices are considered beneficial in patients with reduced calf muscle function, for example, due to immobility or limited ankle mobility, who cannot initially tolerate bandaging due to pain or experience problems with edema control.<sup>24</sup> A recent Cochrane systematic review identified nine randomized trials of IPC to aid venous wound healing (489 patients). In one trial that included 80 subjects, more ulcers healed with IPC than with dressings (62 vs. 28%;  $p = 0.002$ ). IPC plus compression and compression alone were compared in five trials. Two of these (97 patients combined) found increased ulcer healing with IPC plus compression than with compression alone. The remaining three trials (122 patients combined) found conflicting results. Two trials (86 patients) reported no difference between IPC and compression bandages alone. One trial (104 patients) compared different speeds of delivering IPC and found that rapid IPC healed more ulcers than slow IPC (86 vs. 61%). The authors concluded that IPC was more effective than no compression for venous wound healing, with some added benefit from concomitant use with layered banding.<sup>25</sup> Clearly, this is an area that requires additional research.

Traditional IPCs are bulky and the air pump device limits mobility. Recently, a portable IPC was developed (Veno wave), consisting of a rotating gear-motor attached to a flexible sheet via a linkage that generates a repetitive waveform motion with a frequency of six cycles per minute. It has been approved by the Food and Drug Administration for the prevention of DVT. A recent small, two-center, randomized, crossover controlled trial evaluated 32 patients with severe PTS randomized to portable IPC for 8 weeks and regular IPC also for 8 weeks, separated by 4 weeks with no device. The mean Villalta scale score at the end of study period was significantly decreased ( $p = 0.004$ ) for the portable IPC (12.2; SD: 6.3) compared with control (15.0; SD: 6.1).

### Pharmacotherapy

Pharmacological treatment may include anticoagulation therapy, use of anti-inflammatory medication, vasoactive drugs, antibiotics for treatment of infection, and diuretics.

#### Diuretics

Use of low-dose diuretic (hydrochlorothiazide 25–50 mg/d or furosemide 40 mg up to three times daily) for up to a week can be considered as initial treatment for patients with massive edema. Patients should be monitored for volume depletion and electrolyte imbalance.<sup>15</sup> Long-term use is not encouraged.

### Anticoagulation

Poor international normalized ratio (INR) control in patients treated with vitamin K antagonist (VKA) has been associated with an increased incidence of PTS. One study reported an increased risk of PTS (OR: 1.84; 95% CI: 1.13–3.01) in patients whose INR was less than 2 for more than 20% of the time.<sup>26</sup> A previous study had reported a larger risk of PTS, 2.7-fold, in patients whose INR results were subtherapeutic more than 50% of the time.<sup>27</sup> American Heart Association guidelines recommend frequent, regular INR monitoring to avoid subtherapeutic INRs, particularly in the first few months of treatment after DVT diagnosis, to reduce the risk of PTS.<sup>2</sup>

A recent systematic review identified nine articles comparing treatment of DVT using long-term low-molecular-weight heparin (LMWH) only therapy with any comparator and found a risk ratio of 0.66 (95% CI: 0.57–0.77) in favor of LMWH for recanalization of thrombosed veins, as well as a reported 87% risk reduction of development of venous ulcers at 3 months when compared with warfarin.<sup>28</sup> One of those studies reported that patients treated with continued therapeutic dose LMWH, compared with warfarin, had a 23% reduction in symptoms and signs of PTS at 12 weeks.<sup>29</sup> This has led to speculation that the direct oral anticoagulants (DOACs) may also decrease the incidence of PTS, in theory due to their more predictable pharmacodynamics and reliable dosing compared with VKA. This theory is supported by the biological mechanism of a higher incidence of PTS as a result of inappropriate anticoagulation in the first 4 weeks. In this period of time, thrombin generation may retard clot lysis and stimulate connective tissue growth, and that these two factors could lead to persistent fibrotic occlusion and venous damage. However, quality research exploring this concept is lacking.<sup>30</sup> The anti-inflammatory effects of LMWH, demonstrated in an early study with a DVT rat model, might also explain the reported increased symptomatic relief with LMWH than VKA.<sup>31</sup>

### Venoactive Drugs

The use of venoactive drugs such as rutosides, hidrosmin, and defibrotide to treat PTS has been supported by a few randomized trials, but the overall evidence is limited or of low quality due to insufficient blinding, lack of precision, short follow-up duration, and varying methods used to confirm PTS.<sup>32</sup> As a result, the American College of Chest Physicians has recommended against their use<sup>33</sup>; however, the AHA guidelines deemed their effectiveness and safety uncertain.<sup>2</sup>

Horse chestnut seed extract (HCSE) is an herbal supplement that is extracted from the seeds of *Aesculus hippocastanum L*, and has the active component, escin, that inhibits the activity of hyaluronidase and accumulation of leucocytes in CVI-affected limbs. A previous Cochrane review determined that HCSE was an efficacious and safe short-term treatment for CVI reducing leg volume, edema, and pruritus.<sup>34</sup>

A Cochrane review published in 2016 extensively reevaluated phlebotonic herbal supplements (rutoside, French maritime pine bark extract, grape seed extract, diosmin and hidrosmin, disodium flavonate, and centella asiatica)

and synthetic products (calcium dobesilate, naftazone, aminaftone, and chromocarbe). This efficacy analysis included 53 trials (involving 6,013 patients) that studied rutosides (28 trials), hidrosmin and diosmin (10 trials), calcium dobesilate (9 trials), Centella asiatica (2 trials), aminaftone (2 trials), French maritime pine bark extract (2 trials), and grape seed extract (1 trial). Studies evaluating topical phlebotonics, chromocarbe, naftazone, or disodium flavodate were not included. Their findings of moderate-quality evidence showed that phlebotonics may have beneficial effects for reduction of edema and on signs and symptoms related to CVI such as trophic disorders, cramps, restless legs, swelling, and paresthesia. No benefit compared with placebo was found for ulcer healing. Additional high-quality trials focused on clinically important outcomes are needed.<sup>35</sup>

### Pentoxifylline

A Cochrane systematic review evaluating 11 trials using pentoxifylline for venous ulcer healing showed that it is an effective adjunct to compression therapy and may be effective as sole therapy.<sup>36</sup>

### Antibiotics

Patients with cellulitis or infected stasis ulcers should be treated with antibiotics effective against *Staphylococcus* and *Streptococcus* species. Patients should avoid compression garments until the infection is controlled but can reduce edema using leg elevation.<sup>15</sup> An appropriate sampling of tissue should be considered to identify the pathogen or pathogens and select the proper therapy, especially if the infection is recurrent. Options include swabs, needle aspiration, and biopsy (most commonly punch biopsy). A recent meta-analysis on infected wound sample procurement concluded that wound swab may be useful for initial monitoring, the Levine technique being preferred (pressing and rotating swab over 1 cm of tissue for 5 seconds), but biopsies are preferred for evaluation of treatment-resistant wounds and to monitor response. Needle aspiration was not recommended due to unreliability, as it could draw from healthy tissue.<sup>37</sup> The latest clinical practice guidelines from the Society of Vascular Surgery regarding venous wounds recommend against wound culture if no clinical signs of infection are present.<sup>17</sup>

### Exercise Training

There is a paucity of evidence supporting exercise training in the treatment of PTS. However, there is evidence that it does no harm nor aggravates symptoms of PTS.<sup>38</sup> In a prospective study, 42 patients with PTS were randomized to 6 months of exercise training compared with usual care. Exercise training was associated with reduction in PTS severity as assessed by Villalta score, improvement in quality of life, leg strength, and leg flexibility, without adverse events.<sup>39</sup> In another trial, 30 patients with CVI were randomized to 6-month leg muscle-strengthening exercise program or control (all patients were given Class II ECS); exercise was associated with improved calf muscle pump function and dynamic calf muscle strength.<sup>40</sup>

Complex lymphedema therapy (skin care, compression by ESC and/or devices, manual lymphatic drainage, and exercise) has been evaluated in patients with PTS. A small single-center, investigator-blind trial randomized 31 patients with PTS to complex lymphedema therapy or ECS therapy alone. Villalta PTS scores improved from moderate to mild over 3 months with either therapy.<sup>41</sup>

The latest scientific statement from the American Heart Association recommends 6 months of exercise training in patients with PTS who can tolerate it,<sup>2</sup> but additional research is warranted.

### Lifestyle Modifications: Weight Loss, Smoking Cessation, and Leg Elevation

Elevated body mass index (BMI) and obesity are associated with a twofold increased risk of developing PTS.<sup>42</sup> Visceral adiposity has been correlated with the presence and severity of PTS. In a study enrolling 120 patients with DVT who were followed up for 2 years, 49 had PTS by the Villalta scale; higher BMI ( $p = 0.005$ ) and waist circumference ( $p = 0.006$ ) were found among patients with Villalta scale  $\geq 5$  compared with patients without PTS.<sup>43</sup> Weight loss should be encouraged in patients with obesity and DVT, or confirmed PTS.

Although smoking cessation benefits overall cardiovascular health, there are few studies evaluating the benefit in patients with PTS. A case-control trial of 313 women who suffered pregnancy-related DVT compared with 353 controls without DVT reported that daily smoking before the index pregnancy was an independent predictor of PTS.<sup>44</sup>

Patients should elevate their legs above the level of the heart when supine and above the level of their thighs when sitting for 30-minute intervals for at least 3 to 4 hours a day to reduce edema.<sup>45</sup> An early trial evaluating microcirculation in venous disease studied 15 patients with lipodermatosclerosis and 15 controls with laser Doppler flux in different positions and showed enhanced microcirculatory flow velocity with leg elevation.<sup>46</sup> A more recent study used micro-light guide tissue spectrophotometry (a technique that can analyze both arteriolar and micro-venous circulation) in 25 healthy volunteers to establish optimal postsurgical limb positioning to prevent edema, and reported a 28% decrease on superficial venous pooling with leg elevation.<sup>47</sup>

### Conclusion

Compression therapy remains the mainstay and most proven therapy for patients with PTS. ECS are most commonly applied and should be used at least three or more times a week for maximum benefit. If neither ECS nor bandaging is tolerated, adjustable wraps can be applied. In the presence of ulcers, aggressive compression therapy with multilayer bandaging should be considered initially with concomitant pentoxifylline therapy. The strength and duration of compression to achieve maximum efficacy in the prevention and treatment of PTS is under investigation, as it is the choice of initial treatment for DVT. If tolerated, exercise training can be

prescribed for patients with PTS. Smoking cessation, leg elevation, and weight loss are also recommended. Most importantly, education regarding disease presentation, progression, and prognosis is essential for patient compliance.

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