Guidance for the prevention and treatment of the post-thrombotic syndrome

Susan R. Kahn1,5 · Jean-Philippe Galanaud2 · Suresh Vedantham3 · Jeffrey S. Ginsberg4

Abstract The post-thrombotic syndrome (PTS) is a frequent, potentially disabling complication of deep vein thrombosis (DVT) that reduces quality of life and is costly. Clinical manifestations include symptoms and signs such as leg pain and heaviness, edema, redness, telangiectasia, new varicose veins, hyperpigmentation, skin thickening and in severe cases, leg ulcers. The best way to prevent PTS is to prevent DVT with pharmacologic or mechanical thromboprophylaxis used in high risk patients and settings. In patients whose DVT is treated with a vitamin K antagonist, subtherapeutic INRs should be avoided. We do not suggest routine use of elastic compression stockings (ECS) after DVT to prevent PTS, but in patients with acute DVT-related leg swelling that is bothersome, a trial of ECS is reasonable. We suggest that selecting patients for catheter-directed thrombolytic techniques be done on a case-by-case basis, with a focus on patients with extensive thrombosis, recent symptoms onset, and low bleeding risk, who are seen at experienced hospital centers. For patients with established PTS, we suggest prescribing 20–30 mm Hg knee-length ECS to be worn daily. If ineffective, a stronger pressure stocking can be tried. We suggest that intermittent compression devices or pneumatic compression sleeve units be tried in patients with moderate-to-severe PTS whose symptoms are inadequately controlled with ECS alone. We suggest that a supervised exercise training program for 6 months or more is reasonable for PTS patients who can tolerate it. We suggest that management of post-thrombotic ulcers should involve a multidisciplinary approach. We briefly discuss upper extremity PTS and PTS in children.

Keywords Post-thrombotic syndrome · Venous thromboembolism · Deep venous thrombosis · Direct oral anticoagulants (DOAC) · New oral anticoagulants (NOAC)

Introduction

The post-thrombotic syndrome (PTS) is a chronic condition that develops in ~20–50% of patients after deep venous thrombosis (DVT) [1]. It adversely affects health and quality of life, and is costly as measured by health care costs, out of pocket expenditures, and lost productivity.

The objective of this chapter is to provide guidance for the general practitioner, internist, nurse practitioner, pharmacist, and other healthcare professionals on best current practices for the prevention and treatment of PTS.

Background

Traditionally, clinical trials investigating new therapies or management approaches to treat DVT have focused on their effectiveness to prevent recurrent venous thromboembolism (VTE) in the short (3 months) to medium term...
(12 months) after DVT, while their effectiveness to prevent PTS has been ignored. Over the last 10–15 years, however, PTS has been increasingly recognized as a frequent and important outcome of DVT. Recent studies have improved understanding of the epidemiology, risk factors, and health and economic impact of PTS. Recommendations for standardization of the definition of PTS for clinical studies have been published [2], and rigorous clinical trials are underway to evaluate new approaches to preventing and treating PTS. Recently, the first evidence-based guidelines focused solely on PTS were published by the American Heart Association [3].

Methods

To provide guidance on the management of the post-thrombotic syndrome, we first developed a number of pivotal practical questions pertaining to the PTS (Table 1). Questions were developed by consensus from the authors. The literature addressing the questions below was reviewed by searching electronic databases (PubMed, Medline) and the authors’ personal libraries, with a focus on high quality cohort studies and randomized controlled trials published in the last 10 years, where available. For each question, a brief summary and interpretation of pertinent literature and existing guidelines, where available, are provided, followed by guidance for the reader.

Guidance

(1) What is PTS and why is it important (i.e. epidemiology, impact on quality of life, cost)?

PTS is a clinical disorder of pain and disability resulting from chronic venous insufficiency following DVT. PTS is the most frequent complication of DVT. It develops in ~20–50% of patients within 2 years of DVT diagnosis [4, 5], even when patients are adequately treated with anticoagulants, and is severe in 5–10% of cases. Hence on average, about 6 of 10 DVT patients recover without any residual symptoms, 3 of 10 have some degree of PTS, and ~1 of 10 to 1 of 20 develop severe PTS that can include pain leg ulcers. The overall estimated incidence of VTE is 0.7–2 per 1000 person-years and increases with age [6, 7] so that more than one-third of cases occur in persons older than 60 years of age [8]. VTE is a growing public health problem due to increased life expectancy, an increasing proportion of elderly individuals and an expected increase in the prevalence of PTS.

Due to its high prevalence and chronicity, PTS is a costly condition. A Canadian study estimated that the total per-patient cost of PTS over a two-year period was almost 50% higher than for DVT patients without PTS [9]. Costs were largely attributable to frequent healthcare visits and prescription medications. In the United States, annualized median total costs for DVT patients who developed PTS was $20,569 compared with $15,843 in matched controls with DVT and no PTS [10]. Costs are highest in those with PTS who develop venous ulcers, due to surgery, lost workdays and loss of employment [11]. It is estimated that 2 million workdays are lost annually in the United States due to leg ulcers [12].

Studies have shown that compared to DVT patients without PTS, patients with PTS have poorer quality of life [13–16] and scores worsen as severity of PTS increases [17]. Notably, PTS patients report worse quality of life scores than average scores for patients with osteoarthritis, diabetes and chronic lung disease [16].

Guidance Statement Not applicable.

(2) What are the clinical manifestations of PTS and what is its underlying pathophysiology?

The clinical manifestations of PTS are similar to those of primary venous insufficiency and include a constellation of symptoms and signs which vary from patient to patient [18] (Table 2). Typical symptoms include leg pain, a sensation of leg heaviness, pulling or fatigue, and leg swelling. Typical signs may include leg edema, redness, dusky cyanosis when the leg is in a dependent position, telangiectasia, new varicose veins, stasis hyperpigmentation, skin thickening and in severe cases, leg ulcers. The severity of symptoms and signs ranges from minimal discomfort and cosmetic concerns to severe clinical manifestations such as chronic pain, intractable edema, and leg ulceration [1, 19]. The intensity of symptoms and signs increases over the course of the day.

Table 1 Guidance questions to be considered

| Question                                                                 | Guidance                                                                 |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| (1) What is PTS and why is it important (i.e. epidemiology, impact on quality of life, cost)? | PTS is a clinical disorder of pain and disability resulting from chronic venous insufficiency following DVT. PTS is the most frequent complication of DVT. It develops in ~20–50% of patients within 2 years of DVT diagnosis [4, 5], even when patients are adequately treated with anticoagulants, and is severe in 5–10% of cases. Hence on average, about 6 of 10 DVT patients recover without any residual symptoms, 3 of 10 have some degree of PTS, and ~1 of 10 to 1 of 20 develop severe PTS that can include pain leg ulcers. The overall estimated incidence of VTE is 0.7–2 per 1000 person-years and increases with age [6, 7] so that more than one-third of cases occur in persons older than 60 years of age [8]. VTE is a growing public health problem due to increased life expectancy, an increasing proportion of elderly individuals and an expected increase in the prevalence of PTS. Due to its high prevalence and chronicity, PTS is a costly condition. A Canadian study estimated that the total per-patient cost of PTS over a two-year period was almost 50% higher than for DVT patients without PTS [9]. Costs were largely attributable to frequent healthcare visits and prescription medications. In the United States, annualized median total costs for DVT patients who developed PTS was $20,569 compared with $15,843 in matched controls with DVT and no PTS [10]. Costs are highest in those with PTS who develop venous ulcers, due to surgery, lost workdays and loss of employment [11]. It is estimated that 2 million workdays are lost annually in the United States due to leg ulcers [12]. Studies have shown that compared to DVT patients without PTS, patients with PTS have poorer quality of life [13–16] and scores worsen as severity of PTS increases [17]. Notably, PTS patients report worse quality of life scores than average scores for patients with osteoarthritis, diabetes and chronic lung disease [16]. |
| (2) What are the clinical manifestations of PTS and what is its underlying pathophysiology? | The clinical manifestations of PTS are similar to those of primary venous insufficiency and include a constellation of symptoms and signs which vary from patient to patient [18] (Table 2). Typical symptoms include leg pain, a sensation of leg heaviness, pulling or fatigue, and leg swelling. Typical signs may include leg edema, redness, dusky cyanosis when the leg is in a dependent position, telangiectasia, new varicose veins, stasis hyperpigmentation, skin thickening and in severe cases, leg ulcers. The severity of symptoms and signs ranges from minimal discomfort and cosmetic concerns to severe clinical manifestations such as chronic pain, intractable edema, and leg ulceration [1, 19]. The intensity of symptoms and signs increases over the course of the day. |
PTS is thought to develop after DVT due to venous hypertension (i.e. increased venous pressures) [20]. Venous hypertension leads to reduced calf muscle perfusion, increased tissue permeability and the associated clinical manifestations of PTS. Two pathological mechanisms contribute to venous hypertension: persistent (acute, then residual) venous obstruction (RVO) and valvular reflux caused by vein valve damage [21]. 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 [22, 23]. There may also be a genetic predisposition to PTS from gene polymorphisms associated mainly with vein wall remodelling [24].

Guidance Statement  Not applicable.

(3) How is PTS diagnosed?

There is no gold standard laboratory, imaging, or functional 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. Symptoms of PTS can be present in various combinations and may be persistent or intermittent. Symptoms tend to be aggravated by standing or walking and tend to improve with rest and leg elevation. In some patients, it can take a few months for the initial pain and swelling associated with acute DVT to resolve, thus a diagnosis of PTS should be deferred until after the acute phase (i.e. 3–6 months) has passed. Symptoms of PTS usually occur within 3–6 months after DVT, but can occur up to 2 years after DVT [25].

The Villalta PTS scale (sometimes called the Villalta-Prandoni scale) [26] has been adopted by the International Society on Thrombosis and Haemostasis (ISTH) as a standard to diagnose and grade the severity of PTS in clinical studies [2]. The scale’s components (5 symptoms and 6 signs) are each rated on a 4-point severity scale, and the points are summed to produce a total score; a score ≥4 denotes PTS (Table 3). The Villalta PTS scale has been shown to be valid, reproducible, and responsive to clinical change, and is easy to administer [27]. The Villalta PTS scale has been used to diagnose PTS in a number of recent randomized trials of interventions to prevent and treat PTS [28–32]. Additional diagnostic scales have been used to assess PTS, including the CAEP classification and Ginsberg measure; these are discussed in reference 2.

Guidance Statement  We suggest that in patients with a history of VTE, the Villalta PTS scale be used to assess the presence and severity of the PTS.

(4) What are known risk factors for PTS?

While it is not yet possible to precisely predict the absolute risk of PTS in an individual patient with DVT, research done over the last 10 years has provided new information on various risk factors for PTS [1, 33]. This information is summarized below; the strongest risk factors are indicated with*:  

Risk factors apparent at time of DVT diagnosis

- **Age:** Older age increases the risk of PTS.
- **Elevated body mass index (BMI):** Increased risk of PTS.
- **Pre-existing primary venous insufficiency:** Increased risk of PTS [34, 35].
- **Characteristics of initial DVT:** Risk of PTS is higher (2–3-fold) after proximal (especially with involvement of the iliac or common femoral vein) than distal (calf) DVT. Whether DVT was unprovoked vs. secondary (e.g. due to recent surgery, trauma, immobilization or active cancer) does not appear to influence the risk of developing PTS [5, 29].

### Table 2  Typical clinical features of the PTS

| Leg symptoms         | Signs                          |
|----------------------|--------------------------------|
| Heaviness or tiredness | Edema                          |
| Pain                 | Peri-malleolar telangiectasie  |
| Swelling             | Venous ectasia, varicose veins  |
| Itching              | Hyperpigmentation              |
| Cramps               | Redness                        |
| Paresthesia          | Dependent cyanosis             |
| Bursting pain        | Lipodermatosclerosis           |
| Symptom pattern: worse with activity, standing, walking, better with rest, lying down, maximum at end of day | Healed ulcer(s) or open ulcer(s) |

### Table 3  Villalta PTS scale [2, 26]

| Criteria used to diagnose PTS |
|-------------------------------|
| 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)  |
| Points are summed to yield total Villalta-PTS score  |
| 0–4 No PTS  |
| 5–9 Mild PTS  |
| 10–14 Moderate PTS  |
| 15 or more, or presence of ulcer: severe PTS  |
• Gender, Inherited thrombophilia: No consistent relationship with PTS [33, 36].

Risk factors related to treatment of acute DVT
• Quality of oral anticoagulation: PTS risk increases (twofold) if level of anticoagulation is inadequate (e.g. subtherapeutic INR > 50 % time) during the first 3 months of treatment with vitamin K antagonists [37, 38].

Risk factors apparent during follow-up after DVT
• Recurrent ipsilateral DVT: Increases risk of PTS by 4–6-fold, presumably by damaging compromised venous valves or aggravating venous outflow obstruction [4, 5].
• Persistent venous symptoms/signs 1 month after acute DVT: Increased risk of subsequent PTS [5, 39].
• Residual thrombosis on ultrasound (e.g. 3–6 months after acute DVT): Modest (1.5–2-fold) increased risk of PTS [40].
• 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 [41].

Guidance Statement Not applicable.

(5) Is there a best anticoagulant to treat DVT that influences the occurrence of PTS?

It is not known whether use of the new direct, target-specific oral anticoagulants to treat DVT influences the risk of PTS, compared to treatment with low molecular weight heparin (LMWH) and vitamin K antagonists [42]. Interestingly, some data suggest that use of LMWH monotherapy to treat DVT may lead to lower rates of PTS than standard treatment with LMWH followed by vitamin K antagonists [43]. These data require confirmation in large, well-designed RCTs.

Guidance Statement Data are insufficient to make any recommendations regarding choice of anticoagulant, specifically a vitamin K antagonist vs. a target-specific oral anticoagulant, on the outcome of developing PTS.

(6) What are current best approaches to preventing PTS after DVT?

Primary prevention of DVT

Guidance Statement The best way to prevent PTS is to prevent the occurrence of DVT. We therefore suggest the use of pharmacologic or mechanical thromboprophylaxis to prevent VTE in high risk patients and settings, as recommended in evidence-based consensus guidelines [44–46].

Prevention of DVT recurrence

As ipsilateral DVT recurrence is an important risk factor for PTS, preventing recurrent DVT by providing optimal anticoagulation of appropriate intensity and duration for the initial DVT is a key goal [47]. For specific suggestions on optimal anticoagulation to treat DVT, the reader is referred to the chapter in this volume titled ‘Guidance for the treatment of DVT and PE.

Guidance Statement 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.

Elastic compression stockings

Elastic compression stockings (ECS), by reducing edema 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. Two previous small, randomized, open label trials reported that wearing 30–40 mm Hg knee-high ECS for at least 2 years after proximal DVT was effective in preventing PTS [29, 48]. Based on these data, evidence-based consensus guidelines have recommended the use of ECS for at least 2 years after DVT to prevent PTS [47, 49]. However, a recent large (n = 803), multicenter, randomized, placebo-controlled trial showed no evidence of benefit of active compression stockings, worn for 2 years after proximal DVT, to prevent PTS: rates of PTS, recurrent VTE and QOL scores were similar in the active and placebo stockings groups [31]. Further, a secondary analysis of that trial showed no difference in pain scores during the first 60 days after DVT in the active and placebo stockings groups. The placebo-controlled blinded design of this trial is an important methodological strength, owing to the subjective nature of PTS assessment [50].

Guidance Statement Based on these data, we do not suggest the routine use of ECS to prevent PTS in DVT patients, or to relieve acute DVT-related pain. However, because the trials cannot rule out a benefit of ECS in small sub-groups of patients or even to exploit a placebo benefit of ECS in patients with acute DVT-related leg swelling that is bothersome or uncomfortable, a trial of 20–30 mm Hg or 30–40 mm Hg ECS is not unreasonable.

Thrombolysis

Upfront 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 [21, 51]. Catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (catheter-directed thrombolysis + mechanical disruption of thrombus) are likely to be safer and more effective than systemic thrombolytic therapy and could hold promise as a means of preventing PTS, primarily after proximal DVT [52]. In one multicenter randomized controlled trial of modest (n = 189) size, the use of additional CDT in anticoagulated patients with acute DVT involving the iliac and/or upper femoral vein was associated with a 26 % reduction in the risk of developing PTS over 2 years follow-up, with an additional 3 % rate of major bleeding [30]. Larger multicenter trials of PCDT+ standard anticoagulation vs. standard anticoagulation alone to prevent PTS are ongoing [53, 54] and results are expected within 1–2 years. The role of thrombolysis and other endovascular approaches in the management of DVT is discussed in greater depth in the Guidance for the use of Thrombolytic Therapy for DVT and PE chapter in this volume.

Guidance Statement  We suggest that selection of patients for catheter-directed thrombolytic techniques should be done on a case-by-case basis, with a predominant focus on patients with extensive (e.g. iliofemoral) thrombosis, recent onset of symptoms, low risk of bleeding and long life expectancy, [47] who are seen at hospital centers experienced in performing these techniques.

(7) What are current best approaches to treating established PTS?

Compression-based therapies

A number of compression-based therapies have been used with the goals of reducing PTS symptoms (especially leg swelling and discomfort) and improving daily functioning. However, few controlled studies of their effectiveness have been performed, and available controlled studies are small, with limited follow-up time. Therefore, the suggestions below are based primarily on the low risk of harm and the possibility of benefit to at least some patients.

Guidance Statement  We suggest the following management approach for compression-based therapies: Prescribe 20–30 mm Hg ECS to patients with PTS-related leg heaviness or swelling. We suggest knee-length ECS, which have similar physiologic effects to thigh-length ECS and are easier to apply, more comfortable and less costly. Explain to the patient that these are to be worn daily, from waking to retiring. If 20–30 mm Hg ECS do not adequately control PTS symptoms, a stronger pressure stocking (30–40 mm Hg; or 40–50 mm Hg) can be tried [32]. We suggest that the portable, battery-powered Venowave® intermittent pneumatic compression device be tried in patients with moderate to severe PTS whose symptoms are not adequately controlled with ECS alone [28, 47]. We suggest that intermittent pneumatic compression sleeve units (e.g. used for 20–30 min sessions, 2–3 times per day) can be used to help severe, intractable PTS symptoms or severe edema [55], however patients may find these to be cumbersome and the units are expensive.

Pharmacotherapy

Four randomized trials have been performed to evaluate the effectiveness of “venoactive” drugs for PTS: three parallel trials [56–58] and one crossover study [59]. The drugs evaluated were rutosides (thought to reduce capillary filtration and microvascular permeability), defibrotide (down-regulates plasminogen activator inhibitor-1 release and up-regulates prostacyclin, prostaglandin E2, and thrombomodulin), and hidrosm (mechanism of action unknown) [60]. Overall, there is low-quality evidence to support the use of venoactive drugs to treat PTS as studies were limited by a high degree of inconsistency and imprecision [60]. Also, as drug treatment was usually of short duration (e.g. 8 weeks to a few months), potential long-term side effects are unknown.

Guidance Statement  We do not suggest the use of venoactive drugs to treat PTS. Also, due to an absence of evidence and potential for harm, we do not suggest the use of diuretics to treat PTS-related edema.

Exercise and lifestyle

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 six month leg muscle strengthening exercise program led to improved calf muscle function and calf muscle strength [61]. In a two-center Canadian pilot study, a 6 month program of exercise training that consisted of exercises to increase leg strength, leg flexibility and overall cardiovascular fitness improved PTS severity, quality of life, leg strength and leg flexibility, and there were no adverse events [62]. While not definitive, the available data suggest that exercise may benefit patients with PTS.

Common sense advice that is relevant to all patients with chronic venous insufficiency includes: promote venous return by avoiding a sedentary lifestyle, raising the legs on a stool when seated or elevating the legs in bed when lying down; avoid prolonged exposure to heat; maintain a healthy, non-obese body weight; and use a moisturizing cream to avoid skin dryness.

Guidance Statement  We suggest that a supervised exercise training program consisting of leg strengthening...
Table 4 Summary of guidance statements

| Question                                                                 | Guidance statement                                                                 |
|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| (1) What is PTS and why is it important?                                | Not applicable; see text                                                            |
| (2) What are the clinical manifestations of PTS and what is its underlying pathophysiology? | Not applicable; see text                                                            |
| (3) How is PTS diagnosed?                                               | We recommend that in patients with a history of VTE, the Villalta PTS scale be used to assess the presence and severity of the PTS |
| (4) What are known risk factors for PTS?                                | Data are insufficient to make any recommendations regarding choice of anticoagulant, specifically, a vitamin K antagonist vs a target-specific oral anticoagulant, on the outcome of developing PTS |
| (5) Is there a best anticoagulant to treat DVT that influences the occurrence of PTS? | Data are insufficient to make any recommendations regarding choice of anticoagulant, specifically, a vitamin K antagonist vs a target-specific oral anticoagulant, on the outcome of developing PTS |
| (6) What are current best approaches to preventing PTS after DVT?        | For primary prevention                                                            |
|                                                                        | Prevent the index DVT with use of thromboprophylaxis in high-risk patients and settings as recommended in evidence-based consensus guidelines |
|                                                                        | For prevention of recurrent DVT                                                   |
|                                                                        | 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 |
|                                                                        | Value of elastic compression stockings                                           |
|                                                                        | We do not suggest the routine use of ECS to prevent PTS in DVT patients, or to relieve acute DVT-related pain. However, in patients with acute DVT-related leg swelling that is bothersome or uncomfortable, we suggest a trial of 20–30 mm Hg or 30–40 mm Hg ECS to relieve edema |
|                                                                        | Value of thrombolysis                                                            |
|                                                                        | The role of thrombolysis for the prevention of PTS is not yet established. In particular, pharmacomechanical catheter-directed thrombolysis requires further evaluation in properly designed trials. For now, we suggest that selection of patients for these techniques should be done on a case-by-case basis, and mainly considered for select patients with extensive thrombosis, recent onset symptoms, low bleeding risk and long life expectancy |
| (7) What are current best approaches to treating PTS?                   | Elastic compression stockings                                                     |
|                                                                        | We suggest the use of 20–30 mm Hg (or stronger, if ineffective) ECS to reduce edema and improve PTS symptoms |
|                                                                        | We suggest a trial of intermittent pneumatic compression devices in patients with moderate to severe symptomatic PTS |
|                                                                        | Pharmacotherapy                                                                  |
|                                                                        | We do not suggest the use of venoactive drugs to treat PTS. Also, due an absence of evidence and potential for harm we do not suggest the use of diuretics to treat PTS-related edema. |
|                                                                        | Exercise and lifestyle                                                           |
|                                                                        | We suggest that a supervised exercise training program with leg strengthening and aerobic components for 6 or more months be tried in PTS patients who can tolerate it |
|                                                                        | Management of venous ulcers                                                       |
|                                                                        | We suggest a multidisciplinary approach to venous ulcer management, which usually consists of compression therapy, skin care and topical dressings |
|                                                                        | In patients with symptoms of upper extremity PTS, we suggest a trial of a 20–30 mm Hg or 30–40 mm Hg compression sleeve |
| (8) Does PTS occur after upper extremity DVT?                           | Due to potential for benefit and low potential for harm, we suggest a trial of a 20–30 mm Hg or 30–40 mm Hg compression sleeve in patients with symptoms of upper extremity PTS |
| (9) Does PTS occur after DVT in children?                              | At present, we suggest that symptomatic management of PTS in children should generally follow adult guidelines, and that where possible, pediatricians with expertise in thromboembolism should manage pediatric patients with DVT |
and aerobic activity for 6 months or more is reasonable for PTS patients who can tolerate it.

**Venous ulcer management**

Five to 10% of DVT patients develop severe PTS, which can include leg ulcers. Post-thrombotic venous ulcers are treated with compression therapy, leg elevation, topical dressings and sometimes hemorheological agents like pentoxifylline but can be refractory to therapy and tend to recur.

**Guidance Statement** We suggest that ideally, management of patients with post-thrombotic ulcers involves a multidisciplinary approach that includes an internist, dermatologist, vascular surgeon and wound care nurse. For more detailed discussion of venous ulcer management, please refer to recent published reviews [63, 64] and consensus guidelines [3].

**Surgical or endovascular treatments for PTS**

Surgical or endovascular procedures such as venous valve repair, venous bypass and venous stents to treat appropriately selected PTS patients have potential to decrease post-thrombotic manifestations that are attributable to deep vein obstruction or VR [65, 66]. However, because well-designed studies have not been performed to date, experience with these procedures varies substantially among providers, and rates of complications and failure are uncertain, these interventions should not be routinely utilized in unselected PTS populations. Rather, the opportunity to consult with an endovascular subspecialist who is experienced with the assessment and management of complex venous disease may be appropriate to discuss with selected patients with moderate-to-severe PTS who have substantial disability and life limitations. For more detailed discussion of surgical and endovascular treatments for PTS, please refer to a recently published AHA consensus guideline [3].

(8) Does PTS occur after upper extremity DVT?

After upper extremity DVT, 15–25% of patients will develop PTS [67, 68]. As with lower limb PTS, upper extremity PTS can reduce quality of life and limb function [69, 70]. Not surprisingly, dominant arm PTS is associated with worse quality of life and disability than non-dominant arm PTS [69]. 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 thrombolysis, endovascular or surgical treatment of UEDVT results in lower rates of PTS than standard anticoagulation alone.

**Guidance Statement** Due to potential for benefit and low potential for harm, we suggest a trial of a 20–30 mm Hg or 30–40 mm Hg compression sleeve in patients with symptoms of upper extremity PTS.

(9) Does PTS occur after DVT in children?

The incidence of PTS is reported to be as high as 15–25% in children with DVT [71, 72]. There are no pediatric studies that have evaluated the safety and effectiveness of therapies to prevent or treat PTS.

**Guidance Statement** At present, we suggest that symptomatic management of PTS in children should generally follow adult guidelines, and that where possible, pediatricians with expertise in thromboembolism should manage pediatric patients with DVT.

(10) What are the most pressing research needs in the field?

- Mechanistic studies to improve our understanding of the pathophysiology of PTS and to suggest future therapeutic targets
- Development of risk prediction indices to predict risk of PTS at the time of DVT diagnosis, in order to help guide the longitudinal management of patients with DVT
- Study of the role of risk factor modification (e.g. weight reduction, exercise) to prevent or treat PTS
- Assessment of the impact and cost-effectiveness of direct, target specific oral anticoagulants on the risk of PTS
- Assessment of the effectiveness, tolerability and cost-effectiveness of extended LMWH therapy to prevent PTS
- Studies of the effectiveness, safety and cost-effectiveness of PCDT to treat DVT as a means to prevent PTS
- Studies of the effectiveness of ECS and other compression modalities to treat lower extremity PTS, upper extremity PTS and pediatric PTS
- Assessment of the role of CDT/PCDT for prevention of upper extremity PTS and pediatric PTS
- Rigorous evaluation of the safety and long-term effectiveness of endovascular and surgical procedures to treat severe PTS

**Conclusion**

PTS is a frequent complication of DVT that has the potential to reduce quality of life and lead to chronic functional disability. In this chapter, we have tried to provide guidance on key aspects relating to the diagnosis, risk factors, prevention and treatment of PTS (Table 4). Based on the numerous gaps in knowledge of PTS, we have also identified important areas for further research.
Acknowledgments We wish to acknowledge the support provided by Myelin and Associates with the preparation of this manuscript for submission. The work contained in this manuscript was partially funded by support from the following companies: Boehringer Ingelheim, Daiichi Sankyo and Janssen Pharmaceuticals. This guidance document is endorsed by the Anticoagulation Forum’s Board of Directors: Mark Crowther, MD, MSc, FRCPC, Jack E. Ansell, MD, Allison Burnett, PharmD, Nathan Clark, PharmD, Adam Cuker, MD, David Garcia, MD, Scott Kaatz, DO, MSc, FACP, Renato D. Lopes, MD, PhD, Tracy Minichillo, MD, Edith Nutescu, PharmD, FCPP, Lynn Oertel, MS, ANP, CACP, Eva Kline-Rogers, MS, RN, NP, Terri Schnurr, RN, CCRC, Michael Streiff, MD, Diane Wirth, ANP, CACP, BCPS, CACP, Daniel Witt, PharmD, Ann Wittkowsky, PharmD, CACP, FASHP, FCPP.

Compliance with ethical standards

Disclosures S Kahn: None. JP Galanauad: Bayer and Daiichi-Sankyo. S VanDetham: Research support from Covidien, Bayer Healthcare, BSN Medical, Genentech, Cook Inc., Volcano, Inc. J Ginsberg: None.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Kahn SR (2009) How I treat postthrombotic syndrome. Blood 114(21):4624–4631
2. Kahn SR, Peshch H, Vedantham S, Prandoni P, Kearon C (2009) Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 7:879–883
3. Kahn SR, Comerota AJ, Cushman M et al (2014) The post-thrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies a scientific statement from the American Heart Association. Circulation 130(18):1636–1661
4. Prandoni P, Lensing AWA, Cogo A et al (1996) The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 125(1):1–7
5. Kahn SR, Shrier I, Julian JA et al (2008) Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 149(10):698–707
6. Spencer FA, Emery C, Joffe SW et al (2009) Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism: The Worcester VTE study. J Thromb 28(4):401–409
7. Tagalakis V, Patenaude V, Kahn SR, Suissa S (2013) Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE study cohort. Am J Med 126(9):832.e813-821
8. Naess IA, Christiansen SC, Romundstad P, Cnaggeiter SC, Rosendaal FR, Hammerstrom J (2007) Incidence and mortality of venous thromboembolism: a population-based study. J Thromb Haemost 5(4):692–699
9. Guanella R, Ducruet T, Johri M et al (2011) Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost 9(12):2397–2405
10. MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J (2006) Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm 63(20):S5–S15
11. Caprini JA, Botteman MF, Stephens JM et al (2003) Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value Health 6(1):59–74
12. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseeau MR, Eklof B (2006) Chronic venous disease. N Engl J Med 355(5):488–498
13. van Korlaar I, Vossen C, Rosendaal F, Cameron L, Bovill E, Kaptein A (2003) Quality of life in venous disease. Thromb Haemost 90(1):27–35
14. Kahn SR, Ducruet T, Lamping DL et al (2005) Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. Arch Intern Med 165(10):1173–1178
15. Broholm R, Sillesen H, Damsgaard MT et al (2011) Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis. J Vasc Surg 54(6 Suppl):18S–25S
16. Kahn SR, Shbaklo H, Lamping DL et al (2008) Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost 6(7):1105–1112
17. Kahn SR, Hirsch A, Shrier I (2002) Effect of post-thrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 162:1144–1148
18. Kahn SR, Ginsberg JS (2004) Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Int Med 164:17–26
19. Prandoni P, Kahn SR (2009) Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 145(3):286–295
20. Kolbach DN, Neumann HA, Prins MH (2005) Definition of the post-thrombotic syndrome, differences between existing classifications. Eur J Vasc Endovasc Surg 30(4):404–414
21. Vedantham S (2009) Valvular dysfunction and venous obstruction in the post-thrombotic syndrome. Thromb Res 123(4 Suppl):S62–S65
22. Beatrick KB, Eliffe M, Baker N et al (2011) Postthrombotic vein wall remodeling: preliminary observations. J Vasc Surg 53(1):139–146
23. Henke PK, Varma MR, Mouweni DK et al (2007) Fibrotic injury after experimental deep vein thrombosis is determined by the mechanism of thrombogenesis. Thromb Haemost 98(5):1045–1055
24. Bharath V, Kahn SR, Lazo-Langner A (2014) Genetic polymorphisms of vein wall remodeling in chronic venous disease: a narrative and systematic review. Blood 124(8):1242–1250
25. Roumen-Klappe EM, den Heijer M, Janssen MC, van der Vleuten C, Thien T, Wollersheim H (2005) The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. Thromb Haemost 94(4):825–830
26. Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P (1994) Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis 24(1 Suppl):158a
27. Kahn SR (2009) Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. J Thromb Haemost 7:884–888
28. O’Donnell MJ, McRae S, Kahn SR et al (2008) Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS) — a randomized controlled trial. Thromb Haemost 99(3):623–629
29. Prandoni P, Lensing AWA, Prins MH et al (2004) Below-knee elastic compression stockings to prevent the post-thrombotic
30. Enden T, Haig Y, Kleow NE et al (2012) Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliopelvic deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 379(9810):31–38

31. Kahn SR, Shapiro S, Wells PS et al (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 383(9920):880–888

32. Holmes CE, Bambace NM, Lewis P, Callas PW, Cushman M (2014) Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome. Vasc Med 19(1):42–48

33. Rabinovich A, Kahn SR (2014) How to predict and diagnose postthrombotic syndrome. Pol Arch Med Wewn 124(7–8):410–416

34. Galanaud JP, Holcroft CA, Rodger MA et al (2013) Predictors of post-thrombotic syndrome in a population with a first deep vein thrombosis and no primary venous insufficiency. J Thromb Haemost 11(3):474–480

35. Bouman AC, Smits JJ, Ten Cate H, Ten Cate-Hoek AJ (2012) Markers of coagulation, fibrinolysis and inflammation in relation to post-thrombotic syndrome. J Thromb Haemost 10(8):1532–1538

36. Rabinovich A, Cohen JM, Prandoni P, Kahn SR (2014) Association between thrombophilia and the post-thrombotic syndrome: a systematic review and meta-analysis. J Thromb Haemost 12(1):14–23

37. van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutton BA (2005) Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 3(5):939–942

38. Chitsike RS, Rodger MA, Kovacs MJ et al (2012) Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. J Thromb Haemost 10(10):2039–2044

39. Roberts LN, Patel RK, Chitongo PB, Bonner L, Arya R (2013) Presenting D-dimer and early symptom severity are independent predictors for post-thrombotic syndrome following a first deep vein thrombosis. Br J Haematol 160(6):817–824

40. Prandoni P, Frulla M, Sarto D, Concolato A, Girolami A (2005) Vein abnormalities and the post-thrombotic syndrome. J Thromb Haemost 3(2):401–402

41. Rabinovich A, Cohen JM, Kahn SR (2014) The predictive value of markers of fibrinolysis and endothelial dysfunction in the post-thrombotic syndrome. A systematic review. Thromb Haemost 111(6):1031–1040

42. Baglin T (2012) Prevention of post-thrombotic syndrome: a case for new oral anticoagulant drugs or for heparins? J Thromb Haemost 10(8):1702–1703

43. Hull RD, Liang J, Townshend G (2011) Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. Ann Med 124(8):756–765

44. Gould MK, Garcia DA, Wren SM et al (2012) Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e227S–e277S

45. Faile-Ýtter Y, Francis CW, Johanson NA et al (2012) Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e278S–e325S

46. Kahn SR, Lim W, Dunn AS et al (2012) Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e195S–e226S

47. Kearon C, Akl EA, Comerota AJ et al (2012) Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e419S–e494S

48. Brandjes DPM, Buller HR, Heijboer H, Hulsman MV, de Rijk M, Jagt H (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 349:759–762

49. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ (2008) Antithrombotic therapy for venous thromboembolic disease: ACCP evidence-based clinical practice guidelines (8th edition). Chest 133(6 Suppl):e454S–e545S

50. Kahn SR, Shapiro S, Ducruet T et al (2014) Graduated compression stockings to treat acute leg pain associated with proximal DVT: A randomised controlled trial. Thromb Haemost 112(6):1137–1141

51. Comerota AJ, Grewal N, Martinez JT et al (2012) Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. J Vasc Surg 55(3):768–773

52. Watson L, Broderick C, Armon MP (2014) Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev 1:CD002783

53. Vedanathan S, Goldhaber S, Kahn S et al (2013) Rationale and Design of the ATTRACKT Study—a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with proximal deep vein thrombosis. Am Heart J 165(4):523–530

54. DUTCH CAVA-trial: Catheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT. Clinicaltrials.gov identifier NCT00970619. Accessed 3 Sept 2014

55. Ginsberg JS, Magier D, MacKinnon B, Gent M, Hirsh J (1999) Intermittent compression units for severe post-phlebitic syndrome: a randomized crossover study. CMAJ 160:1303–1306

56. de Jongst AB, Jonker JJ, Huisman MV, ten Cate JW, Azar AJ (2014) A double blind three center clinical trial on the short-term efficacy of 0-(beta-hydroxyethyl)-rutosides in patients with post-thrombotic syndrome. Thromb Haemost 62(3):826–829

57. Coccheri S, Andreozzi GM, D’Addato M, Gensini GF (2004) Effects of defibrotide in patients with chronic deep insufficiency. Phlebology 9(1):37–40

58. Ginsburg ES, Farahmand B, Khoury N, Gerber JS (2009) Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome: A randomized controlled two-centre trial. CMAJ 183(1):37–44

59. Monreal M, Callejas JM, Martorell A, Lisbona C, Lerma R (1999) A prospective study of the long-term efficacy of two different venoactive drugs in patients with post-thrombotic syndrome. Phlebology 9(1):37–40

60. Comerota AJ, Akl EA, Kahn SR (2012) Pharmacologic and compression therapies for postthrombotic syndrome: A systematic review of randomized controlled trials. Chest 141(2):308–320

61. Padberg JR, Johnston MV, Sisto SA (2004) Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. J Vasc Surg 39(1):79–87

62. Kahn SR, Shrier I, Shapiro S et al (2011) Six-month exercise treatment and the development of the post-thrombotic syndrome: a randomized controlled two-centre trial. CMAJ 183(1):37–44

63. O’Meara S, Cullum N, Nelson EA, Dumville JC (2012) Compression for venous leg ulcers. Cochrane database of systematic reviews 11:CD00265

64. Jull AB, Arroll B, Parag V, Waters J (2012) Pentoxifylline for treating venous leg ulcers. Cochrane database of systematic reviews 12:CD001733
65. Neglen P, Hollis KC, Raju S (2006) Combined saphenous ablation and iliac stent placement for complex severe chronic venous disease. J Vasc Surg 44(4):828–833
66. Nayak L, Hildebolt CF, Vedantham S (2012) Postthrombotic syndrome: feasibility of a strategy of imaging-guided endovascular intervention. J Vasc Interv Radiol 23(9):1165–1173
67. Elman ER, Kahn SR (2006) The post-thrombotic syndrome after upper extremity deep venous thrombosis: a systematic review. Thromb Res 117(6):609–614
68. Prandoni P, Bernardi E, Marchiori A et al (2004) The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. BMJ 329(7464):484–485
69. Kahn SR, Elman EA, Bornais C, Blostein M, Wells PS (2005) Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. Thromb Haemost 93(3):499–502
70. Czihal M, Paul S, Rademacher A, Bernau C, Hoffmann U (2012) Impact of the postthrombotic syndrome on quality of life after primary upper extremity deep venous thrombosis. VASA. Zeitschrift fur Gefasskrankheiten 41(3):200–204
71. Goldenberg NA, Donadini MP, Kahn SR et al (2010) Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. Haematologica 95(11):1952–1959
72. Monagle P, Chan AK, Goldenberg NA et al (2012) Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e737S–e801S