Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

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Summary

Background **Post-thrombotic syndrome (PTS) is a common and burdensome complication of deep venous thrombosis (DVT). Previous trials suggesting benefit of elastic compression stockings (ECS) to prevent PTS were small, single-centre studies without placebo control. We aimed to assess the efficacy of ECS, compared with placebo stockings, for the prevention of PTS.**

Methods **We did a multicentre randomised placebo-controlled trial of active versus placebo ECS used for 2 years to prevent PTS after a first proximal DVT in centres in Canada and the USA. Patients were randomly assigned to study groups with a web-based randomisation system. Patients presenting with a first symptomatic, proximal DVT were potentially eligible to participate. They were excluded if the use of compression stockings was contraindicated, they had an expected lifespan of less than 6 months, geographical inaccessibility precluded return for follow-up visits, they were unable to apply stockings, or they received thrombolytic therapy for the initial treatment of acute DVT. The primary outcome was PTS diagnosed at 6 months or later using Ginsberg's criteria (leg pain and swelling of ≥1 month duration). We used a modified intention to treat Cox regression analysis, supplemented by a prespecified per-protocol analysis of patients who reported frequent use of their allocated treatment. This study is registered with ClinicalTrials.gov, number NCT00143598, and Current Controlled Trials, number ISRCTN71334751.**

Findings **From 2004 to 2010, 410 patients were randomly assigned to receive active ECS and 396 placebo ECS. The cumulative incidence of PTS was 14·2% in active ECS versus 12·7% in placebo ECS (hazard ratio adjusted for centre 1·13, 95% CI 0·73–1·76; p=0·58). Results were similar in a prespecified per-protocol analysis of patients who reported frequent use of stockings.**

Interpretation **ECS did not prevent PTS after a first proximal DVT, hence our findings do not support routine wearing of ECS after DVT.**

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Introduction

Post-thrombotic syndrome (PTS) is a chronic disorder that develops in 25–50% of patients after deep venous thrombosis (DVT).[1,2] Its clinical features range from minor limb swelling and discomfort to severe leg pain, intractable oedema, irreversible skin changes, and leg ulceration. PTS reduces quality of life[3,4] and imposes a substantial economic burden on patients and society.[5,6]

Prevention of PTS is important since treatments are not very effective.[7,8] Ideally, PTS is averted entirely by primary prevention of the initial DVT with the judicious use of thromboprophylaxis. However, thromboprophylaxis remains underused and the occurrence of at least half of all cases of DVT are unpredictable, hence are not preventable. Therefore, prevention of PTS after DVT is an important goal.

Elastic compression stockings (ECS) have the potential to prevent PTS by reducing venous hypertension and reflux, which are thought principal factors in the pathophysiology of PTS.[9] The findings of two previous randomised trials[10,11] suggested that wearing ECS for 2 years after proximal DVT halved the risk of developing PTS. However, both trials were small, done in a single centre, and were not placebo-controlled. Stockings are cumbersome to apply, and can be hot, constricting, and itchy. They can cost $100 or more per pair, need to be replaced twice a year due to wear and tear, and might not be covered by public health care plans. Furthermore, a survey of thrombosis physicians showed a lack of agreement on the benefits of ECS or the optimum timing, indication, and duration of their use.[12] In view of the above, we believed that a large, placebo-controlled trial was needed to provide definitive evidence of efficacy, or lack of efficacy, of ECS. This would allow physicians to make informed, evidence-based decisions on the use of compression stockings in patients with DVT. We therefore did the SOX trial, a multicentre, randomised, placebo-controlled trial to establish whether ECS prevent PTS after proximal DVT. We also assessed the effect of ECS on severity of PTS, recurrent venous thromboembolism, venous valvular reflux, and quality of life.

Methods

Participants

Between June, 2004, and February, 2010, we enrolled patients in 24 centres in Canada and the USA. The study originally had a two by two factorial design that tested a second intervention, celecoxib versus placebo taken twice-daily for 30 days. Because of concerns about the safety of COX-2 inhibitors[13] it was decided to abandon this intervention after 26 patients were enrolled and redesign the study as a parallel group trial of active versus placebo ECS.[14]

Patients presenting with a first symptomatic, proximal DVT (with or without concurrent distal DVT or pulmonary embolism) were potentially eligible to participate. Proximal DVT, which was defined as DVT in the popliteal or more proximal deep leg veins, had to be objectively confirmed with ultrasound within the previous 14 days. Patients were excluded if they had a contraindication to the use of compression stockings (eg, allergy or severe arterial claudication), an expected lifespan of less than 6 months, geographical inaccessibility precluding return for follow-up visits, were unable to apply stockings, or received thrombolytic therapy for the initial treatment of acute DVT. The study was approved by the research ethics boards at all participating centres, and written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned to study groups with a web-based randomisation system (TrialStat, Jubilant Clinsys, Ottawa, ON, Canada), which ensured concealed allocation. Randomisation was stratified by centre and used varying block sizes of four and eight. At randomisation, an alert was sent to the stocking manufacturer's central distribution centre (Sigvaris, St Laurent, QC, Canada) with the patient's treatment code, leg measurements, and mailing address. A pair of active or placebo stockings was then shipped directly to the patient. This procedure was repeated during follow-up.

Treatment allocation was masked from patients, health-care providers, study personnel, and study statisticians. To assess masking, the patient, health-care providers, and study personnel were asked to state at the end of the study which treatment they believed the patient had been assigned to receive: active ECS, placebo ECS, or uncertain.

Procedures

Patients were randomly assigned to receive active 30–40 mm Hg graduated ECS or placebo stockings with an identical appearance but less than 5 mm Hg compression at the ankle (appendix). Stockings were applied within 2 weeks of DVT diagnosis and were replaced every 6 months, or earlier if stockings had torn or leg size had

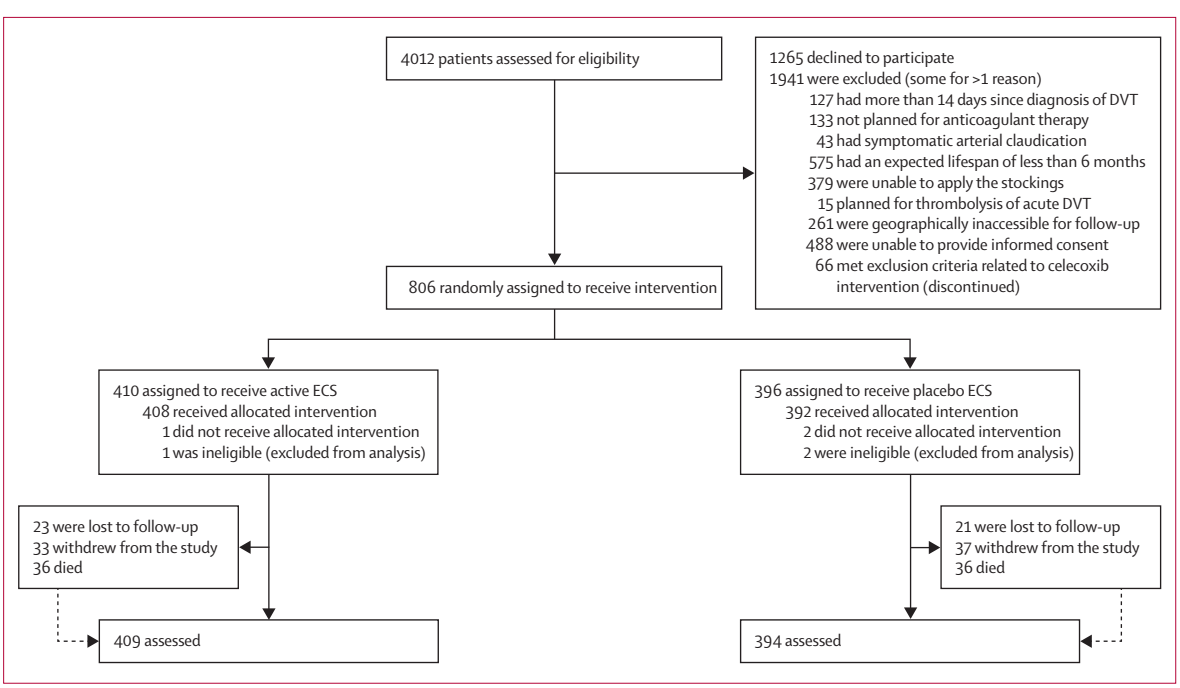

Figure 1: **Trial profile**

Three patients were ineligible and excluded from the analysis (in the active ECS group, one patient had no DVT [did not receive study stockings] and in the placebo ECS group, one patient had previous DVT [did not receive study stockings] and one was moribund [received study stockings]). Three patients did not receive their allocated intervention. Because of leg shape, one patient in each group could not be fitted with stockings; they did not receive stockings but continued in the trial. One patient in the placebo ECS group received active ECS at the baseline visit due to an error at the stockings distribution centre—the patient insisted on using the same type of stockings throughout the trial without knowing if it was active or placebo. ECS=elastic compression stockings. DVT=deep venous thrombosis.

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See **Online** for appendix

changed. Patients were asked to wear the stocking on the affected leg from waking until retiring for 2 years, and were encouraged to keep active.

Co-interventions (anticoagulants, non-steroidal anti-inflammatory drugs) and use of non-study stockings were recorded at each study visit. Data on results of international normalised ratio tests were not collected.

	Active stockings group (n=409)	Placebo stockings group (n=394)
Age, years	55·4 (15·3)	54·8 (15·8)
Age category		
<40 years	67 (16·4%)	67 (17·0%)
40–65 years	222 (54·3%)	217 (55·1%)
>65 years	120 (29·3%)	110 (27·9%)
Men	255 (62·4%)	228 (57·9%)
Outpatients	355 (86·8%)	344 (87·3%)
White ethnic origin	371 (90·7%)	354 (89·9%)
Body-mass index, kg/m²	29·0 (6·1)	28·9 (6·1)
Time from DVT diagnosis to randomisation, days	4·8 (4·1)	4·6 (3·8)
Characteristics of DVT		
Right	180 (44·0%)	173 (43·9%)
Left	222 (54·3%)	216 (54·8%)
Bilateral	7 (1·7%)	5 (1·3%)
Most proximal extent of DVT*		
Iliac vein	44 (10·8%)	49 (12·4%)
Common femoral vein	109 (26·7%)	107 (27·2%)
Femoral vein	128 (31·3%)	123 (31·2%)
Popliteal vein	128 (31·3%)	115 (29·2%)
Villalta score at baseline	8·2 (4·4)	8·7 (4·8)
Concurrent pulmonary embolism	57 (13·9%)	57 (14·5%)
Venous thrombosis risk factors		
Surgery, past 3 months	77 (18·8%)	64 (16·2%)
Trauma, past 3 months	42 (10·3%)	51 (12·9%)
Immobilised in past month	67 (16·4%)	61 (15·5%)
Active cancer†	52 (12·7%)	46 (11·7%)
Pregnant, post partum, oral contraceptives, or hormonal replacement therapy‡	37 (24·0%)	55 (33·1%)
Family history of venous thromboembolism	85 (20·8%)	82 (20·8%)
DVT treatment		
Low molecular weight heparin	388 (94·9%)	384 (97·5%)
Unfractionated heparin	31 (7·6%)	21 (5·3%)
Warfarin	330 (80·7%)	317 (80·5%)
Investigational anticoagulant§	15 (3·7%)	11 (2·8%)
Duration of heparin, days	8 (6–11)	8 (6–10)
Duration of warfarin, days	186 (113–240)	180 (100–214)
Duration of investigational anticoagulant§, days	189 (183–647)	205 (182–546)
Duration of oral anticoagulation (warfarin or investigational), days	186 (113–253)	182 (104–220)

Data are n (%), mean (SD), or median (IQR). DVT=deep vein thrombosis. *In the case of bilateral DVT, the leg with the most proximally extensive DVT was used as the index leg. †Diagnosed within past 6 months, treatment ongoing, metastatic, or palliative. ‡In women only (active ECS, 154 women; placebo ECS, 166 women). §Some patients were participants in concurrent studies comparing investigational anticoagulants (oral dabigatran, oral rivaroxaban, or subcutaneous idraparinux) with standard anticoagulation.

Table 1: **Baseline characteristics**

Patients attended follow-up visits at 1, 6, 12, 18, and 24 months, and were instructed to not wear study stockings to the visits. Visits were scheduled in the afternoon when possible to allow PTS signs to become fully evident. Frequency of stocking use between visits was recorded (number of days per week [response options were every day, 3–6 days per week, 1–2 days per week, or less than once per week] and numbers of hours per day).

In the original study protocol, the primary outcome was the proportion of patients with PTS at the 24 month study visit. Before any analyses, the study's steering committee decided to change the primary outcome to the cumulative incidence of PTS (ie, time to first event) from 6 to 24 months follow-up to optimally use all available outcome data (this change did not affect the study's sample size). PTS was diagnosed with Ginsberg's criteria of ipsilateral pain and swelling of at least 1 month's duration that are typical in character (worse at the end of the day or with prolonged sitting or standing, and better after a night's rest and leg elevation).[15] Local study investigators were required to confirm each case of PTS.

As secondary outcomes, we recorded cumulative incidence and severity of PTS with Villalta's scale, that grades the intensity (0 points=absent, 1=mild, 2=moderate, 3=severe) of five patient-rated symptoms (pain, cramps, heaviness, pins and needles, and itching) and six physical signs (pretibial oedema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, and redness).[16–18] The presence of leg ulcers was also recorded. Physical signs were assessed by study nurses or physicians with the aid of a full-colour visual guide.[18] A higher total Villalta's score suggests greater severity of PTS (a score ≥5 or a venous ulcer suggests PTS; score of 5–9, mild PTS; 10–14, moderate PTS; >15 or venous ulcer, severe PTS).

Additional secondary outcomes included objectively confirmed recurrent venous thromboembolism, death, adverse events, venous valvular reflux, and quality of life. All suspected recurrent venous thromboembolism events and deaths were independently adjudicated by two physicians from whom treatment allocation was masked (for diagnostic criteria see appendix). Adverse events were classified as likely or unlikely to be due to study stockings. Venous valvular reflux at the popliteal vein was assessed as present or absent at the 12 month visit with a standardised venous ultrasound procedure (for description of procedure see appendix).[19,20] Quality of life was measured at each study visit with validated generic (SF-36)[21] and venous-disease specific (VEINES-QOL/Sym)[22,23] questionnaires.

Statistical analysis

We estimated that the cumulative incidence of the primary outcome would be 30% in the placebo ECS group and 20% in the active ECS group over the 2 year follow-up—ie, a risk reduction of 33%.[15,24] These event rates were

converted into exponential distribution instantaneous hazard rates and the corresponding sample size was obtained by use of the approach of Schoenfeld and Richter,[25] as implemented by the program PS Power and Sample Size.[26] The total sample size needed to detect a difference between groups with a two-tailed α of 0·05 and 80% power was 800, which included adjustment for a projected 25% rate of loss-to-follow up, including deaths.

The Data Safety Monitoring Board regularly reviewed study recruitment, patient retention, and safety outcomes. A single, planned, formal masked interim analysis to consider early stopping for efficacy was done after 364 patients completed follow-up, and employed a Lan-DeMets α-spending approach using an O'Brien-Fleming spending function.[27] Based on the results of this analysis, the Data Safety Monitoring Board recommended that patient recruitment should continue to complete the originally planned sample size of 800 patients.

Cumulative incidences of PTS (primary analysis) were compared in a modified intention-to-treat analysis with Cox regression adjusted for centre. Losses to follow-up, withdrawals, and deaths were censored as of last date of follow-up. This was supplemented by a prespecified per-protocol analysis of patients who reported frequent use of their allocated treatment. Patients were classified as frequent users if they used study stockings for at least 3 days per week at three or more of five study visits, or at two or more study visits if there were fewer than five visits. We did prespecified subgroup analyses by age, sex, body-mass index (BMI), and proximal extent of index DVT. In secondary analyses, we compared the cumulative incidence of PTS as assessed by a Villalta score of 5 or higher at the 6 month visit or later[18] using Cox regression adjusted for centre. For both groups, we also described severity of PTS, the proportion who developed venous ulcers, recurrent venous thromboembolism, death from venous thromboembolism, adverse events attributed to study stockings, and venous valvular reflux at 12 months. *t* tests were used to compare within-patient changes in quality of life scores from baseline to time of last follow-up. In sensitivity analyses to assess the effect of missing quality of life data, logistic regression was done to estimate the probability of missingness for each timepoint, by treatment group. Baseline variables age, sex, inpatient status, ethnicity, BMI, concurrent pulmonary embolism, trauma, surgery, immobilisation, cancer, and extent of DVT were used as independent predictors in the model. We then did a weighted analysis based on the inverse probability of missingness using a generalised estimated equation.[28] Since the results were similar to the unweighted analyses, the latter results are reported.

All statistical tests were two-sided and significance was set at $p<0·05$. Analyses were done with SAS version 9.3. This study is registered with ClinicalTrials.gov, number NCT00143598, and Current Controlled Trials, number ISRCTN71334751.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Three patients were identified as ineligible soon after randomisation and were excluded from further analysis (ie, modified intention-to-treat). Baseline characteristics were similar between the two groups (table 1). Overall, 483 (60·1%) of

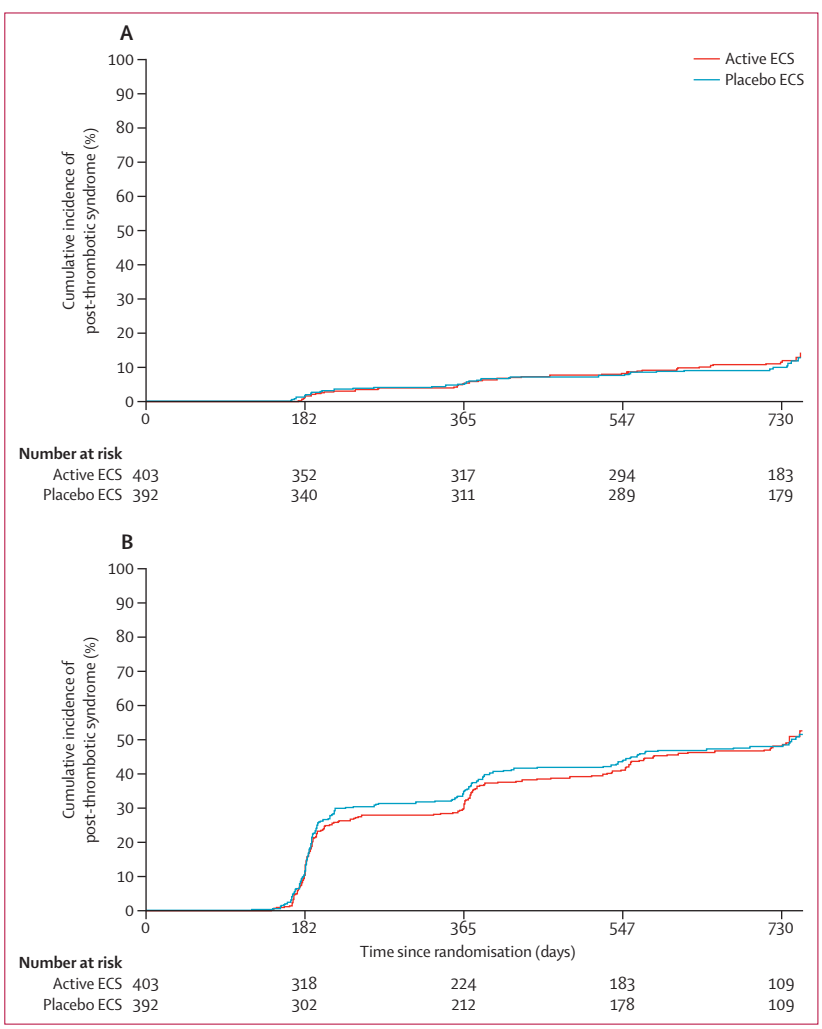

Figure 2: **Cumulative incidence of post-thrombotic syndrome**

The primary outcome (A; Ginsberg's criteria) was first assessed at the 6 month visit and each 6 months thereafter. Cumulative incidence of PTS (at 750 days) was 14·2% in active ECS versus 12·7% in placebo ECS (hazard ratio [HR] adjusted for centre 1·13, 95% CI 0·73–1·76; p=0·58). The secondary outcome (B), PTS diagnosed using Villalta's criteria, was first assessed at the 6 month visit and each 6 months thereafter. Cumulative incidence of PTS by Villalta's criteria (Villalta score ≥5 or ulcer at or after the 6 month visit; at 750 days) was 52·6% in active ECS versus 52·3% in placebo ECS (HR adjusted for centre 1·00, 95% CI 0·81–1·24; p=0·96). For both criteria, data from patients who withdrew consent or who were lost to follow-up were censored at the time of the last follow-up assessment, and patients who stopped study stockings but agreed to follow-up were included in the intention-to-treat analysis. PTS=post-thrombotic syndrome. ECS=elastic compression stockings.

803 patients were men, mean age was 55·1 years (SD 15·5), and 699 (87·1%) of 803 were outpatients. Mean time from DVT diagnosis to randomisation was 4·7 days (SD 3·9). The most proximal extent of DVT was iliac vein in 93 (11·6%) of 803 patients, common femoral vein in 216 (26·9%), femoral vein in 251 (31·3%), and popliteal vein in 243 (30·3%).

The cumulative incidence of PTS (Ginsberg's criteria) during study follow-up was 14·2% in the active ECS group versus 12·7% in the placebo ECS group (figure 2, table 2). In secondary analyses, there were no between-group differences in the cumulative incidence of PTS defined with Villalta's scale (figure 2), distribution of PTS severity category, or rate of ipsilateral leg ulcers. Rates of recurrent episodes of venous thromboembolism, ipsilateral DVT, and death were similar in both groups, as was the prevalence of ipsilateral venous valvular reflux at 12 months (table 2). Mean Villalta total scores, symptom scores, sign scores, and severity category at each study visit were similar between groups (appendix).

Generic and disease-specific quality-of-life scores were similar between groups at each visit (appendix). Within-patient changes in quality-of-life scores from baseline to last follow-up visit did not differ between groups. SF-36 physical component score improved by 8·4 points (SD 13·6) for active ECS versus 9·9 (SD 13·2) for placebo ECS (difference between groups of –1·53 points, 95% CI –3·44 to 0·39; p=0·12). SF-36 mental component score improved by 1·6 points (SD 12·3) for active ECS versus 1·8 (SD 11·4) for placebo ECS (difference of –0·23 points, 95% CI –1·94 to 1·47; p=0·79). VEINES-QOL score improved by 5·8 points (SD 7·5) for active ECS versus 5·9 (SD 7·1) for placebo ECS (difference of –0·12 points, 95% CI –1·11 to 0·86; p=0·81).

Most patients received standard anticoagulant therapy consisting of 5–10 days of heparin (usually subcutaneous low molecular weight heparin) and warfarin for 3–6 months or longer to treat their acute DVT. Median duration of anticoagulation was similar in the two groups (186 days [IQR 113–253] for active ECS and 184 days [104–220] for placebo ECS; table 1). Similar proportions of patients in each group reported taking oral anticoagulants, heparins, and non-steroidal anti-inflammatory drugs at each visit. Temporary use of non-study stockings was uncommon (appendix).

Use of study stockings at each visit was similar between groups. Overall, at 1 month, 734 (96·1%) of 764 patients reported wearing their stockings, and, of these, 660 (86·4%) of 764 used them for 3 or more days per week; this decreased to 378 (69·1%) of 547 and 304 (55·6%) of 547, respectively, by the 24 month visit. When used, stockings were worn for about 10–11 h per day (appendix).

Attendance at study visits was similar in both groups (appendix). Over the course of the study, 33 patients in

	Active stockings (n=409)	Placebo stockings (n=394)	Hazard ratio* (95% CI)
Primary outcome			
Number of post-thrombotic syndrome events as assessed by Ginsberg's criteria† (cumulative incidence‡)	44 (14·2%)	37 (12·7%)	1·13 (0·73–1·76)
Secondary outcomes			
Number of post-thrombotic syndrome events as assessed by Villalta's criteria§ (cumulative incidence‡)	176 (52·6%)	168 (52·3%)	1·00 (0·81–1·24)
Villalta severity category¶			
None (score <5)	185 (51·3%)	178 (51·4%)	··
Mild (5–9)	119 (33·0%)	111 (32·1%)	··
Moderate (10–14)	30 (8·3%)	37 (10·7%)	··
Severe (>14 or ulcer)	27 (7·5%)	20 (5·8%)	··
Ipsilateral leg ulcer‖	17 patients (4·2%); 17 ulcers	16 patients (4·1%); 17 ulcers	··
Recurrent venous thromboembolism	33 patients (8·1%); 45 events (36 DVT, 9 pulmonary embolism)	38 patients (9·6%); 44 events (32 DVT, 12 pulmonary embolism)	··
Recurrent ipsilateral DVT	16 patients (3·9%); 18 events	17 patients (4·3%); 17 events	··
Ipsilateral venous valvular reflux at 12 months**	120/291 (41·2%)	117/283 (41·3%)	··
Death††	36 (8·8%)	36 (9·1%)	··

DVT=deep vein thrombosis. *Adjusted for centre. Of the 803 patients in the intention-to-treat analysis, 795 were included in the time-to-event analysis. The eight patients (six in the active stockings group and two in the placebo stockings group) who were not included are those for whom no follow-up data were available after the baseline visit. †Pain and swelling of 1 or more month's duration that is typical in character (worse at the end of the day or with prolonged sitting or standing, and better after a night's rest and leg elevation).[15] ‡Cumulative incidence as of 750 days follow-up. §Villalta score ≥5 or ulcer at or after the 6 month visit.[16,18] ¶Highest Villalta score at or after 6 month visit (missing for 48 patients in each group). Patients with a venous ulcer whose total Villalta score was less than 15 were attributed a score of 15.[18] ‖In the active stockings group, two cases of leg ulcer were noted at the 1 month visit, six at the 6 month visit, seven at the 12 month visit, and two at the 24 month visit. In the placebo stockings group, five cases of leg ulcer were noted at the 1 month visit, seven at the 6 month visit, two at the 12 month visit, two at the 18 month visit, and one at the 24 month visit. **A total of 574 patients underwent ultrasound assessment for venous valvular reflux at 12 months. ††No deaths in either group were judged by investigators to be definitely or probably due to pulmonary embolism, or judged by adjudicators to be attributable (primary or contributing cause) to pulmonary embolism.

Table 2: **Outcomes by treatment group**

the active ECS group withdrew from the study (ie, did not wish further contact) compared with 37 in the placebo group and 23 were lost to follow-up compared with 21 in the placebo group.

A comparison of the cumulative incidence of PTS in patients in each group who reported frequent use of stockings (per-protocol analysis) yielded similar results (hazard ratio for primary outcome, adjusted for centre, 0·96, 95% CI 0·53–1·74; appendix). Prespecified subgroup analyses by age, BMI, and extent of DVT did not detect differences between the study groups. For sex, the test for interaction was marginally statistically significant (p=0·047), suggesting treatment benefit for women (figure 3). To explore this finding, in post-hoc analyses we assessed whether stockings use differed by sex; at each study visit, men reported more common use of stockings than women (appendix) and 286 (59·2%) of 483 men versus 162 (50·6%) of 320 women met our definition of frequent users of stockings.

There were no serious adverse events attributable to stockings in either group. Minor adverse events (rash, itching) occurred in eight patients in the active ECS group and seven patients in the placebo ECS group.

In the active ECS group, 202 (59%) of 345 patients, 300 (76%) of 394 research nurses, and 334 (87%) of 382 site investigators provided either a wrong guess or answered "uncertain" about whether patients were wearing active or placebo stockings, suggesting that they remained unaware of treatment allocation. The proportion of correct responses in the active ECS group for patients was 41% (143 of 345), research nurses 24% (94 of 394), and site investigators 13% (48 of 382).

In the placebo ECS group, 279 (83%) of 336 patients, 336 (88%) of 380 research nurses, and 341 (92%) of 371 site investigators provided either a wrong guess or answered "uncertain" about whether patients were wearing active or placebo stockings, suggesting that they remained unaware of treatment allocation. The proportion of correct responses in the placebo ECS group for patients was 17% (57 of 336), research nurses 12% (44 of 380), and site investigators 8% (30 of 371).

Discussion

Our findings show that wearing a graduated ECS did not reduce the incidence of PTS at 2 years in patients with a first proximal DVT, compared with wearing placebo stockings. Similarly, ECS did not affect the occurrence of venous ulcers, rate of recurrent venous thromboembolism, prevalence of venous valvular reflux at 12 months, or generic or venous disease specific quality of life. These findings were consistent across subgroups defined by age, BMI, and extent of DVT. We believe a true subgroup effect for sex is unlikely because the test of interaction p value was only slightly significant and the CIs surrounding the hazard ratios for men and women overlapped and crossed the null. Frequency of use of study stockings was very high initially, diminished over time, and was similar in the two groups. In a prespecified per-protocol analysis that focused on patients who used stockings more commonly, we did not identify evidence of benefit of active ECS. In post-hoc analyses, use of a more strict definition of frequent use (daily use at all study visits) similarly did not show evidence of benefit of active ECS (data not shown). Taken together, our findings suggest that ECS do not alter the natural history of development of PTS after DVT.

The cumulative incidence of PTS in both groups was lower than that reported in some previous studies. This is probably attributable to our use of Ginsberg's definition of PTS as our primary outcome, because this measure has been shown to capture more severe forms of PTS.[29] However, the incidence of PTS defined by Villalta criteria (secondary outcome) was similar in our study with that reported in previous prospective studies.[3,11,30] We did not identify that active ECS were effective using either the Ginsberg or Villalta measure's definition of PTS. We believe it is a strength of our trial that both measures were used to assess PTS, because this enhances comparability of our results with those of other studies.

Additional strengths of our trial are its large size, multicentre design, 2 year length of follow-up, and that several strategies were used to protect against bias, including randomisation with allocation concealment, use of a placebo stocking to achieve masking, and use of validated instruments to assess PTS and quality of life. Also, we measured stocking compliance throughout the study and assessed masking at the end of each patient's participation on the trial.

Limitations of our study are that 114 (14%) of 803 patients withdrew or were lost to follow-up; however, these rates were similar in the two groups and consistent with our

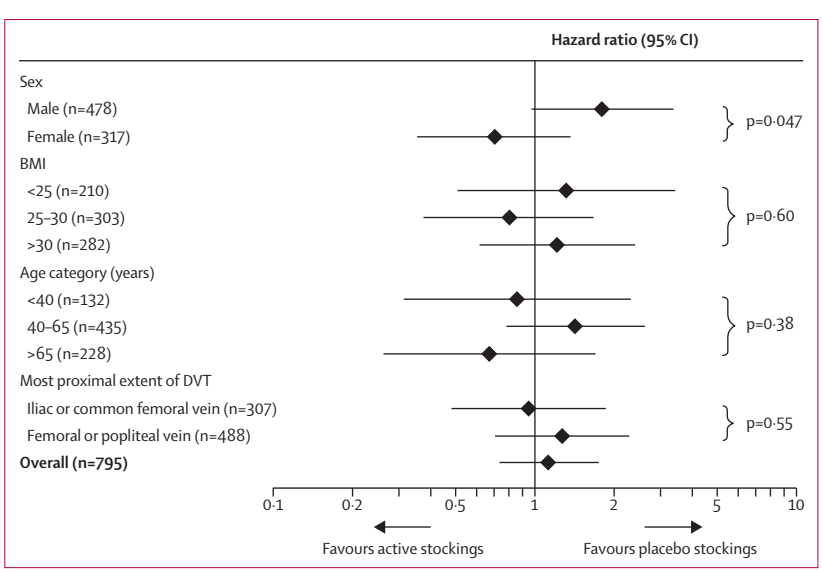

Figure 3: **Analysis of prespecified subgroups**
For all subgroup treatment effects, 95% CIs overlapped each other and the null. Test of interaction p value was p=0·047 for sex, p=0·38 for age, p=0·60 for BMI, and p=0·55 for extent of deep venous thrombosis. BMI=body-mass index.

Panel: **Research in context**

Systematic review

At the time of applying for funding of the SOX trial, in September, 2003, we did a computer database search for individual trials and systematic reviews of the use of compression stockings started early after deep venous thrombosis (DVT) diagnosis to prevent the post-thrombotic syndrome (PTS). The terms stockings, compression stockings, post-thrombotic syndrome, and post-phlebitic syndrome were used to search PubMed and the Cochrane Database of Systematic Reviews. Only one study was identified: a trial by Brandjes and colleagues[10] in which 194 patients with symptomatic proximal DVT were randomly assigned to receive daily use of knee-length custom-made 40 mm Hg elastic compression stockings (ECS), applied within 2–3 weeks of DVT diagnosis for at least 2 years, versus no stockings. Use of stockings reduced the incidence of mild to moderate PTS from 47% to 20% and of severe PTS from 23% to 11%. In 2004, after the SOX trial began, Prandoni and colleagues[11] published the results of a trial of off-the-rack 30–40 mm Hg ECS used for 2 years to prevent PTS after a first episode of proximal DVT. OF 180 patients, those randomly assigned to receive ECS had a 24·5% incidence of PTS, compared with 49·1% in controls. Both of the above trials were single centre, open-label studies. A new search of the scientific literature in May, 2013, did not identify additional published trials of ECS used early after DVT to prevent PTS.

Interpretation

In a first, large (803 patients), multicentre, placebo-controlled trial, we noted that wearing 30–40 mm Hg graduated ECS did not reduce the incidence of PTS at 2 years in patients with a first proximal DVT, compared with wearing placebo stockings. Similarly, ECS did not affect the occurrence of venous ulcers, rate of recurrent venous thromboembolism, prevalence of venous valvular reflux at 12 months, or generic or venous-disease-specific quality of life. Our findings were consistent across subgroups and among frequent ECS users. Therefore, our results do not support routine wearing of ECS after DVT to prevent PTS.

pretrial projections. Adherence to study stockings tended to diminish over follow-up, which could have affected treatment efficacy. However, the results of our per-protocol analyses focusing on frequent users and daily users, were similar to that of our intention-to-treat analysis, which increases confidence in our finding of no effect of active ECS. We acknowledge that the subgroup results must be interpreted with caution since our sample size calculation did not include the detection of subgroup effects. Although results of sensitivity analyses to account for missing quality-of-life data did not differ from complete case analysis, we acknowledge that quality of life of patients who withdrew or were lost to follow-up might have differed from those who remained in the study.

We used a number of strategies to reduce unmasking of treatment assignment. Active and placebo stockings looked identical. Study stockings were shipped directly to the patients, who were instructed to not wear them to study visits to maintain masking of allocation from assessors.[31] Most patients, research nurses, and site investigators remained unaware of treatment allocation. Although partial unmasking might have happened in the active stocking group, because two-fifths of patients correctly guessed their treatment assignment, this further reinforces rather than weakens our finding of lack of treatment effect of active ECS.

Our findings differ from those of two previous randomised trials (panel), which showed substantial benefit of 30–40 mm Hg ECS to prevent PTS after proximal DVT.[10,11] These studies were open label, single centre, and smaller than our study. In the study by Brandjes and colleagues[10] of 194 patients randomly assigned to wear a made-to-measure 40 mm Hg knee-length ECS for at least 2 years versus no stocking, mild-to-moderate PTS (assessed with a Villalta-like scale) occurred in 20% of patients versus 47%, and severe PTS in 11% versus 23%. In the study by Prandoni and colleagues[11] of 180 patients randomly assigned to wear so-called off-the-rack 30–40 mm Hg knee length ECS for 2 years versus no stocking, PTS (assessed with Villalta's scale, with positive criteria required on at least two consecutive visits) was recorded in 25% versus 49% of patients and severe PTS in 4% versus 12%. In these studies, stockings were replaced every 6 months, as in our study. The lower rates of PTS in the treatment groups than the control groups in these studies could be due to, at least in part, their open-label design. Although these previous trials masked allocations from assessors, assessment of PTS was based on both patient-reported symptoms and clinician-assessed signs. As apparent benefits of a treatment might derive from a placebo effect, which typically is strongest in measures of subjective symptoms,[32] the use of a placebo stocking control in our study was intended to account for a placebo effect of active stockings. We sought other potential reasons for differences between our results and those of the previous studies. The characteristics of patients in our trial (eg, age, sex distribution, DVT risk factors, anatomical extent of DVT, and duration of anticoagulation) were similar to those of the previous studies. Compliance with ECS might have been greater in the previous trials than in our study, but because of differences in how often use was measured and reported in the three studies, this is uncertain. Differences might relate to the particular brand of active ECS used in our study, but we believe this is unlikely since the compression strength used was the same as in the previous trials.

We believe it is unlikely that our trial's null results can be attributed to a therapeutic benefit of placebo ECS, because placebo stockings were manufactured to have no therapeutic effect (5 mm Hg or less at the ankle), and the 2 year cumulative incidence of Villalta-defined PTS in both the active and placebo stockings groups in our study was similar to that in the control arms of the previous trials that reported benefit of stockings.[10,11]

We believe that our results are generalisable to the broad population of patients with proximal DVT in whom use of ECS would be considered. As noted above, the characteristics of patients in our trial were similar to those of the previous ECS trials[10,11] and to published cohorts and population-based studies of patients with DVT.[2,33]

Our findings that ECS started at the time of acute DVT do not prevent PTS are consistent with a small randomised trial that used ECS 1 year after proximal

DVT and identified no difference in rates of PTS compared with wearing a sham stocking that was one to two sizes too large.[15] Similarly, in patients with proximal DVT who wore ECS for 6 months and were then randomly assigned to stopping stockings or using them for an additional 18 months, there was no difference in rates of PTS at 2 years.[34] Although these and our results suggest that ECS might not affect the natural history of PTS development after DVT, whether compression stockings might be of benefit to improve symptoms of established PTS or of acute DVT warrants assessment in future studies.

Contributors

SRK was involved in study design, data collection, data interpretation, writing, and critical review and final approval of the report. PSW, MAR, MJK, DRA, VT, and JSG were involved in study design, data collection, and critical review and final approval of the report. SSh was involved in study design, data analysis, data interpretation, and critical review and final approval of the report. AHH was involved in data collection, data analysis, data interpretation, writing, and critical review and final approval of the report. TD and CH were involved in data analysis, data interpretation, and critical review and final approval of the report. MJ, SSo, M-JM, EY, RSm, SSc, JK, CK, IC, TW, CD, RH, SK, RSe, SR, SD, LO, and TLO were involved in data collection and critical review and final approval of the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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