Thigh-length versus below-knee compression elastic stockings for prevention of the post-thrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial

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**Words in the summary**: 199

**Words in the text** (including references and tables): 3889
Abstract
Although below-knee compression elastic stockings (CES) are effective for prevention of the post-thrombotic syndrome (PTS), a substantial proportion of patients with deep venous thrombosis (DVT) still develop the PTS. In an open-label, randomized clinical trial, we compared thigh-length with below-knee CES for prevention of the PTS. 267 patients with the first episode of proximal DVT were randomized to wear either thigh-length or below-knee CES for 2 years. After 3, 6, 12, 18, 24 and 36 months, they were assessed for PTS manifestations according to the Villalta scale. PTS developed in 44 (32.6%) of the 135 patients randomized to thigh-length CES, and in 47 (35.6%) of the 132 allocated to below-knee CES, for an adjusted hazard ratio of 0.93 (95% CI, 0.62 to 1.41). Severe PTS developed in 3 patients in each group. Stockings-related side-effects developed in 55 (40.7%) of the 135 patients allocated to thigh-length CES, and in 36 (27.3%) of those randomized to the below-knee group (p=0.017), and led to premature discontinuation of their use in 29 (21.5%) and 18 (13.6%) patients, respectively. We conclude that thigh-length CES do not offer a better protection against PTS than below-knee CES and are less well tolerated (Clinical Trial number: NCT00426075).
Introduction

Compression elastic stockings (CES) have been shown to offer substantial protection against the development of the post-thrombotic syndrome (PTS) in patients with proximal deep venous thrombosis (DVT). Although the precise mechanism by which stockings reduce the risk of the PTS is unknown, they are likely to counterbalance the effects of venous hypertension resulting from persistent venous obstruction and/or valve damage and assist the muscle pump function. The latest international guidelines recommend the use of CES in all patients with proximal DVT for at least two years.

In two randomized studies in patients with proximal deep venous thrombosis, the use of below-knee CES for at least two years was associated with some 50% reduction in the incidence of the PTS compared to patients without CES. However, despite this large reduction, 25% of patients still develop post-thrombotic manifestations, which are severe in 2 to 5%.

In clinical practice, many physicians recommend the use of thigh-length CES over below knee CES, especially in patients with extensive proximal DVT, because of a perceived higher degree of protection against the development of the PTS. In order to assess the potential benefit of thigh-length over below-knee CES for prevention of the PTS, we performed a multicenter randomized study in patients with a first episode of proximal DVT. In both study arms patients were encouraged to use their stockings for two years. The Villalta scale was used for the classification of PTS.
Methods

Study design and outcomes

This randomized clinical trial compared the efficacy of thigh-length CES with that of below-knee CES, given for two years, for prevention of the PTS in patients with a first episode of proximal-vein thrombosis. The primary analysis concerned the 3-year cumulative incidence of the PTS. In addition, compliance to the assigned CES and their tolerability was assessed.

Patients

Patients referred to eight Italian university or hospital ceters with symptomatic proximal DVT, as confirmed by compression ultrasonography, between October 2005 and September 2007 were potentially eligible for the study. Patients were excluded if they had recurrent ipsilateral DVT, pre-existing leg ulcers or signs of chronic venous insufficiency, bilateral thrombosis, a short life expectancy or had a contraindication for the use of stockings (e.g. advanced-stage peripheral arterial insufficiency or allergy to stockings).

Patients who passed the screen of inclusion and exclusion criteria were asked to participate in the study after receiving detailed written information about study hypotheses and procedures. Study patients had to give written informed consent to participate in the study in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of each participating center.
**Anticoagulant treatment**

Patients were treated with low-molecular-weight heparin, overlapping with and followed by at least three months of vitamin K antagonist therapy (International Normalized Ratio [INR], 2.0 to 3.0), except for selected patients with active cancer or pregnancy, in which a LMWH mono-therapy was employed.

The duration of anticoagulant treatment followed international guidelines with individual adaptation based on patient’s preferences and risk profile. In general, patients with transient risk factors were scheduled to receive up to three months of oral anticoagulant therapy, while patients with unprovoked thrombosis received at least six months of treatment, and those with permanent risk factors, such as active cancer, were treated for the entire study period. The individual quality of oral anticoagulation was considered satisfactory if the INR was within or above the therapeutic range in more than 70% of determinations.

**Study procedures**

At baseline, a clinical history was taken, detailing the presence of risk factors for venous thrombosis (i.e., active cancer, recent [< 3 months] trauma or surgery, prolonged [> 7 days] immobilization from medical illnesses, pregnancy or puerperium, ongoing hormonal therapy). The search for thrombophilic abnormalities was left to discretion of attending physicians.

At the time of hospital discharge, on average 4-5 days after admission, patients were randomly allocated to wear either a thigh-
length or a below-knee graded CES of the affected leg, preceded by elastic bandages in the first few days at discretion of attending physicians. Randomization was done according to a computer-generated list that was accessible only to a trial nurse who informed study physicians on treatment allocation after patients had provided informed consent. Randomization was stratified by center, and permuted blocks of varying sizes were used.

Elastic stockings were supplied by Sigvaris AG, St.Gallen, Switzerland, and produced a pressure of 30 to 40 mm Hg at the ankle, were flat knitted and made of the combination of cotton, latex, and rubber/polyamide. Both thigh-length and below-knee stockings were available in three sizes. Patients received two stockings, which were replaced by identical garments every six months. The stocking had to be used during the day, for a period of two years.

Patients were discharged with a letter for their family physician, indicating that they had accepted to participate in a randomized study on CES. Both patients and their family physicians were given a card with the telephone numbers of the thrombosis clinic.

Follow-up and assessment of recurrent thromboembolism
Patients were followed-up for up to three years. The study was stopped when the last recruited patient completed the 3-year study period.

Patients were asked to visit the study center at three and six months from the index event and then every six months. In the
interval between scheduled visits, patients were asked to report to the study center if a deterioration of symptoms or signs occurred. Patients who could not attend follow-up examinations at the study center were visited at home.

Patients were asked to return to the center if they developed symptoms suggestive of recurrent venous thromboembolism. The diagnosis of recurrent thromboembolic events was made as previously described. For all patients who died during follow-up, the date and cause of death were retrieved.

Assessment of the post-thrombotic syndrome

Patients were instructed not to wear their stocking on the day of assessment and not to reveal their treatment allocation to the assessor. Each PTS assessment was done by study personnel aware of the side of the index venous thrombosis, but unaware of the treatment allocation and of the results of previous measurements. Only the side of the index venous thrombosis was considered for the development of the PTS.

The presence and severity of post-thrombotic signs and symptoms was assessed at predefined times (3, 6, 12, 24 and 36 months after the acute episode) using the Villalta scale. Briefly, the presence of five leg symptoms (i.e., pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (i.e., pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness and pain during calf compression) was scored. For each item, a score of 0 up to 3 was assigned using the contralateral
unaffected leg as denominator for all evaluations. The presence of a venous ulcer of the lower limb indicated severe PTS regardless of the sum of the remaining signs and symptoms. In the absence of a venous ulcer, patients were classified as having severe PTS if they had a score of 15 or more on two consecutive visits, at least three months apart. A total score of 5 to 14 on two consecutive visits, at least three months apart, indicated mild PTS. All other patients, including those who had a score higher than 4 on a single examination, were interpreted as not having a post-thrombotic syndrome.

An independent adjudication committee, whose members were not involved in the clinical assessments and who were unaware of treatment allocation, evaluated the scoring forms at the end of follow-up and classified the outcome status of the patients.

Compliance, adverse effects, and cointerventions

Patients were asked to document their use of the CES, the occurrence of side-effects, and cointerventions. For this purpose, they were instructed to report every day on a booklet the duration they wore the assigned stocking, use of not permitted stockings, occurrence of possible adverse effects (such as itching, erythema, or other forms of allergic reaction), use of analgesic or anti-inflammatory drugs (including aspirin), and to bring it to the study physicians on the day of visits. Compliance was defined as satisfactory if stockings were reportedly used for at least 70% of daytime.
Analysis

Based on the assumption that the overall 3-year rate of PTS would be around 30% in the below-knee group, 313 patients would be required in each group to give a power of 0.80 and a two-sided significance level of 0.05 for the detection of 33% risk reduction (from 30 to 20%) with the thigh-length CES.

An interim analysis was planned after inclusion of approximately 250 patients to review these assumptions. Based on the obtained findings (HR 0.93; 95% CI, 0.62 to 1.41) the assumed reduction in the rate of overall PTS with the use of full-length CES was deemed unlikely to be achieved. Indeed, a sample size of 3951 patients in each group would have been necessary to confer a statistically significant value to the observed trend in favor of the full-length garments. Thus, continuation of the study was deemed futile and inclusion of patients was stopped.

The primary analysis was conducted on an intention-to-treat basis. Cumulative incidences of PTS were calculated according to Kaplan-Meier. Patients were censored after the last visit in case of loss to follow up or death. Hazard ratios (HR) and their 95% confidence interval (CI) for the effects of thigh-length vs below-knee CES were calculated using Cox’s regression models and adjusted for age, gender, clinical presentation of DVT (unprovoked or secondary) and extent of the index thrombotic episode (popliteal only or common femoral vein [with or without the involvement of the popliteal vein]).
The chi-square test was used for comparison of compliance and tolerability. P-values lower than 0.05 were regarded as statistically significant.

All calculations were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

Patients

Between October 2005 and September 2007, 363 potentially eligible patients with acute proximal DVT were considered for inclusion. Of these, 89 were excluded because of poor life expectancy (n=36), previous ipsilateral DVT (n=22), pre-existing leg ulcers or venous insufficiency (n=13), current use of elastic stockings (n=11), bilateral thrombosis (n=4) or known skin reactions to elastic stockings (n=3). Of the remaining 274 patients, 267 (97%) agreed to participate and were randomized to the thigh-length (n=135) or below-knee (n=132) CES. The baseline characteristics of the patients in the two treatment arms were similar (Table 1). Figure 1 shows a flow diagram that maps inclusion and progress of study participants.

During the study period, 11 patients were lost to follow-up (8 in the thigh-length and 3 in the below-knee study group), and 31 died (14 in the thigh-length, and 17 in the below-knee study group, respectively). In none of the patients death was attributed to PE. The average duration of follow-up was 32.5 + 8.3 months in the thigh-length, and 32.6 + 8.2 months in the below-knee group.
During the study period, 12 patients in each group (8.9% in the thigh-length and 9.0% in the below-knee group) developed non-fatal recurrent VTE, with the involvement of the initially affected leg in 6 and 9 patients, respectively.

Post-thrombotic syndrome
Post-thrombotic sequelae developed in 44 of the 135 (32.6%) patients (severe in 3) assigned to thigh-length, and in 47 of the 132 (35.6%) patients allocated to below-knee CES (severe in 3), a difference of 3% (95% CI -14.2 to 8.3). The cumulative incidence of the PTS after three years was 33.9% (95% CI, 25.7 to 42.1) in the thigh-length and 36.7 % (95 CI%, 28.3 to 45.2) in the below-knee group (Figure 2). The HR for the PTS in the thigh-length as compared to the below-knee group was 0.92 (95% CI, 0.61 to 1.38). After adjustment for the baseline characteristics, the HR remained unchanged (0.93; 95% CI, 0.62 to 1.41).

Among patients with the DVT involving the popliteal vein alone 19 (of 51, 37.3%) developed PTS in the thigh-length and 23 (of 64, 35.9%) in the below-knee group  (HR 1.01; 95% CI, 0.55 to 1.85), while these incidences were 25 (of 84, 29.8%) and 24 (of 68, 35.3%), respectively, among patients with a more proximal location of DVT (HR 0.86; 95% CI, 0.49 to 1.51).

Adverse effects, compliance, and cointerventions
Stockings-related side-effects (i.e. itching, erythema, or other forms of allergic reaction) developed in 55 (40.7%) of the 135 patients
allocated to the thigh-length CES, and in 36 (27.3%) of those randomized to the below-knee group (p=0.017), and led to premature discontinuation of their use in 29 (21.5%) and 18 (13.6%) patients, respectively (p=0.11).

Compliance was good in 90 of 135 patients (66.7%) in the thigh-length CES group versus 109 of 132 patients (82.6%) in the below-knee CES group (p=0.003). When the analysis was confined to patients who did not prematurely discontinue the use of their stocking, compliance was good in 79 of 106 patients (74.5%) in the thigh-length, and in 97 of 114 (85.1%) in the below-knee group (p=0.063). Among the 199 patients who were compliant with their CES, the adjusted HR for PTS was 1.1 (95% CI 0.69 to 1.76).

Analgesic and/or anti-inflammatory drugs were used for variable periods of time (ranging between few days and three weeks) by 10 patients belonging to the thigh-length group and 7 allocated to the below-knee study group.

Of the patients allocated to the thigh-length group, oral anticoagulants were administered for up to six months in 88 (65.2%) and for longer periods in the remaining 47; the corresponding figures in the below-knee group were 88 (66.7%) and 44, respectively. The quality of oral anticoagulant treatment was similar in both groups; an INR within or above the targeted therapeutic range (INR, 2-0-3.0) on at least 70% of measurements was reached in 90 (66.7%) patients allocated to thigh-length and 88 (66.7%) patients belonging to the below-knee CES group.
Discussion

Despite appropriate anticoagulant therapy, 25 to 50% of patients develop long-term post-thrombotic sequelae after an episode of DVT.\textsuperscript{12} Established PTS remains a significant cause of chronic illness, with considerable socio-economic consequences for both patients and health care providers.\textsuperscript{13,14} Among factors that have been found to be associated with an increased risk of PTS are proximal location of the initial thrombosis – especially the ilio-femoral location, the development of recurrent ipsilateral DVT and the inadequacy of oral anticoagulant therapy.\textsuperscript{9,15,16} The incidence of the PTS is reduced by use of graduated compression stockings.\textsuperscript{1,8,9} However, uncertainty remains about the choice of the most suitable type of stocking, as in proper studies on the value of elastic stockings for prevention of PTS only below-knee stockings were used.\textsuperscript{8,9} Thigh-length CES are generally perceived as more effective, especially in patients with the most proximal involvement of the venous system,\textsuperscript{4} but are more expensive and may not be as practical and tolerable as the below-knee CES. In order to assess the relative role of these two types of garments, we decided to conduct a head-to-head comparison.

We failed to show any advantage of the thigh-length over the below-knee stockings. After completion of the 3-year follow-up, PTS developed in 32.6% of patients randomized to thigh-length and in 35.6% allocated to below-knee stockings, for an adjusted HR of 0.93 (95% CI, 0.62 to 1.41). Although the confidence intervals are relative wide and potentially allow for a 30 to 40% reduction in the
incidence of PTS in patients wearing the thigh-length CES, such a reduction is unlikely, due to the point estimates, that are close to unity. Even when the analysis was confined to patients compliant with their stocking and to those with the involvement of the common femoral vein, no benefit of thigh-length over below-knee stockings was observed (HR 1.1, 95% CI 0.69 to 1.76; and 0.86; 95% CI, 0.49 to 1.51, respectively).

The slight difference in the proportion of patients allocated to below-knee stockings who developed PTS between this (35%) and our previous investigation (25%)\(^9\) most likely reflects the difference in patients’ age. Age was indeed found to be an important predictor of PTS development,\(^9,17\) and in the current investigation patients’ age (mean, 67 to 69) was substantially higher than that (mean, 60 to 63) recorded in the previous one. Interestingly enough, in both studies the rate of severe PTS was consistently low.

Not unexpectedly, the thigh-length stockings were significantly less well tolerated. Indeed, a higher proportion of patients allocated to thigh-length CES developed stockings-related side-effects (40.7 vs 27.3%), which led to premature discontinuation in 21.5 and 13.6%, respectively. In addition, only 67% of the patients allocated to thigh-length CES used their garments for at least 70% of daytime, as compared to 83% of patients allocated to the below-knee CES.

Some methodological issues require comment. Only patients with proximal DVT who were admitted to hospital departments were eligible for the current investigation, hence not necessarily can the
study conclusions be generalized to those patients who are managed entirely out of hospital. Because of the open design of the study, precautions were taken to avoid bias in the assessment of the PTS. Therefore, an investigator who was not involved in the care of the patient and who was unaware of previous findings, assessed the patient and completed the scale for PTS. For this purpose, patients were instructed not to wear their garments on the day of assessment and not to disclose information on treatment allocation to the assessor. Another physician independently collected information on protocol compliance at each follow-up visit. In addition, a blinded adjudication committee evaluated the scoring forms at the end of follow-up. Finally, the length of CES use (two years) was decided in agreement with the latest ACCP guidelines, and the diagnosis of the PTS was based on a validated scale, which has a good correspondence with patient's perception of quality of life and has a high reproducibility.

Below-knee CES should be regarded as the stockings of choice for prevention of the PTS in patients with proximal DVT. Indeed, they have similar effectiveness as thigh-length stockings, while having a better tolerability and lower cost. Indeed, the below-knee garments that were used in this study are currently marketed in Europe at the price of approximately €42 as compared to €75 (that is, 56% less expensive) for the thigh-length ones.

Although a considerable proportion of patients wearing below-knee stockings still develop the PTS, the rate of severe sequelae is acceptably low. Whether aggressive treatment of the initial
thrombosis can further decrease the PTS rate remains to be demonstrated, as does the assessment of the optimal duration of elastic stockings for its prevention.

**Authors contribution**

P. Prandoni, S. Villalta, A.W.A. Lensing and M.H. Prins designed the study and wrote the paper. R. Quintavalla, C. Bova, B. Cosmi, S. Siragusa, E. Bucherini, F. Astorri, S. Cuppini and F. Dalla Valle recruited the study patients. F. Noventa and M.H. Prins analyzed data. P. Prandoni was the responsible for administrative, technical and logistic support. All the authors agreed on the final version of the manuscript.

**Potential financial conflicts of interest**

None disclosed.

**Role of the Funding Source**

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.
References


**Additional Investigators of the Canano Study** (all in Italy), in the order of contributed patients: V. Vedovetto, S. Barbar, E. Campello, M. Milan, L. Filippi (Padova, 69); A. Rocci (Parma, 59); P. Chiappetta, R. Pellegrini, E. Fiaschi, G. Vallone, E. D' Amico, A. Noto (Cosenza, 30); C. Pili, E. Costantini, M. Gasperon, G. Palareti (Bologna, 28); A. Malato, G. Saccullo (Palermo, 23); F. Ventura, C. Brini (Faenza, 21); G. Bitti (Fermo, 20); M. Marzolo, E. Ramazzina, S. Zamboni (Rovigo, 17).
Table 1. Main characteristics of the study patients

<table>
<thead>
<tr>
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<th>Thigh-length CES (n=135)</th>
<th>Below-knee CES (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (mean, range)</td>
<td>67 (20-94)</td>
<td>69 (21-90)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>69 (51.1)</td>
<td>73 (55.3)</td>
</tr>
<tr>
<td><strong>Obesity (BMI &gt; 30)</strong></td>
<td>26 (19.2)</td>
<td>28 (21.2)</td>
</tr>
<tr>
<td><strong>Thrombophilia</strong> in tested</td>
<td>30/93 (32.3)*</td>
<td>25/89 (28.1)**</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unprovoked</td>
<td>80 (59.3)</td>
<td>82 (62.1)</td>
</tr>
<tr>
<td>Secondary</td>
<td>55 (39.6)</td>
<td>50 (37.9)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent trauma or surgery</td>
<td>22 (16.3)</td>
<td>16 (12.1)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12 (8.9)</td>
<td>15 (11.4)</td>
</tr>
<tr>
<td>Medical diseases</td>
<td>12 (8.9)</td>
<td>14 (10.6)</td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td>7 (5.2)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Pregnancy or puerperium</td>
<td>2 (1.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><strong>Location of DVT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Popliteal only</td>
<td>51 (37.8)</td>
<td>64 (48.5)</td>
</tr>
<tr>
<td>Common femoral (with or without popliteal)</td>
<td>84 (62.2)</td>
<td>68 (51.5)</td>
</tr>
<tr>
<td><strong>DVT treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH/VKA***</td>
<td>124 (91.9)</td>
<td>120 (90.9)</td>
</tr>
<tr>
<td>UFH/VKA</td>
<td>11 (8.1)</td>
<td>12 (9.1)</td>
</tr>
<tr>
<td>VKA duration, months</td>
<td>10.3 + 9.2</td>
<td>9.6 + 8.6</td>
</tr>
<tr>
<td>(mean + SD)</td>
<td></td>
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</tbody>
</table>
LMWH=low-molecular-weight heparin; UFH=unfractionated heparin; VKA=vitamin K antagonists. Numbers in parentheses are percentages, unless otherwise indicated
* FVL in 11 patients, PTM in 10, APL in 4, deficiency in AT in 2, deficiency in prot  S in 1, and combined abnormalities in 2; ** FVL in 11 patients, PTM in 7, APL in 4, and combined abnormalities in 3; *** 11 patients with cancer in each group were treated with LMWH mono-therapy
Legenda of the two figures:

Figure 1. *Flow diagram of the study*

Figure 2. *Cumulative incidence of the post-thrombotic syndrome in the two study groups*
Figure 1

Eligible patients
N = 363

Patients excluded (N = 96)
- life expectancy < 6 mo. 36
- previous ipsilateral DVT 22
- venous insufficiency 13
- current use of stockings 11
- bilateral DVT 4
- allergy to stockings 3
- refusal of consent 7

Randomized patients
N = 267

Thigh-length CES
N = 135
Died 14
Lost 8
Rec. VTE 12

Below-knee CES
N = 132
Died 17
Lost 3
Rec. VTE 12

Overall PTS 44
Severe PTS 3

Overall PTS 47
Severe PTS 3
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