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Brandjes, D.P.M.; Büller, H.R.; Heijboer, H.; Huisman, M.V.; de Rijk, M.; Jagt, H.; ten Cate, J.W.

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Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis

Dees P M Brandjes, Harry R Büller, Harriët Heijboer, Menno V Huisman, Monique de Rijk, Henriëtte Jagt, Jan Wouter ten Cate

Summary

Background Post-thrombotic syndrome varies from mild oedema to incapacitating swelling with pain and ulceration. We investigated the rate of post-thrombotic syndrome after a first episode of deep-vein thrombosis and assessed the preventive effect of direct application of a sized-to-fit graded compression stocking.

Methods Patients with a first episode of venogram-proven proximal deep-vein thrombosis were randomly assigned no stockings (the control group) or made-to-measure graded compression elastic stockings for at least 2 years. Post-thrombotic syndrome was assessed with a standard scoring system that combined clinical characteristics and objective leg measurements. Patients were assessed every 3 months during the first 2 years, and every 6 months thereafter for at least 5 years. The cumulative incidence of mild-to-moderate post-thrombotic syndrome was the primary outcome measure.

Findings Of the 315 consecutive outpatients considered for inclusion, 44 were excluded and 77 did not consent to take part. 194 patients were randomly assigned compression stockings (n=96) or no stockings (n=98). The median follow-up was 76 months (range 60–96) in both groups. Mild-to-moderate post-thrombotic syndrome (score ≥ 3 plus one clinical sign) occurred in 19 (20%) patients in the stocking group and in 46 (47%) control-group patients ($p < 0.001$). 11 (11%) patients in the stocking group developed severe post-thrombotic syndrome (score ≥ 4), compared with 23 (23%) patients in the control group ($p < 0.001$). In both groups, most cases of post-thrombotic syndrome occurred within 24 months of the acute thrombotic event.

Interpretation About 60% of patients with a first episode of proximal deep-vein thrombosis develop post-thrombotic syndrome within 2 years. A sized-to-fit compression stocking reduced this rate by about 50%.

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Centre for Haemostasis, Thrombosis, Atherosclerosis, and Inflammation Research, Academic Medical Centre (D P M Brandjes MD, H R Büller MD, H Heijboer MD, M V Huisman MD, H Jagt RN, Prof J W ten Cate MD); **and Department of Medicine, Slotervaart Ziekenhuis** (D P M Brandjes, M de Rijk RN), **Amsterdam, Netherlands**

Correspondence to: Dr Dees P M Brandjes, Centre for Haemostasis, Thrombosis, Atherosclerosis, and Inflammation Research, Academic Medical Centre F4-237, 1105 AZ Amsterdam, Netherlands

Introduction

During the past 20 years much progress has been made in the diagnosis and treatment of venous thrombosis and its acute complications. However, the long-term consequence of venous thrombosis—post-thrombotic syndrome—is little understood. This syndrome varies from mild oedema with little discomfort to incapacitating limb swelling with pain and ulceration. It is generally believed that it takes 5–10 years before post-thrombotic syndrome becomes clinically manifest.^{1,2} Previous studies have reported frequencies of the syndrome of between 5% and 100%.^{3–9} This wide range probably reflects the small size of these retrospective studies, with different periods of follow-up and selection criteria. Interpretation of the findings of these studies is hampered by the lack of an established definition of post-thrombotic syndrome. Thus, the precise incidence and the time of onset of post-thrombotic syndrome after deep-vein thrombosis is not known.

Post-thrombotic syndrome is probably caused by a combination of venous hypertension, which results from outflow obstruction and damage to venous valves, and abnormal microcirculation.¹ Strategies to reduce the outflow obstruction, such as vascular surgery and thrombolytic therapy, have not been effective.^{7,10,11} Bandages are commonly used in the treatment of patients with established post-thrombotic symptoms.¹² Brakkee and Kuiper¹³ suggested that early application of external compression in patients with acute deep-vein thrombosis may prevent post-thrombotic syndrome by stimulating the development of collaterals, reducing the transcapillary filtration, and increasing fibrinolytic activity.

We aimed to document prospectively the cumulative rate of post-thrombotic syndrome after a first episode of proximal deep-vein thrombosis and to assess the preventive effect of direct application of a sized-to-fit graded compression stocking.

Methods

Consecutive outpatients who were referred by their family doctors to the Academic Medical Centre or the Slotervaart Ziekenhuis, Amsterdam, Netherlands, with a first episode of venogram-proven proximal deep-vein thrombosis were considered for inclusion in our study. Proximal-vein thrombosis included thrombi involving the popliteal vein or above, irrespective of concomitant calf-vein thrombi.¹⁴

Our exclusion criteria were: a life expectancy of less than 6 months; paralysis of the leg; bilateral thrombosis; leg ulcers or extensive varicosis; and current use of compression stockings.

All eligible patients were told about the study design and the duration of follow-up, and were asked to give informed consent to take part. The study was approved by the ethics and research committees of both institutions.

Randomisation was done by a sealed envelope technique in blocks of eight. Eligible patients were randomly allocated sized-

	Subjective criteria		Objective criteria	
	Symptom	Score	Sign	Score
Mild-to-moderate PTS (score ≥ 3)*	Spontaneous pain in calf	1	Calf circumference increased by 1 cm	1
	Spontaneous pain in thigh	1	Ankle circumference increased by 1 cm	1
	Pain in calf on standing/walking	1	Pigmentation	1
	Pain in thigh on standing/walking	1	Venectasia	1
	Oedema of foot/calf	1	Newly formed varicosis	1
	"Heaviness" of leg	1	Phlebitis	1
Severe PTS (score ≥ 4)	Spontaneous pain and pain on standing/walking	1	Calf circumference increased by 1 cm	1
	Oedema of calf	1	Pigmentation, discolouration, and venectasia	1
	Impairment of daily activities	1	Venous ulcer	4

PTS=post-thrombotic syndrome. *Including one objective criterion.

Table 1: Scoring system for mild-to-moderate or severe post-thrombotic syndrome

to-fit graded elastic compression stockings (40 mm Hg at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf) or no stockings (the control group). All patients initially received heparin treatment in hospital for at least 5 days after hospital discharge, coumadin was continued on an outpatient basis for 3 months.

The stocking (knee-length on the affected leg, Neo Durelma, Varitex, Haarlem, Netherlands) was 57% cotton, 24% latex rubber, and 19% polyamide threads. The stocking was custom-made for each patient and applied 2–3 weeks after the first episode of proximal-vein thrombosis. Each patient received two stockings, which were replaced every 6 months. Patients were asked to wear the stockings during the day only for at least 2 years; after this time patients could choose whether to continue to use the stockings.

Patients were followed up every 3 months at the outpatient clinic during the first 2 years, and every 6 months thereafter for at least 5 years. Patients were asked not to wear their stockings on the day of assessment. Each assessment was done by an independent investigator who was unaware of the measurements recorded at the previous assessment and who was not involved in the final scoring.

An independent research nurse assessed compliance at the end of each 3 month follow-up assessment during the first 2 years. She interviewed the patient and used a four-point scale to record compliance—wearing the stocking always, usually (>80% of the time), sporadically, or never.

We also assessed the frequency of recurrent symptomatic venous thromboembolism during the follow-up period. Patients were asked to contact the thrombosis unit as soon as any symptoms of recurrent venous thromboembolism developed. Recurrent thrombosis was documented by contrast venography, scanning of the leg with iodine-125-labelled fibrinogen, or ultrasonography. Pulmonary embolism was documented by lung scanning or angiography.

We used previously defined clinical characteristics and objective leg measurements to assess the presence of mild-to-moderate or severe post-thrombotic syndrome at each follow-up visit. Subjective criteria such as pain in the calf during rest (spontaneous) or upon standing or walking, and objective criteria, such as an increase in leg circumference, new varicosis, or venous ulcers were scored. Because of the lack of an accepted definition for post-thrombotic syndrome, these symptoms and signs were scored and recorded on a specially designed form that combined components of earlier scoring systems.^{7,15} This scoring system had been tested in a previous study of patients with post-thrombotic syndrome.¹⁶

To differentiate between post-thrombotic syndrome and symptoms associated with the initial thrombotic event, patients who had post-thrombotic symptoms during the first 3 months of the study were not classified as cases of post-thrombotic syndrome; this diagnosis was made only after 6 months.

Post-thrombotic syndrome was classified as mild-to-moderate if a score of 3 or higher plus at least one objective symptom was recorded on two consecutive 3-month follow-up visits (table 1). Post-thrombotic syndrome was classified as severe in patients with a score of 4 or higher on two consecutive 3-month follow-up visits (table 1).

All patients were followed up to the end of the study, irrespective of whether they met the criteria for a mild-to-moderate or severe post-thrombotic syndrome. The scoring forms were interpreted by an independent adjudication committee, unaware of treatment allocation and the clinical condition of the patient. The committee first assessed whether the criteria for a severe post-thrombotic syndrome were met, and subsequently whether the patient had mild-to-moderate post-thrombotic syndrome. For patients with a first manifestation of post-thrombotic signs and symptoms at 24 months, an additional follow-up visit was done 3 months later.

The primary outcome measure was the cumulative incidence of mild-to-moderate post-thrombotic syndrome.

At the time we planned this study, little information about the true incidence of post-thrombotic syndrome was available. Based on the assumption that the cumulative 6-year rate of mild-to-moderate post-thrombotic syndrome would be 40% or more in the patients who did not wear stockings, we calculated that about 100 patients would be required in each group to give a power of 0.80 and a significance level of 0.05 in detecting a 50% risk reduction with the early application of compression stockings.

We used the method of Kaplan-Meier for the primary analysis of the cumulative rate of mild-to-moderate post-thrombotic syndrome; statistical significance was assessed by the method of Mantel-Haenszel.¹⁷ Patients who died or were lost to follow-up were censored. The same methods were used for the analysis of the cumulative rate of severe post-thrombotic syndrome.

Results

315 consecutive outpatients with a first episode of venogram-proven symptomatic acute proximal deep-vein thrombosis were considered for inclusion. We excluded 44 patients: 20 had a life expectancy of less than 6 months; 11 had leg paralysis; ten already wore elastic stockings; and three had leg ulcers, extensive varicosis, or bilateral thrombosis. 77 patients refused to give their consent to take part. Thus, 194 patients were randomly assigned made-to-measure graded compression elastic stockings for at least 2 years or no stockings (figure 1).

The two groups were well matched in terms of clinical characteristics at baseline (table 2). The mean age of the patients was 60 years (SD 17), 86 (44%) were women, and the majority had calf-vein thrombosis with concomitant extension into the femoral vein.

All patients were followed up for at least 60 months (median 76 [range 60–96]). During this period, 35 patients died: 19 in the stocking group and 16 in the control group. Causes of death were malignant disease (13 patients), cardiovascular disease (12), respiratory insufficiency (four), and other (six). Four patients in the stocking group and two in the control group were lost to follow-up. None of these patients had developed symptoms of a post-thrombotic syndrome at their last follow-up visit (at 8, 9, 21, and 24 months in the stocking group and at 6 and 9 months in the control group).

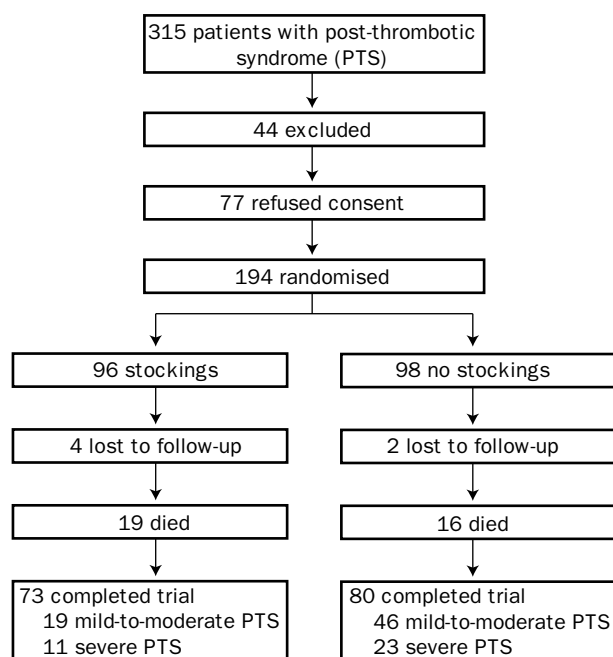


Figure 1: Trial profile

Patients were lost to follow-up because of emigration and withdrawal of consent.

Mild-to-moderate post-thrombotic syndrome occurred in 19 (20%) of the 96 patients in the stocking group, and in 46 (47%) of the 98 patients in the control group ($p < 0.001$). Life-table analysis of the time to occurrence of mild-to-moderate post-thrombotic syndrome in both groups is shown in figure 2. In both groups, most of the patients who developed post-thrombotic syndrome did so within the first 24 months. 11 (11%) patients in the stocking group and 23 (23%) in the control group developed severe post-thrombotic syndrome ($p < 0.001$). Venous ulceration was observed in four patients (one in the stocking and three in the control group). Six patients in the stocking group and ten in the control group developed severe post-thrombotic syndrome after an initial mild-to-moderate episode, with a delay of 16.5 and 11.7 months, respectively. Five patients in the stocking group and 13 in the control group presented with severe post-thrombotic syndrome without a preceding episode of mild post-thrombotic syndrome; in most of these patients the syndrome occurred in the first 24 months. The cumulative rate of severe post-thrombotic syndrome is shown in figure 2.

	Compression stockings (n=96)	No compression stockings (n=98)
Mean (SD) age in years	60 (17)	59 (17)
Median (range) days since onset of symptoms	5 (0-9)	5 (0-10)
M/F	54/42	55/44
Underlying disorders		
Diabetes mellitus	5 (5%)	5 (5%)
Peripheral arterial disease	0	1 (1%)
Idiopathic thrombosis	46 (48%)	48 (49%)
Location of thrombus at entry		
Calf and popliteal	11 (12%)	14 (14%)
Calf, popliteal, and femoral	76 (79%)	75 (77%)
Popliteal and femoral	6 (6%)	2 (2%)
Femoral only	3 (3%)	7 (7%)

Table 2: Clinical characteristics of patients at baseline

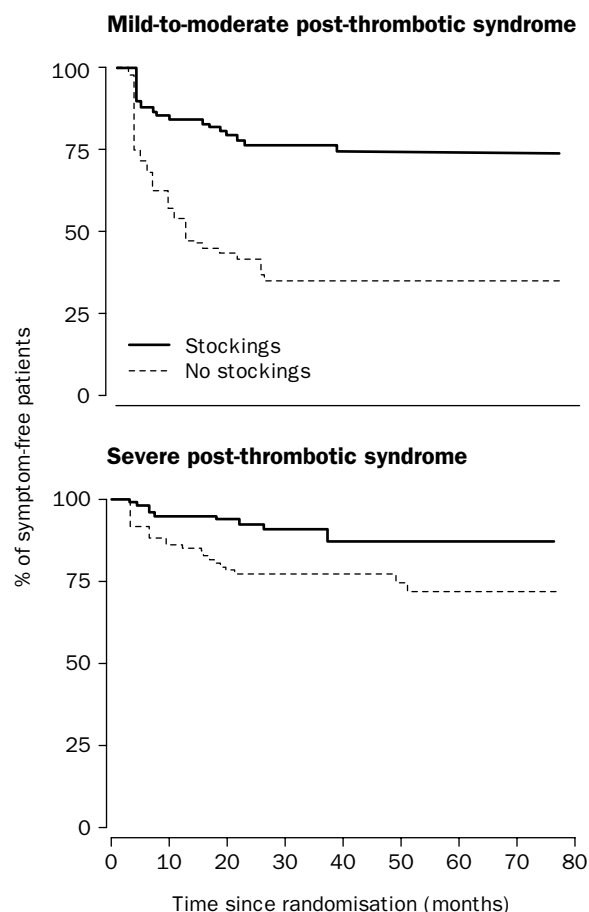


Figure 2: Proportions of patients without symptoms of mild-to-moderate or severe post-thrombotic syndrome

During follow-up, 14 (14.6%) of the 96 patients in the stocking group had documented recurrence of venous thromboembolism, compared with 13 (13.3%) of the 98 patients in the control group; the between-group difference was not significant. Recurrent venous thrombosis was confirmed in 20 patients by repeat venography, and by I^{125} -labelled fibrinogen scanning or ultrasonography in the other seven patients. The median period between the initial event and the recurrent episode was 14.5 months (range 2-30) in the stocking group versus 12 months (3-60) in the control group. Of the 14 patients in the stocking group with recurrent thrombosis, three had severe post-thrombotic syndrome compared with two of the 13 patients in the control group.

Our assessment of compliance showed that of the 96 patients in the stocking group, seven did not wear or only occasionally wore their stockings, 16 usually wore their stockings, and 73 always wore their stockings. Although compliance was not formally assessed after the first 2 years, most of the patients continued to wear their stockings.

Discussion

During the French-British war in the sixteenth century, the French surgeon Ambroise Paré was released from captivity after he used compression bandages to cure the leg of an English army commander.¹⁸ Nowadays, bandages are commonly used in patients with established post-thrombotic symptoms. Our data indicate that in patients with a first episode of proximal deep-vein thrombosis, the

cumulative 6-year incidence of mild-to-moderate post-thrombotic syndrome is about 50%. In the group without stockings, 23 (23%) patients developed a severe post-thrombotic syndrome, half of whom had an initial mild-to-moderate episode. An important finding was that most of these cases became clinically manifest within the first 2 years of the acute thrombotic event, which contrasts with the general belief that it takes 5–10 years for the syndrome to become evident.^{1,2}

The use of a sized-to-fit graded compression stocking, applied within 2–3 weeks of the initial diagnosis, reduced the rate of mild-to-moderate and severe post-thrombotic syndrome by about 50%. Furthermore, most patients in the stocking group who developed post-thrombotic syndrome did so within the first 30 months. The use of compression stockings did not affect the rate of recurrent venous thrombosis, which suggests that the mechanism of recurrent thrombotic disease differs from that of post-thrombotic syndrome.

In this study, made-to-measure compression stockings were applied directly after the acute thrombotic episode and renewed every 6 months. Rogers and Lutchter¹¹ showed that these elastic stockings increase venous flow velocity and decrease transcapillary filtration.¹¹ However, the precise mechanism of these stockings in the prevention of post-thrombotic syndrome is not known and was not investigated in our study.

Several issues about our study design require comment. First, given the inevitable non-blinded design, bias in the assessment of post-thrombotic syndrome cannot be excluded. However, we used a quantitative scoring form, derived from patients known to have post-thrombotic syndrome, which was completed without knowledge of the previous assessment and included objective measurements. The scoring forms were interpreted by an independent adjudication committee. Furthermore, the syndrome was deemed to be present only if the patient's score met the criteria for mild-to-moderate or severe post-thrombotic syndrome on two consecutive 3-monthly follow-up visits. Second, because of the lack of a generally accepted definition of post-thrombotic syndrome, the observed effects of stockings might simply reflect the natural course of the disease. However, we used stringent criteria for the classification of severe post-thrombotic syndrome, which included a venous ulcer or a combination of symptoms and clinical indications. Using this definition, we observed a 50% reduction in severe post-thrombotic syndrome among the patients who wore compression stockings, which was similar to the reduction in the mild-to-moderate score. Thus, we believe that our scoring system accurately measured post-thrombotic syndrome. Since there is no established objective method for the clinical assessment of post-thrombotic syndrome, we decided to limit the outcome measurement to the clinical score. Third, can our findings be generalised? The baseline characteristics—particularly mean age, sex distribution, delay between onset of symptoms and referral, and the extent of the venous thrombosis—of the

77 patients who refused to give informed consent were similar to those of the 194 enrolled patients. Therefore, we believe that our findings are relevant for all patients with symptomatic proximal-vein thrombosis. Finally, our study did not investigate how long compression stockings should be applied to achieve the observed preventive effect. Most of the patients wore their stockings during the first 2 years, and continued to do so after this period. A reasonable assumption, given the low rate of post-thrombotic syndrome after 24 months in the control group (figures 2, 3), is that stockings should be applied for a minimum of 2 years.

We conclude that about 60% of patients with symptomatic proximal deep-vein thrombosis will develop post-thrombotic syndrome, usually within 2 years of the acute thrombotic episode. The use of sized-to-fit compression stockings reduces the rate of this syndrome by about 50%.

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