

Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: A randomized controlled trial

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Objective: Compression stockings are widely applied after acute proximal deep vein thrombosis, but their efficacy in preventing the post-thrombotic syndrome remains controversial. This study assessed the effect of prolonged compression therapy after a standard treatment of 6 months after acute deep vein thrombosis.

Methods: Of 900 patients screened, we randomly allocated 169 patients with a first or recurrent proximal deep vein thrombosis after receiving 6 months of standard treatment to wear compression stockings or not. Primary efficacy analysis was performed on the end point of emerging skin changes (C4-C6 according to the CEAP classification). Secondary analysis was done on symptoms associated with post-thrombotic syndrome. All analyses were done according to the intention-to-treat principle.

Results: The primary end point occurred in 11 patients (13.1%) in the treatment group compared with 17 (20.0%) in the control group (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.28-1.28; $P = .19$). Mean follow-up was 3.2 years and 2.9 years, respectively. Five additional patients in the control group required compression therapy owing to post-thrombotic signs and symptoms not included in the primary end point. No venous ulceration was observed in either group. Within subgroup analyses of the primary end point, we observed a large sex-specific difference between women (HR, 0.11; 95% CI, 0.02-0.91) and men (HR, 1.07; 95% CI, 0.42-2.73). Symptom relief was significant in favor of compression treatment during the first year but not thereafter.

Conclusion: Prolonged compression therapy after proximal deep vein thrombosis significantly reduces symptoms and may prevent post-thrombotic skin changes. Whether these findings translate to the prevention of advanced disease states with ulcerations remains unclear. (*J Vasc Surg* 2008;47:1015-21.)

Clinical research in the field of venous thromboembolism in recent years has focused mainly on diagnostic strategies and drug regimens in the early- and middle-term stage of the disease.¹⁻³ The long-term course of the disease has received less scientific attention, although its main manifestation—post-thrombotic syndrome (PTS)—has potential important implications for patients and society because of substantial consumption of health care resources.⁴

The reported incidence of PTS varies widely between 5% (most ≤ 2 to 4 years)⁵ and 50% (most \leq first 6 months).⁶ An important reason for this discrepancy is the lack of a generally accepted definition of PTS, which range from clinical signs with trophic skin changes⁵ to a suggestion of mixed scores with clinical signs and symptoms.⁶⁻⁸ Other reasons for the discrepancy are differences in populations and settings with respect to the extension of deep vein thrombosis (DVT) and different treatment strategies for the acute disease.^{5-7,9}

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So far, only three randomized controlled trials (RCT) concerning compression therapy for the prevention of PTS have been conducted.⁶⁻⁸ The investigators of two larger RCTs reported effect sizes of about 50% risk reductions in favor of compression.^{6,7} One smaller trial used placebo-stockings as a control and found no benefit of compression.⁸ These trials incorporated symptoms into their definition of the primary end point. Early symptoms, however, may be due to an acute or subacute DVT and are not yet a sign of PTS.¹⁰ Incorporating early symptoms after DVT into the outcome definition of PTS therefore leads to an apparently high incidence of end points. Furthermore, efficacy assessment of compression therapy should differentiate between symptoms of DVT, which decline over time, and symptoms that persist or evolve as a part of the “full clinical picture” of PTS.

In contrast with previous trials, we aimed to address the genuine effect of stockings to prevent PTS. We randomized patients only 6 months after the initial diagnosis and treatment of DVT and introduced end point definitions that are carefully based on clinical signs (ie, skin changes as a surrogate marker) and symptoms.

METHODS

Patients. Recruitment period lasted from June 1997 until June 2004. Patients who were generally symptomatic were initially referred by hospital interns or primary care

physicians to our institution for exclusion or confirmation of DVT. All patients with confirmed DVT completed a recommended standard therapy before screening for study inclusion. Therapy consisted of heparin in the initial phase, followed by oral anticoagulation (target international normalized ratio 2.0 to 3.0) and compression stockings (ankle pressure, 26.3 to 36.1 mm Hg) for at least 6 months. Medical care in this prestudy period was provided by the primary care physician. After finishing these 6 months of therapy, patients were screened for study inclusion. Inclusion criteria were age >18 years and first or recurrent proximal DVT confirmed by duplex ultrasound (DUS) imaging. Proximal DVT was defined as thrombosis of the popliteal vein or more proximal (eg, femoral and iliac vein). Exclusion criteria were chronic venous insufficiency C4 to C6 by the CEAP classification (corresponding to skin changes ascribed to venous disease with or without active or healed ulcer),¹¹ advanced malignancy or death anticipated to occur ≤ 2 years, long-lasting immobilization, geographic inaccessibility, dementia, peripheral arterial disease contraindicating compression therapy, anticipated lack of compliance, or refused informed consent.

Treatment allocation to compression stocking (intervention) or no stocking (control) was concealed and performed by a study nurse not involved in the trial by means of a computer-generated randomization list. Subsequent medical care, including exceptional oral anticoagulation >6-months standard treatment period was left to the discretion of the primary care physician. The single-center trial was approved by the local ethical committee, and informed consent was obtained from all patients before to inclusion.

Baseline examination. At study inclusion, DUS imaging of the affected leg was performed in all patients by one experienced investigator (C. J.). The deep venous system, consisting of the common femoral vein, proximal femoral vein, popliteal vein and posterior tibial vein, and the main superficial trunks (great and small saphenous vein) were evaluated for patency and presence of reflux. Patency was divided into three categories: open, partially, and completely occluded.

Reflux was tested with a standardized compression/decompression method, as described elsewhere.^{12,13} Pathologic reflux was defined as a more than twofold normal reflux time in the deep vein segments¹³ and >1 second reflux time in the superficial veins. The clinical assessment included the examination of the malleolar region for the presence of hyperpigmentation, eczema, atrophic blanche, dermatoliposclerosis, or ulceration. A medical history for the presence of five PTS-associated symptoms accurately described in a study by Widmer et al¹⁴ as pain, heaviness, sensation of heat, tension, and tiredness of the affected limb was taken, and additional diagnoses were recorded.

Intervention. Patients in the intervention group were reinstructed about wearing compression stockings during the day, defined as from getting up in the morning until bedtime. Prescribed stockings were bought by the patients and reimbursed for up to two pairs per year by their insurance companies. The type of recommended stocking

was a ready-to-wear, flat-knitted, below knee stocking with an applied pressure at the ankle of 26.3 to 36.1 mm Hg.

Follow-up examinations. Clinical follow-up examinations, as described for baseline, were done by three specialists in vascular medicine who were blinded to the results of the DUS examination but not for treatment allocation. Follow-up examinations took place every 3 months in the first year after inclusion and every 6 months thereafter until an end point developed or the patient reached the end of follow-up. When recurrent DVT was suspected, DUS imaging was performed. Criteria for diagnosing recurrent DVT were (1) noncompressibility of a previously not affected vein segment, (2) elevated thrombotic burden in a previously thrombosed segment compared with the findings at entry, or (3) the presence of a floating thrombus tip. Patients with recurrent DVT during follow-up were censored from further analyses because of the need for compression stocking.

Adherence to treatment. Adherence to wearing the stocking (or not wearing in the control group) was verified by a study nurse at every visit. Full adherence was defined if a patient acknowledged wearing the stocking for ≥ 6 days per week, partial adherence for 4 to 5 days, and nonadherence for <4 days a week.

Outcome. The primary end point was defined as the occurrence of emerging post-thrombotic skin changes according to C4 or higher. Any skin-related end point detected for the first time had to be confirmed by a consensus of two outcome assessors at a second visit 3 months later. This second date was used as the event date for analysis. The secondary end point focused on PTS-associated symptoms. Symptom status was registered at every follow-up visit. A patient was considered symptomatic if at least one of five PTS-associated symptoms was present. In all patients of the control group who resumed using compression stockings during follow-up, the exact reason for compression, such as swelling of the leg or pain, was registered. All patients in the control group who developed post-thrombotic skin changes according to C4 or higher were encouraged to wear compression stockings to avoid progression of chronic venous insufficiency.

Statistical analysis. At the time our trial was started, little information about the incidence of PTS was available. We calculated a sample size assuming a 45% incidence of PTS in the control group over an average follow-up duration of 3 years, with an assumed 50% relative risk reduction of compression stockings and a dropout of 10%. With 80% power and a two-sided significance level of $P = .05$, 85 patients were needed per treatment arm.

No interim analyses were performed. Primary efficacy analysis was done according to the intention-to-treat principle using the end point of emerging post-thrombotic skin changes. Kaplan-Meier analysis with the log-rank test was used to test the null hypothesis of equality of the survival curves for the intervention and control arm. We performed extended analyses on the primary outcome with adjustment for baseline covariates with Cox regression. The prespecified predictor variables were ipsilateral previous DVT, the

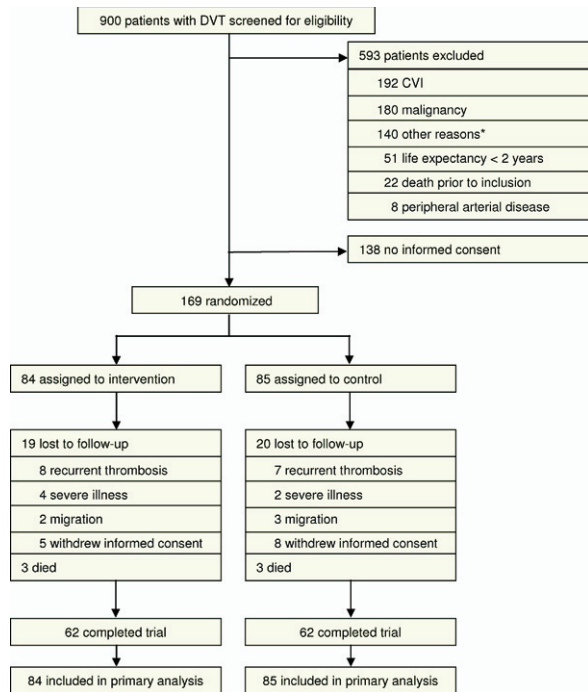


Fig 1. Trial profile. *CVI*, Chronic venous insufficiency C4 to C6 (CEAP classification)¹⁰; *DVT*, proximal deep vein thrombosis. *Other reasons included frailty, dementia, and living too remote from the study center.

extension of the thrombus, the presence of obstruction and reflux at baseline DUS imaging at the same leg, age, and sex. Completeness of follow-up was calculated as suggested by Clark.¹⁵ We conducted subgroup analyses for the prespecified predictor variables by testing interactions with treatment in the Cox model.¹⁶

To deal with treatment crossover during follow-up, we additionally performed an as-treated analysis using time-dependent covariates. We used the counting process notation of the Cox model and reallocated patients in the intervention group who stopped wearing the stocking to the control group thereafter, and vice versa for the control group patients who started to wear a stocking.

A repeated measurement analysis to assess differences in the presence or absence of symptoms during follow-up was performed according to treatment allocation (analysis of secondary end points). A marginal generalized linear model of repeated follow-up measurements within a patient was used.¹⁷ The baseline symptom status was included as a covariate in the model, and an interaction of treatment with time reflected potential change of treatment on symptoms over time. A crude as well as adjusted analysis including the same prespecified covariates as with the primary end point analysis was performed. We used R 2.1.1 software (The R Foundation for Statistical Computing, <http://www.r-project.org/foundation/>) for all statistical analyses.

Table I. Baseline characteristics of patients included

Characteristics	Intervention (n = 84)	Control (n = 85)
Age, median (IQR) years	64.1 (52.9-72.5)	63.8 (45.3-70.8)
Sex, No. (%)		
Male	54 (64.3)	45 (52.9)
Female	30 (35.7)	40 (47.1)
BMI, median (IQR) kg/m ²	25.6 (24.2-28.7)	25.9 (22.9-28.1)
Side of DVT, No. (%)		
Left	49 (58.3)	44 (51.8)
Right	35 (41.7)	41 (48.2)
Previous DVT, No. (%) ^a		
No DVT	63 (75.0)	68 (80.0)
Same Leg	18 (21.4)	13 (15.3)
Contralateral leg	2 (2.4)	4 (4.7)
Location of DVT, No. (%)		
Popliteal	26 (30.9)	29 (34.1)
Popliteal and femoral	44 (52.4)	38 (44.7)
Popliteal, femoral, and iliac	14 (16.7)	18 (21.2)
DUS finding in any vein segment, No. (%)		
Obstruction	50 (59.5)	49 (57.6)
Reflux	79 (94.0)	82 (96.5)
Obstruction and reflux	49 (58.3)	51 (60.0)
Obstruction or reflux	81 (96.4)	83 (97.6)

BMI, Body mass index; *DUS*, duplex ultrasound; *DVT*, proximal deep vein thrombosis; *IQR*, interquartile range.

^aOne value missing in the intervention group.

RESULTS

A total of 900 consecutive patients with proximal DVT were screened. Of these, 593 were excluded for clinical reasons and 138 were considered noncompliant or refused to give informed consent (Fig 1). The latter group was similar to the study population concerning age, sex, and thrombus extension. The intention-to-treat population consisted of 169 patients, 84 of whom were randomized to the intervention group and 85 to the control group. The number of patients lost to follow-up was similar in both groups, and 62 patients completed the trial as intended in each group. Table I reports the distribution of baseline characteristics according to treatment allocation. Some baseline imbalances were recognized for sex and same-leg previous DVT. Completeness of follow-up was 84.5% in the intervention group and 75.4% in the control group. Mean length of follow-up was 3.2 years (range, 2 months-6.8 years) in the intervention group and 2.9 years (range, 1.5 months-7.0 years) in the control group.

Primary end point. Overall, the primary end point developed in 11 patients (13.1%) in the intervention group, and in 17 (20.0%) in the control group. Two of the 17 patients in the control group with post-thrombotic skin changes developed C4b with dermatoliposclerosis, no patients in either group developed venous ulcer (C5). Three patients in each group died (Table II). Kaplan-Meier curves for rates of freedom from post-thrombotic skin changes are given for both treatment arms for the whole study popula-

Table II. Primary end point

	Intervention (n = 84)	Control (n = 85)	HR ^a (95% CI)	P	HR ^b (95% CI)	P
PT-s, crude effect	11 (13.1%)	17 (20.0%)	0.60 (0.28-1.28)	.19	0.65 (0.31-1.40)	.27
PT-s, adjusted ^c			0.61 (0.28-1.31)	.20	0.65 (0.30-1.42)	.28

CI, Confidence interval; HR, hazard ratio; PT-s, post-thrombotic skin changes.

^aHazard ratio from Cox model, intention to treat analysis.

^bHazard ratio from Cox model, as-treated (treatment as time-dependent covariate).

^cAdjusted for previous deep vein thrombosis, age, and sex.

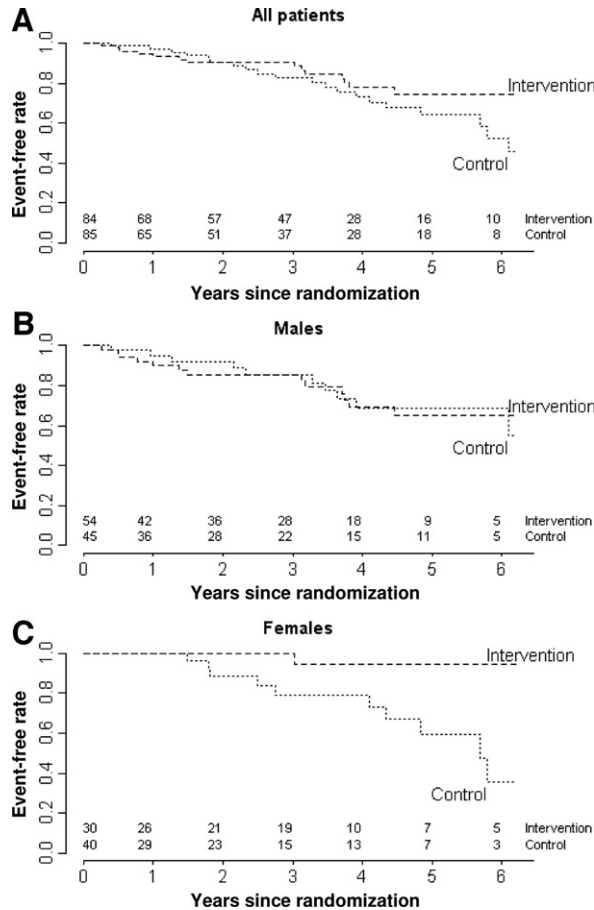


Fig 2. Kaplan-Meier estimates of survival without post-thrombotic skin changes in the intervention (dotted line) and control groups (dashed line). **A**, Survival free of post-thrombotic skin changes for the whole study population. **B**, Treatment effects specific to men. **C**, Treatment effects specific to women.

tion and for men and women separately (Fig 2). In the intention-to-treat analysis, the relative hazard for the primary end point of intervention against control was 0.60 (95% confidence interval [CI], 0.28-1.28, $P = .19$) and after adjustment for baseline imbalances 0.61 (95% CI, 0.28-1.31, $P = .20$; Table II).

Seven patients in each group had a crossover from their assigned treatment. Five of the seven crossovers in the control group were caused by development of post-thrombotic pain,

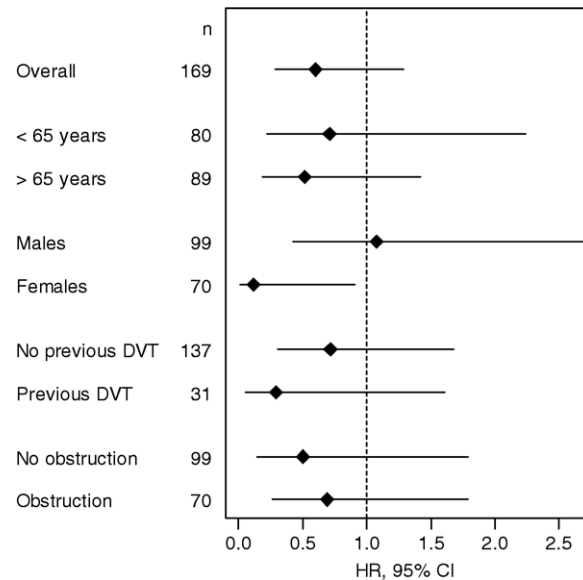


Fig 3. Subgroup-analysis of primary end point. CI, Confidence interval; DVT, ipsilateral deep vein thrombosis; HR, hazard ratio.

swelling, or venous claudication, and all the remaining in both groups were because of patients' wishes. The median time of crossover was early in the control group at a median 4 months (range, 3-7 months) but late in the intervention group at 33 months (range, 3-56 months). In the as-treated analysis, the unadjusted relative hazard for the primary end point of intervention vs control was 0.65 (95% CI, 0.31-1.40; $P = .27$; Table II).

Subgroup analyses for the primary end point showed that the stocking effect was significantly different within gender strata but not within strata of the remaining pre-specified covariates. Although men did not show any benefit from the intervention (hazard ratio, 1.07; 95% CI, 0.42-2.73), women showed a significant benefit (hazard ratio, 0.11; 95% CI, 0.02-0.91; Figs 2 and 3). Baseline characteristics, including body mass index as well as side and extent of DVT, were equally distributed in men and women.

Secondary end point. In 12.2% (77 of 629) of follow-up visits in the intervention group and 16.5% (93 of 563) of follow-up visits in the control group, patients reported on at least one of the five PTS associated symptoms at any follow-up visit occasion. In both groups, there

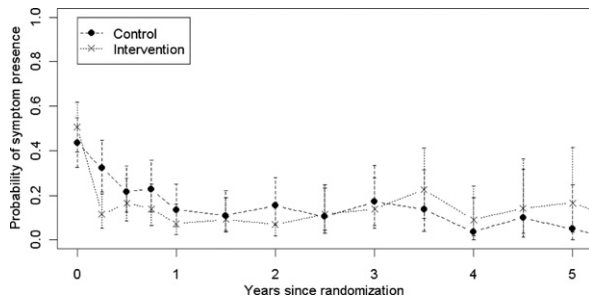


Fig 4. Probability of presence of symptoms over time in controls (*circles*) and intervention group (*crosses*). Symptom presence means at least one of five symptoms present at any follow-up examination. Error bars indicate 95% confidence interval per treatment arm.

was a marked reduction of symptom complaints during the first 12 months (Fig 4). After an initial 65% relative risk reduction (odds ratio [OR], 0.35; 95% CI, 0.17-0.73) by the intervention at 3 months, the effect decreased to 54% (OR, 0.46; 95% CI, 0.23-0.90) at 1 year. Thereafter, no reduction in symptom complaints was registered in either group.

Adherence. In the intervention group, nonadherence to stocking treatment was recorded at 8.4% of follow-up visits. Men indicated in 11% and women in 3.6% of follow-up visits nonadherence to compression stocking treatment. Modeling noncompliance as a function of sex showed that noncompliance was about four times more frequent in men than women (OR, 4.1; 95% CI, 1.0-16.0; $P = .05$).

DISCUSSION

This open, randomized controlled trial investigated the long-term benefit of compression stockings beyond the 6 months of standard compression after DVT of the lower extremities. Unlike two previous trials,^{6,7} this study did not begin immediately after the diagnosis of DVT, where compression therapy was considered mandatory. In addition, only post-thrombotic skin changes based on the standardized C-part of the CEAP classification¹¹ were used in this study for the definition of the primary end point. Although post-thrombotic skin changes were reduced by 40%, this finding did not reach statistical significance. Nevertheless, the observed effect size was close to that obtained in the two main previous trials of similar size and comparable applied compression pressure as our study, as well as a Cochrane review, where a risk reduction of about 50% for all degrees of severity of PTS was reported.^{6,7,18}

We need to emphasize several important differences in the trial concepts that may further explain the findings of our trial. The trials of Brandjes et al⁷ and Prandoni et al⁶ used scoring systems based on the combination of different clinical signs and symptoms. We instead used the CEAP classification¹¹ for assessment of post-thrombotic skin changes for the primary end point. To our knowledge, this now generally accepted classification of chronic venous changes^{19,20} has not yet been used in comparable PTS

intervention trials. Our rationale was to have a more reliably measurable end point that is less prone to misclassification.

To strengthen the primary end point and to avoid misinterpretation of acute and subacute DVT symptoms as PTS, we did not incorporate symptoms in the primary end point. Our primary end point thus relied explicitly on post-thrombotic skin changes, and symptoms were analyzed as a secondary end point. Symptoms such as cramps, pruritus, paraesthesia, or “heaviness” are very unspecific²¹ and are probably not suitable to describe long-term consequences in a cohort. This is underlined by the rapid decrease of symptoms during the first year and the prevalence of symptoms of about 10% during extended follow-up in our study. Furthermore, edema of the foot or calf region and redness or pain in the calf, as incorporated in scoring systems for the definition of PTS, are also unspecific.^{6,7} During the early course of thromboembolism, they may represent rather symptoms and signs of acute or subacute DVT rather than those of PTS. The inclusion of these clinical signs into widely accepted diagnostic scores for acute DVT, such as the Wells-Score, may underline this fact.²²

The CEAP classification has also some limitations and may lack discrimination because it does not allow for a more detailed grading of the severity of skin lesions. Differentiation between mild, moderate, or severe PTS, as used in the work of Brandjes et al⁷ and Prandoni et al,⁶ is not provided. This drawback was recently ameliorated by a refined classification that now allows the differentiation between pigmentation or eczema (4a) and lipodermatosclerosis or atrophy blanche (4b), or both, the more advanced stage of chronic venous insufficiency.²³

We considered only skin alterations according to C4a and C4b or higher as the primary end point, although others have defined less specific C2 and C3 as mild PTS.²⁴ This restriction inevitably results in a lower incidence of the primary end point. The rationale behind our decision is that in large epidemiologic studies of asymptomatic individuals without a history of DVT, manifestations of C1 to C3 were found in more than 80%.^{25,26} In our opinion, these mostly harmless venous alterations are not sufficiently relevant to justify their classification as true PTS.

Finally, we based our subgroup analyses on a priori set hypothesis and showed no difference in the primary end point for all prespecified treatment covariates but sex. In women, but not in men, stockings were highly effective in the prevention of post-thrombotic skin alterations. The incidence of end points in the control group was not sex specific, however. A possible but perhaps not the only explanation of this differential effect is lower adherence of men to compression stocking therapy.

The strength of the presented study is that enrolment only started 6 months after the diagnosis of DVT, with the aim that signs and symptoms related to PTS are less contaminated with signs and symptoms of the acute disease. By using DUS imaging for the assessment of the whole venous system, we were able to document post-thrombotic damage of the veins in almost all of the included patients, which

underlines that a true at-risk population was investigated. We did not include patients with a distal DVT to avoid a lower risk population for PTS but did include patients with previous DVT assuming that they present an increased risk for PTS. We used an approach to treatment that is very close to real life by using ready-to-wear stockings and leaving final responsibility for replacement of stockings to the patient. Finally, in contrast with previous studies, the standardized well-established CEAP scoring system was used to classify disease.

Our study does have several limitations. In particular, it lacks adequate power to show a significant difference for the primary outcome. Several factors may have restricted the power of this trial. Our primary end point definition led to a much lower number of events. Furthermore, the inclusion criteria led to the selection of a population of patients with less advanced skin alterations, where the compression therapy might be less effective than in more advanced C categories. The relatively large number of patients not eligible for the trial might also limit a generalized application of our findings to other populations with DVT.

Although a good adherence was documented, the therapeutic effect of the intervention was additionally diluted by poorer adherence, particularly in men. Furthermore, the five crossover patients in the control group who resumed wearing stockings owing to symptomatic PTS were not considered in our primary end point even though they presented the classical type of PTS but without progressive skin changes. The mortality rate in our trial was much lower than in those of Brandjes et al⁷ and Prandoni et al,⁶ which is in the line with the strict exclusion criteria.

Patients were not blinded because the nature of the intervention precluded effective blinding of patients through placebo stockings. They all had a 6-month experience with verum stockings, so that the application of sham stockings was not an alternative. Blinding of outcome assessors was not done because an experienced outcome assessor would certainly identify typical skin imprints induced by compression stockings, even if we had advised patients in the intervention group to abstain from wearing stockings at the day of the clinical visit.

CONCLUSION

We found that prolonged compression therapy by ready-to-wear compression stockings may reduce post-thrombotic skin changes, an objective early sign of PTS, by about 40% compared with noncompression. Our trial, however, was insufficiently powered to demonstrate a statistically significant effect. We found an additional effect of symptom reduction from prolonged compression therapy in the early phase of the study. The efficacy of treatment in men and women differed to a great extent. In our study population, women—but not men—showed a benefit from compression therapy; however, owing to the uncertainty of subgroup results, this effect has to be treated with caution and needs future attention. Our compliance data, underlined by a low and equally distributed number of

crossovers, indicate that a fairly good acceptance of this harmless but effective therapy can be anticipated with a minimal effort of two short visits a year. Finally, identification of a high-risk patient population for the development of PTS, which probably could profit most from prolonged compression therapy, should be the focus of future studies.

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AUTHOR CONTRIBUTIONS

Conception and design: MA, CJ, KA

Analysis and interpretation: MA, CJ, MK, HB, KJ

Data collection: MA, CJ, CT

Writing the article: MA, MK, CT, KJ

Critical revision of the article: MA, CJ, MK, CT, HB, KJ

Final approval of the article: MA, CJ, MK, CT, HB, KJ

Statistical analysis: MK

Obtained funding: KJ

Overall responsibility: KJ

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