

The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing

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The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on
Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing

The purpose of this scientific statement is to provide an up-to-date overview of the postthrombotic syndrome (PTS), a frequent, chronic complication of deep venous thrombosis (DVT), and to provide practical recommendations for its optimal prevention, diagnosis, and management. The intended audience for this scientific statement includes clinicians and other healthcare professionals caring for patients with DVT.

Methods

Members of the writing panel were invited by the American Heart Association Scientific Council leadership because of their multidisciplinary expertise in PTS. Writing Group members have disclosed all relationships with industry and other entities relevant to the subject. The Writing Group was subdivided into smaller groups that were assigned areas of statement focus according to their particular expertise. After systematic review of relevant literature on PTS (in most cases, published in the past 10 years) until December 2012, the Writing Group incorporated this information into this scientific statement, which provides evidence-based recommendations. The American Heart Association Class of Recommendation and Levels of Evidence grading algorithm (Table 1) was used to rate the evidence and was subsequently applied to the draft recommendations provided by the writing group. After the draft statement was approved by the

panel, it underwent external peer review and final approval by the American Heart Association Science Advisory and Coordinating Committee. External reviewers were invited by the American Heart Association. The final document reflects the consensus opinion of the entire committee. Disclosure of relationships to industry is included with this document (Writing Group Disclosure Table).

Introduction

Background

DVT refers to the formation of blood clots in ≥ 1 deep veins, usually of the lower or upper extremities. PTS, the most common long-term complication of DVT, occurs in a limb previously affected by DVT. PTS, sometimes referred to as postphlebotic syndrome or secondary venous stasis syndrome, is considered a syndrome because it manifests as a spectrum of symptoms and signs of chronic venous insufficiency, which vary from patient to patient.¹ These can range from minor leg swelling at the end of the day to severe complications such as chronic debilitating lower-limb pain, intractable edema, and leg ulceration,² which may require intensive nursing and medical care. PTS increases healthcare costs and reduces quality of life (QoL).^{3,4} The purposes of this scientific statement are to provide current best practice guidelines pertaining to PTS and to serve as an additional resource to healthcare professionals who manage patients with DVT and PTS.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on May 16, 2014. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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Table 1. Classification of Recommendations and Levels of Evidence

		SIZE OF TREATMENT EFFECT				
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
				Procedure/ Test	Treatment	
				COR III: No benefit	No Proven Benefit	
				COR III: Harm	Excess Cost w/o Benefit or Harmful	
				Harmful to Patients or Harmful		
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses 	
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies 	
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care 	
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/administered/ other is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases [†]		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important key clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Epidemiology and Burden of PTS

Incidence and Prevalence of PTS

Despite advances in the primary and secondary prevention of DVT, DVT affects 1 to 3 of 1000 people in the general population annually.^{5,6} Well-designed prospective studies with long-term follow-up (ie, ≥12 months) report that 20% to 50% of patients with DVT develop PTS sequelae. In most cases, PTS develops within a few months to a few years after symptomatic DVT.^{7–12} However, some studies have reported that the cumulative incidence of PTS continues to increase, even 10 to 20 years after DVT diagnosis.^{11,12} About 5% to 10% of patients develop severe PTS, which may include venous ulcers.^{7,8,11,13}

Schulman et al¹¹ have shown that the probability of developing a venous ulcer over 10 years after DVT was almost 5%. It is projected that the number of adults in the United States with venous thromboembolism (of which DVT is the predominant form) will double from 0.95 million in 2006 to 1.82 million in 2050¹⁴; therefore, improved prevention and treatment of DVT are critical in decreasing the incidence of PTS.

Impact on Healthcare Costs and QoL

PTS adversely affects QoL and reduces productivity,³ leading to substantial burden to patients and the healthcare system.^{4,15,16} In a Canadian study that assessed the economic consequences of DVT over a 2-year period, the total per-patient cost of PTS

Table 2. Clinical Characteristics of PTS

Symptoms	Clinical Signs
Pain	Edema
Sensation of swelling	Telangiectasia
Cramps	Venous dilatation/ectasia
Heaviness	Varicose veins
Fatigue	Redness
Itching	Cyanosis
Pruritis	Hyperpigmentation
Paresthesia	Eczema
Bursting pain	Pain during calf compression
Venous claudication	Lipodermatosclerosis
	Atrophie blanche
	Open or healed ulcers

PTS indicates postthrombotic syndrome.

was Canadian \$4527, a cost that was almost 50% higher than for patients with DVT without PTS.⁴ This cost increase was largely attributable to greater use of healthcare visits and prescription medications. The average annual cost of PTS treatment in the United States was estimated at ≈\$7000 per patient per year.¹⁵ Caprini et al¹⁷ provided cost analyses of mild to moderate and severe PTS over time. During the first year of diagnosis, the annual cost of mild to moderate PTS was \$839 compared with \$341 in subsequent years, whereas severe PTS cost \$3817 per patient in the first year (all had open ulcers) compared with \$3295 (open ulcers) and \$933 (healed ulcers) per year in subsequent years. The high cost of treating venous ulcers is due largely to surgery, lost workdays, and loss of employment. It is estimated that 2 million workdays are lost annually in the United States as a result of leg ulcers.¹⁸

In the assessment of burden of illness for chronic conditions such as PTS, QoL is an important consideration. Ideally, both generic QoL (ie, overall health state) and disease-specific QoL should be assessed. Studies have shown that compared with DVT patients without PTS, patients with PTS have poorer venous disease-specific QoL,^{3,19–22} and scores worsen significantly with increasing severity of PTS.¹⁹ It is notable that generic physical QoL for patients with PTS is worse than that for people with chronic diseases such as osteoarthritis, angina, and chronic lung disease.³

Clinical Manifestations and Pathophysiology

Characteristic Symptoms and Signs of PTS

PTS, a form of secondary venous insufficiency, is characterized by a range of symptoms and signs (Table 2). Typical symptoms of lower-extremity PTS include pain, swelling, heaviness, fatigue, itching, and cramping (often at night) in the affected limb (upper-extremity PTS is discussed later in Upper-Extremity PTS). Symptoms differ from patient to patient, may be intermittent or persistent, usually worsen by the end of the day or with prolonged standing or walking, and improve with rest or limb elevation. Venous symptoms associated with the initial DVT can persist for several months and may transition to chronic symptoms without a symptom-free period.⁸ PTS may also present as venous claudication, likely caused by persistent



Figure 1. Clinical manifestations and spectrum of postthrombotic syndrome (PTS). **A** and **B**, Edema and hyperpigmentation. **C**, PTS 3 months after the onset of iliofemoral deep venous thrombosis (DVT; treated with anticoagulation alone). The patient has venous claudication, swelling, bluish discoloration, and pigment changes of the left lower extremity. CEAP (clinical, etiological, anatomic, pathophysiological) classification is C4a. His Villalta score is 16. **D**, Lower extremity of a patient with PTS 6 years after acute DVT showing edema, hyperpigmentation, and lipodermatosclerosis. His CEAP classification is C4b and Villalta score is 15. **E**, Edema, redness, hyperpigmentation, and lipodermatosclerosis. **F**, Hyperpigmentation and a healed venous ulcer.

venous obstruction of a major venous confluence (iliofemoral or popliteal veins). Such patients report bursting leg pain during exercise that can resemble arterial claudication.²³

Typical signs of PTS are similar to those of other chronic venous diseases. These range from perimalleolar (or more extensive) telangiectasia, pitting edema, brownish hyperpigmentation of the skin, venous eczema, and secondary varicose veins to signs of more severe PTS such as atrophie blanche (white scar tissue), lipodermatosclerosis (fibrosis of subcutaneous tissues of the medial lower limb), and leg ulceration (Figure 1).

Pathophysiology of PTS

Although the pathogenesis of PTS is complex and has not been fully characterized, venous hypertension appears to play a central role (Figure 2). Venous pressure is dependent on the weight of the blood column between the right atrium and the foot (hydrostatic pressure). Normally, when an individual is

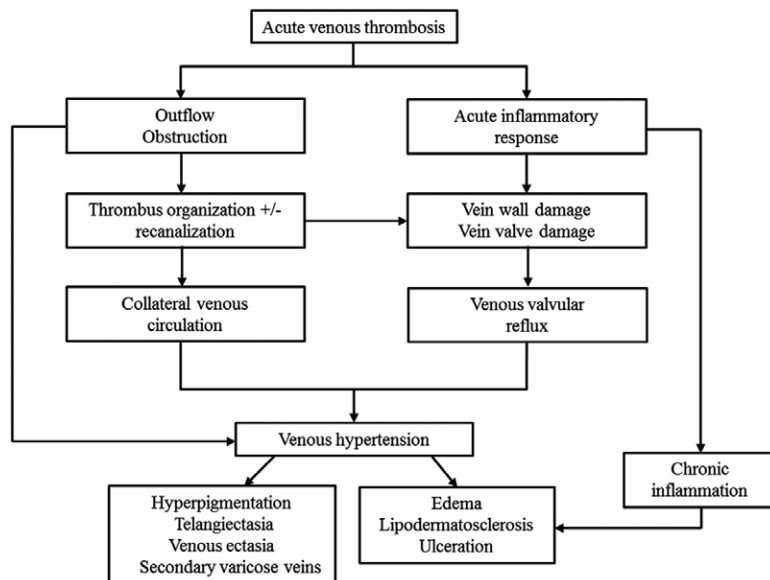


Figure 2. Proposed pathophysiology of postthrombotic syndrome.

at rest in the supine position, venous pressure is low because dynamic pressure derived from the pumping action of the heart maintains movement of the blood through arteries and veins.²⁴ When an individual is upright (sitting or standing) but motionless, venous pressure is highest, increasing to up to 80 to 90 mmHg. While an individual is walking at a rate of 1.7 mph, venous pressure is incrementally reduced to a mean of 22 mmHg.²⁵ Blood is ejected by contraction of the leg muscles, which are assisted by competent venous valves working to return blood proximally from the distal leg to the heart after exercise, thus preventing reflux and limiting accumulation of blood in the lower-extremity veins.²⁴ Therefore, any damage to the venous valves impedes venous return to the heart, leading to venous hypertension and consequent leg pain and swelling.

In the case of PTS, ambulatory venous hypertension can occur from outflow obstruction as a result of the thrombus or valvular incompetence (reflux). After DVT, recanalization of the thrombosed veins, which occurs through a combination of fibrinolysis, thrombus organization, and neovascularization,²⁶ is often incomplete, resulting in residual venous obstruction, which may interfere with calf muscle pump function and cause damage to venous valves, ultimately leading to venous valvular incompetence. In this situation, there is insufficient reduction in venous pressure with walking, resulting in ambulatory hypertension.²⁴

The literature on whether PTS development is predominantly the consequence of outflow obstruction, venous valvular reflux, or both is conflicting, which may reflect, in part, the limited ability to quantify venous obstruction and reflux. Prandoni et al²⁷ found that PTS developed more frequently in patients who had persistent venous obstruction within the first 6 months after an episode of acute proximal DVT (relative risk [RR], 1.6; 95% confidence interval [CI], 1.0–2.4), a result that was replicated by the same group in a second study.²⁸ Similarly, Roumen-Klappe et al²⁹ reported that persistent venous obstruction was an important predictor of PTS 3 months after DVT (RR, 1.7; 95% CI, 1.0–2.2). In the Catheter-Directed Venous Thrombolysis Trial (CaVenT),

which assessed the efficacy of catheter-directed thrombolysis (CDT) using alteplase in patients with acute DVT extending above the popliteal vein, the absolute risk of PTS was reduced by 14.4% (95% CI, 0.2–27.9) in the CDT group.³⁰ Iliofemoral patency was noted in 65.9% of patients randomized to CDT compared with 47.4% of those who received conventional anticoagulant therapy,³⁰ but the prevalence of valvular reflux was similar in the 2 groups.³¹ In contrast, Haenen et al³² reported a significant positive correlation between increasing severity of PTS and prevalence of reflux in the proximal femoral vein ($P<0.001$), distal femoral vein ($P<0.05$), and popliteal vein ($P<0.05$). These investigators also noted that venous obstruction alone or in combination with reflux had no relation to the presence of severe PTS. Yamaki et al³³ and Asbeutah et al³⁴ have similarly reported that reflux appears to be more important than persistent obstruction in the pathophysiology of PTS.

Other models focus on vein wall damage and acute and chronic inflammation as potential drivers of PTS.^{18,35} Sustained venous hypertension can cause structural and biochemical abnormalities of the vein wall, resulting in pathological effects in the skin and subcutaneous tissues such as edema, hyperpigmentation, varicose veins, and ulceration.²⁴ Several studies have reported associations between elevated levels of various inflammation markers and PTS development^{35,36} (see Role of Biomarkers to Predict PTS).

Although the pathogenesis of PTS remains incompletely elucidated, there is mounting interest in the early use of pharmacomechanical therapy in patients with iliofemoral DVT to restore venous blood flow and to preserve valve function with the expectation that such treatment will reduce the risk of PTS (see Treatment of PTS). Further understanding of the pathophysiology of PTS will lead to more optimal prevention and management of the syndrome.

Diagnosis of PTS

There is no single gold standard test to diagnose PTS. PTS is diagnosed primarily on clinical grounds when characteristic

symptoms and signs (Table 2) occur in a patient with prior DVT. Because PTS is a chronic condition that often demonstrates a waxing-and-waning pattern, the recommendation is to wait at least 3 months for the initial pain and swelling associated with acute DVT to resolve; therefore, a diagnosis of PTS should generally be deferred until after the acute phase (up to 6 months) has passed.

Clinical Tools to Diagnose PTS

A number of clinical tools or scales have been used to help diagnose and define PTS. Of these, 3 were developed specifically to diagnose PTS after objectively diagnosed DVT: the Villalta scale,³⁷ Ginsberg measure,⁹ and Brandjes scale.³⁸ The others, developed for chronic venous disease in general, include the CEAP (clinical, etiological, anatomic, pathophysiological) classification,³⁹ Venous Clinical Severity Score (VCSS),⁴⁰ and Widmer scale.⁴¹ The general characteristics of each clinical scale are described below. Tables 3–5 show the individual components and scoring of the various scales.

Villalta Scale

The Villalta scale is a clinical measure that incorporates the assessment of 5 subjective (patient-rated) venous symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and 6 objective (clinician-rated) venous signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression), as well as the presence or absence of ulcer, in the DVT-affected leg^{13,37} (Table 3). The Villalta scale shows good correlation with generic and disease-specific QoL scores,^{3,19} as well as anatomic and physiological markers of PTS.^{27,44} A potential shortcoming of the Villalta scale (which

also applies to other scales discussed below) is its relative non-specificity; symptoms and signs could be due, at least in part, to nonvenous conditions or primary venous insufficiency.⁴⁵ In addition, although the presence of ulcer is noted, ulcer size and number are not. Nonetheless, the Villalta scale has been widely and successfully used to diagnose PTS,^{21,35,46,47} to classify its severity, and to evaluate treatment,^{48–50} including in randomized, controlled trials (RCTs).^{30,51} In an effort to standardize the definition of PTS for research purposes, the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation recommended the Villalta scale as the most appropriate measure to diagnose and rate the severity of PTS,¹³ as has a recent systematic review.⁵² Kahn et al¹³ provide a more detailed description of the Villalta scale and recommendations on how to administer it.

Ginsberg Measure

The Ginsberg measure⁹ defines PTS by the presence of daily leg pain and swelling that persists for at least 1 month, is typical in character (worse with standing or walking and relieved by rest or leg elevation), and occurs at least 6 months after acute DVT. This measure was used as the primary PTS outcome measure in the recently published Compression Stockings to Prevent the Post-Thrombotic Syndrome (SOX) trial.⁵³ Although the measure does not rate the severity of PTS, it correlates well with QoL scores and identifies more severe PTS than the Villalta scale.^{52,54} Potential shortcomings include a lack of sensitivity for milder forms of PTS and the fact that it is not quantitative.

Brandjes Scale

The Brandjes scale, similar to the Villalta scale, assesses a number of subjective and objective criteria, including leg circumference.³⁸ On the basis of scores determined in 2 consecutive visits 3 months apart, patients are classified as having no PTS, mild to moderate PTS, or severe PTS. This scale was used to assess PTS in 1 study.³⁸

Table 3. Villalta Scale

	None	Mild	Moderate	Severe
5 Symptoms				
Pain	0 Points	1 Point	2 Points	3 Points
Cramps	0 Points	1 Point	2 Points	3 Points
Heaviness	0 Points	1 Point	2 Points	3 Points
Paresthesias	0 Points	1 Point	2 Points	3 Points
Pruritus	0 Points	1 Point	2 Points	3 Points
6 Clinical Signs				
Pretibial edema	0 Points	1 Point	2 Points	3 Points
Hyperpigmentation	0 Points	1 Point	2 Points	3 Points
Venous ectasia (venules or varicose veins)	0 Points	1 Point	2 Points	3 Points
Redness	0 Points	1 Point	2 Points	3 Points
Skin induration	0 Points	1 Point	2 Points	3 Points
Pain on calf compression	0 Points	1 Point	2 Points	3 Points
Venous ulcer		Absent		Present

Total score of 0 to 4 indicates no postthrombotic syndrome (PTS); score of ≥5 indicates PTS. PTS severity: total score of 5 to 9, mild PTS; score of 10 to 14, moderate PTS; and score of ≥15 or venous ulcer present, severe PTS.

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Table 4. Clinical Component of CEAP Classification

Class	Clinical Signs
0	No visible or palpable signs of venous disease
1	Telangiectasiae or reticular veins
2	Varicose veins; distinguished from reticular veins by a diameter of ≥3 mm
3	Edema
4	Changes in skin and subcutaneous tissue secondary to CVD, now divided into 2 classes to better define the differing severity of venous disease:
4a	Pigmentation or eczema
4b	Lipodermatosclerosis or atrophie blanche
5	Healed venous ulcer
6	Active venous ulcer

CEAP indicates clinical, etiological, anatomic, pathophysiological; and CVD, cardiovascular disease.

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Table 5. Revised VCSS

Attribute	None=0	Mild=1	Moderate=2	Severe=3
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning): presumes venous origin		Occasional pain or other discomfort (ie, not restricting regular activity)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or other discomfort (ie, limits most regular activities)
Varicose veins (>4 mm in diameter): varicose veins must be ≥3 mm in diameter to qualify in the standing position		Few: scattered (ie, isolated branch varicosities or clusters); also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema: presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation: presumes venous origin; does not include focal pigmentation resulting from other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution (above lower third) and recent pigmentation
Inflammation: more than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Severe cellulitis (lower third and above) or significant venous eczema
Induration: presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hyperdermatitis); includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Entire lower third of leg or more
Active ulcer number	0	1	2	>2
Active ulcer duration (longest active)	N/A	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2–6 cm	Diameter >6 cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance with stockings



Absence of venous disease is defined by a score of ≤3; a score of ≥8 defines severe disease. VCSS indicates Venous Clinical Severity Score.

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CEAP Classification

The CEAP classification was developed to diagnose and compare treatment outcomes in patients with chronic venous disorders.⁴³ CEAP categorizes venous disease according to clinical, etiologic, anatomic, and pathophysiologic attributes. There are 7 clinical classes, which correspond with objective clinical signs (Table 4). Although CEAP has been used to diagnose PTS,^{12,29,35,55} there is no agreed-on cutoff that defines the diagnosis,⁵² it has a limited ability to monitor change over time, and it does not incorporate assessment of PTS symptom severity. Therefore, CEAP is not an ideal scoring system to diagnose and follow up the course of PTS.

The VCSS

The VCSS (Table 5),⁵⁶ recently revised by Vasquez et al,⁴⁰ combines key elements of CEAP with additional criteria such as use of compression therapy and number and duration of ulcers, thus allowing assessment of change with treatment. The VCSS scoring system assesses the severity of 9 clinical signs of chronic venous disease. VCSS elements are weighted toward more severe manifestations, and only 1 symptom (pain) is assessed; hence, this measure has not been used in many studies to diagnose incident PTS.

Widmer Classification

The Widmer classification, developed to grade chronic venous disease into classes I, II, and III according to the presence of clinical signs, has also been used to diagnose PTS⁴¹ and to assess the effectiveness of compression therapy in patients with stage I and II PTS.⁵⁷

A comparison of the various PTS classifications and their relationships with invasive venous pressure measurement was performed by Kolbach et al.⁴⁴ In general, agreement among the different clinical measures is modest. For example, there is poor to moderate agreement between the Villalta scale and CEAP, and VCSS shows poor correlation with other scoring systems.⁴⁴ A study by Kahn et al⁵⁴ found that the proportion of patients classified as having PTS according to the Villalta scale was almost 5 times higher than that classified by the Ginsberg measure (37% versus 8.1%, respectively), with the Ginsberg measure tending to be less sensitive for mild PTS. Jayaraj and Meissner⁵⁸ recently reported good correlation between the Villalta scale and VCSS for mild and moderate PTS but not for severe PTS.

The variability in the measures used to define PTS has limited the ability to compare results across studies. Because the Villalta scale was developed specifically for PTS and

Table 6. Risk Factors for PTS

Risk Factor	Author, Year	Risk Estimate	Strength/Consistency of Risk Association
Present at the time of DVT diagnosis			
Older age	Wik et al, ⁶¹ 2012	OR, 3.9 (95% CI, 1.8–8.3) if >33 y at time of pregnancy	++
	Tick et al, ⁴⁶ 2008	RR, 0.6 (95% CI, 0.4–0.9); >60 y	
	Kahn et al, ⁸ 2008	0.30 Villalta scale increase per 10 y	
	Schulman et al, ¹¹ 2006	Increased risk if age ≥60 y	
	van Dongen et al, ⁴⁷ 2005	RR, 2.56 (95% CI, 1.39–4.71); >65 y	
	Prandoni et al, ⁵¹ 2004	RR, 1.36 (95% CI, 1.15–1.60) per 10-y age increase	
Sex	Tick et al, ⁶² 2010	RR, 1.4 (95% CI, 0.9–2.2); male	+/-
	Kahn et al, ⁸ 2008	0.79 Villalta scale increase for female vs male	
	Tick et al, ⁴⁶ 2008	RR, 1.5 (95% CI, 1.3–1.8); female	
	Stain et al, ¹⁰ 2005	OR, 1.6 (95% CI, 1.0–2.3); male	
Increased BMI/obesity	Galanaud et al, ⁴⁵ 2013	OR, 2.63 (95% CI, 1.47–4.70); BMI ≥30 kg/m ²	++
	Kahn et al, ⁸ 2008	0.14 Villalta scale increase per unit BMI increase	
	Tick et al, ⁴⁶ 2008	RR, 1.5 (95% CI, 1.2–1.9); BMI >30 kg/m ²	
	Kahn et al, ⁶³ 2005	0.16 Villalta scale increase per unit BMI increase	
	van Dongen et al, ⁴⁷ 2005	OR, 1.14 (95% CI, 1.06–1.23); BMI >25 kg/m ²	
	Stain et al, ¹⁰ 2005	OR, 1.6 (95% CI, 1.0–2.4); BMI >25 kg/m ²	
DVT localization	Ageno et al, ⁶⁴ 2003	OR, 3.54 (95% CI, 1.07–12.08); BMI >28 kg/m ²	++
	Wik et al, ⁶¹ 2012	OR, 6.3 (95% CI, 2.0–19.8); proximal postnatal thrombosis, up to 3 mo postpartum	
	Kahn et al, ⁸ 2008	2.23 Villalta scale increase for iliac or CFV vs distal	
	Tick et al, ⁴⁶ 2008	RR, 1.4 (95% CI, 1.1–1.8); iliac or CFV vs popliteal	
	Stain et al, ¹⁰ 2005	OR, 2.1 (95% CI, 1.3–3.7); proximal vs distal DVT	
	Asbeutah et al, ³⁴ 2004	Increased risk if proximal vs distal	
	Gabriel et al, ⁶⁵ 2004	Increased risk if proximal+distal DVT	
	Mohr et al, ⁶⁶ 2000	RR, 3.0 (95% CI, 1.6–4.7); proximal vs distal DVT	
	Prandoni et al, ⁷ 1996	No relation between extent of DVT and PTS	
Thrombophilia	Labropoulos et al, ⁶⁷ 2008	Increased risk if DVT was extensive	-
	Spiezia et al, ⁶⁸ 2010	HR, 1.23 (95% CI, 0.92–1.64); antithrombin, protein C and S deficiencies, lupus anticoagulant, FVL and prothrombin gene mutation; compared with noncarriers of thrombophilia	
	Tick et al, ⁴⁶ 2008	RR, 1.1 (95% CI, 0.9–1.4); FVL RR, 1.2 (95% CI, 0.9–1.4); prothrombin gene mutation	
	Kahn et al, ⁶³ 2005	RR, 0.33 (95% CI, 0.2–0.7); FVL or prothrombin gene mutation	
	Stain et al, ¹⁰ 2005	OR, 0.9 (95% CI, 0.6–1.3); FVL OR, 0.8 (95% CI, 0.4–1.7); prothrombin gene mutation OR, 2.0 (95% CI, 0.8–5.1); FVIII	
Varicose veins at baseline	Galanaud et al, ⁴⁵ 2013	OR, 2.2 (95% CI, 1.1–4.3); primary venous insufficiency at baseline	++
	Ten Cate-Hoek et al, ⁶⁹ 2010	RR, 3.2 (95% CI, 1.2–9.1)	
	Tick et al, ⁴⁶ 2008	RR, 1.5 (95% CI, 1.2–1.8)	
Smoking daily before pregnancy	Wik et al, ⁶¹ 2012	OR, 2.9 (95% CI, 1.3–6.4)	++
Asymptomatic DVT	Wille-Jørgensen et al, ⁷⁰ 2005	Metanalysis RR, 1.58 (95% CI, 1.24–2.02); after postoperative asymptomatic DVT	+/-
	Lonner et al, ⁷¹ 2006	No increase in risk after asymptomatic proximal or distal DVT	
	Persson et al, ⁷² 2009	PTS uncommon sequel to asymptomatic DVT after minor surgery	
Surgery within last 3 mo	Tick et al, ⁴⁶ 2008	RR, 1.1 (95% CI, 0.9–1.3)	-

(Continued)

Table 6. Continued

Risk Factor	Author, Year	Risk Estimate	Strength/Consistency of Risk Association
Provoked vs unprovoked DVT	Labropoulos et al, ⁷³ 2010	RR, 2.9 (95% CI, 1.5–5.7)	+/-
	Tick et al, ⁴⁶ 2008	RR, 0.9 (95% CI, 0.7–1.2)	
	Kahn et al, ⁸ 2008	Not an independent predictor	
	Stain et al, ¹⁰ 2005	OR, 1.0 (95% CI, 0.6–1.7)	
	Prandoni et al, ⁵¹ 2004	Not an independent predictor	
Present during follow-up			
Poor INR control	Chitsike et al, ⁷⁴ 2012	OR, 1.84 (95% CI, 1.13–3.01); INR <2 for >20% of the time	++
	van Dongen et al, ⁴⁷ 2005	OR, 2.71 (95% CI, 1.44–5.10); TTR <50%	
Ipsilateral DVT recurrence	Bouman et al, ⁷⁵ 2012	OR, 6.3 (95% CI, 1.5–26.9)	++
	Labropoulos et al, ⁷³ 2010	RR, 1.6 (95% CI, 1.4–2.2)	
	Kahn et al, ⁸ 2008	1.78 Villalta scale increase if previous vs no previous ipsilateral DVT (95% CI, 0.69–2.87)	
	van Dongen et al, ⁴⁷ 2005	OR, 9.57 (95% CI, 2.64–34.7)	
	Prandoni et al, ⁵¹ 2004	RR, 3.32 (95% CI, 1.04–10.62)	
	Prandoni et al, ⁷ 1996	RR, 6.4 (95% CI, 3.1–13.3)	
Residual thrombus	Vedovetto et al, ²⁸ 2013	RR, 1.92 (95% CI, 1.39–2.64) residual thrombus alone, 1.83 (95% CI 1.26–2.66) residual thrombus+popliteal valve reflux	+
	Comerota et al, ⁷⁶ 2012	Direct linear correlation of Villalta score with residual thrombus ($P=0.0014$).	
	Galanaud et al, ⁴⁵ 2013	OR, 2.1 (95% CI, 1.1–3.7)	
	Tick et al, ⁶² 2010	RR, 1.6 (95% CI, 1.0–2.5); proximal veins	
	Prandoni et al, ²⁷ 2005	RR, 1.56 (95% CI, 1.01–2.45); common femoral and the popliteal vein	
	Incomplete resolution of leg symptoms and signs at 1 mo after DVT	Kahn et al, ⁸ 2008	
LMWH vs OAC	Hull et al, ⁷⁷ 2011	RR, 0.66 (95% CI, 0.57–0.77)	+
Increased D-dimer level	Latella et al, ⁷⁸ 2010	OR, 1.05 (95% CI, 1.01–1.10); for 100- μ g/L difference in D-dimer	+
	Stain et al, ¹⁰ 2005	OR, 1.9 (95% CI, 1.0–3.9); D-dimer >500 μ g/L	
Elevated levels of markers of inflammation	Bouman et al, ⁷⁵ 2012	OR, 8.0 (95% CI, 2.4–26.4); CRP >5 mg/L 12 mo after DVT	+
	Roumen-Klappe et al, ³⁵ 2009	RR, 2.4 (95% CI, 1.5–3.9); IL-6 VOR >0.8 mm Hg/min per 1% (surrogate of PTS) at 90 d	
		RR, 1.4 (95% CI, 1.1–3.3); CRP VOR >0.8 mm Hg/min per 1% (surrogate of PTS) at 90 d	
	Shbaklo et al, ³⁶ 2009	OR, 1.66 (95% CI, 1.05–2.62); IL-6 at 4 mo above median value of controls	
		OR, 1.63 (95% CI, 1.03–2.58); ICAM-1 at 4 mos above median value of controls	
Duration of oral anticoagulation	Schulman et al, ¹¹ 2006	No difference in risk: 6 wk vs 6 mo of OAC	–
	Stain et al, ¹⁰ 2005	No difference in risk: 6.6–12 vs >12 mo	
Intensity of oral anticoagulation	Kahn et al, ⁶³ 2005	No difference in risk: INR 1.5–1.9 vs 2.0–3.0 \geq 3 mo after DVT	–
Physical activity	Shrier et al, ⁷⁹ 2009	RR, 1.65 (95% CI, 0.87–3.14); for mild- to moderate-intensity exercise within 1 mo after DVT	–
		RR, 1.35 (95% CI, 0.69–2.67); for high-intensity exercise within 1 mo after DVT	–

BMI indicates body mass index; CFV, common femoral vein; CI, confidence interval; CRP, C-reactive protein; dist, distal; DVT, deep vein thrombosis; FVIII, factor VIII; FII, G20210A prothrombin gene mutation; FVL, factor V Leiden; HR, hazard ratio; ICAM, intercellular adhesion molecule; IL-6, interleukin-6; INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulants; OR, odds ratio; prox, proximal; PTS, postthrombotic syndrome; RR, relative risk; TTR, time in the therapeutic range; VOR, venous outflow resistance; –, no apparent association; +/-, variable or inconsistent association; +, consistent association of low magnitude; and ++, consistent association of higher magnitude

has undergone assessment of its validity and reliability for PTS diagnosis and PTS severity classification, we endorse its use for this purpose, in line with the recommendations of the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation.¹³

Objective Diagnosis of PTS

In patients with a characteristic clinical presentation of PTS but no history of previous DVT, compression ultrasonography can be done to look for evidence of prior DVT such as lack of compressibility of the popliteal or common femoral veins or reflux of venous valves on continuous-wave Doppler.^{9,59,60} In carefully selected patients in whom iliac vein obstruction is suspected on clinical grounds (eg, chronic severe aching or swelling of the entire limb, lack of respiratory phasicity of the common femoral vein Doppler waveform), imaging of the iliac vein using cross-sectional modalities (computed tomography, magnetic resonance imaging) or contrast venography with or without intravascular ultrasound can be performed. In such patients, the imaging finding of iliac vein thrombosis can confirm the diagnosis of PTS and guide therapeutic options. However, venography is invasive, so it is not routinely recommended for patients with mild symptoms that do not significantly affect daily functioning. It is important to highlight that many patients have demonstrable residual venous abnormalities after DVT (eg, venous reflux, venous hypertension, internal venous trabeculation) yet have no symptoms of PTS. In the absence of characteristic clinical features of PTS, PTS should not be diagnosed.

Risk Factors for PTS

To date, known risk factors can generally be divided into 1 of 2 categories: factors apparent at the time of DVT diagnosis and those that manifest during follow-up (Table 6).

PTS Risk Factors Apparent at the Time of DVT Diagnosis

Patient Characteristics

Elevated body mass index and obesity increase the risk of developing PTS by as much as 2-fold.^{8,10,45–47,63} Older age also increases the risk of PTS.^{8,11,46,47} There is no consistent association between sex and PTS; an almost equal number of studies have shown men or women to be at higher risk for PTS.^{8,10,46,62} Recent work on the risk of PTS after pregnancy-associated DVT reported that age >33 years at the time of index pregnancy is a predictor of PTS (odds ratio [OR], 3.9; 95% CI, 1.8–8.3), as is daily smoking (OR, 2.9; 95% CI, 1.3–6.4).⁶¹

DVT Characteristics

The extent (ie, size and location) of initial DVT is an important predictor of risk of PTS. Kahn et al⁸ noted that extensive thrombosis in the common femoral or iliac vein was a strong predictor of higher Villalta PTS scores over 2 years. A study by Tick et al⁴⁶ reported that DVT in the femoral and iliac veins was associated with an increased risk of PTS compared with popliteal vein thrombosis (RR, 1.3; 95% CI, 1.1–1.6), perhaps because of more rapid and complete resolution of thrombosis in distal vein segments.⁶² In a study by Labropoulos et al⁶⁷

of patients with a first episode of acute DVT, PTS was more frequent and more severe when the iliac vein was occluded in conjunction with other veins. In the previously noted study of PTS after pregnancy-related DVT, the strongest predictor of PTS was proximal thrombosis that occurred postpartum (OR, 6.3; 95% CI, 2.0–19.8).⁸⁰

Risk Factors Apparent During DVT Treatment and Follow-Up

Recurrent ipsilateral DVT has been shown in numerous studies to be an important risk factor for PTS. The variability in the magnitude of effect across studies (ORs, 1.6–10) is probably attributable to differences in study populations and definitions of PTS. However, all are consistent in showing ipsilateral recurrence to be predictive of future PTS (Table 6).^{7,8,47,51,73,75}

Residual thrombosis after treatment of DVT has also been shown to be a predictor of PTS.^{27,28,62,76} In patients with a first episode of DVT, the risk of PTS was 1.6-fold higher (95% CI, 1.0–2.5) in those with residual proximal thrombosis compared with those without this finding.⁶² A recent study by Comerota et al⁷⁶ documented a statistically significant correlation between residual thrombus after CDT and PTS severity. This finding highlights the importance of preventing recurrent DVT and the need to critically evaluate the utility of therapeutic strategies aimed at restoration of venous blood flow as potential means of preventing PTS.

The contribution of residual vein thrombosis versus popliteal valve incompetence to the risk of PTS was recently assessed in 290 patients with a first episode of proximal DVT.²⁸ The RR of PTS (assessed with the Villalta scale) was 1.92 (95% CI, 1.39–2.64) in patients with residual vein thrombosis alone, 1.11 (95% CI, 0.66–1.89) in patients with popliteal valve incompetence, and 1.83 (95% CI, 1.26–2.66) in patients with both findings, suggesting that residual vein thrombosis is a stronger determinant of PTS.

In the Venous Thrombosis Outcomes (VETO) study, a prospective cohort study by Kahn et al,⁸ the presence of residual venous symptoms and signs 1 month after DVT diagnosis was strongly predictive of subsequent PTS. Patients whose residual symptoms at 1 month were mild, moderate, or severe had average Villalta scores over 2 years of follow-up that were higher by 2, 5, and 7 points, respectively, compared with patients without residual symptoms at 1 month. This suggests that the pathophysiological progenitor of PTS occurs in the first few weeks after DVT.

Finally, 2 studies reported that subtherapeutic anticoagulation with warfarin (international normalized ratio [INR] <2.0) increased the risk of PTS. In 1 recent study, patients had an almost 2-fold increased risk of developing PTS if their INR during the first 3 months of therapy was subtherapeutic >20% of the time (OR, 1.84; 95% CI, 1.13–3.01).⁷⁴ These findings were consistent with an earlier study that reported that patients whose INR results were subtherapeutic >50% of the time had a 2.7-fold higher risk of PTS.⁴⁷

Risk Factors Not Likely to Be Associated With PTS

Total duration of anticoagulation does not appear to influence the risk of PTS. In a multicenter trial comparing 6 weeks and

6 months of warfarin treatment, the risk of PTS was similar in both groups.¹¹ Similarly, Stain et al¹⁰ observed that duration of anticoagulant therapy (< 6, 6–12, or >12 months) did not influence the risk of PTS. Level of education and income were not significantly correlated with PTS, nor was the nature of the initial DVT event (provoked versus unprovoked).^{10,12,44,46,51,56,72,81} In some studies, asymptomatic DVT (eg, detected by systematic imaging in the course of a clinical trial) was associated with subsequent development of PTS,⁷⁰ whereas in others it was not.^{71,72} Finally, inherited or acquired thrombophilia has generally not been shown to increase the risk of developing PTS,^{10,45,46,51,81} although 1 study showed a protective effect.⁶³

In summary, key risk factors for PTS include older age, higher body mass index, recurrent ipsilateral DVT, more extensive DVT, greater symptom severity at 1 month, and subtherapeutic anticoagulation, especially in the first few months after DVT. Further research on predictors of PTS is needed, including the development and validation of PTS risk prediction models. Whether risk factor modification such as weight reduction may have a role in preventing PTS has not been studied.

Role of Biomarkers to Predict PTS

Recent research efforts have focused on the role of inflammatory biomarkers such as interleukin-6, C-reactive protein, and intercellular adhesion molecule-1 as predictors of PTS. Shbaklo et al³⁶ reported that patients with PTS had significantly higher mean levels of interleukin-6 and intercellular adhesion molecule-1 than those without PTS. Roumen-Klappe et al³⁵ noted that higher levels of interleukin-6 and C-reactive protein were associated with greater venous outflow resistance 3 months after DVT, but their association with clinical PTS was weak or absent. In a recent prospective cohort study, C-reactive protein levels >5 mg/L 12 months after the index DVT independently predicted PTS (OR, 8.0; 95% CI, 2.4–26.4).⁷⁵ In 2 studies, persistently elevated levels of D-dimer, an indirect marker of coagulation activation, were predictive of PTS when measured at various intervals after DVT,^{10,78} especially when measured when the patient was off anticoagulant treatment. It is not yet known whether the aforementioned biomarkers may have clinical utility to identify patients with acute DVT who are at risk for PTS.

Prevention of PTS

Importance of Primary and Secondary Prevention of DVT to Prevent PTS

Primary Prevention

Because PTS is a consequence of DVT and thromboprophylaxis is an effective means of preventing DVT, it is clear that use of pharmacological or mechanical thromboprophylaxis in high-risk patients and settings as recommended in evidence-based consensus guidelines^{82–84} will prevent cases of PTS.

Secondary Prevention

Although thromboprophylaxis is effective, its use reduces the incidence of venous thromboembolism by only one half to two thirds. Moreover, nearly 50% of venous thromboembolism

events occur unpredictably and are therefore not preventable with thromboprophylaxis. Hence, strategies that focus on preventing the development of PTS after DVT are more likely to be effective in reducing the frequency of PTS than are attempts to prevent the index DVT. Because ipsilateral DVT recurrence is an important risk factor for PTS, preventing recurrent DVT by providing anticoagulation of appropriate intensity and duration for the initial DVT is an important goal.⁸⁵ In addition, appropriate thromboprophylaxis should be used when clinically warranted if long-term anticoagulation is discontinued.

Recommendations for Primary and Secondary Prevention of DVT to Prevent PTS

1. Use of thromboprophylaxis in patients at significant risk for DVT is recommended as a means of preventing PTS (*Class I; Level of Evidence C*).
2. Providing anticoagulation of appropriate intensity and duration for treatment of the initial DVT is recommended as a means of reducing the risk of recurrent ipsilateral DVT and consequent PTS (*Class I; Level of Evidence B*).

Optimizing Anticoagulation Delivery to Prevent PTS

As discussed, subtherapeutic anticoagulation with vitamin K antagonists has been associated with the development of PTS,^{47,74} with an almost 3-fold higher risk in those who had an INR <2.0 for >50% of the time. This occurred in about one third of patients, usually in the first few weeks of treatment. A dose-response effect was noted such that patients who spent more time in the subtherapeutic INR range had the highest incidence of PTS.

There has been interest in whether low-molecular-weight heparins (LMWHs), which have anti-inflammatory and anticoagulant properties,⁸⁶ could have a role in preventing PTS. In a systematic review of 5 randomized trials that compared long-term (≥3 months) LMWH with warfarin for DVT treatment, Hull et al⁷⁷ reported a risk ratio of 0.66 (95% CI, 0.57–0.77) in favor of LMWH for complete recanalization of thrombosed veins, and LMWH-treated patients had a lower incidence of venous ulceration. It should be noted that none of the included trials assessed PTS with accepted, validated clinical scales. Furthermore, although LMWH is safe and effective, it is costly and requires administration by daily subcutaneous injection.

As noted above, Kahn et al⁸ reported that the severity of venous symptoms and signs as early as 4 weeks after DVT were strongly predictive of the subsequent development of PTS. Together with the observation that inadequate initial oral anticoagulation increases the risk of PTS, these findings suggest that the treatment delivered during the first few weeks after DVT may be fundamental to determining long-term outcome, perhaps by tilting the physiological balance in favor of endogenous thrombus reduction, by preventing or reducing damage to the valves and microcirculation, or by limiting inflammation. The interesting hypothesis has been raised that new oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban, with their rapid onset and more predictable pharmacokinetics than vitamin K antagonists, could be associated with a reduced incidence of PTS.⁸⁷ However, this has not yet been tested.

Recommendations for Optimizing Anticoagulation Delivery to Prevent PTS

1. In patients whose DVT is treated with a vitamin K antagonist, frequent, regular INR monitoring to avoid subtherapeutic INRs, especially in the first few months of treatment, is recommended to reduce the risk of PTS (Class I; Level of Evidence B).
2. Compared with LMWH followed by a vitamin K antagonist, the effectiveness of LMWH used alone to treat DVT as a means to reduce the risk of PTS is uncertain (Class IIb; Level of Evidence B).
3. Compared with a vitamin K antagonist, the effectiveness of the new oral anticoagulants (ie, oral thrombin or factor Xa inhibitors) to treat DVT as a means to reduce the risk of PTS is unknown (Class IIb; Level of Evidence C).

Compression to Prevent PTS

Until recently, elastic compression stockings (ECS) have been considered a mainstay for PTS prevention despite sparse and conflicting data supporting their use. Six RCTs of the use of ECS to prevent PTS that include data on a total of nearly 1500 patients have been published. Summaries of these trials are given in Table 7.^{9,12,38,51,53,88}

Brandjes et al³⁸ randomized 194 patients with proximal DVT within 2 to 3 weeks after diagnosis to 21- to 40-mmHg knee-high stockings or no stockings and followed them up for up to 2 years. The primary outcome, development of mild to moderate PTS assessed with a modified version of the Villalta scale, occurred in 20% of the stocking group and 47% of the control group. Severe PTS developed in 11% of the stocking group compared with 23% of the control group. Using a similar study design, Prandoni et al⁵¹ randomized 180 patients with symptomatic proximal DVT to 30- to 40-mmHg stockings or no stockings. After 2 years of follow-up, 25% of the patients in the stocking group developed PTS, assessed with the Villalta scale, compared with 49% of the control group. Only 3% of the stocking group developed severe PTS compared with 11% of the control group.

In contrast to the trials above that initiated stockings soon after DVT diagnosis, 2 studies enrolled patients 6 months¹² and 1 year⁹ after DVT diagnosis. In the first study, all patients wore ECS for the first 6 months after DVT diagnosis, and in the second study, patients did not begin to use ECS until study enrollment, 1 year after DVT diagnosis. In neither study did the use of knee-high 26- to 36-mmHg or 20- to 30-mmHg ECS, respectively, reduce the rate of PTS compared with no stockings, suggesting that extending the use of stockings beyond the first 6 months or late initiation of stockings is not of benefit to reduce the incidence of PTS.

Partsch et al⁸⁸ compared early ambulation in combination with compression stockings (n=18) or Unna boots (n=18) with bed rest and no compression (n=17) in patients with acute DVT. All patients wore ECS for at least the first year of follow-up. At 2 years, the 2 early ambulation groups had lower Villalta scores, although the number of patients who met Villalta criteria for PTS was not reported. Given the design of this study, it cannot be discerned whether early compression or early ambulation was responsible for the apparent benefit.

The SOX trial was the only multicenter, double-blind, placebo-controlled trial of ECS.⁵³ This trial enrolled 806 patients an average of 4.7 days after a first episode of symptomatic proximal DVT and randomized them to 30- to 40-mmHg knee-high ECS or placebo stockings with no compression for 2 years. The primary outcome was the Ginsberg definition of PTS, namely persistent daily leg pain and swelling for at least 1 month. There was no statistically significant difference in the primary outcome between those randomized to active ECS and those randomized to placebo (hazard ratio, 1.13; 95% CI, 0.73–1.76).⁵³ Secondary analyses showed no effect of active ECS on PTS as defined by the Villalta scale, PTS severity, venous ulcers, venous thromboembolism recurrence, venous valvular reflux, or QoL. Subgroup analyses did not identify benefit of active ECS for subgroups defined by age, sex, body mass index, extent of DVT, or frequency of stocking use. These results suggest that the use of ECS does not alter the natural history of the development of PTS after DVT and that the benefit of ECS reported in previous studies may

Table 7. RCTs of Graduated Compression Stockings to Prevent PTS

Study, Year	Sample Size, n	Blinding	Time of Intervention After DVT	Type of Stocking	Duration of Follow-Up, y	Primary Outcome
Brandjes et al, ³⁸ 1997	96 Stockings, 98 no stockings	No	2–3 wk	30 mmHg at ankle; knee high	Up to 5	PTS by modified Villalta
Ginsberg et al, ⁹ 2001	24 Active stockings, 23 placebo stockings	Double-blinded	1 y	20–30 mmHg knee-high	Up to 9	Daily pain and swelling
Prandoni et al, ⁵¹ 2004	90 Stockings, 90 no stockings	No	5–10 d	30–40 mmHg	Up to 5	PTS by Villalta scale
Aschwanden et al, ¹² 2008	84 Stockings, 85 no stockings	No	6 mo	26–36 mmHg knee-high	Up to 7	Skin changes (CEAP ≥4)
Partsch et al, ⁸⁸ 2004	18 Stockings plus walking, 18 Unna boot plus walking, 17 bed rest	No	At admission	30 mmHg thigh-length	2	PTS by Villalta scale
Kahn et al, ⁵³ 2014	410 Active stockings, 396 placebo stockings	Double-blinded	4 d	30–40 mmHg knee-high	Up to 2	Daily pain and swelling

CEAP indicates clinical, etiological, anatomic, pathophysiological; DVT, deep venous thrombosis; PTS, postthrombotic syndrome; and RCT, randomized, controlled trial.

have been due, at least in part, to reporting or observer bias as a consequence of their open-label design. Alternatively, the placebo stockings used in the SOX study may have had some therapeutic effect.

Adverse events associated with stocking use are rare. In the study by Prandoni et al,⁵¹ itching, erythema, or discomfort (6%) and difficulty putting on the stockings (1%) were the principal recorded complaints. Compliance, which was defined as wearing stockings at least 80% of the time over the 2-year study period, was 93% in that trial. No serious adverse events were attributed to stockings in the SOX trial, and minor adverse events such as rash or itching occurred in <2% of patients in both groups. At 2 years, 56% of patients reported frequent use of their stockings, defined as wearing them for ≥ 3 days each week. Although not reported in these trials, it should be noted that ECS may aggravate symptoms in patients with arterial inflow limitation from peripheral arterial disease; hence, caution is urged in prescribing ECS to such patients.

On the basis of existing evidence, ECS are a low-risk intervention that may be useful for controlling the symptoms of acute DVT. However, whether ECS prevent PTS is now in doubt because the highest-quality evidence provided by the SOX trial suggested no benefit.

Recommendations for Compression to Prevent PTS

- 1. The effectiveness of ECS for PTS prevention is uncertain, but application of ECS is reasonable to reduce symptomatic swelling in patients with a diagnosis of proximal DVT (Class IIb; Level of Evidence A).**

Thrombolysis/Endovascular Therapies to Prevent PTS

Systemic anticoagulation alone does not reduce the risk of PTS. Earlier and more complete thrombus clearance producing an “open vein” can relieve venous outflow obstruction, preserve valvular function, and reduce venous hypertension.^{76,89} Therefore, from a pathophysiological standpoint, pharmacological thrombolysis, mechanical thrombectomy, or their combination is attractive for PTS prevention in patients with acute proximal DVT.^{90,91} However, the evidence for thrombolysis, whether systemic or CDT, or pharmacomechanical CDT (PCDT) for the prevention of PTS is currently insufficient to support its routine first-line use in most patients with DVT.^{85,90,92}

Systemic thrombolysis as an upfront treatment for DVT is not recommended for the prevention of PTS. Although several studies have compared systemically delivered thrombolytics with anticoagulation alone for DVT, few evaluated the occurrence of PTS as a primary outcome.^{93–96} Although this limited number of studies suggested a reduction in PTS, the risk of major bleeding was greater with systemic thrombolysis than with anticoagulation alone or CDT.^{96,97} Moreover, there is a nontrivial failure rate of systemic thrombolysis resulting, in part, from the poor concentration and penetration of thrombolytics within the thrombus itself.⁹⁸

CDT and PCDT evolved to overcome the limitations of systemic thrombolysis and the invasiveness of surgical thrombectomy.^{90,99} However, given the known risks of thrombolytic therapy and the uncertainty surrounding the estimates of risks

and benefit from the many CDT/PCDT studies that were of low to medium quality, CDT and PCDT are not currently recommended for routine first-line use for the purpose of PTS prevention in the general DVT patient population. Rather, these are promising techniques that should be considered in experienced centers for selected patients with acute symptomatic iliofemoral DVT (defined as DVT involving the common femoral vein or iliac vein, with or without involvement of additional veins) who, after careful evaluation, are considered to be at low risk for bleeding complications.¹⁰⁰ It should be noted that CDT or PCDT may be indicated in specific situations apart from PTS prevention such as for limb salvage in the rare patient with acute limb-threatening DVT, for early symptom relief in patients with particularly severe pain and swelling resulting from iliofemoral DVT or rapid DVT progression despite initial anticoagulation, or for organ salvage in patients with acute inferior vena cava thrombosis compromising end organs (eg, extending to renal vein thrombosis). The reader is referred to other guidelines for recommendations in these situations.^{92,100,101}

Most of the evidence supporting CDT or PCDT for the prevention of PTS stems from nonrandomized, single-center studies or registries.^{76,96,102–106} However, the recent Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) and Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trials provide more robust, although still limited, data on CDT and PCDT. CaVenT was an open-label RCT of 209 patients with acute proximal DVT comparing CDT plus standard anticoagulation with standard anticoagulation alone. There was a statistically significant ($P=0.047$) 26% relative reduction in risk of PTS at 2 years associated with CDT. However, 41% of CDT patients still developed PTS, indicating that CDT does not eliminate the risk of PTS. In addition, imbalances in the adequacy of anticoagulation and use of ECS between groups (both greater in the CDT group) may have influenced the results.³⁰ The TORPEDO trial evaluated PCDT plus anticoagulation versus anticoagulation alone in 183 patients with symptomatic DVT and found that PCDT significantly reduced the risk of PTS (7% versus 30%; $P<0.001$).¹⁰⁷ This study had a number of limitations, including the use of a nonvalidated measure of PTS, lack of blinding precautions for the clinical assessments, systematic differences in the use of antiplatelet therapy in the 2 treatment arms, and adjudication of crossovers as treatment failures. The multicenter, National Institutes of Health–sponsored Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial (anticipated enrollment, $n=692$; expected completion, 2016) will be the largest and most definitive study to date to address the role of CDT and PCDT in acute proximal DVT for the prevention of PTS.¹⁰⁸ Table 8 summarizes the CaVenT, TORPEDO, and ATTRACT trials.

Surgical thrombectomy might be considered in select patients with extensive acute proximal DVT who are not candidates for CDT or PCDT because of bleeding risk (Figure 3). In a recent meta-analysis, 8 studies, all from the 1970s through 1990s, were identified that addressed surgical thrombectomy versus systemic anticoagulation for the prevention of PTS. In

Table 8. RCTs of CDT and Other Endovascular Procedures to Prevent PTS After Proximal DVT

Study, Year	Patients	Intervention	Duration of Follow-up, mo	Primary Outcome	Main result	Comments
CaVenT (Enden et al, ³⁰ 2012)	209 Patients (63% male; mean age, 52 y) with a first episode of acute iliofemoral DVT; symptom onset within previous 21 d; recruited from 20 centers in Norway	CDT* plus anticoagulation (n=108) vs anticoagulation alone (control group; n=101); patients were asked to wear ECS (class II) daily for 24 mo	24	Coprietary outcomes: iliofemoral patency at 6 mo; PTS (defined by Villalta score ≥ 5 or ulcer present) at 24 mo	Iliofofemoral patency achieved in 65.9% (58 of 90) of CDT group vs 47.4% (45 of 99) of control group ($P=0.012$) PTS occurred in 41.1% (37 of 90) of CDT group vs 55.6% (55 of 99) of control group ($P=0.047$)	20 Bleeding complications in CDT group; 3 major and 5 clinically relevant. No bleeding events in control group. At 6 mo, 61% of CDT group had INR in therapeutic range vs 53% of control group; at 24 mo, results were 65% vs 50%, respectively. At 6 mo, 79% of CDT group used ECS daily vs 69% of control group; at 24 mo, results were 63% vs 52%, respectively.
TORPEDO (Sharifi et al, ¹⁰⁷ 2012)	183 Patients (56% male; mean age, 61 y) with symptomatic proximal DVT (femoropopliteal vein or more proximal venous segments); recruited from 1 US center	PEVI† plus anticoagulation (n=93) vs anticoagulation alone (control group; n=91); patients were asked to wear ECS (30–40 mm Hg) for a minimum of 6 mo and up to 2 y	30 (mean)	PTS (presence of ≥ 2 new symptoms: leg burning, pain, aches, discomfort, restlessness, and tingling, plus any of these signs: edema plus venous reflux on Doppler; skin hyperpigmentation or lipodermatosclerosis; healed or active ulcer	PTS occurred in 6.8% (6 of 88) of PEVI group vs 29.6% (24 of 81) of control group ($P<0.001$).	Bleeding events not reported. ECS compliance at 6-mo follow-up was similar in the PEVI and control groups (27.2% vs 28.4%). Anticoagulation time in the therapeutic range not provided.
ATTRACT (Vedantham et al, ¹⁰⁸ 2013)	692 (Projected), patients with symptomatic proximal DVT (iliac, common femoral, and/or femoral vein), to be enrolled at 40–60 US centers	PCDT with intrathrombus delivery of rtPA (maximum total dose, 35 mg) plus anticoagulation vs anticoagulation alone (control group); all patients asked to wear ECS (30–40 mm Hg) for 2 y	24	Cumulative incidence of PTS (defined by Villalta score of ≥ 5 or ulcer present) any time from the 6-mo follow-up visit to the 24-mo visit (inclusive)	Not yet available	Estimated completion of study: May 2016

ATTRACT indicates Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis; CaVenT, Catheter-Directed Venous Thrombolysis Trial; CDT, catheter-directed thrombolysis; DVT, deep venous thrombosis; ECS, elastic compression stockings; INR, international normalized ratio; PCDT, pharmacomechanical catheter-directed thrombolysis; PEVI, percutaneous endovenous intervention; PTS, postthrombotic syndrome; RCT, randomized, controlled trial; rtPA, recombinant tissue-type plasminogen activator; and TORPEDO, Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion.

*CDT using alteplase (0.01 mg·kg⁻¹·h⁻¹ for maximum of 96 hours; maximum dose, 20 mg/24 h). Mean duration of CDT was 2.4 days. Use of adjunctive angioplasty and stents to establish flow and obtain <50% residual stenosis left to the discretion of the operator.

†PEVI group: procedure performed within 24 hours of presentation and initiation of anticoagulation. All patients received inferior vena cava filter. Treatment consisted of ≥ 1 of a combination of thrombectomy, manual thrombus aspiration, balloon venoplasty, stenting, or local catheter-directed low-dose thrombolytic therapy with tPA 1 mg/h for 20 to 24 hours, followed by 81 mg aspirin per day for ≥ 6 months and, in the case of stent placement, clopidogrel 75 mg/d for 2 to 4 weeks.

the pooled analysis of 611 patients, surgical thrombectomy was associated with a 33% RR reduction (95% CI, 13–48) in the incidence of PTS.¹⁰⁹ However, we underline that there have not been any contemporary trials comparing surgical thrombectomy with systemic anticoagulation or CDT/PCDT.

For further discussion and procedural details for CDT, PCDT, surgical thrombectomy, and use of inferior vena cava filters in the management of acute iliofemoral DVT, the reader is referred to a recent American Heart Association scientific statement by Jaff et al.¹⁰⁰



Figure 3. Operative photograph of thrombus retrieved from a patient with phlegmasia cerulea dolens after surgical iliofemoral venous thrombectomy. Photograph courtesy of Dr Comerota.

Recommendations for Thrombolysis and Endovascular Approaches to Acute DVT for the Prevention of PTS

1. CDT and PCDT, in experienced centers, may be considered in select patients with acute (≤ 14 days) symptomatic, extensive proximal DVT who have good functional capacity, ≥ 1 -year life expectancy, and low expected bleeding risk (*Class IIb; Level of Evidence B*).
2. Systemic anticoagulation should be provided before, during, and after CDT and PCDT (*Class I, Level of Evidence C*).
3. Balloon angioplasty with or without stenting of underlying anatomic venous lesions may be considered after CDT and PCDT as a means to prevent rethrombosis and subsequent PTS (*Class IIb; Level of Evidence B*).
4. When a patient is not a candidate for percutaneous CDT or PCDT, surgical thrombectomy, in experienced centers, might be considered in select patients with acute (≤ 14 days) symptomatic, extensive proximal DVT who have good functional capacity and ≥ 1 -year life expectancy (*Class IIb; Level of Evidence B*).
5. Systemic thrombolysis is not recommended for the treatment of DVT (*Class III; Level of Evidence A*).

Treatment of PTS

Graduated Stockings and Intermittent Compression to Treat PTS

A number of compression-based therapies have been used in patients with PTS with the goals of reducing symptoms (particularly limb swelling) and improving daily functioning, but few controlled studies of their effectiveness have been performed. Anecdotally, some patients describe improvement with the use of compression, but the published studies have methodological limitations and statistical imprecision that preclude confident conclusions about their effectiveness in patients with PTS. Accordingly, the recommendations below are based primarily on the low risk of harm and the possibility of benefit to at least some patients with PTS.

Graduated ECS

Two small, randomized trials comprising a total of 115 patients have evaluated the ability of 30- to 40-mmHg graduated

ECS to reduce symptoms in patients with PTS.^{9,49} In 1 study, patients with PTS were randomized to receive active 30- to 40-mmHg stockings (knee-high or thigh-high stockings) versus placebo stockings and were followed up for clinical change every 3 months.⁹ The proportions of patients exhibiting failure of therapy were similar in both arms (61.1% active stockings versus 58.8% placebo; $P=NS$). The second study was an open-label, assessor-blind RCT in which patients with PTS were randomized to wear or not to wear 30- to 40-mmHg knee-high ECS.⁴⁹ No benefit was observed with use of ECS. No studies have directly addressed the comparative efficacy of thigh-high versus knee-high ECS to treat PTS.

Although most patients exhibit some degree of compliance with ECS with education on their use, limitations of ECS can include patient nonadherence resulting from difficulty in donning the garments, discomfort, allergic hypersensitivity of the skin, and cost. However, because the risk of major harm with ECS therapy is low and some patients report clinical improvement with their use, a trial of ECS may be reasonable in patients with PTS and without contraindications.

Intermittent Compression Devices

Two small, crossover RCTs evaluated the use of intermittent compression devices for the treatment of PTS. One study of 15 patients with severe PTS found that a 4-week period of daily use of an intermittent pneumatic compression device at 50 mmHg improved edema in 80% of the patients.¹¹⁰ Disadvantages of intermittent pneumatic compression therapy are its expense and inconvenience, in particular, the need to pump the affected limb for several hours each day. The second study evaluated a lightweight, portable, battery-powered, cuff-like compression device (VenoWave device).⁵⁰ In this 2-center, placebo-controlled, double-blind, crossover RCT of 32 patients with severe PTS and no ulcer, 31% of patients who used the device daily for 8 weeks were clinically improved compared with 13% in the placebo arm ($P=0.11$).

Despite the statistical imprecision of these estimates of efficacy resulting from the small numbers of patients studied, the potential for benefit is likely to outweigh harm. Hence, a trial of an intermittent compression device may be reasonable for patients with moderate or severe PTS and edema.

Recommendations for the Use of Graduated ECS and Intermittent Compression to Treat PTS

1. A trial of ECS may be considered in patients with PTS who have no contraindications (eg, arterial insufficiency) (*Class IIb; Level of Evidence C*).
2. For patients with moderate or severe PTS and significant edema, a trial of an intermittent compression device is reasonable (*Class IIb; Level of Evidence C*).

Pharmacotherapy to Treat PTS

Only 4 randomized trials have been performed to evaluate the effectiveness of pharmacological therapy for PTS: 3 parallel trials^{49,111,112} and 1 crossover study.¹¹³ The drugs evaluated were rutosides (thought to reduce capillary filtration rate and microvascular permeability to proteins), defibrotide (down-regulates plasminogen activator inhibitor-I release and up-regulates prostacyclin, prostaglandin E₂, and thrombomodulin),

and hidrosmin (unknown mechanism of action).¹¹⁴ The main features of these studies are shown in Table 9.

de Jongste et al¹¹¹ reported statistically significant improvement in leg tiredness in patients treated with rutosides compared with patients treated with placebo, but pain, heaviness, and swelling were only moderately relieved. Monreal et al¹¹³ showed that both hidrosmin and rutosides reduced symptoms but that hidrosmin produced greater improvement. Statistically significant improvement in pain and edema scores was observed by Coccheri et al¹¹² with defibrotide versus placebo, whereas claudication, skin pigmentation, and lipodermatosclerosis were unchanged. Finally, a similar proportion of patients treated with compression stockings alone, rutosides alone, and a combination of compression stockings and rutosides showed symptom improvement (70%, 65%, and 63%, respectively) or deterioration (15%, 23%, and 23%) in the study by Frulla et al.⁴⁹ Notably, in the only study in which

follow-up continued for 6 additional months after treatment completion, the drug effect virtually disappeared.¹¹³

Three of 4 studies reported on side effects, which were mostly mild and balanced between groups.^{49,111,112} In the de Jongste et al¹¹¹ study, 7 of 41 patients (17%) in the rutosides group and 4 of 42 (12%) in the placebo group reported headache, hair loss, swollen fingers, muscle stiffness, rash, or dizziness. In the Coccheri et al study,¹¹² 3% in both groups reported nausea, vomiting, or syncope, and a case of laryngeal edema occurred in the defibrotide group. Gastric pain was reported by 6 of 80 patients (8%) taking rutosides in the study by Frulla et al.⁴⁹ Because drug treatment was usually of short duration, potential long-term side effects are unknown.

Overall, there is low-quality evidence to support the use of venoactive drugs (rutosides, hidrosmin, and defibrotide) to treat PTS, and all studies present a high degree of inconsistency and imprecision.¹¹⁴ More rigorous studies using

Table 9. Pharmacotherapy for the Treatment of PTS

Study, Year	Design	Population	Intervention	Control	Follow-Up	Results
de Jongste et al, ¹¹¹ 1989	Parallel-group RCT	83 Patients with PTS of ≥ 6 -mo duration; minimum 10-mm difference in calf/ankle circumference between PTS leg and other leg	HR 1200 mg daily (4 equal doses) for 8 wk	Placebo 4 times daily; use of GCS not allowed	8 wk (4- and 8-wk follow-up visits)	Greater improvement of symptoms* seen in HR group at 4 and 8 wk (only tiredness was statistically significant, $P=0.02$). Greater reduction in mean calf (-6.7 mm) and ankle (-3.4 mm) circumference at 8 wk in HR group.
Monreal et al, ¹¹³ 1994	Crossover RCT	29 Patients with PTS of ≥ 12 -mo duration; minimum 20-mm difference in calf/ankle circumference between PTS leg and other leg	Hidrosmin 600 mg daily (3 equal doses) for 6 mo; HR 900 mg daily (3 equal doses) for 6 mo	All subjects took both study drugs; all were encouraged to use GCS	18 mo; study period of 6 mo and then follow-up every 3 mo	Improvement of symptoms† with both drugs. Small reduction in calf/ankle circumference with hidrosmin. Ulcer healing with both drugs.
Coccheri et al, ¹¹² 2004	Parallel-group RCT	288 Patients with CEAP class C2-C4 venous disease; only 64% had history of DVT	Defibrotide, 800 mg daily (2 equal doses) for 12 mo	Placebo twice a day; GCS used by both groups	12 mo (follow-up visits every 2 mo)	Improvement in symptoms,‡ statistically significant for pain ($P=0.01$) and edema ($P=0.03$). Decreased mean ankle circumference over 12 mo in treatment group ($P=0.0013$)
Frulla et al, ⁴⁹ 2005	Parallel-group RCT (3 arms)	120 Patients with PTS (defined by Villalta scale) and previous proximal DVT	HR 1,000 mg twice daily (soluble powder) alone or combined with GCS (30-40 mm Hg) for 12 mo	GCS (30-40 mm) for 12 mo	12 mo (follow-up visits at 3,6,12 mo)	1) PTS improvement§: 26/40 HR, 25/40 CGS + HR, 28/40 GCS alone 2) PTS worsening: 9/40 HR, 9/40 GCS + HR, 6/40 GCS alone

CEAP indicates clinical, etiologic, anatomic, pathophysiologic; DVT, deep venous thrombosis; HR, 0-(β -hydroxyethyl)-rutosides; GCS, graduated compression stockings; PTS, postthrombotic syndrome; and RCT, randomized clinical trial.

*Symptoms assessed with a nonvalidated scale assigning a value of 0 (absent) to 3 (severe) per item.

†Symptoms assessed with the validated Kakkar and Lawrence scale.

‡Symptoms assessed with a nonvalidated scale assigning a value of 0 (absent) to 2 (severe) per item.

§Symptoms assessed with the validated Villalta scale.

validated measures of clinically important outcomes, including QoL, are needed to assess the safety, effectiveness, and sustainability of pharmacological treatments for PTS.

Recommendations for Pharmacotherapy to Treat PTS

- 1. The effectiveness and safety of rutosides, hidrosmin, and defibrotide to treat PTS are uncertain (Class IIb; Level of Evidence B).**

Exercise Training to Treat PTS

Exercise does not appear to aggravate leg symptoms after DVT or to increase the risk of PTS.^{79,115} Indeed, many patients with PTS report improvement in their symptoms with exercise, which may be related to improved calf muscle function and ejection of venous blood from the limb. Two small trials have assessed the potential benefits of exercise in patients with PTS. In a study of 30 patients with chronic venous insufficiency (half had prior DVT), a 6-month leg muscle strengthening exercise program was associated with improved calf muscle pump function and dynamic calf muscle strength.¹¹⁶ In a 2-center Canadian pilot study, 42 patients with PTS were randomized to 6 months of exercise training (including components to increase leg strength and flexibility and overall cardiovascular fitness) or control. Exercise training was associated with improvement in PTS severity, QoL, leg strength, and leg flexibility, and there were no adverse events.⁴⁸

In summary, although the role of exercise training to prevent or treat PTS is not definitively established, available data suggest that exercise does not harm and may benefit patients with DVT and PTS. Further research on the role of exercise after DVT is warranted.

Recommendations for Exercise Training to Treat PTS

- 1. In patients with PTS, a supervised exercise training program consisting of leg strength training and aerobic activity for at least 6 months is reasonable for patients who are able to tolerate it (Class IIa; Level of Evidence B).**

Venous Ulcer Management

Up to 10% of patients with DVT develop severe PTS, which can include leg ulcers (Figure 4). The probability of developing an ulcer increases with PTS duration, with up to 5% of patients with DVT having ulcers by 10 years.¹¹ Leg ulcers are costly, slow to heal, and disabling and reduce QoL.¹⁶

The mainstay of treatment for venous ulcers is compression therapy. A systematic review of 7 RCTs reported that chronic venous ulcers healed more quickly with compression compared with primary dressings alone, noncompression bandages, and usual care without compression.¹¹⁸ This review also suggested that single-component compression may be less effective than multicomponent compression and that multicomponent compression systems containing an elastic bandage are more effective than those composed mainly of inelastic constituents.

There has been interest in the use of pentoxifylline, a hemorheological agent that increases microcirculatory blood

flow and ischemic tissue oxygenation, to treat venous ulcers.¹¹⁹ A meta-analysis of 11 trials reported that pentoxifylline 400 mg 3 times daily was more effective than placebo for complete healing of or significant improvement in ulcer (RR, 1.70; 95% CI, 1.30–2.24), and pentoxifylline plus compression was more effective than placebo plus compression (RR, 1.56; 95% CI, 1.14–2.13).¹²⁰ However, more adverse effects, mostly gastrointestinal (eg, nausea, indigestion, diarrhea), were reported in those receiving pentoxifylline (RR, 1.56; 95% CI, 1.10–2.22).

Other important measures to treat venous ulcers include maintaining a moist environment to optimize wound healing, providing a protective covering, controlling dermatitis, and aggressively preventing and treating infection.^{121,122}

The role of exercise in healing venous ulcers is unknown. Exercise increases venous hypertension, theoretically worsening the conditions leading to ulceration. However, as discussed above, some patients with PTS note improvement in their symptoms with exercise, and supervised calf muscle exercise has been associated with improved hemodynamics in patients with venous ulcers.¹¹⁶ More work is needed to determine whether exercise can help speed ulcer healing.

Finally, the role of surgical and endovascular procedures to remove or ablate incompetent superficial veins in the treatment of venous ulcers remains controversial.^{123–127} Neovalue reconstruction may be considered as a surgical treatment for refractory venous ulcers. A study by Lugli et al¹²⁸ reported on 40 neovalue constructions in 36 patients with resistant venous ulceration resulting from venous valve incompetence; of these, 32 patients had PTS and 4 had primary valve agenesis. During a median follow-up of 28 months, ulcer healing occurred in 36 of 40 limbs (90%), and recurrent ulceration occurred in 3 of 40 limbs (8%).

Recommendations for Venous Ulcer Management

- 1. Compression should be used to treat venous ulcers in preference to primary dressing alone, noncompression bandage, or no compression (Class I; Level of Evidence A).**
- 2. Multicomponent compression systems are more effective than single-component systems (Class I; Level of Evidence B).**
- 3. Pentoxifylline can be useful for treating venous ulcers on its own or with compression (Class IIa; Level of Evidence A).**
- 4. Neovalue reconstruction may be considered in patients with refractory postthrombotic venous ulcers (Class IIb; Level of Evidence C).**

Endovascular and Surgical Treatment for PTS

Surgical or endovascular procedures to treat appropriately selected patients with PTS have potential to decrease postthrombotic morbidity attributable to deep venous obstruction or venous valve incompetence (Table 10). However, well-designed studies have not been performed because experience with these procedures is limited and only the most severely affected patients are treated. Furthermore, some of the published experience predates the development of objective reporting standards for outcome assessment of patients undergoing procedures for chronic venous disease.



Figure 4. Various degrees of postthrombotic venous ulcers. **A**, Healing ulcer, medial malleolus of left leg required. **B**, Healed venous ulcer (this patient also has psoriasis, accounting for reddish skin abnormality on the lateral portion of anterior calf). **C**, A 30-year-old woman with severe postthrombotic syndrome of the right lower extremity, demonstrating a small, round, open, weeping ulcer, along with pronounced subcutaneous fibrosis. Reprinted from Nayak et al¹¹⁷ with permission from SIR. Copyright © 2012, SIR. Published by Elsevier Inc. **D**, Round, open, active ulcer of ≈1-in diameter. **E**, Large healed ulcer with pronounced subcutaneous fibrosis and resulting deformity in skin architecture. **F**, Patient with advanced postthrombotic morbidity who suffered from iliofemoral and vena caval occlusion. This patient presented with a large venous ulcer of the right lower extremity. Sequential photographs at 1, 2, and 3 months show the progressive benefit of sustained multilayer compression for the management of venous leg ulcers. Photographs in **A**, **B**, **D**, and **E** are courtesy of Dr Vedantham. Photograph in **F** is courtesy of Dr Comerota.

As a first principle, detection and elimination of iliac vein obstruction may be worth considering for patients with moderate to severe PTS. Below, we describe the endovascular and surgical means to do this. An important consideration when evaluating procedural results is that there often is uncorrected disease distal to the most proximal reconstruction, which will mitigate the clinical response to the procedure. Interventions to correct reflux might be considered in a highly symptomatic patient once it is known that the iliac vein is open.

Infrainguinal Venous Obstruction

Saphenopopliteal or Saphenotibial Bypass

Using the patent saphenous vein to bypass an occluded femoral or popliteal venous segment was initially reported by Warren

and Thayer¹²⁹ and subsequently by Husni¹³⁰ and others.^{131–136} The total number of patients reported is only 125, with follow-up ranging from 6 to 125 months. Bypass patency ranges from 50% to 97%, and clinical benefit is reported in 31% to 75%. The most contemporary series by Coleman et al¹³⁷ confirms a primary patency rate of 69%; 82% experienced complete or nearly complete resolution of venous claudication; and 59% experienced healing of their ulcers.

Iliofemoral Obstruction

Femoro-Femoral Bypass

Palma and Esperon¹³⁸ were the first to report autogenous femoro-femoral bypass using the contralateral saphenous vein in patients with unilateral iliac vein obstruction; reports from

Table 10. Endovascular, Surgical, and Hybrid Approaches to the Treatment of PTS*

	Indication	Approach
Endovascular approaches	Iliocaval/iliofemoral obstruction	Venoplasty and stenting
	Correction of superficial reflux	Endovenous thermal ablation
Surgical approaches	Infrainguinal venous obstruction	Saphenopopliteal bypass
		Saphenotibial bypass
	Iliofemoral obstruction	Femoro-femoral bypass
		Femoroiliac bypass
Iliocaval bypass		
Correction of reflux	Femoral-caval bypass	
	Segmental vein valve transfer via axillofemoral/popliteal transplant or venous transposition	
	Ligation of femoral vein	
Hybrid approaches	Femoral and iliac vein reconstruction	Surgical endophlebectomy of common femoral vein with patch angioplasty and endoluminal balloon venoplasty and stenting of iliac veins and vena cava Adjunctive arteriovenous fistula to maintain patency Surgical disobliteration of common femoral vein to more effectively drain infrainguinal venous system and provide inflow to recanalized iliac veins

PTS indicates postthrombotic syndrome.

*Note: experience with these procedures is limited, and only the most severely affected patients are considered for treatment. Outcomes of these procedures are highly dependent on operator (surgical) expertise, and if not available locally, referral to a center with expertise is recommended. See the Endovascular and Surgical Treatment for PTS section for more detailed discussion.

others followed.^{131–136,139–142} After follow-up ranging from 6 to 144 months, autogenous bypass patency ranged from 37% to 100%, and 25% to 100% had clinical improvement. Prosthetic femoro-femoral bypasses were used in patients without adequate saphenous veins.^{134,139,143–148} After follow-up ranging from 1 to 123 months, patency and clinical success were 25% to 100%. Of note, reports with the best patency and clinical success had the smallest number of patients and shortest follow-up.

Garg et al¹⁴⁹ reported 26 patients undergoing femoro-iliac/iliocaval bypass and 9 patients having femoro-caval bypass. At a median follow-up of 41 months, 53% of patients had no or minimal swelling and no activity limitations. Ulcers were healed in 83% of patients (10 of 12 patients) at 12 months, but half recurred at a mean of 48 months. Procedure type significantly correlated with persistent postthrombotic symptoms: relative odds were 0.5 in femoro-femoral bypasses, 0 in short bypasses, 0.6 in femoro-caval bypasses, 3 in complex bypasses, and 7 in hybrid reconstructions.

Endovascular Procedures for Iliocaval Obstruction

Central venous outflow obstruction of the iliofemoral venous segment results in the highest venous pressures and most severe PTS morbidity. A number of reports describe the technical success rate and short-term outcome after percutaneous relief of iliac vein obstruction. The largest, most carefully studied cohort was that of Neglen et al,¹⁵⁰ who reported results of venoplasty and stenting in 464 limbs of patients with PTS followed up for at least 5 years. Ulcer healing occurred in 55%. Resting arm-foot pressure differential and QoL significantly improved after venoplasty and stenting. Procedure-related thrombosis occurred in 2.6%.

Complex Reconstructions

Hybrid Surgical and Endovenous Iliofemoral/Caval Reconstruction

Patients with common femoral vein and iliac vein segment with or without caval obstruction have been treated with surgical

endophlebectomy of the common femoral vein with patch angioplasty and endoluminal balloon venoplasty and stenting of the iliac veins and vena cava. An adjunctive arteriovenous fistula is used to maintain patency. Operative disobliteration of the common femoral vein is performed to drain the infrainguinal venous system more effectively and to provide inflow to the recanalized iliac veins. Comerota¹⁵¹ recently reported results of 16 limbs (14 patients) with incapacitating PTS involving the common femoral and iliac veins (12 patients) and bilateral common femoral vein and iliofemoral segments (2 patients). Seven procedure-related complications occurred: bleeding (3), thrombosis (3), and acute lymphedema (1). All patients had at least 6 months of follow-up (mean, 26 months). All 3 patients with recalcitrant venous ulcers experienced healing without recurrence. QoL, Villalta, and VCSS scores significantly improved after the procedure.

Surgical Procedures to Correct Reflux

Segmental Vein Valve Transfer: Axillofemoral/Popliteal Transplantation or Venous Transposition

Transplanting a segment of axillary vein with a competent valve or valves to an incompetent postthrombotic infrainguinal vein or transposing an incompetent femoral vein below a competent profunda vein valve or saphenous vein valve has been shown to reduce the clinical severity of chronic venous disease. A report by Masuda and Kistner¹⁵² summarized long-term outcomes (follow-up, 4–21 years; mean follow-up, 11 years). Thirty-seven percent of patients (6 of 16 patients) with PTS versus 73% of patients (16 of 22 patients) with primary venous insufficiency had good to excellent results, defined by ability to resume full activity, either with stockings or without stockings. Neovale reconstruction for patients with refractory venous ulceration is discussed above in Venous Ulcer Management.

Endovascular Approaches to Address Reflux

Two studies have reported the use of endovenous thermal ablation to eliminate saphenous vein reflux as a source of venous

hypertension in patients with PTS who continue to be symptomatic after iliac vein obstruction has been addressed.^{117,153} Both suggest that at least some patients experience symptom improvement with this approach, but both studies had significant methodological limitations. Hence, this approach cannot be strongly recommended at present. Prospective studies of this and other endovascular strategies to treat PTS are needed.

Harms of Endovascular and Surgical Approaches

Complications associated with endovascular and open surgical venous reconstruction depend on the magnitude of the underlying disease and patient comorbidities. Focal, single-segment obstruction is generally associated with good success and low complication rates. Conversely, patients with multi-level venous occlusion who require open surgical procedures as part of the overall treatment strategy face acute failure rates of up to 10% to 20%, with a 10% rate of hemorrhagic complications and 5% to 10% rate of wound complications.^{154,155}

Summary

Open surgical and endovenous procedures that correct central postthrombotic venous occlusion or infrainguinal venous valvular incompetence may be offered to patients with severe PTS in an attempt to reduce postthrombotic morbidity and to improve QoL. However, Level of Evidence A data do not exist; therefore, only weak recommendations (mostly Level of Evidence C) can be made.

We emphasize that outcomes of these procedures are highly dependent on operator (surgical) expertise and that, if not available locally, referral to a center with expertise is recommended. Selection of patients for these procedures should take into account the surgical risk, clinical severity of PTS, specific venous anatomy, and expected life span.

Recommendations for Endovascular and Surgical Treatment of PTS

- 1. For the severely symptomatic patient with iliac vein or vena cava occlusion, surgery (eg, femoro-femoral or femoro-caval bypass) (Class IIb; Level of Evidence C) or percutaneous endovenous recanalization (eg, stent, balloon angioplasty) (Class IIb; Level of Evidence B) may be considered.**
- 2. For severely symptomatic patients with postthrombotic occlusion of their common femoral vein, iliac vein, and vena cava, combined operative and endovenous disobliteration may be considered (Class IIb; Level of Evidence C).**
- 3. For severely symptomatic patients with PTS, segmental vein valve transfer or venous transposition may be considered (Class IIb; Level of Evidence C).**

Special Populations

Upper-Extremity PTS

Upper-extremity DVT (UEDVT) comprises DVT of the subclavian, axillary, or brachial veins. Although PTS develops after UEDVT, reported incidences are variable, in part because there is no accepted standard for its diagnosis, and range from 7% to 46%, with a systematic review of 7 studies reporting a

weighted mean incidence of 15%.¹⁵⁶ Risk factors for upper-extremity PTS are not well characterized. In a prospective study of 53 patients with first UEDVT followed up for 5 years, more than a quarter of patients developed PTS by 2 years. Residual thrombus on ultrasound predicted the development of PTS (hazard ratio, 4.0; 95% CI, 1.1–15.0). Subclavian and axillary thromboses were also associated with PTS but did not achieve statistical significance (hazard ratio, 2.9; 95% CI, 0.8–10.7).¹⁵⁷ Of interest, the incidence of PTS appears to be lower after catheter-associated UEDVT than after spontaneous UEDVT or UEDVT resulting from extrinsic compression.¹⁵⁸

As with lower-extremity PTS, upper-extremity PTS can reduce QoL and upper-extremity function.^{159,160} Furthermore, dominant-arm PTS appears to be associated with worse QoL and disability than nondominant-arm PTS.¹⁵⁹

Data to guide the management of upper-extremity PTS are sparse. There have been no trials of compression sleeves or bandages to prevent or treat upper-extremity PTS. Similarly, it is uncertain whether thrombolysis or endovascular or surgical treatment of UEDVT results in lower rates of PTS than standard anticoagulation. A prospective evaluation of a small group of patients treated for effort-induced UEDVT with thrombolysis, thoracic inlet decompression, percutaneous transluminal angioplasty, and subclavian vein stenting reported that those with complete venous patency after treatment were asymptomatic on follow-up,¹⁶¹ and a retrospective study of 30 patients with UEDVT treated with catheter-directed lysis showed that none developed severe PTS and 6 (21%) developed mild PTS.¹⁶² However, another study comparing systemic thrombolysis with anticoagulation alone in 95 patients with UEDVT showed similar rates of PTS in both groups.¹⁶³

Further study is needed to determine the incidence and risk factors for upper-extremity PTS, to develop a standardized scoring system for its diagnosis, and to test modalities to prevent and manage this condition.

Because of a lack of studies on compression bandages, compression sleeves, or venoactive drugs to prevent or treat PTS after UEDVT, it is not possible to make specific recommendations on the prevention or treatment of upper-extremity PTS. Please refer to the Recommendations for Primary and Secondary Prevention of DVT to Prevent PTS and the Recommendations for Optimizing Anticoagulation Delivery to Prevent PTS for general approaches to preventing PTS. Please refer to Kearon et al⁸⁵ for management of acute UEDVT.

Pediatric PTS

A systematic review of the literature revealed 19 studies reporting the frequency of PTS in children with DVT.¹⁶⁴ Among a total of 977 patients with UEDVT/lower-extremity DVT, the weighted mean frequency of PTS was 26% (95% CI, 23–28). When restricted to the 9 prospective analyses,^{165–173} this frequency was 17% (95% CI, 14–20). Only 1 prospective study has subsequently been published, in which the cumulative incidence of PTS was 23% after a follow-up period ranging from 1 to 5 years.¹⁷⁴ Variation in estimates of PTS frequency across studies may be attributable to the heterogeneity of study designs and methods of PTS measurement and variable intervals from DVT occurrence to PTS assessment. In addition, although a recent retrospective study suggested

that change in PTS severity (as measured by modified Villalta score) is common over time,¹⁷⁵ it is unclear whether this is a true reflection of natural history or is explained by poor test-retest reliability of the instrument itself.

In its recent recommendations on definition of pediatric PTS,¹⁷⁶ the Pediatric/Perinatal Subcommittee of the *International Society on Thrombosis and Haemostasis* Scientific and Standardization Committee concurred with the Scientific and Standardization Committee's adult PTS recommendation that evaluation of PTS after lower-extremity DVT should consist of both objective (ie, signs) and subjective (ie, symptoms) criteria but recognized limitations in the degree to which subjective criteria can be reliably assessed in pediatrics, particularly among young children. Nevertheless, for standardized pediatric PTS assessment, it recommended the use of either the Manco-Johnson instrument (training video is available at www.kids-dott.net) or the modified Villalta score.¹⁷⁷ Given the lack of published data on test-retest reliability of pediatric PTS assessment, it was also recommended that a diagnosis of definitive PTS in children be restricted to concordance on 2 independent PTS evaluations performed at least 3 months apart.

Lack of a pediatric, venous disease-specific QoL outcome instrument is an additional limitation in understanding the physical and psychosocial impacts of PTS in children. National Institutes of Health-funded efforts are underway to evaluate associations between pediatric PTS instrument findings and QoL outcome measures after UEDVT/lower-extremity DVT in children (M.J. Manco-Johnson, N.A. Goldenberg, and S.R. Kahn, personal communication, April 25, 2014).

Limited evidence exists on the prognostic factors for PTS in children. An early study implicated elevated levels of hypercoagulability and inflammation biomarkers (eg, factor VIII, D dimer) as predictors of poorer outcome,¹⁷³ and a small prospective series suggested a protective effect of acute thrombolytic approaches to treat occlusive proximal limb DVT.¹⁷² Recently, a 2-institution cohort study reported preliminary findings that the acute presence of the lupus anticoagulant (assessed by dilute Russell viper venom time) was associated with a significantly increased risk of clinically significant PTS.¹⁷⁴

As a result of the paucity of studies in this area, it is not possible to make specific recommendations on the prevention or treatment of pediatric PTS. Please refer to the Importance of Primary and Secondary Prevention of DVT to Prevent PTS and the Optimizing Anticoagulation Delivery to Prevent PTS sections for general approaches to preventing PTS.

Summary

PTS is a frequent, chronic, burdensome, and costly complication of DVT. This scientific statement has evaluated the body of literature on the pathophysiology, epidemiology, prevention, diagnosis, and treatment of PTS to make evidence-based recommendations to guide clinicians and other healthcare professionals. It is acknowledged that the body of evidence to guide management of PTS is incomplete and that therefore many recommendations rely on lower levels of evidence.

Research Needs

The results of the ATTRACT study on the role of CDT and PCDT in preventing PTS after acute proximal DVT¹⁰⁸ are

eagerly awaited. There is also a pressing need for research on the following aspects of PTS:

Pathophysiology and Risk Factors

- Better elucidation of the pathophysiology of PTS
- Development of PTS risk prediction models that integrate clinical and biomarker information
- Investigation of the association between inflammation and thrombophilia and PTS to identify new therapeutic targets for preventing PTS
- Role of risk factor modification (eg, weight reduction, exercise) in preventing or improving PTS

Diagnosis and Measurement of PTS

- Assessment of test-retest reliability of pediatric PTS measures
- Development of a pediatric, venous disease-specific QoL instrument to improve the understanding of the physical and psychosocial impacts of PTS in children

Prevention of PTS

- The role of CDT and PCDT in the prevention of upper-extremity PTS and pediatric PTS
- The effectiveness of ECS and other compression modalities for the prevention of upper-extremity PTS and pediatric PTS
- The effectiveness of anti-inflammatory agents, statins, long-term LMWHs, and new oral anticoagulants to reduce the occurrence of PTS after DVT

Treatment of PTS

- Studies of the effectiveness of ECS and other compression modalities in treating lower-extremity PTS, upper-extremity PTS, and pediatric PTS
- Well-designed studies of the safety, effectiveness, and sustainability of pharmacological treatments for PTS
- Rigorous evaluation of the safety and long-term effectiveness of endovascular and/or surgical procedures to treat severe PTS
- Investigation of the role of exercise in treating PTS

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*Modest.
†Significant.

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KEY WORDS: AHA Scientific Statements ■ mechanical thrombolysis ■ postphlebotic syndrome ■ postthrombotic syndrome ■ thrombolytic therapy ■ thrombosis ■ venous insufficiency ■ venous thrombosis



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