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Incidence and Cost Burden of Post-Thrombotic Syndrome

Aneel A. Ashrani[1] and **John A. Heit**[1,2]

[1]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

[2]Division of Cardiovascular Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN.

Abstract

Post-thrombotic syndrome (PTS) is a long-term complication of deep-vein thrombosis (DVT), manifesting as swelling, pain, edema, venous ectasia, and skin induration of the affected limb. PTS has been estimated to affect 23–60% of individuals with DVT, frequently occurring within 2 years of the DVT episode. Symptomatic DVT, post-operative asymptomatic DVT, and recurrent DVT are all risk factors for the development of PTS. Treatment of PTS is often ineffective and treatment-related costs represent a healthcare burden. Therefore, prevention of DVT is essential to reduce PTS, and thus improve outcomes and reduce overall healthcare costs. Although recommended by guidelines, appropriate DVT prophylaxis remains considerably underused. This review evaluates the incidence, risk factors, and economic impact of PTS. Increasing the awareness of PTS, and the methods to prevent this complication may help reduce its incidence, improve long-term outcomes in patients, and decrease resulting costs associated with treatment.

Keywords

anticoagulant therapy; deep-vein thrombosis; post-thrombotic syndrome; venous leg ulcers

Introduction

Post-thrombotic syndrome (PTS) is a long-term complication of deep-vein thrombosis (DVT). The term venous stasis syndrome (VSS) is sometimes used to describe the symptoms of PTS when observed in patients without a prior history of DVT. The classic symptoms of PTS are dependent swelling, pain, edema, venous ectasia, and skin induration of the affected limb [1]. Severe PTS can lead to painful intractable venous leg ulcers which decrease mobility, and require medical and nursing care [1]. Even in less severe cases, the quality of life (QoL) and functional status of affected patients may be impaired [2, 3].

In a population-based study, the estimated annual incidence of VSS and venous ulcer was estimated as 76 and 18 per 100,000 person-years, respectively [4]. Between 23–60% of patients with symptomatic DVT are likely to suffer from PTS within 2 years and up to 10%

Address correspondence to: Aneel A. Ashrani, Stabile 6-60 Hematology Research, Mayo Clinic, 200 First Street, Southwest, Rochester, MN 55905, USA, ashrani.aneel@mayo.edu, Tel.: +1 507 284 4634, Fax: +1 507 266 9302..

Conflicts of interest

No potential financial conflicts of interest.

will develop venous ulcers within 1–2 years [5–10], with rates further increasing thereafter [11]. Although PTS may become apparent soon after DVT, it is notable that the cumulative incidence of PTS continues to increase for 20 years after an initial DVT event [12]. This highlights the fact that the risk of PTS persists long-term.

The socioeconomic impact of chronic venous diseases is significant, with the estimated annual direct cost of VSS being at least US $200 million [4]. In addition, the indirect costs of VSS are prohibitive, as an estimated 2 million workdays are lost annually in the US because of leg ulcers [13]. It is anticipated that the costs of PTS would be even higher than those of VSS alone, due to the prior presence of DVT in patients with PTS. Despite the high cumulative incidence of PTS and its impact on healthcare costs and patient's QoL, it still remains a largely unresolved problem. The aim of this article is to review the existing data on the incidence, risk factors and cost of PTS, and to identify measures that could prevent it. Prevention of PTS would in turn improve long-term patient outcomes and reduce medical care costs in these patients.

Clinical characteristics of PTS

Pathophysiology

It has been postulated that venous hypertension and abnormal microcirculation leading to tissue hypoxia are the main predisposing factors for PTS, resulting in valvular destruction, venous incompetence, and/or persistent venous outflow obstruction (**Fig. 1**) [14]. DVT is usually responsible for venous valve damage, either due to thrombus-induced inflammation or from physical scarring, leading to valvular incompetence [13]. In addition, incomplete vein recanalization following DVT may obstruct venous outflow leading to collateral circulation via superficial and perforator veins, which gradually become incompetent and varicose [14]. These processes lead to venous hypertension, which can be assessed by ambulatory venous pressure measurement, and which has both diagnostic and prognostic significance for PTS [15–18]. Moreover, a strong association has between noted between severe PTS and valvular incompetence [19–22]. However, many patients with severe reflux have only mild symptoms of PTS, suggesting that additional factors may be contributing to the development of symptomatic PTS [21].

Clinical features

Symptoms associated with PTS include pain (especially related to exertion), cramps, heaviness, paresthesias, and pruritus in the affected limb. The characteristic signs include affected limb edema, telangiectasia, venous ectasia, skin hyper-pigmentation, skin induration (lipodermatosclerosis) and, eventually, skin ulceration [14, 23].

Diagnosis

PTS is the most common cause of venous ulcer development [12]. However, it can only be diagnosed 3–6 months after an acute episode of DVT; once the symptoms of DVT are no longer evident. Diagnosis of PTS should be based on the presence of typical clinical features, as listed in **Table 1** [24]. The presence of venous valvular reflux and demonstration of venous hypertension supports a diagnosis of PTS in symptomatic patients [14] (Table 1).

Various clinical scales have been developed to help diagnose PTS. These include the Widmer scale [25], the Villalta scale [24], the Ginsberg measure [26], and scoring schemes based on the Clinical–Etiology–Anatomic–Photophysiologic (CEAP) system [27, 28].

The Widmer scale was initially meant to grade chronic venous insufficiency and took only clinical signs into account. These were graded into classes I (ankle flare, subclinical edema), II (edema, pigmentation, lipodermatosclerosis, skin atrophy), or III (leg ulcer, current or past). The Villalta scale grades the severity of five symptoms (pain, cramps, heaviness, pruritus, and paresthesias) and six signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain on calf compression) from 0–3. A total score of ≥5–14 indicates mild-to-moderate PTS, and a score ≥15 or presence of a venous ulcer indicates severe PTS. The Ginsberg measure defines PTS by the presence of daily leg pain and swelling for 1 month, occurring 6 months or more after a DVT event, made worse by standing/walking and relieved by rest/leg elevation. The CEAP scoring system comprises of three components – a venous clinical severity score, a venous segmental disease score, and a venous disability score. The venous clinical severity score has nine clinical characteristics (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, compressive therapy use, active ulcers and, if ulcers are present, the number of ulcers, their duration and size), which are graded from 0–3 (absent/asymptomatic, mild, moderate, severe) with specific criteria to avoid overlap or arbitrary scoring. The venous segmental disease score combines the anatomic and pathophysiologic components of CEAP, where 11 major venous segments are graded according to presence of reflux and/or obstruction on venous imaging findings. The venous disability score is a modification of the existing 0–3 CEAP disability score.

However, these scoring systems have not been fully validated [29]. Moreover, agreement between the different clinical measures is poor. For example, a prospective cohort of patients with a history of symptomatic DVT assessed the level of PTS by both the Villalta and Ginsberg measures which were then correlated to patient-reported QoL and venous valvular reflux [29]. The proportion of patients classified as PTS was almost 5-times higher according to the Villalta scale than by the Ginsberg measure (37% vs. 8.1%, respectively), and the agreement between the two measures was poor (κ=0.22). Although both the measures demonstrated a graded association with QoL, patients with PTS defined by the Ginsberg measure had a worse QoL, indicating that the Ginsberg measure identifies more severe disease. In this study, presence of valvular reflux was not significantly associated with PTS or with QoL. Similarly, poor to moderate agreement between the Widmer, CEAP and the Villalta scales were noted by Kolbach et al. [30].

Incidence of PTS

Studies have reported a wide variability in the 10-year cumulative incidence of PTS after an acute DVT event, ranging between 20–100% [2, 31]. Estimates of the 2-year cumulative incidence of PTS also vary enormously, ranging between 23–60% (**Table 2**) [5, 7–9, 11, 26, 32, 33]. The estimated cumulative incidence of severe PTS after approximately 5-years, is in the range of 1–30%, although estimates of around ≤10% are more common [5, 7, 9].

Differences in the definition of PTS, in the test characteristics of PTS scales used and in study design contribute to this wide variation in incidence. As the agreement between the PTS scales is poor, making an accurate estimate of the burden of PTS is challenging [29, 30]. Symptoms of PTS tend to occur mostly within the first 2-years of the incident DVT. For example, Prandoni et al. [5] reported a cumulative incidence of PTS of 22.8%, 2 years after incident DVT (95% confidence interval [CI]: 18–27.5) and 28% after 5 years (95% CI: 23–33) [5].

Although PTS may become apparent soon after DVT, it is notable that the cumulative incidence of PTS continues to increase long after the initial DVT event, and in some cases as long as 20 years [5, 8, 11, 12]. In a population based retrospective cohort study of patients who had DVT and/or PE from 1966–1990, the cumulative incidence of PTS increased from 7% after 1 year, to 14% after 5 years, to 20% after 10 years, and to 27% after 20 years [12]. This highlights the fact that the risk of PTS persists long-term.

Symptoms of VSS and venous reflux have been reported in up to three-fourths of VSS patients who have no history of DVT [4, 33–35]. Moreover, approximately 10% of patients with incident venous thromboembolism (VTE) have a diagnosis or evidence of VSS on physical examination *prior* to the incident VTE event [12]. It has been suggested that undiagnosed prior DVT should be suspected in patients with no known history of DVT, especially if the patient underwent surgery or prolonged immobilization [2]. Alternatively, VSS without prior history of DVT could reflect central venous hypertension, secondary to obesity, congestive heart failure, chronic lung disease/pulmonary hypertension, serious liver disease, or chronic renal disease/nephrotic syndrome. Although VSS can occur with no prior history of DVT, DVT is the most important risk factor leading to VSS [12].

Risk factors for the development of PTS

Several risk factors have been identified which influence the probability of developing PTS. These risk factors are related to the VTE and patient characteristics. DVT has a greater influence, compared with pulmonary embolism (PE), on the likelihood of developing PTS. A population based retrospective cohort study of 1,527 patients with incident DVT or PE showed that patients with DVT (with or without PE) were 2.4-times more likely to develop PTS, than were those with PE alone (95% CI: 1.7–3.2 fold) [12]. A similar finding of higher odds of PTS following incident DVT with or without PE compared with incident PE alone, has been noted in other studies [11, 36]. Postoperative asymptomatic DVT is also associated with a higher risk of PTS. A systematic review of studies reported that the relative risk (RR) of developing PTS was 1.58 (95% CI: 1.24–2.02) in patients with asymptomatic postoperative DVT, compared with those without postoperative DVT [37]. DVT was considered asymptomatic if it was diagnosed using a sensitive screening test in patients without symptoms. Interestingly, the odds of PTS in the leg contralateral to that affected by symptomatic DVT were 2.6-fold higher than in those individuals with no history of symptomatic DVT [36], and could reflect occult venous thrombosis in the inferior vena cava or in the test leg, central venous hypertension, or other mechanisms leading to PTS. Similarly, Kahn et al. [38] reported a high prevalence of PTS in the leg contralateral (and presumably unaffected) to the one affected by DVT (37% and 17% PTS prevalence in the

DVT leg and the contralateral leg, respectively) [38]. The risk of PTS appears to be higher with left leg DVT compared to right leg DVT [11, 36], and may be secondary to the May-Thurner syndrome (i.e., the anatomic compression of the left iliac vein by the overlying right iliac artery).

Recurrent DVT also significantly increases the risk of PTS. When 355 patients with a first episode of DVT were followed up for 8 years, the hazard ratio of PTS was 6.4 (95% CI: 3.1–13.3) in patients with recurrent DVT, compared with patients with no recurrence [5]. Other studies have noted a 2.6–9.6-fold increased risk of PTS with recurrent DVT [9, 39]. However, data on the risk of PTS by DVT location are conflicting, with some studies noting an increased risk of PTS in patients with proximal DVT [9, 40, 41] whereas others have either shown no risk [5], or an increased PTS risk with isolated calf DVT [42]. Similar conflicting data exist for the role of residual vein thrombosis/venous outflow obstruction in PTS, with two recent studies noting an association between residual vein thrombosis and venous outflow obstruction and PTS [43, 44], whereas another study did not [45].

A strong association between severe PTS and venous valvular incompetence has been observed [19–22, 44], and a high peak-reflux velocity in the proximal deep veins may be an independent predictor of advanced symptoms of PTS [46]. A study investigating the causes of leg ulcers in 382 patients found that venous insufficiency was the main cause of the leg ulcers in 54% of patients, and it was a contributory cause in a considerable additional proportion of patients [47]. However, many patients with severe valvular incompetence have only mild symptoms of PTS, suggesting that additional factors may contribute to the development of symptomatic PTS [21].

The association of PTS with advancing age has been observed by some investigators [36, 39, 43] but not others [9, 38]. Varicose veins are an independent risk factor for PTS or VSS [34, 36, 48, 49] as is an increasing body mass index (BMI) [34, 36, 39, 45, 48–50].

Consequences of PTS

QoL

Patients with PTS often suffer from pain, cramps, swelling, and itching. These symptoms usually worsen when standing and walking, therefore impacting on the QoL of these patients and limiting their daily activities. Several studies have confirmed the negative impact of PTS on patient QoL [2, 14, 32, 51, 52], using either generic (e.g., SF-36) or disease-specific (e.g., VEINES-QOL/Sym) QoL measures. The disease-specific VEINES-QOL measure was developed specifically for chronic venous diseases and has been validated for PTS [28, 52, 53]. A study conducted by Kahn et al. [2] showed that the VEINES-QOL score was significantly lower in PTS patients with prior history of DVT, compared with DVT patients without PTS (44.5 ± 11.6 vs. 54.8 ± 5.4, respectively; $P < 0.001$). The QoL was worse in patients with more severe PTS. Kahn et al. [3] also demonstrated that patients with chronic venous disease with a prior history of VTE had a poorer QoL compared with individuals with other forms of chronic venous disease, after controlling for a number of factors, including age, gender, and BMI. Moreover, patients with upper extremity DVT can develop PTS that impacts their QoL. A pilot study that included 24 patients with upper extremity

DVT noted that one-half of these patients had symptoms of PTS, and had a poorer QoL compared with those without PTS [45]; a subsequent study further reinforced these findings. PTS, age, proximal DVT and inpatient status all independently predicted QoL scores in a multivariate analysis, but PTS was the principal determinant of health-related QoL after 2 years [28]. In this study, patients who developed PTS had poorer QoL at all visits and the QoL scores all significantly worsened with increasing severity of PTS ($P < 0.001$) [28].

Specific aspects of PTS are associated with reduced physical QoL and impaired activities of daily living. A case-control study involving a total of 265 participants examined the association between VTE, VSS, venous outflow obstruction and venous valvular incompetence, with QoL and activities of daily living using questionnaires, physical examinations, and vascular laboratory tests. Adjusted for age, gender, BMI and time since VTE event, impaired lower extremity activities of daily living (either walking/bending or decreased capacity for lower extremity activities) was associated with prior VTE, VSS, and venous outflow obstruction [51]. Impaired physical QoL, specifically increased lower extremity pain but not mental QoL, was associated with VSS and with a trend towards association with prior VTE.

Costs

A retrospective Swedish study of 257 patients with DVT and 241 control participants investigated the cost of long-term sequelae of DVT over 15 years. The study found that, based on 1990–1991 prices, the healthcare costs of primary DVT alone were approximately $6,000 per DVT complication, and that PTS complications added an additional 75% or $4,300 to this cost. These costs included the costs of treating recurrent VTE and varicose veins [54].

Two studies have reported the healthcare costs of PTS treatment in the US (**Table 3**) [54–57]. The first, a literature-based Markov model, revealed that the total additional cost for treating PTS after 15 years was approximately $3,000. Furthermore, PTS contributed 74–81% of the total cost of treating DVT [55]. The second study, based on actual claims data for patients with a diagnosis of PE or DVT, estimated that the mean incremental adjusted healthcare costs of developing PTS was approximately $7,000 per patient/year [56]. A small study in Brazil reported much lower estimates of treatment costs for PTS. It found the mean annual cost per patient to be approximately $400 for mild-to-moderate PTS, and $1,200 for severe PTS [57].

Venous ulcers are the most expensive complication of PTS to treat. In the Swedish study discussed previously, the average cost of treating a venous ulcer was estimated to be $7,900 [54]. A more recent US study from 1999 calculated the average cost of treating a venous ulcer at $10,000 per patient/year [58]. The indirect costs of PTS are significant. One study performed in 1994 showed that patients with venous ulcers, particularly younger individuals, were absent more often from work, had more job losses, and had adverse financial consequences [59]. The study estimated that 2 million workdays are lost annually in the US due to venous ulcers.

Although estimates of the healthcare costs of treating PTS vary among different studies, it is widely acknowledged that PTS impacts greatly on the costs of treating DVT. However, the current treatment options for PTS are not always effective. Therefore, a better strategy may be the prevention of PTS.

Treatment of PTS

Currently few methods are available to treat PTS and evaluation of these strategies has been largely limited to four randomized trials [60]. The main treatment approach is to use physical methods to counteract raised venous pressure.

One of the suggested physical approaches currently listed in the American College of Chest Physicians (ACCP) guidelines for PTS treatment is a course of intermittent pneumatic compression stockings for patients with severe edema of the leg (Grade 2B recommendation) [60]. In a crossover trial, 15 patients with PTS used intermittent compression units at either therapeutic pressure (50 mmHg) or placebo pressure (15 mmHg) twice-daily for 20 minutes. After 2 months, the symptom scores (evaluated using a patient questionnaire) were significantly improved ($P = 0.007$). The treatment was also considered ‘successful’ if the patient preferred the therapeutic pressure and stated that they would continue using the compression device, and that there was at least some difference between therapeutic and placebo pressures. By this definition, the treatment was considered ‘successful’ for 80% (12/15) of patients treated (95% CI: 52–96) [61].

The other method suggested in the guidelines is the use of graduated compression stockings (GCS) for patients with mild edema of the leg as a result of PTS (Grade 2C recommendation) [60]. The use of properly fitted GCS is generally considered beneficial, but the extent of the effects is unclear [62]. However, use of GCS is limited because they can be hot, expensive, difficult for older and less agile patients to put on, and cosmetically unappealing.

A lower-limb venous return assist device called Venowave™, has recently been evaluated for the treatment of severe PTS in a small randomized crossover study, where eligible subjects were randomly allocated to receive Venowave™ for 8 weeks and a control device for 8 weeks [63]. Of the 26 participants who completed both the trial periods, 10 participants receiving Venowave™ reported benefit from the device with moderate or greater improvement in symptoms of PTS, as compared with 4 participants receiving the control device ($P = 0.11$). The QoL measurements at the end of the study period were significantly better for Venowave™ compared with control (mean VEINES-QOL score 52.5 ± 5.8 vs. 50.2 ± 6.2, respectively; $P = 0.004$). The symptoms and signs of PTS, as measured by the Villalta scale at the end of study period was significantly better for Venowave™ compared with control (mean PTS score 12.2 ± 6.3 vs. 15.0 ± 6.1, respectively; $P = 0.004$). This could be a promising alternative therapy for patients with severe PTS when used alone or in combination with GCS.

Rutosides are a group of compounds derived from horse chestnut. When used to treat PTS, rutosides have shown some evidence of reduced calf and ankle swelling. Therefore, rutosides are recommended for patients with persistent venous ulcers, together with local

care and compression (Grade 2B recommendation) [60]. The use of other drugs, such as low-molecular-weight heparins (LMWHs), unfractionated heparin (UFH) and dermatan sulphate, have not been fully evaluated.

Surgical interventions have been evaluated to manage chronic venous ulcers related to PTS. These include venous surgery to eradicate reflux in superficial veins. Several clinical trials have demonstrated that surgery performed to eradicate venous reflux in superficial veins notably reduced the recurrence rate of ulcers in a follow-up period of up to 3 years (Barwell et al., 2000; Zamboni et al., 2003; Barwell et al., 2004). Furthermore, as tissue pressures are increased in the affected limbs of patients with PTS, the role of fasciotomy in addition to surgical correction of superficial venous reflux was evaluated in a small study for the treatment of venous ulcers (Christenson, 2007). The addition of fasciotomy promoted healing in 11 out of 12 ulcers (92%), compared to only four out of 11 (36%) ulcers treated with surgical correction of superficial venous reflux alone (p=0.049) (Christenson, 2007).

Cell-based therapies have also been tested to manage chronic venous ulcers. Apligraf® is a bilayered skin substitute (BSS) composed of allogeneic keratinocytes and fibroblasts, and is FDA-approved for the treatment of chronic refractory venous ulcers. In a study of 293 patients, treatment with BSS was more effective than compression therapy in achieving healing of venous ulcers (63% vs 49%, p=0.02), with a shorter median time to healing (61 days vs 181 days; p=0.003). While the mechanism of action has not yet been elucidated, it has been hypothesized that the release of chemokines and growth factors (such as interleukin-8 and human granulocyte-macrophage colony-stimulating factor (GM-CSF)) involved in wound healing may play a role. Indeed, topical recombinant human GM-CSF, followed by the application of a compression dressing for management of venous skin ulcers resulted in complete healing of 90.4% of ulcers in 38 patients, with no observed systemic or local side-effects (Jaschke et al., 1999).

Thus, there are a number of different options available for the management of PTS. Implementation of guidelines for the diagnosis and treatment of venous leg ulcers may improve patient outcomes [64]. For example, patients with venous ulcers in the US were 6.5-times and in the UK twice more likely to heal if a guideline was followed [64].

Prevention of PTS

In 2005, the estimated annual incidence of symptomatic VTE events in the US was approximately 600,000 [65]. VTE events, such as DVT or PE, are commonly associated with surgery or trauma. However, over half the patients who developed in-hospital VTE did not undergo surgery [66]. This suggests that medical patients are also at high-risk of VTE and, consequently at high-risk of developing PTS.

Mechanical methods

Some studies have suggested that the use of GCS to help prevent PTS is effective in patients with confirmed DVT [6, 7, 67]. Brandjes et al. [7] randomized 194 patients with proximal DVT, who initially received heparin and then coumadin for 3 months, to either GCS (n = 96) or no stockings (n = 98) for 2 years. The GCS were knee-length on the affected leg,

customized for each patient, worn during the day only, replaced every 6 months, and worn for at least 2 years. After this time patients could choose whether to continue using the stockings or to stop. After a median follow-up of 6 years, 20% of patients in the GCS group experienced mild-to-moderate PTS, compared with 47% of those in the control group ($P < 0.001$). Severe PTS occurred in 11% of the GCS group and 23% of the control group ($P < 0.001$). Approximately half of the patients who developed severe PTS did so after an initial bout of mild PTS, indicating the need for measures to prevent progression of the disease [7].

This result was confirmed in a similarly designed study of 180 patients with a first episode of symptomatic proximal DVT [6]. Here, a 50% reduction in the incidence of PTS within 2 years was observed in patients given GCS to wear during the day (hazard ratio 0.49; 95% CI: 0.29–0.84; $P = 0.011$). However, both of these studies were limited by the lack of a double-blind design. A combined analysis of the available randomized studies on the use of GCS found that they reduced the incidence of PTS from 54% to 25% (RR 0.47; 95% CI: 0.36–0.61) [67]. Another study that assessed PTS development 2-years after an initial DVT episode found that the combination of ambulation with the use of GCS immediately after DVT results in significantly better outcomes when compared with bed rest ($P < 0.01$) [68]. The average daily number of hours the stockings were worn was not specified, but patients wore the stockings for an average of 27 months in the bed rest group, compared with 12 months in ambulatory group [68].

By contrast, a study of patients enrolled a year after an episode of proximal DVT did not report any significant benefits of GCS [33]. In this study, patients were encouraged to wear GCS as much as possible during waking hours. A limitation of this study was the low number of patients involved; stricter criteria to diagnose PTS were used than in some of the other studies [33]. The authors advised against the routine use of GCS shortly after DVT except in patients with severe symptoms as GCS have a poor fit once the acute swelling dissipates, and advocated further trials to determine the benefits of GCS in patients with symptomatic PTS.

Antithrombotic therapy

PTS can develop after symptomatic DVT despite oral anticoagulant therapy [11, 35, 38]. Schulman et al. [11] randomized 897 patients to secondary prophylaxis with warfarin or dicoumarol after a first episode of DVT or PE, either for 6 weeks or for 6 months. Among the 545 patients evaluated after 10 years, signs of PTS were observed in 56.3% of them, with 6% having severe PTS. The duration of anticoagulation did not have a statistically significant effect on the likelihood of developing PTS [11]. In another study of 93 patients with DVT who wore GCS for a year and who were treated with LMWHs or UFH, and subsequently on oral anticoagulant therapy for 3 months, the cumulative incidences of PTS after 1 year, 2 years, and 6 years were 49%, 55%, and 56%, respectively [44]. Thus, based on the data available, thromboprophylaxis after DVT does not sufficiently prevent PTS, and therefore prevention of DVT is required.

Thrombolytic therapy

The goal of standard anticoagulation therapy is to prevent further propagation of DVT. Dissolution of the clot is undertaken naturally by the fibrinolytic system of the body, although the extent of this is variable. This frequently results in loss of valvular competence, with the development of PTS as a consequence. The rationale for using thrombolytic therapy in the treatment of DVT is to attempt to lyse the clot so as to maintain vein patency and valve competence, and hence reduce the incidence of PTS. Although the results from case series and small randomized clinical trials are interesting, this hypothesis has not yet been proven by appropriately powered studies [69].

Johansson et al. [70] treated 19 patients with acute DVT with streptokinase, of whom, 7 (37%) had complete thrombus resolution and restoration of venous flow. When followed up 6–50 months after the acute DVT, 8 patients demonstrated normal venogram and valve function studies, all of whom were also free from post-thrombotic symptoms [70]. Arnesen et al. [71] randomized 42 patients with extensive acute DVT to either systemic streptokinase or heparin. Significant thrombolysis was noted in 71.4% patients treated with streptokinase and in 23.8% heparin-treated patients ($P = 0.002$) [71]. The mean angiographic score decreased by 52.3% in the streptokinase group but only 20.6% in the heparin group ($P < 0.01$). Long-term data were available in 35 patients; 44% of patients treated with streptokinase had a normal venogram compared with 0% treated with heparin ($P = 0.004$). A total of 44% of patients treated with streptokinase had major PTS, as compared with 67% of heparin treated patients. Turpie et al. [72] conducted a similar small randomized study comparing systemic tissue plasminogen activator versus UFH for the initial treatment of DVT, and demonstrated that 58% of the patients receiving tissue plasminogen activator over 4 hours had >50% lysis of the thrombus, compared with 0% who received placebo plus heparin [72]. With long-term follow-up, 25% of patients in whom >50% lysis was achieved had symptoms of PTS, compared with 56% of patients in whom lysis was <50% ($P = 0.07$). Although suggestive and hypothesis-generating, the above studies are too small to draw any definitive conclusions regarding the role of systemic thrombolytics in reducing PTS.

Catheter directed thrombolytic therapy may be safer and more effective in thrombus dissolution than systemic thrombolytic therapy, but its role in reducing PTS is still unproven. A post-therapy follow-up survey compared 68 iliofemoral DVT registry patients treated with catheter directed thrombolysis with 30 individuals with iliofemoral DVT, who were identified by medical record review and treated with anticoagulation alone [73]. This study noted that patients treated with catheter directed thrombolysis had a better overall physical functioning ($P = 0.046$), less health distress ($P = 0.022$), and fewer post-thrombotic symptoms ($P = 0.006$). Within the thrombolysis group, venographically successful lysis correlated with improved QoL ($P = 0.038$). In another prospective non-randomized study, 51 patients were given the option to choose between conventional therapy and a multimodality therapy regimen which included catheter-directed lysis followed by percutaneous transluminal balloon angioplasty and stenting for residual iliac stenoses [74]. This study showed a significant improvement in long-term venous symptom resolution in the multimodality treatment group compared with conventional therapy (78% vs. 30%, respectively; $P = 0.0015$) [74]. Other investigators outlining their experience with catheter

directed thrombolysis have reported excellent vein patency rates and better valve function, but did not report whether that led to reduced PTS [75–77].

Prevention of DVT

Several studies have shown convincing evidence that the incidence of DVT is significantly reduced by the use of appropriate thromboprophylaxis. Current guidelines recommend thromboprophylaxis to prevent DVT in patients undergoing major surgery, specific groups of hospitalized medical patients, trauma patients, and those admitted to intensive care units [78]. The guidelines give specific recommendations about the dose and duration of the currently available thromboprophylaxis options to be used, such as LMWHs, low-dose UFH, fondaparinux, adjusted-dose vitamin K antagonist, or mechanical prophylaxis [78]. The LMWHs enoxaparin and dalteparin are effective in preventing VTE in surgical [79, 80] and medical patients [81–83]. A meta-analysis showed that both UFH and LMWHs are responsible for a 56% risk reduction of DVT of the lower limbs, but the LMWHs were associated with a lower-risk of major bleeding (RR 0.48; 95% CI: 0.23–1.00) [84]. In surgical patients, the LMWHs also significantly reduced the risk of clinical VTE, compared with UFH (RR 0.71; 95% CI: 0.51–0.99), with a trend for less major-bleeding (RR 0.89; 95% CI: 0.75–1.05), and total bleeding (RR 0.92; 95% CI: 0.79–1.07) [85]. Furthermore, in patients undergoing orthopedic surgery, the LWMHs are more effective than vitamin K antagonists in preventing total and proximal DVT (RR 1.51; 95% CI: 1.27–1.79 and RR 1.51; 95% CI: 1.04–2.17, respectively), with comparable rates of major bleeding [86].

A study in acutely ill medical patients who did not have an indication for VTE prophylaxis showed that use of the synthetic pentasaccharide fondaparinux resulted in a 46.7% RR reduction for VTE-risk compared with placebo (95% CI: 7.7–69.3), with major bleeding occurring in 0.2% of patients in both groups [87]. Fondaparinux was also found to be effective in surgical patients, although in this group of patients it was associated with a higher-rate of major bleeding [88]. Thus, the use of effective methods for the prevention of DVT may be key to preventing long-term complications, such as PTS.

Cost-effectiveness of thromboprophylaxis for reducing PTS

Although a number of cost-effectiveness studies have been performed on the use of the LMWHs for VTE prophylaxis, the costs of long-term sequelae are often excluded.

A US-based cost-effectiveness comparison study comparing the LMWH enoxaparin with warfarin prophylaxis took a more comprehensive approach, and included long-term DVT complications after total hip replacement surgery [89]. According to this study, when only the short-term consequences of DVT were included in the analysis, thromboprophylaxis with enoxaparin was cost-effective, resulting in a net cost of $133 per patient, for a net increase of 0.04 quality-adjusted life years (QALYs) per patient ($3,733 per QALY saved, compared with warfarin). When the long-term consequences of DVT were included the benefits of enoxaparin compared with warfarin were even more notable; enoxaparin resulted in a net lifetime saving of $89 per patient, and saved 0.16 QALYs per patient (about 2 quality-adjusted life months; **Fig. 2**) [89]. The authors concluded that when the long-term

costs were included, the results suggested that thromboprophylaxis with the LMWH enoxaparin is more cost-effective than thromboprophylaxis with warfarin.

Future directions

Estimating the true incidence of PTS in VTE requires further work. This can only be accomplished with standardizing the criteria for the diagnosis of PTS that focuses on patient symptoms and clinical signs, and will thus help to standardize research in the field. Strategies to reduce the risk of PTS need further evaluation. As individuals with recurrent VTE appear to be at a higher risk for PTS, the role of prolonged duration of anticoagulation for the treatment of idiopathic VTE in reducing the risk of PTS needs systematic evaluation. Multicenter trials of catheter-directed thrombolysis to prevent PTS in patients with extensive proximal DVT are under way to test whether restoring vein patency and preserving venous valve function reduces the risk of PTS with an acceptable risk burden of hemorrhage.

Conclusions

PTS is the most common long-term complication of DVT, but knowledge and awareness of the condition remains poor. GCS are effective in reducing the risk of PTS but the best strategy for preventing PTS is to prevent the development of DVT. Anticoagulant therapy can reduce the incidence of DVT in at-risk patients and has a good safety profile. Prevention of DVT is likely to reduce the incidence of PTS, which in turn would decrease the cost-burden of the medical care associated with PTS, and improve the QoL of patients suffering with PTS.

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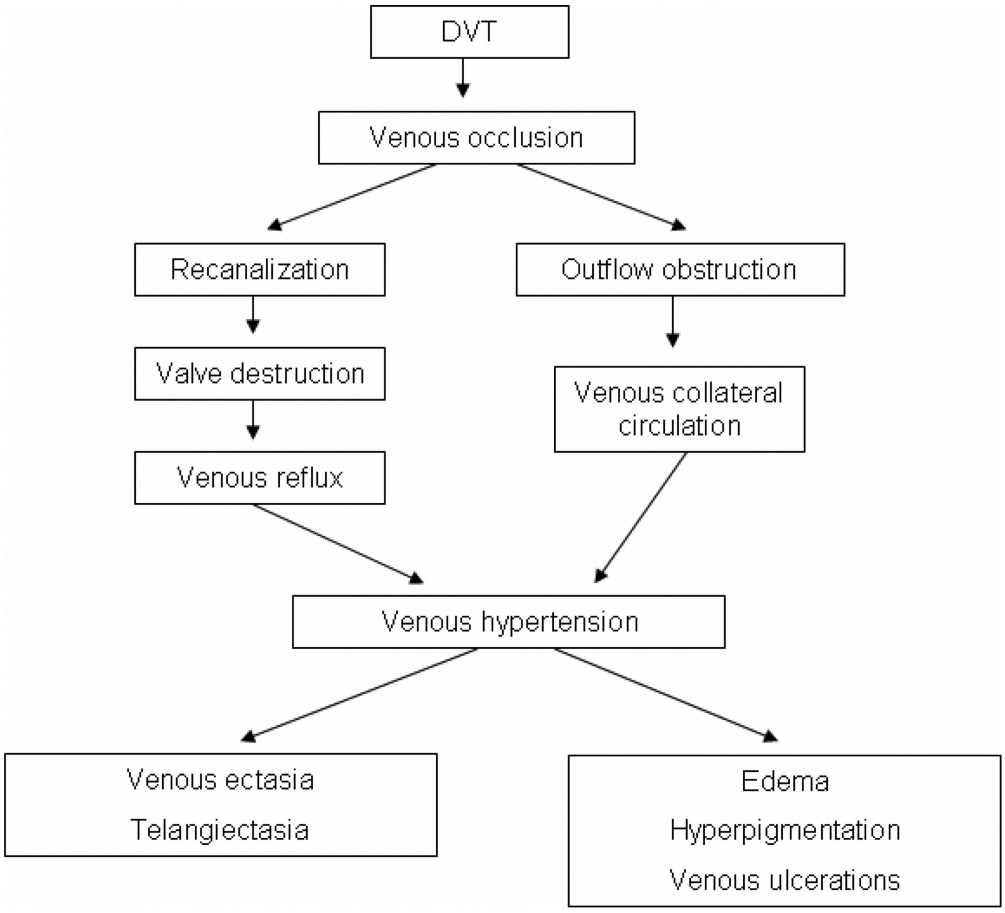

Fig. 1.

Sequence of events leading to post-thrombotic syndrome.

DVT = deep-vein thrombosis.

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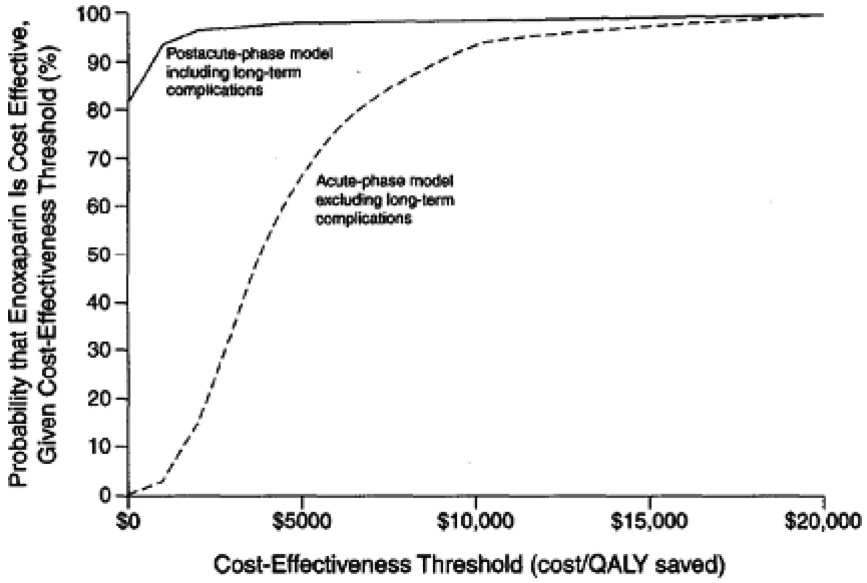

Fig. 2.

The probability of enoxaparin being cost-effective against the cost-effectiveness threshold for 2 models, including and excluding long-term complications [89].

QALY = quality-adjusted life years.

Reproduced from “Results of an economic model to assess the cost-effectiveness of enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States” by Botteman MF, Clinical Therapeutics vol. 24(11):1960-86 copyright 2002, with permission from Elsevier.

Table 1

Characteristics of post-thrombotic syndrome

Symptoms	Clinical signs
Swelling	Edema[a]
Pain[a]	Telangiectasia
Cramps[a]	Venous dilatation/ectasia[a]
Heaviness[a]	Hyperpigmentation[a]
Paresthesia[a]	Open or healed ulcers
Pruritus[a]	Redness[a]
Bursting pain	Cyanosis
	Lipodermatosclerosis (skin induration)[a]
	Eczema
	Varicose veins
	Pain during calf compression[a]

[a]Symptom or sign according to Villalta scale. Post-thrombotic syndrome (PTS) score is based on the cumulative rating of the five symptoms and signs signs, with each rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). Total score: 0–4 = no PTS; 5–14 = mild-to-moderate PTS; ≥15 or presence of venous ulcer = severe PTS [24].

Table 2

Frequency of post-thrombotic syndrome

Study [Ref]	Number of patients	Type of patient	Follow-up, years	Treatment	Frequency of PTS, %	
					All	Severe
Prandoni et al., 1996 [5]	355	Consecutive outpatients	8	GCS	29	9
Brandjes et al., 1997 [7]	194	Consecutive outpatients	6	GCS/no GCS	31/70	11/23
Franzeck et al., 1996 [8]	39	Low-risk patients (no previous DVT or PE)	12	54% with regular GCS	36	8
Stain et al., 2005 [9]	406	Patients receiving VKAs after symptomatic VTE	5	GCS	43	1.4
Ginsberg et al., 2001 [33]	110 (symptomatic DVT)/82 (asymptomatic DVT)	1 year after confirmed proximal DVT	1	GCS	27/4	NR
Ginsberg et al., 2000 [26]	25 (proximal DVT)	Hip or knee arthroplasty within previous 2–7 years	5	Different prophylactic regimens	4	NR
	66 (distal DVT)				6.1	
	164 (no DVT)				4.3	
Schulman et al., 2006 [11]	897	Objectively verified DVT (cancer patients excluded)	10	VKAs	56	6

DVT = deep-vein thrombosis; GCS = graduated compression stockings; NR = not reported; PE = pulmonary embolism; PTS = post-thrombotic syndrome; VKAs = vitamin K antagonists; VTE = venous thromboembolism.

Table 3

Cost studies about post-thrombotic syndrome

Study [Ref]	Country	Mean additional cost per person with PTS after 15 years (US $)	Mean annual costs per person with PTS (US $)
Bergqvist et al., 1997 [54]	Sweden	4,300	-
Caprini et al., 2003 [55]	USA	~3,000	-
MacDougall et al., 2006 [56]	USA	-	~7,000
Ramacciotti et al., 2006 [57]	Brazil	-	400 (mild-to-moderate) 1,200 (severe)

PTS = post-thrombotic syndrome.