

Relationship Between Deep Venous Thrombosis and the Postthrombotic Syndrome

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The postthrombotic syndrome (PTS) is a frequent complication of deep venous thrombosis (DVT). Clinically, PTS is characterized by chronic, persistent pain, swelling, and other signs in the affected limb. Rarely, ulcers may develop. Because of its prevalence, severity, and chronicity, PTS is burdensome and costly. Preventing DVT with the use of effective thromboprophylaxis in high-risk patients and settings and minimizing the risk of ipsilateral DVT recurrence are likely to reduce the risk of development of PTS. Daily use of compression stockings after DVT might reduce the incidence and severity of PTS, but consistent and convincing data about their effectiveness are not available. Future research should focus on standardizing diagnostic criteria for PTS, identifying patients at high risk for PTS, and rigorously evaluating the role of thrombolysis in preventing PTS and of compression stockings in preventing and treating PTS. In addition, novel therapies should be sought and evaluated.

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The postthrombotic syndrome (PTS) is a chronic condition that develops in 20% to 50% of patients within 1 to 2 years of symptomatic deep venous thrombosis (DVT). A severe form, which can include venous ulcers, occurs in one quarter to one third of patients with PTS.^{1,2} Because of its prevalence and chronicity, PTS is costly to society and is a cause of substantial patient morbidity.

In this article, we critically review the evidence informing current understanding of the pathophysiology, epidemiology, diagnosis, and management of PTS. The burden of PTS from both a patient and a societal perspective is discussed. Using standard criteria to grade the quality of the available evidence, we provide recommendations for the prevention and treatment of PTS. This article also acknowledges controversies in the field and key areas of ongoing and future research.

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CLINICAL PRESENTATION AND PATHOPHYSIOLOGY OF PTS

Patients with PTS complain of pain, heaviness, swelling, cramps, itching, or tingling in the affected limb. Typically, symptoms are aggravated by standing or walking and improve with rest and recumbency. On physical examination, edema, telangiectasias, hyperpigmentation, eczema, and varicose collateral veins are often present. In severe cases, lipodermatosclerosis and ulceration may result³⁻⁶ (**Table 1**).

The pathophysiology of PTS is incompletely understood, but it is thought that the acute thrombus itself, associated mediators of inflammation, and the process of vein recanalization in the weeks after DVT induce damage to venous valves, leading to valvular incompetence (reflux). Valvular incompetence, persistent venous obstruction, or both cause venous hypertension,⁶⁻⁸ which leads to edema, tissue hypoxia, and, in some cases, skin ulceration.^{6,7} A number of clinical studies have suggested that valvular reflux in the proximal veins, particularly the pop-

Table 1. Clinical Features of Postthrombotic Syndrome

| Leg Symptoms* | Signs |
|---------------|----------------------------|
| Heaviness | Edema |
| Pain | Telangiectasia |
| Swelling | Venous ectasia |
| Itching | Varicose veins |
| Cramps | Venous dilation |
| Paresthesia | Hyperpigmentation |
| Bursting pain | Stasis dermatitis (eczema) |
| | Redness |
| | Dependent cyanosis |
| | Lipodermatosclerosis |
| | Healed ulcer |
| | Open ulcer |

*Symptom pattern: worsened by activity, standing; improved by rest, recumbency.

lital vein, is associated with clinical manifestations of PTS.⁹⁻¹³ Therefore, preventing valve damage and reducing venous hypertension are likely to be important in preventing PTS.

FACTORS THAT PREDICT THE DEVELOPMENT OF PTS AFTER DVT

Recurrent DVT

The only clearly identified risk factor for PTS is recurrent, ipsilateral DVT, which increases the risk of PTS as much as 6-fold.^{1,14-17} Recurrent DVT probably causes additional damage to already compromised venous valves and further venous outflow obstruction.

Characteristics of the Initial DVT

There is little correlation between the venographic severity of the initial thrombus and subsequent development of PTS.^{1,18} In some studies, the risk of PTS was higher in patients with proximal rather than distal (calf) DVT,¹⁹⁻²² while in others the site of the initial thrombus did not influence the subsequent development of PTS.^{1,18,23-25} In prospective studies, reported rates of PTS after distal DVT have ranged from 20% to 80%.²⁵⁻³¹ Hence, calf DVT is associated with a significant risk of subsequent PTS.

Asymptomatic DVT

Whether asymptomatic DVT (ie, detected by routine screening) leads to PTS is controversial. One study found that the frequency of PTS 2 to 7 years after hip or knee arthroplasty was similarly low (approximately 5%) in patients whose routine predischarge venogram showed proximal DVT, calf DVT, or no DVT.³² All patients with DVT received 6 to 12 weeks of anti-coagulant therapy. Other investigators have also found low rates of PTS after asymptomatic DVT.^{33,34} Conversely, some groups have shown that as many as 25% to 33% of patients with asymptomatic DVT develop PTS.^{35,36} Differences in patient selection, study design, and definition of PTS may explain these discrepant results, but if confirmed, this would support the clinical relevance of asymptomatic DVT in studies of thromboprophylaxis³⁷ and would provide a rationale for reducing the risk of such thrombi.^{38,39}

Patient Characteristics

In prospective studies, clinical features such as delay in initiating treatment for DVT; risk factors for thrombosis; family history of thrombosis; protein C, protein S, or antithrombin deficiency; or the presence of the lupus anticoagulant have not been found to increase the risk of developing PTS.^{1,14} In retrospective studies, factors predictive of PTS were increasing age, female sex, hormone therapy, varicose veins, abdominal surgery, and increased body mass index.^{40,41}

DIAGNOSIS OF PTS

There is no gold standard test for the diagnosis of PTS. In patients with objectively confirmed DVT and a typical clinical presentation, PTS is usually the correct diagnosis. As it usually takes 3 to 6 months after acute DVT for the initial pain and swelling to resolve, a diagnosis of PTS should be deferred until after this time. Objective evidence of venous valvular incompetence by Doppler ultrasound or by plethysmography helps to confirm the diagnosis in symptomatic patients.^{10,11,20,25,42} However, a diagnosis of PTS should

not be made in the absence of clinical symptoms; while most patients with symptomatic PTS have valvular incompetence, many with valvular incompetence do not have PTS.⁴³

Three clinical scales for the diagnosis of PTS are available^{32,44,45} and have been used in a number of clinical studies. They are presented in detail in **Table 2**.^{32,44-46}

IMPACT OF PTS

Population-Based Studies: Incidence and Prevalence

The prevalence of PTS is influenced by the incidence of DVT. Despite advances in its prevention and treatment, the annual incidence of venous thromboembolism (VTE) (ie, DVT and pulmonary embolism) has not decreased and is 1.0 to 1.6 per 1000 persons per year, with a per-person lifetime incidence of 2% to 5%.⁴⁷⁻⁵¹ Approximately 250000 new cases of VTE occur in the United States each year.⁴⁸ The population burden of PTS is difficult to estimate because of varying definitions of PTS and a tendency to undercode chronic conditions. In a recent study, cumulative rates of venous stasis were 7.3% at 1 year, 14.3% at 5 years, 19.7% at 10 years, and 26.8% at 20 years after DVT; the cumulative risk of ulcer was 3.7% by 20 years.¹⁹ It is estimated that more than one quarter of the at least 170000 new cases of venous stasis syndrome per year represent PTS.⁵²

Clinical Studies: Frequency of PTS After DVT

The frequency of PTS after objectively diagnosed DVT is difficult to estimate. Many studies have used surrogate end points such as reflux or abnormal results of venography without consideration of clinical symptoms and signs, and few have used validated PTS scores.

Nonetheless, a few prospective studies have provided key information on the frequency of PTS after symptomatic DVT. In a longitudinal cohort study of patients with a first episode of acute symptomatic DVT, Prandoni et al¹ found that

Table 2. Clinical Scales for the Diagnosis of Postthrombotic Syndrome

| PTS Scale | Criteria Used to Diagnose PTS | Test Characteristics | Developed Specifically for PTS | Rates Severity of PTS |
|---------------------------------------|--|--|--------------------------------|-----------------------|
| Ginsberg et al ³² | Pain and swelling of limb of ≥ 1 -mo duration, typical character (worse at end of day or with prolonged sitting/standing, better after night's rest and leg elevation) that occurs ≥ 6 mo after acute DVT and Objective evidence of valvular incompetence (diagnosed via plethysmography or venous Doppler) • If both criteria are present, PTS is diagnosed • Global Rating Questionnaire to rate overall improvement or worsening of PTS over time | Not assessed | Yes | No |
| Villalta et al ⁴⁵ | 5 Symptoms (pain, cramps, heaviness, pruritus, paresthesia) 6 Signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) Each rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) Points are summed Total score: 0-4: No PTS 5-14: Mild/moderate PTS ≥ 15 , or presence of ulcer: Severe PTS | Interobserver agreement: $\kappa = 0.80$ for symptoms, 0.77 for signs, 0.75 for total score Area under ROC curve: None vs mild/moderate, 0.93 Mild/moderate vs severe, 0.98 | Yes | Yes |
| CEAP classification ^{44,46*} | Patients with chronic venous disease classified into 1 of 7 clinical classes (class 0-6) according to presence of clinical signs; each class may include signs present in lower-order class Class: 0, Symptoms only; no visible or palpable signs of venous disease 1, Telangiectasias, reticular veins, malleolar flare 2, Varicose veins 3, Edema, no skin changes 4, Skin changes (eg, pigmentation, eczema, lipodermatosclerosis) 5, Skin changes with healed ulcer 6, Skin changes with active ulcer Each clinical class is then subclassified as to: Etiology (congenital, primary, secondary) Anatomy (superficial, deep, perforator veins) Pathophysiology (reflux, obstruction, both) | Not assessed | No† | No‡ |

Abbreviations: CEAP, Clinical-Etiology-Anatomic-Pathophysiologic; DVT, deep venous thrombosis; PTS, postthrombotic syndrome; ROC, receiver operating characteristic.

*Modifications of CEAP (Clinical Severity Score, Venous Segmental Disease Score) have been proposed.⁴⁶

†Developed for chronic venous disease in general.

‡Increasing CEAP class is intended to reflect increased severity of signs of chronic venous disease; symptoms and their severity are not considered.

the cumulative incidence of PTS was 17.3% after 1 year (severe in 3%), 23% after 2 years, 28% after 5 years (severe in 9%), and 29% after 8 years. In a subsequent trial to evaluate the use of compression stockings to prevent PTS in patients with symptomatic proximal DVT, mild to moderate PTS occurred in 20% of patients assigned to stockings and in 47% of controls, and severe PTS occurred in 11% and 23%, respectively.² The frequency of PTS in the stockings group was similar to that in the study by Prandoni et al, in which all patients were encouraged to wear compression stockings. In both studies, most cases of PTS occurred within 2 years of DVT. In contrast, in a recent study

by Ginsberg and colleagues,⁵³ 27% of patients (none of whom used stockings) had developed PTS by 1 year after a first episode of symptomatic proximal DVT, but among patients who were free of PTS 1 year after DVT, only 5% subsequently developed PTS (average follow-up, 55 months). However, the Ginsberg et al study used stricter diagnostic criteria for PTS: in addition to symptoms, objective demonstration of valvular incompetence was required.

In summary, the frequency of PTS after symptomatic DVT ranges from 15% to 50%. In most cases, PTS develops within 1 to 2 years after DVT. Severe PTS occurs in 5% to 10% of patients after DVT. **Table 3** pro-

vides a synopsis of prospective studies of the frequency of PTS after symptomatic DVT,* and **Table 4**, after asymptomatic DVT.^{32-36,53,56,57}

Cost of PTS

Although there is little direct-cost information available, PTS undoubtedly incurs high direct costs and indirect costs such as loss of productivity. A Swedish study estimated that the average cost of treating PTS was US \$4700, or 75% of the cost of treating the primary DVT.⁵⁸ Extrapolations can be made from the

*References 1, 2, 10, 20, 21, 23, 25, 27-29, 53-55

Table 3. Prospective Studies of the Frequency of Postthrombotic Syndrome After Symptomatic DVT

| Source | DVT Type | No.* | Duration of Follow-up, y | % Regular Stocking Use | Definition of PTS | Frequency of PTS, % | | |
|---|------------------------|----------|--------------------------|-------------------------|--|---------------------|---------|-------|
| | | | | | | All | Severe† | Ulcer |
| Strandness et al, ²³ 1983 | Any | 65 Limbs | 3 (Mean) | 74 | Pain, edema, skin changes, ulcer | 67 | 28 | 5 |
| Kakkar and Lawrence, ²⁵ 1985 | Any | 97 Limbs | 2 (Total) | NR | 10-Point scoring system based on symptoms and signs | 84 | 8 | NR |
| Monreal et al, ²¹ 1993 | First episode | 84 Limbs | 3 (Total) | NR | 10-Point scoring system based on symptoms and signs | 56 | 20 | 6 |
| Johnson et al, ⁵⁴ 1995 | Any | 83 Limbs | 3 (Median) | 47 | Edema, skin changes, ulcer | 41 | 13 | 2 |
| Prandoni et al, ¹ 1996 | First episode | 355 | 8 (Total) | 100 | Villalta et al scale ⁴⁵ | 29 | 9 | NR |
| Brandjes et al, ² 1997‡ | First episode proximal | 194 | 6 (Median) | 100 (n = 96)/0 (n = 98) | Villalta et al scale ⁴⁵ | 31/70 | 11/23 | 1/3 |
| Franzeck et al, ¹⁰ 1997 | Any | 39 | 12 (Mean) | 54 | CEAP scale ⁴⁴ | 36 | 8 | 3 |
| AbuRahma et al, ⁵⁵ 1998 | First episode proximal | 87 | 5 (Mean) | NR | Edema, skin changes, ulcer | 36 | 25 | 8 |
| Masuda et al, ²⁷ 1998 | Distal | 23 | 3 (Median) | NR | CEAP scale ⁴⁴ | 57 | 5 | 0 |
| Meissner et al, ²⁰ 1998 | First episode | 73 Limbs | 4½ (Mean) | NR | CEAP scale ⁴⁴ | 73 | 21 | 3 |
| Saarinen et al, ²⁸ 2000 | Any | 28 | 2 (Total) | 12 | Pain, edema, skin changes, ulcer | 73 | 35 | 7 |
| Ginsberg et al, ⁵³ 2001 | First episode proximal | 110 | 1 | 0 | Chronic persistent leg pain and swelling and valvular incompetence | 27 | NR | NR |
| Haenen et al, ²⁹ 2001 | Any | 79 Limbs | 2 (Total) | NR | CEAP scale ⁴⁴ | 77 | 20 | 0 |

Abbreviations: CEAP, Clinical-Etiology-Anatomic-Pathophysiologic; DVT, deep venous thrombosis; NR, not reported; PTS, postthrombotic syndrome.

*Number of patients unless otherwise specified.

†Severe PTS includes ulcers, when frequency of ulcers was reported.

‡Randomized trial of stockings vs no stockings after DVT; data presented by treatment group (stockings/no stockings).

costs of treating chronic venous insufficiency and venous ulcers, since a proportion of these cases represent PTS.^{52,59-61} In a recent Canadian study, patients with venous ulcers composed 6% of home care clientele but consumed 18% of supply expenditures, and the annual cost of their care was more than \$1 million.⁶² The direct cost of treating chronic venous insufficiency exceeds \$300 million per year in the United States,⁵² with similar costs in Britain, Belgium, France, Germany, Italy, and Spain.^{4,63-65} The indirect costs of PTS are also likely to be significant, since PTS often affects persons of working age. It is estimated that, for leg ulcers, 2 million workdays are lost annually in the United States.⁶⁶

Impact of PTS on Quality of Life

For chronic conditions such as PTS, assessment of quality of life can provide important information on burden of illness.^{3,67,68} Despite the availability of easy-to-use, validated measures of generic quality of life,^{68,69} few studies have quantified the long-term impact of DVT, or of PTS, on quality of life. An early study showed that almost 90% of patients were disabled and unable to work because of leg symptoms 10 or more years after

iliofemoral DVT.⁷⁰ In a study of patients who had DVT 6 to 8 years earlier, those with PTS had poorer health perceptions, worse physical functioning, and more severe role limitations, as measured by the SF-36 Health Survey quality-of-life questionnaire.¹⁵ Recently, in the course of conducting the Venous Insufficiency Epidemiologic and Economic Study (VEINES), our group developed and validated the VEINES-QOL/Sym questionnaire, a venous disease-specific quality-of-life measure,⁷¹ and showed that by 2 years after DVT, patients with PTS had significantly worse quality of life than those without PTS, and scores worsened with increasing severity of PTS.⁷²

MANAGEMENT OF PTS

Preventing PTS

Thromboprophylaxis. Postthrombotic syndrome can be averted with the use of thromboprophylaxis to prevent DVT in high-risk patients and settings, as recommended in regularly updated consensus guidelines.⁷³ However, audits consistently demonstrate that thromboprophylaxis is underused.⁷⁴⁻⁷⁷ Furthermore, existing thromboprophylaxis regi-

mens do not eliminate the risk of VTE.⁷³ New antithrombotic drugs may be more effective than existing regimens in preventing VTE in high-risk patients.⁷⁸⁻⁸⁴ Since the publication of the last consensus guidelines in 2001,⁷³ newer classes of drugs such as synthetic pentasaccharides have demonstrated promising results in phase 3 trials of VTE prevention when compared with conventional heparins.⁷⁹⁻⁸² Unfortunately, nearly 50% of VTE events occur unpredictably and therefore cannot be prevented with thromboprophylaxis.^{74,85} Hence, strategies that focus on preventing the development of PTS after DVT are more feasible and more likely to be effective in reducing the burden of PTS than are attempts to prevent the index DVT. Since ipsilateral DVT recurrence is a risk factor for PTS, preventing recurrent DVT by optimizing the intensity and duration of anticoagulation for an initial DVT, taking into account the patient's risk of recurrence and of bleeding,⁸⁶⁻⁸⁸ is an important goal.

Role of Thrombolysis. The use of thrombolytic therapy in addition to heparin for the treatment of acute DVT leads to higher rates of vein patency and better preservation of valve function than does the use of hepa-

Table 4. Prospective Studies of the Frequency of Postthrombotic Syndrome in Patients Screened for Asymptomatic DVT

| Source | Patient Population | DVT Detection | DVT Treatment | Duration of Follow-up, y | % Regular Stocking Use | Definition of PTS | No. * | Frequency of PTS, % | | |
|--|----------------------------------|---------------|-------------------|--------------------------|------------------------|--|-------------------------------------|--|----------|----------|
| | | | | | | | | All | Severe† | Ulcer |
| Mudge et al, ⁵⁷ 1988 | Elective major abdominal surgery | FUS | NR | 10 (Total) | NR | Any 3 of varicose veins, edema, pigmentation, eczema, liposclerosis, ulcers | 26 DVT 108 No DVT | 8 1 | NR NR | 0 NR |
| Francis et al, ⁵⁶ 1988 | THA or TKA | CV | 3-6 mo A/C | 4 (Mean) | NR | Symptoms (swelling, pain, varicosities, ulcer) or signs (edema, ulcer, pigmentation, varicose veins) | 19 DVT (limbs) 78 No DVT (limbs) | 58 38 | NR NR | NR NR |
| Andersen and Wille-Jørgensen, ³³ 1991 | Surgery (unspecified) | FUS, TS | 3-6 mo A/C | 5 (Median) | 28 (DVT) 0 (No DVT) | Symptoms and signs | 29 DVT (limbs) 32 No DVT (limbs) | 38 (Edema) 46 (Varicose veins) 31 (Pigmented skin) 50 (Edema) 16 (Varicose veins) 19 (Pigmented skin) | NR NR | 0 0 |
| McNally et al, ³⁵ 1994 | THA | CV | ≥3 mo A/C | 5 (Total) | NR | Scoring system based on symptoms and signs | 8 DVT 32 No DVT | 88 16 | 25 3 | NR NR |
| Warwick et al, ³⁴ 1996 | THA | FUS, CV | Yes (duration NR) | 16 (Mean) | NR | Scoring system based on symptoms and signs | 98 DVT (limbs) 36 No DVT (limbs) | 47 44 | 3 6 | NR NR |
| Siragusa et al, ³⁶ 1997 | THA or TKA | CV | 3 mo A/C | 3 (Mean) | NR | Villalta et al scale ⁴⁵ and valvular incompetence | 46 DVT 52 No DVT | 24 4 | 2 NR | 2 NR |
| Ginsberg et al, ³² 2000 | THA or TKA | CV | 1.5-3 mo A/C | 5 (Mean) | NR | Chronic persistent leg pain and swelling and valvular incompetence | 91 DVT 164 No DVT | 5 4 | NR NR | NR NR |
| Ginsberg et al, ⁵³ 2001 | Major orthopedic surgery | CV | NR | 1 (Total) | NR | Chronic persistent leg pain and swelling and valvular incompetence | 82 DVT | 4 | NR | NR |

Abbreviations: A/C, anticoagulant therapy; CV, contrast venography; DVT, deep venous thrombosis; FUS, fibrinogen I 125 uptake scan; NR, not reported; PTS, postthrombotic syndrome; THA, total hip arthroplasty; TKA, total knee arthroplasty; TS, technetium Tc 99m fibrinolytic scintigraphy.

*Number of patients, unless otherwise specified.

†Severe PTS includes ulcers, when frequency of ulcers was reported.

rin alone. However, there is no definitive evidence that thrombolysis leads to lower rates of PTS compared with the use of heparin and warfarin alone⁸⁹ (**Table 5**).^{26,90-95} Furthermore, thrombolytic trials or registries of treated patients have tended to ignore long-term outcomes such as PTS.^{89,96-98} Large controlled trials of standard anticoagulation vs catheter-directed thrombolysis, which may be safer and more effective than systemic therapy,⁹⁷ are required to definitively address this issue.

Elastic Compression Stockings. Graduated elastic compression stockings (ECSs) assist the calf muscle pump, reduce venous hypertension

and reflux, and thereby reduce edema and improve tissue microcirculation.⁹⁹⁻¹⁰³ Knee-length and thigh-length ECSs have equal physiologic effects, but the former are easier to apply and more comfortable.¹⁰⁴

Notwithstanding their physiologic effects, data on the clinical effectiveness of ECSs in preventing PTS are scarce and inconclusive. Evidence supporting their effectiveness comes primarily from the trial by Brandjes et al² of 194 patients with symptomatic proximal DVT. Patients were randomly allocated to daily use of 30- to 40-mm Hg knee-length ECSs for at least 2 years, or no stocking. Use of ECSs resulted in a decrease from 47% to 20% of mild

or moderate PTS, and from 23% to 11% of severe PTS, diagnosed with the scale of Villalta et al⁴⁵ (see Table 2). As a result of this trial, it has become common clinical practice to prescribe ECSs for patients with DVT, particularly proximal DVT.¹⁰⁵ However, a recent randomized trial conducted by Ginsberg and colleagues⁵³ showed no benefit of daily ECSs in preventing or treating PTS. This study used a more specific measure of PTS than that of Brandjes et al² (see Table 2), and control patients wore sham stockings. Because of the small number of patients with PTS, benefit (or harm) of up to 30% compared with the control group could not be excluded.

Table 5. Prospective Studies of the Frequency of Postthrombotic Syndrome After Thrombolysis for Symptomatic DVT*

| Source | Study Type | DVT Type | Symptom Duration Before Lysis, d | Intervention Groups | No. Enrolled | No. Followed Up | Follow-up, y | Definition of PTS | Frequency of PTS, % | P Value |
|-------------------------------------|--------------------------------|----------|----------------------------------|---|----------------------------|----------------------------|--------------|--|---|---------|
| Common et al, ⁹⁴ 1976 | Randomized trial | Any | <14 | SK UFH | 25 25 | 15 12 | 0.5 | Symptoms and signs | 33 50 | NR |
| Elliot et al, ⁹¹ 1979 | Randomized trial | Proximal | <8 | SK | 26 | 21 | 1.6 | Symptoms and signs | 6% With complete lysis developed PTS; 89% with incomplete lysis developed 92 PTS | NR |
| Arnesen et al, ⁹² 1982 | Randomized trial | Proximal | NR | UFH SK | 26 21 | 21 17 | 6.5 | Signs including ulcer | 24 (0 Ulcer) 67 (17 Ulcer) | NR |
| Schulman et al, ⁹⁵ 1984 | Randomized, single-blind trial | Proximal | <7 | High-dose SK Low-dose SK | 39 41 | 35 35 | 3 | Symptoms and signs | 57 (3 Ulcer) 69 (3 Ulcer) | <.05 |
| Schulman et al, ²⁶ 1986 | Randomized trial | Calf | <7 | SK UFH | 19 17 | 18 17 | 5 | Clinical score incorporating symptoms and signs | 35 61 | NR |
| Turpie et al, ⁹³ 1990 | Randomized double-blind trial | Proximal | <7 | rtPA 2-chain infused over 4 h rtPA 1-chain infused over 8 h UFH | 12 29 42 | 7 20 19 | 3 | Persistent pain and swelling of limb plus valvular reflux by objective testing | (Results not presented by intervention group) 25% Of patients with >50% lysis had PTS 56% Of patients with <50% lysis had PTS | .07 |
| Schweizer et al, ⁹⁰ 2000 | Randomized trial | Proximal | <9 | rtPA (local) UK (local) UK SK UFH | 50 50 50 50 50 | 50 50 46 46 46 | 1 | Symptoms and signs incorporated into scale into 4 levels of severity | 78 74 64 46 82 | <.001† |

Abbreviations: DVT, deep venous thrombosis; NR, not reported; PTS, postthrombotic syndrome; rtPA, recombinant tissue plasminogen activator; SK, streptokinase; UFH, unfractionated heparin; UK, urokinase.

*Thrombolysis and heparin administered systemically intravenously unless otherwise stated.

†In favor of systemic thrombolysis.

These results, while not definitive, question the generalizability of the results of the Brandjes et al study, which had unusually high rates of PTS in the control group and dramatic reductions in both relative and absolute risk of PTS in the stocking group.

Stockings are difficult to apply, uncomfortable, and expensive, and require replacement every few months. Because of the uncertainty regarding their value in preventing PTS after DVT, further research on their effectiveness is required.

Treating PTS

Available treatments for established PTS are limited. Regular use

of ECSs may improve symptoms and swelling. Severe intractable PTS can be managed with long-term use of an intermittent compression extremity pump.^{106,107} Postthrombotic venous ulcers are managed with compression therapy, leg elevation, topical dressings, and sometimes surgery.^{4,108-111} Ulcers are often recalcitrant and tend to recur,¹⁰⁹ causing pain and suffering to patients^{112,113} and incurring high costs to society.^{66,114} The short-term use of “venoactive” medications such as horse chestnut seed extract or hydroxyethyl rutosides appears to be effective in reducing symptoms of chronic venous insufficiency^{115,116}; however, their long-term effectiveness and safety and their value in pa-

tients with PTS are unknown. There is no proven role for the long-term use of diuretics to treat PTS-related edema.

RECOMMENDATIONS REGARDING PREVENTION AND TREATMENT OF PTS

The following recommendations for the prevention and treatment of PTS are based on our review of the literature. Levels of evidence, using an adaptation of the categories proposed by Guyatt et al¹¹⁷ in the sixth American College of Chest Physicians consensus conference on antithrombotic therapy (**Table 6**), are used when appropriate.

General Recommendations

- Physicians should actively screen patients with DVT for PTS during follow-up.

The diagnosis of PTS should primarily be based on the presence of typical symptoms and signs, since objective evidence of venous valvular incompetence has low specificity for PTS. However, the presence of valvular incompetence helps to confirm the diagnosis of PTS (and rule out other conditions) in symptomatic patients.

Prevention of PTS

- Prevention of the index DVT will prevent PTS.
- Prevention of ipsilateral DVT recurrence is likely to decrease the risk of developing PTS and prevent worsening of PTS (grade 1C).
- In patients with proximal DVT, the risk of developing PTS may be reduced with daily use of knee-length, 30- to 40-mm Hg ECSs (grade 2B).
- The effects of ECSs after distal DVT and the optimal duration of ECS use are not known.
- There is no convincing evidence that systemic thrombolysis prevents PTS (grades 2B and 2C). Catheter-directed thrombolysis requires further evaluation in properly designed trials before it is endorsed as being effective in reducing the risk of PTS.

Treatment of PTS

- Compression stockings may reduce swelling in some patients with PTS and should be tried. Their benefit in this setting is extrapolated from studies of patients with chronic venous disease⁴ but has not been definitively shown in the setting of PTS.
- Severe, intractable PTS can be improved with long-term use of an intermittent compression extremity pump (grade 1A). There is no proven role for venoactive medications or diuretics in the management of PTS.

FUTURE DIRECTIONS

Further work needs to be done to increase our understanding of PTS and

Table 6. Grades of Recommendations*

| Grade of Recommendation | Clarity of Risk/Benefit | Methodologic Strength of Supporting Evidence | Strength of Recommendation |
|-------------------------|-------------------------|--|----------------------------|
| 1A | Clear | Randomized trials; consistent results; no methodologic flaws | Strong |
| 1B | Clear | Randomized trials; inconsistent results and/or methodologic flaws† | Strong |
| 1C | Clear | Observation studies | Intermediate |
| 2A | Unclear | Randomized trials; consistent results; no methodologic flaws | Intermediate |
| 2B | Unclear | Randomized trials; inconsistent results and/or methodologic flaws | Weak |
| 2C | Unclear | Observation studies | Very weak |

*Adapted from Guyatt et al.¹¹⁷

†Flaws include randomized clinical trials with lack of blinding, subjective outcomes, and/or large loss to follow-up.

to test potentially effective preventive and therapeutic interventions. The frequency of PTS in different DVT patient populations (asymptomatic vs symptomatic, proximal vs distal, thrombophilia) should be evaluated in prospective studies of consecutive patients, using a systematic approach to PTS diagnosis. Enumeration of the direct and indirect costs of PTS, identification of key factors that influence costs, and quantification of the impact of PTS on quality of life will allow better estimation of its population burden and more accurate evaluation of the cost-effectiveness of various preventive and therapeutic regimens. Large-scale controlled trials are needed to evaluate the effectiveness, optimal timing, strength, and duration of use of compression stockings in preventing and treating PTS. Multi-center trials of catheter-directed thrombolysis to prevent PTS in patients with extensive proximal DVT are also required. Finally, the value of venoactive agents, diuretics, and anti-inflammatory medications should be studied.

THE VENOUS THROMBOSIS OUTCOMES STUDY

The Venous Thrombosis Outcomes Study is an ongoing Canadian multicenter prospective cohort study being conducted by our group. Its objectives are to estimate the incidence and timing of PTS within 2 years after objectively confirmed DVT and to identify clinical and genetic risk factors that predict its development. Quality of life is being evalu-

ated with the VEINES-QOL/Sym questionnaire,⁷¹ and direct and indirect costs of PTS are being quantified by means of data obtained from multiple sources (patient diaries, patient interviews, hospital chart, health insurance databases).¹¹⁸ This study will help to enumerate the patient and societal burden of PTS and will identify key variables that most influence quality of life and costs.

SUMMARY

Because of its prevalence, severity, and chronicity, PTS is costly and burdensome to patients and society. It is likely to become more prevalent, since the incidence of DVT has not decreased. The availability of newer, more effective antithrombotic agents may lead to a reduction in the future incidence of DVT, and thereby PTS, in certain settings. The overall frequency of PTS after symptomatic DVT ranges from 20% to 50%; severe PTS occurs in 5% to 10% of patients with DVT. Preventing ipsilateral DVT recurrence is likely to reduce the risk of PTS. There is no proven role for thrombolysis in preventing PTS. Daily use of graduated compression stockings after DVT may reduce the risk of PTS and may prevent the worsening of established PTS. Prevention of PTS is the key to reducing its morbidity, since, at present, treatment options for PTS are extremely limited.

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