

Relationship Between Deep Venous Thrombosis and the Postthrombotic Syndrome

Susan R. Kahn, MD, MSc, FRCPC; Jeffrey S. Ginsberg, MD, FRCPC

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.

Arch Intern Med. 2004;164:17-26

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.

From the Department of Medicine, McGill University, Center for Clinical Epidemiology & Community Studies, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec (Dr Kahn); and Department of Medicine, McMaster University, McMaster University Medical Center, Hamilton, Ontario (Dr Ginsberg). The authors have no relevant financial interest in this article.

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 250 000 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 170 000 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	12	7	3	Persistent pain and swelling of limb plus valvular reflux by objective testing	(Results not presented by intervention group)	.07
				rtPA 1-chain infused over 8 h	29	20				
				UFH	42	19				
Schweizer et al, ⁹⁰ 2000	Randomized trial	Proximal	<9	rtPA (local)	50	50	1	Symptoms and signs incorporated into scale into 4 levels of severity	78 74 64 46 82	<.001†
				UK (local)	50	50				
				UK	50	46				
				SK	50	46				
				UFH	50	46				

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.

Accepted for publication January 24, 2003.

This work was supported in part by an unrestricted educational grant from Organon-Sanofi Synthelabo. Dr Kahn is a recipient of a Clinical Research Scientist Award from the Fonds de la Recherche en Santé du Québec, Montreal. Dr Ginsberg is a recipient of a Career Investigator Award from the Heart and Stroke Foundation of Ontario, Toronto, and a Research Chair from the Canadian Institutes of Health Research/AstraZeneca, Ottawa, Ontario.

We thank Joan Sobel, PhD, for her help with development of the tables.

Corresponding author: Susan R. Kahn MD, MSc, FRCPC, Department of Medicine, McGill University, Center for Clinical Epidemiology & Community Studies, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote Ste Catherine, Room A-127, Montreal, Quebec, Canada H3T 1E2 (e-mail: susan.kahn@mcgill.ca).

REFERENCES

- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med.* 1996;125:1-7.
- Brandjes DPM, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet.* 1997;349:759-762.
- Kahn SR, Solymoss S, Lamping DL, Abenham L. Long-term outcomes after deep vein thrombosis: postphlebotic syndrome and quality of life. *J Gen Intern Med.* 2000;15:425-429.
- Kurz X, Kahn SR, Abenham L, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management: summary of an evidence-based report of the VEINES task force. *Int Angiol.* 1999;18:83-102.
- Bernardi E, Prandoni P. The post-thrombotic syndrome. *Curr Opin Pulm Med.* 2000;6:335-342.
- Hopkins NF, Wolfe JH. ABC of vascular diseases: deep venous insufficiency and occlusion. *BMJ.* 1992;304:107-110.
- Ackroyd JS, Browse NL. The investigation and surgery of the post-thrombotic syndrome. *J Cardiovasc Surg (Torino).* 1986;27:5-16.
- Negus D. The post-thrombotic syndrome. *Ann R Coll Surg Engl.* 1970;47:92-105.
- Markel A, Manzo RA, Bergelin RO, Strandness DE Jr. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. *J Vasc Surg.* 1992;15:377-382.
- Franzcek UK, Schalch I, Bollinger A. On the relationship between changes in the deep veins evaluated by duplex sonography and the post-thrombotic syndrome 12 years after deep vein thrombosis. *Thromb Haemost.* 1997;77:1109-1112.
- Franzcek UK, Schalch I, Jäger KA, Schneider E, Grimm J, Bollinger A. Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich study). *Circulation.* 1996;93:74-79.
- Lindhagen A, Bergqvist D, Hallböök T, Efsing HO. Venous function five to eight years after clinically suspected deep venous thrombosis. *Acta Med Scand.* 1985;217:389-395.
- Haenen JH, Janssen MC, van Langen H, et al. The postthrombotic syndrome in relation to venous hemodynamics, as measured by means of duplex scanning and strain-gauge plethysmography. *J Vasc Surg.* 1999;29:1071-1076.
- Prandoni P, Villalta S, Bagatella P, et al. The clinical course of deep-vein thrombosis: prospective long-term follow-up of 528 symptomatic patients. *Haematologica.* 1997;82:423-428.
- Beyth RJ, Cohen AM, Landefeld CS. Long-term outcomes of deep-vein thrombosis. *Arch Intern Med.* 1995;155:1031-1037.
- McColl MD, Ellison J, Greer IA, Tait RC, Walker ID. Prevalence of the post-thrombotic syndrome in young women with previous venous thromboembolism. *Br J Haematol.* 2000;108:272-274.
- Saarinén J, Sisto T, Launkka J, Salenius J-P, Tarkka M. Late sequelae of acute deep venous thrombosis: evaluation five and ten years after. *Phlebology.* 1995;10:106-109.
- Browse NL, Clemenson G, Thomas ML. Is the postphlebotic leg always postphlebotic? relation between phlebographic appearances of deep-vein thrombosis and late sequelae. *BMJ.* 1980;281:1167-1170.
- Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ III. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc.* 2000;75:1249-1256.
- Meissner MH, Caps MT, Zierler BK, et al. Determinants of chronic venous disease after acute deep venous thrombosis. *J Vasc Surg.* 1998;28:826-833.
- Monreal M, Martorell A, Callejas JM, et al. Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study. *J Intern Med.* 1993;233:233-238.
- Lindner DJ, Edwards JM, Phinney ES, Taylor LM Jr, Porter JM. Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis. *J Vasc Surg.* 1986;4:436-442.
- Strandness DE Jr, Langlois Y, Cramer M, Randlett A, Thiele BL. Long-term sequelae of acute venous thrombosis. *JAMA.* 1983;250:1289-1292.
- Philbrick JT, Becker DM. Calf deep venous thrombosis: a wolf in sheep's clothing? *Arch Intern Med.* 1988;148:2131-2138.
- Kakkar VV, Lawrence D. Hemodynamic and clinical assessment after therapy for acute deep vein thrombosis: a prospective study. *Am J Surg.* 1985;150:54-63.
- Schulman S, Granqvist S, Juhlin-Dannfelt A, Lockner D. Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase. *Acta Med Scand.* 1986;219:349-357.
- Masuda EM, Kessler DM, Kistner RL, Eklof B, Sato DT. The natural history of calf vein thrombosis: lysis of thrombi and development of reflux. *J Vasc Surg.* 1998;28:67-74.
- Saarinén J, Kallio T, Lehto M, Hiltunen S, Sisto T. The occurrence of the post-thrombotic changes after an acute deep venous thrombosis: a prospective two-year follow-up study. *J Cardiovasc Surg (Torino).* 2000;41:441-446.
- Haenen JH, Wollersheim H, Janssen MC, et al. Evolution of deep venous thrombosis: a 2-year follow-up using duplex ultrasound scan and strain-gauge plethysmography. *J Vasc Surg.* 2001;34:649-655.
- Meissner MH, Caps MT, Bergelin RO, Manzo RA, Strandness DE Jr. Early outcome after isolated calf vein thrombosis. *J Vasc Surg.* 1997;26:749-756.
- McLafferty RB, Moneta GL, Passman MA, Brant BM, Taylor LM Jr, Porter JM. Late clinical and hemodynamic sequelae of isolated calf vein thrombosis. *J Vasc Surg.* 1998;27:50-57.
- Ginsberg JS, Gent M, Turckstra F, et al. Post-thrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. *Arch Intern Med.* 2000;160:669-672.
- Andersen M, Wille-Jørgensen P. Late complications of asymptomatic deep venous thrombosis. *Eur J Surg.* 1991;157:527-530.
- Warwick D, Perez J, Vickery C, Bannister G. Does total hip arthroplasty predispose to chronic venous insufficiency? *J Arthroplasty.* 1996;11:529-533.
- McNally MA, McAlinden MG, O'Connell BM, Molan RA. Postphlebotic syndrome after hip arthroplasty: 43 patients followed at least 5 years. *Acta Orthop Scand.* 1994;65:595-598.
- Siragusa S, Beltrametti C, Barone M, Piovella F. Clinical course and incidence of post-thrombotic syndrome after profound asymptomatic deep vein thrombosis: results of a transverse epidemiologic study [in Italian]. *Minerva Cardioangiol.* 1997;45:57-66.
- Heit JA, Elliott CG, Trowbridge AA, et al. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2000;132:853-861.
- Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med.* 2001;135:858-869.
- Davidson BL, Lensing AW. Prolonged prophylaxis after joint replacement: another step sideways? *Ann Intern Med.* 2000;132:914-915.
- Biguzzi E, Mozzi E, Alatri A, Taioli E, Moia M, Mannucci PM. The post-thrombotic syndrome in young women: retrospective evaluation of prognostic factors. *Thromb Haemost.* 1998;80:575-577.
- Wille-Jørgensen P, Jørgensen T, Andersen M, Kirchhoff M. Postphlebotic syndrome and general surgery: an epidemiologic investigation. *Angiology.* 1991;42:397-403.
- Killewich LA, Bedford GR, Beach KW, Strandness DE Jr. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg.* 1989;9:89-97.
- Milne AA, Stonebridge PA, Bradbury AW, Ruckley CV. Venous function and clinical outcome following deep vein thrombosis. *Br J Surg.* 1994;81:847-849.
- Porter JM, Moneta GL. International Consensus Committee on Chronic Venous Disease. Reporting standards in venous disease: an update. *J Vasc Surg.* 1995;21:635-645.
- Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome [abstract 158]. *Haemostasis.* 1994;24(suppl 1):157.
- Rutherford RB, Padberg FT Jr, Comerota AJ, Kist-

- ner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg.* 2000;31:1307-1312.
47. Coon WW, Willis PW III, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation.* 1973;48:839-846.
 48. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med.* 1991; 151:933-938.
 49. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158:585-593.
 50. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost.* 2001;86:452-463.
 51. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med.* 1992;232:155-160.
 52. Heit JA, Rooke TW, Silverstein MD, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg.* 2001;33:1022-1027.
 53. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med.* 2001; 161:2105-2109.
 54. Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one-to six-year follow-up. *J Vasc Surg.* 1995;21:307-312.
 55. AbuRahma AF, Stickler DL, Robinson PA. A prospective controlled study of the efficacy of short-term anticoagulation therapy in patients with deep vein thrombosis of the lower extremity. *J Vasc Surg.* 1998;28:630-637.
 56. Francis CW, Ricotta JJ, Everts CM, Marder VJ. Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty. *Clin Orthop.* July 1988;232:271-278.
 57. Mudge M, Leinster SJ, Hughes LE. A prospective 10-year study of the post-thrombotic syndrome in a surgical population. *Ann R Coll Surg Engl.* 1988;70:249-252.
 58. Bergqvist D, Jendteg S, Johansen L, Persson U, Ödegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. *Ann Intern Med.* 1997;126:454-457.
 59. Scott TE, LaMorte WW, Gorin DR, Menzoian JO. Risk factors for chronic venous insufficiency: a dual case-control study. *J Vasc Surg.* 1995;22: 622-628.
 60. Hafner J, Kuhne A, Schar B, et al. Factor V Leiden mutation in postthrombotic and non-postthrombotic venous ulcers. *Arch Dermatol.* 2001;137:599-603.
 61. Gaber Y, Siemens HJ, Schmeller W. Resistance to activated protein C due to factor V Leiden mutation: high prevalence in patients with post-thrombotic leg ulcers. *Br J Dermatol.* 2001;144: 546-548.
 62. Harrison MB, Graham ID, Friedberg E, Lorimer E, Ottawa-Carleton Regional Leg Ulcer Team. A regional planning study: assessing the population with leg and foot ulcers. *Can Nurse.* 2001; 97:18-23.
 63. Bosanquet N. Costs of venous ulcers: from maintenance therapy to investment programmes. *Phlebology.* 1992;7(suppl 1):44-46.
 64. Van den Oever R, Hepp B, Debbaut B, Simon I. Socio-economic impact of chronic venous insufficiency: an underestimated public health problem. *Int Angiol.* 1998;17:161-167.
 65. Abenheim L, Kurz X, VEINES Group. The VEINES study (Venous Insufficiency Epidemiologic and Economic Study): an international cohort study on chronic venous disorders of the leg. *Angiology.* 1997;48:59-66.
 66. Phillips T, Stanton B, Provan A, Lew R. A study of the impact of leg ulcers on quality of life: financial, social, and psychological implications. *J Am Acad Dermatol.* 1994;31:49-53.
 67. Lamping DL. Measuring health-related quality of life in venous disease: practical and scientific considerations. *Angiology.* 1997;48:51-57.
 68. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care.* 1989;27(3, suppl): S217-S232.
 69. Ware J, Kosinski M, Keller SD. *SF-36® Physical and Mental Health Summary Scales: A User's Manual.* Boston, Mass: Health Institute, New England Medical Center; 1994.
 70. O'Donnell TF Jr, Browse NL, Burnand KG, Thomas ML. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res.* 1977; 22:483-488.
 71. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenheim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg.* 2003; 37:410-419.
 72. Kahn SR, Hirsch A, Shrier I. Effect of post-thrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med.* 2002;162:1144-1148.
 73. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest.* 2001; 119(suppl 1):132S-175S.
 74. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. *Chest.* 2001;120:1964-1971.
 75. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* 1999;353:1386-1389.
 76. Stratton MA, Anderson FA, Bussey HI, et al. Prevention of venous thromboembolism: adherence to the 1995 American College of Chest Physicians consensus guidelines for surgical patients. *Arch Intern Med.* 2000;160:334-340.
 77. Bratzler DW, Raskob GE, Murray CK, Bumpus LJ, Piatt DS. Underuse of venous thromboembolism prophylaxis for general surgery patients: physician practices in the community hospital setting. *Arch Intern Med.* 1998;158:1909-1912.
 78. Turpie AGG, Gallus AS, Hoek JA, Pentasaccharide Investigators. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med.* 2001; 344:619-625.
 79. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet.* 2002;359:1721-1726.
 80. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet.* 2002;359:1715-1720.
 81. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med.* 2001;345:1298-1304.
 82. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med.* 2001; 345:1305-1310.
 83. Heit JA, Colwell CW, Francis CW, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. *Arch Intern Med.* 2001;161:2215-2221.
 84. Lee A, Agnelli G, Büller H, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. *Circulation.* 2001;104:74-78.
 85. Cogo A, Bernardi E, Prandoni P, et al. Acquired risk factors for deep-vein thrombosis in symptomatic outpatients. *Arch Intern Med.* 1994;154: 164-168.
 86. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med.* 1999;340:901-907.
 87. Schulman S. Optimal duration of oral anticoagulant therapy in venous thromboembolism. *Thromb Haemost.* 1997;78:693-698.
 88. Couturaud F, Kearon C. Treatment of deep vein thrombosis. *Semin Vasc Med.* 2001;1:43-54.
 89. Wells PS, Forster AJ. Thrombolysis in deep vein thrombosis: is there still an indication? *Thromb Haemost.* 2001;86:499-508.
 90. Schweizer J, Kirch W, Koch R, et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol.* 2000;36:1336-1343.
 91. Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. *Br J Surg.* 1979;66:838-843.
 92. Arnesen H, Høiseth A, Ly B. Streptokinase of heparin in the treatment of deep vein thrombosis: follow-up results of a prospective study. *Acta Med Scand.* 1982;211:65-68.
 93. Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis: results of a randomized trial. *Chest.* 1990;97(4, suppl):172S-175S.
 94. Common HH, Seaman AJ, Rösch J, Porter JM, Dotter CT. Deep vein thrombosis treated with streptokinase or heparin: follow-up of a randomized study. *Angiology.* 1976;27:645-654.
 95. Schulman S, Lockner D, Granqvist S, Bratt G, Paul C, Nyman D. A comparative randomized trial of

- low-dose versus high-dose streptokinase in deep vein thrombosis of the thigh. *Thromb Haemost.* 1984;51:261-265.
96. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med.* 1984;76:393-397.
 97. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology.* 1999; 211:39-49.
 98. Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med.* 1990;88:235-240.
 99. O'Donnell TF Jr, Rosenthal DA, Callow AD, Ledig BL. Effect of elastic compression on venous hemodynamics in postphlebotic limbs. *JAMA.* 1979; 242:2766-2768.
 100. Pierson S, Pierson D, Swallow R, Johnson G Jr. Efficacy of graded elastic compression in the lower leg. *JAMA.* 1983;249:242-243.
 101. Jones NA, Webb PJ, Rees RI, Kakkar VV. A physiological study of elastic compression stockings in venous disorders of the leg. *Br J Surg.* 1980; 67:569-572.
 102. Noyes LD, Rice JC, Kerstein MD. Hemodynamic assessment of high-compression ho-
 - siery in chronic venous disease. *Surgery.* 1987; 102:813-815.
 103. Evers EJ, Wuppermann T. Effect of different compression therapies on the reflux in deep veins with a post-thrombotic syndrome. *Vasa.* 1999;28: 19-23.
 104. Benkö T, Cooke EA, McNally MA, Mollan RAB. Graduated compression stockings: knee length or thigh length. *Clin Orthop.* February 2001; 383:197-203.
 105. Kahn SR, Elman ER, Rodger MA, Wells PS. Use of elastic compression stockings after deep venous thrombosis: a comparison of practices and perceptions of thrombosis physicians and patients. *J Thromb Haemost.* 2003;1:500-506.
 106. Ginsberg JS, Brill-Edwards P, Kowalchuk G, Hirsh J. Intermittent compression units for the post-phlebotic syndrome: a pilot study. *Arch Intern Med.* 1989;149:1651-1652.
 107. Ginsberg JS, Magier D, MacKinnon B, Gent M, Hirsh J. Intermittent compression units for severe post-phlebotic syndrome: a randomized crossover study. *CMAJ.* 1999;160:1303-1306.
 108. Weingarten MS. State-of-the-art treatment of chronic venous disease. *Clin Infect Dis.* 2001; 32:949-954.
 109. Alguire PC, Mathes BM. Chronic venous insufficiency and venous ulceration. *J Gen Intern Med.* 1997;12:374-383.
 110. Gilliland EL, Wolfe JHN. ABC of vascular diseases: leg ulcers. *BMJ.* 1991;303:776-779.
 111. Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2001;(2):CD000265.
 112. Krasner D. Painful venous ulcers: themes and stories about their impact on quality of life. *Ostomy Wound Manage.* 1998;44:38-49.
 113. Smith JJ, Guest MG, Greenhalgh RM, Davies AH. Measuring the quality of life in patients with venous ulcers. *J Vasc Surg.* 2000;31:642-649.
 114. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. *Angiology.* 1997;48:67-69.
 115. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet.* 1996; 347:292-294.
 116. Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency: a criteria-based systematic review. *Arch Dermatol.* 1998; 134:1356-1360.
 117. Guyatt G, Schunemann H, Cook D, Jaeschke R, Pauker S, Bucher H. Grades of recommendation for antithrombotic agents. *Chest.* 2001; 119(1, suppl):3S-7S.
 118. Kahn SR, Ducruet T, Johri M, for the Venous Thrombosis Outcomes (VETO) Study Investigators. Resource utilisation and loss of productivity during the 4 months following a diagnosis of deep venous thrombosis [abstract]. *J Thromb Haemost.* 2003;1 (7, suppl 1):abstract 181.