Randomized Placebo Controlled Trial of Compression Stockings to Prevent the Post-Thrombotic Syndrome

Susan R. Kahn, M.D., M.Sc., Stan Shapiro, Ph.D., Philip S Wells, M.D., M.Sc., Marc A. Rodger, M.D., M.Sc., Michael J. Kovacs, M.D., David R Anderson, M.D., Vicky Tagalakis, M.D., M.Sc., Adrielle H Houweling, M.Sc., Thierry Ducruet, M.Sc., Christina Holcroft, Sc.D., Mira Johri, Ph.D., MPH, Susan Solymoss, M.D., Marie-José Miron, M.D., Erik Yeo, M.D., Reginald Smith, Pharm D, Sam Schulman, M.D., Ph.D., Jeannine Kassis, M.D., Clive Kearon, MB, Ph.D., Isabelle Chagnon, M.D., Turnly Wong, M.D., Christine Demers, M.D., Rajendar Hanmiah, M.D., Scott Kaatz, D.O., M.Sc., Rita Selby, MBBS, M.Sc., Suman Rathbun, M.D., Sylvie Desmarais, M.D., Lucie Opatrny, M.D., M.Sc., M.H.C.M., Thomas L. Ortel , M.D., Ph.D. and Jeffrey S. Ginsberg, M.D. for the SOX Trial investigators

Corresponding author: Susan R. Kahn, MD MSc, Centre for Clinical Epidemiology, Jewish General Hospital, 3755 Cote Ste. Catherine Room H420.1, Montreal QC CANADA H3T 1E2

susan.kahn@mcgill.ca

Published

Kahn, S. R., S. Shapiro, et al. (2014). "Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial." The Lancet 383(9920): 880-888.

Authors' affiliations: See next page

Funding: Funded by Canadian Institutes of Health Research (MCT 63142, MOP 102610), with active and placebo stockings provided as in-kind support by Sigvaris.

Word count, abstract: 267

Word count, manuscript: 4061

Trial registration: clinicaltrials.gov (NCT00143598) and Current Controlled Trials (ISRCTN71334751)

Key words: randomized controlled trial; deep vein thrombosis; elastic compression stockings; post-thrombotic syndrome; quality of life; device trial; placebo control; sham device

Authors' affiliations

Susan R Kahn, MD MSc: Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

Stan Shapiro, PhD: Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada; Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada

Philip S Wells, MD MSc: Department of Medicine, University of Ottawa/Ottawa Hospital, Ottawa, ON Canada; Ottawa Hospital Research Institute, Ottawa, ON Canada

Marc A Rodger, MD MSc: Thrombosis Program, Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; Ottawa Hospital Research Institute, Ottawa, ON, Canada

Michael J Kovacs, MD: Division of Hematology, London Health Sciences Centre, London, ON, Canada

David R Anderson, MD: Department of Medicine, Dalhousie University, Halifax, NS, Canada; Capital Health, Halifax, NS, Canada

Vicky Tagalakis, MD MSc: Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

Adrielle H Houweling, MSc: Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

Thierry Ducruet, MSc: Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

Christina Holcroft, ScD: The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA; Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts, USA

Mira Johri, PhD MPH: International Health Unit (USI), University of Montreal Hospital Research Centre (CR-CHUM), Montreal, QC, Canada; Department of Health Administration, Faculty of Medicine, University of Montreal, Montreal, QC, Canada

Susan Solymoss, MD: Division of Hematology, Montreal General Hospital, Montreal, QC, Canada; St. Mary's Hospital, Montreal, QC, Canada

Marie-José Miron, MD: Department of Medicine, Hôpital Notre-Dame, Montreal, QC, Canada

Erik Yeo, MD: Division of Hematology, University Health Network, Toronto, ON, Canada

Reginald Smith, Pharm D: Divisions of Cardiology and Thrombosis, Victoria Heart Institute Foundation, Victoria, BC, Canada

Sam Schulman, MD PhD: Department of Medicine, McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; Karolinska Institute, Stockholm, Sweden

Jeannine Kassis, MD: Division of Hematology, Hôpital Maisonneuve-Rosemont, QC, Canada

Clive Kearon, MB PhD: Department of Medicine, McMaster University, Hamilton, ON, Canada.

Isabelle Chagnon, MD: Department of Medicine, Hôpital du Sacré-Coeur, University of Montreal, Montreal, QC, Canada

Turnly Wong, MD: Department of Medicine, St. Boniface General Hospital, University of Manitoba, Winnipeg, Manitoba, Canada

Christine Demers, MD: Division of Hematology, CHU de Quebec, Quebec, QC, Canada

Rajendar Hanmiah, MD: Division of General Internal Medicine, St. Joseph's Hospital, Hamilton, ON, Canada

Scott Kaatz, DO MSc: Academic Hospital Medicine, Hurley Medical Center, Flint, Michigan, USA

Rita Selby, MBBS, FRCPC, MSc: Departments of Medicine and Clinical Pathology, Sunnybrook Health Sciences Centre & University Health Network, University of Toronto, Toronto, ON, Canada

Suman Rathbun, MD: Department of Medicine, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, USA

Sylvie Desmarais, MD: Department of Medicine, Hôpital Pierre-Boucher, Longueuil, QC, Canada

Lucie Opatrny, MD MSc MHCM: Vice-President Professional Services, St. Mary's Hospital Center, Montreal, QC, Canada

Thomas L Ortel, MD PhD: Division of Hematology, Duke University Medical Center, Durham, North Carolina, USA

Jeffrey S Ginsberg, MD: Department of Medicine, McMaster University, Hamilton, ON, Canada

ABSTRACT

Background: The post-thrombotic syndrome (PTS) is a frequent and burdensome complication of deep venous thrombosis. Previous trials suggesting benefit of elastic compression stockings (ECS) to prevent PTS were small, single-center studies without placebo control. We studied the effectiveness of ECS, compared with placebo (sham) stockings, to prevent PTS.

Methods: We conducted a multicenter randomized placebo-controlled trial of active ECS vs. placebo ECS used for 2 years to prevent PTS after a first proximal deep venous thrombosis. Active ECS were knee-length with 30-40 mm Hg compression. Placebo ECS looked identical but lacked therapeutic compression. The primary outcome was PTS diagnosed at 6 months or later using Ginsberg's criteria (leg pain and swelling of ≥1 month duration). A modified intention to treat Cox regression analysis was performed. Secondary outcomes were incidence and severity of PTS assessed with Villalta's scale, venous ulcers, venous thromboembolism recurrence, venous valvular reflux, and change in generic and disease-specific quality of life.

Findings: From 2004-2010, 410 patients were randomized to active ECS and 396 to placebo ECS. The cumulative incidence of PTS was 14·2% in active ECS vs. 12·7% in placebo ECS (HR 1·13; 95% CI 0·73, 1·76; p=0·58). Results were similar in a pre-specified per-protocol analysis of patients who reported frequent use of stockings. There were no differences between groups in any secondary outcome.

Interpretation: ECS did not prevent PTS after a first proximal deep venous thrombosis or influence severity of PTS, rate of recurrent venous thromboembolism, or quality of life.

Funding: Canadian Institutes of Health Research, with active and placebo stockings provided as in-kind support by Sigvaris.

BACKGROUND

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

Prevention of PTS is key as 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 underutilized and at least half of all cases of DVT occur unpredictably, hence are not preventable. Therefore, prevention of PTS after the occurrence of DVT is an important goal.

Elastic compression stockings (ECS) have the potential to prevent PTS by reducing venous hypertension and reflux, which are considered principal factors in the pathophysiology of PTS.[9] Two randomized trials reported that wearing ECS for two years after proximal DVT halved the risk of developing PTS.[10, 11] However, both trials were small, performed in single centers, 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 may 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 optimal timing, indication, and duration of their use.[12] In light of the above, we believed that a large, placebo-controlled trial was needed to provide definitive evidence of effectiveness, or lack of effectiveness of ECS. This would allow physicians to make informed, evidence-based decisions regarding their use in DVT patients. We therefore conducted the SOX Trial, a multicenter, randomized, placebo-controlled trial to determine whether ECS prevent PTS after proximal DVT. We also assessed the effect of

ECS on severity of PTS, recurrent venous thromboembolism (VTE), venous valvular reflux, and quality of life.

METHODS

We enrolled patients in 24 Canadian and United States centres between June 2004 and February 2010. The study was approved by the research ethics boards at all participating centres, and written informed consent was obtained from all patients.

The study originally had a 2 by 2 factorial design that tested a second intervention, celecoxib vs. 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 vs. placebo ECS.[14]

Study Population

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 have been objectively confirmed by ultrasound within the previous 14 days. Patients were excluded if they had a contraindication to the use of compression stockings (e.g. allergy or severe arterial claudication), an expected lifespan of less than 6 months, geographic inaccessibility precluding return for follow-up visits, were unable to apply stockings, or received thrombolytic therapy for the initial treatment of acute DVT.

Study Interventions

Patients were randomly assigned to active 30-40 mm Hg graduated ECS or to an identical appearing placebo (sham) stocking that had less than 5 mm Hg compression at the ankle (see web extra materials for stockings specifications and procedures to train study personnel on their sizing and use). 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 changed. Patients were asked to wear the stocking on the affected leg from waking to retiring for two years, and were encouraged to keep active.

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

Randomization and masking

Patients were randomised using a web-based randomization system (TrialStat, Jubilant Clinsys) that ensured concealed allocation. Randomization was stratified by centre and used varying block sizes of four and eight. At randomization, an alert was sent to the stocking manufacturer's central distribution centre (Sigvaris Corp; St. Laurent, QC) 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, and this procedure repeated during follow-up.

Patients, healthcare providers, study personnel and study statisticians were blinded to treatment allocation. To evaluate blinding, at the end of the study the patient, healthcare providers and study personnel were asked to indicate which treatment they believed the patient had been assigned to: active ECS, placebo ECS, or uncertain.

Study Outcomes

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 manifest more fully. Frequency of stocking use between visits was recorded (number of days per week [response options: every day; 3-6 days per week; 1-2 days per week; or less than once per week], 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. Prior to the conduct of any analyses, the study's Steering Committee decided to change the primary outcome to the cumulative incidence of PTS (i.e. time to first event) from 6 to 24 months follow-up in order to optimally use all available outcome data (this change did not affect the study's sample size). PTS was diagnosed using Ginsberg's criteria of ipsilateral pain and swelling of at least one 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 using Villalta's scale, that grades the intensity (0 points=absent, 1 point=mild, 2 points=moderate, 3 points=severe) of five patient-rated symptoms (pain, cramps, heaviness, pins and needles, itching) and six physical signs (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, redness).[16-18] The presence of leg ulcers is also documented. Physical signs were assessed by study nurses or physicians with the aid of a full-color Visual Guide.[18] A higher total Villalta's score indicates greater severity of PTS (a score ≥5 or a leg ulcer indicates PTS; score of 5–9, mild PTS; 10–14, moderate PTS; greater than 15 or venous ulcer, severe PTS).

Additional secondary outcomes included objectively confirmed recurrent VTE, death, adverse events, venous valvular reflux, and quality of life. All suspected recurrent VTE events and deaths were independently adjudicated by two blinded physicians (for diagnostic criteria, see web extra materials). 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 using a standardized venous ultrasound procedure (for description of procedure, see web extra materials).[19, 20] Quality of life was measured at each study visit using validated generic (SF-36)[21] and venous-disease specific (VEINES-QOL/Sym)[22, 23] questionnaires.

Sample Size and 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 two year follow-up, i.e. 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 following the approach of Schoenfeld and Richter,[25] as implemented by the program "PS Power and Sample Size".[26] The total sample size required to detect a difference between groups with a 2-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 blinded interim analysis to consider early stopping for efficacy was performed after 364 patients completed follow-up, and employed a Lan-DeMets alpha 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 using 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 pre-specified 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 3 or more of 5 study visits, or at 2 or more study visits, if there were fewer than 5 visits. We conducted pre-specified subgroup analyses by age, sex, body mass index, 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 VTE, death from VTE, 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 performed to estimate the probability of missingness for each time point, by treatment group. Baseline variables age, sex, inpatient status, ethnicity, body mass index, concurrent pulmonary embolism, trauma, surgery, immobilization, cancer, and extent of DVT were used as independent predictors in the model. We then conducted a weighted analysis based in the inverse probability of missingness using a generalized estimated equation.[28] Given that the results were similar to the unweighted analyses, the latter results are reported.

All statistical tests were 2-sided and significance was set at $P<0{\cdot}05$. Analyses were performed using SAS version 9·3 (SAS Institute Inc.).

Role of the funding source

The funding sources had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, in the writing of the report, or the decision to submit the paper for publication.

Susan Kahn, Thierry Ducruet, Adrielle Houweling and Christina Holcroft had complete access to the data, and Susan Kahn had final responsibility for the decision to submit the manuscript.

RESULTS

Study Population

Between June 2004 and February 2010, 806 patients were randomly assigned to active ECS (410 patients) or placebo ECS (396). Three patients found to be ineligible soon after randomization were excluded from further analysis (i.e. modified intention-to-treat) (Figure 1). Baseline characteristics were similar in the two groups (Table 1). Overall, 60·1% (483/803) of patients were male, mean age was 55·1 years (SD, 15·5) and 87·1% (699/803) were out-patients. Mean time from DVT diagnosis to randomization was 4·7 (SD 3·9) days. The most proximal extent of DVT was iliac vein in 11·6% (93/803), common femoral vein in 26·9% (216/803), femoral vein in 31·3% (251/803), and popliteal vein in 30·3% (243/803).

Outcomes

The cumulative incidence of PTS (Ginsberg's criteria) during study follow-up was 14·2% (43 events in 409 patients) in the active ECS group vs. 12·7% (38 events in 394 patients) in the placebo ECS group (hazard ratio (HR) 1·13; 95% CI 0·73–1·76; p=0·58) (Figure 2a). In secondary analyses, there were no between-group differences in the cumulative incidence of PTS defined using Villalta's scale (52·6% in active ECS vs. 52·3% in placebo ECS; HR 1·00; 95% CI 0·81–1·24; p=0·96) (Figure 2b), distribution of PTS severity category, or rate of ipsilateral leg ulcers. Rates of recurrent episodes of VTE, 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 (web extra Table S-1).

Generic and disease-specific quality of life scores were similar between groups at each visit (Table S-2). 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 (SD 13·6) points for active ECS vs. 9·9 (SD 13·2) points for placebo ECS (difference between groups of -1·53 points [95% CI -3·44–0·39; p=0·12]). SF-36 mental component score improved by 1·6 (SD 12·3) points for active ECS vs. 1·8 (SD 11·4) points for placebo ECS (difference of -0·23 points [95% CI -1·94–1·47; p=0·79]). VEINES-QOL score improved by 5·8 (SD 7·5) points for active ECS vs. 5·9 (SD 7·1) points for placebo ECS (difference of -0·12 points [95% CI -1·11– 0·86; p=0·81]).

Co-interventions

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 [interquartile range (IQR) 113, 253] in active ECS and 184 days [IQR 104, 220] in 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 infrequent (Table S-3).

Frequency of stockings use and attendance at study visits

Use of study stockings at each visit was similar between groups. Overall, at 1 month, 96·1% (734/764) of patients reported wearing their stockings, and of these, more than 80% (660/764) used them for 3 or more days per week; this decreased to 69·1% (378/547) and 55·6% (304/547), respectively, by the 24 month visit. When used, stockings were worn an average of 10-11 hours a day (Table S-4).

Attendance at study visits was similar in both groups (Table S-5). Over the course of the study, 33 patients in the active ECS group withdrew from the study (i.e. did not wish further contact) and 23 were lost to follow-up, compared with 37 and 21, respectively, in the placebo ECS group.

Per-protocol and subgroup analyses

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 (HR for primary outcome, adjusted for center, 0·96; 95% CI 0·53- 1·74) (Table S-6). Prespecified subgroup analyses by age, body mass index and extent of DVT did not detect differences between the active ECS and placebo ECS 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 frequent use of stockings than women (Table S-4a) and 59·2% (286/483) of men vs. 50·6% (162/320) of women met our definition of frequent users of stockings.

Adverse events

There were no serious adverse events attributed to stockings in either group. Minor adverse events (rash, itching) occurred in 8 patients in the active ECS and 7 patients in the placebo ECS group.

Blinding

In the active ECS group, 59% (202/345) of patients, 76% (300/394) of research nurses and 87% (334/382) of 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 percentage of correct responses in the active ECS group for patients, research nurses and site investigators were 41% (143/345), 24% (94/394) and 13% (48/382), respectively

In the placebo ECS group, 83% (279/336) of patients, 88% (336/380) of research nurses and 92% (341/371) of 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 percentage of correct responses in the placebo ECS group for patients, research nurses and site investigators were 17% (57/336), 12% (44/380) and 8%

(30/371), respectively.

DISCUSSION

We found that wearing a graduated ECS did not reduce the incidence of PTS at 2 years in patients with a first proximal DVT, compared to wearing placebo stockings. Similarly, ECS did not influence the occurrence of venous ulcers, rate of recurrent VTE, 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, body mass index and extent of DVT. We believe a true subgroup effect for sex is unlikely as the test of interaction p-value was only marginally significant and the confidence intervals 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 frequently, we did not find 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 likely to be attributable to our use of Ginsberg's definition of PTS as our primary outcome, as 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 to that reported in previous prospective studies. [3, 11, 30] We did not find 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, as this enhances comparability of our results with those of other studies.

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

Limitations of our study are that 14% (114/803) of patients withdrew or were lost to follow-up, however, these rates were similar in the two groups and consistent with our pre-trial projections. Adherence to study stockings tended to diminish over follow-up, which could have impacted on treatment efficacy. However, the results of our per-protocol analyses focusing on frequent users, and daily users, were similar to that of our intent 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 as our sample size calculation did not include the detection of subgroup effects. While 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 may have differed from those who remained in the study.

We used a number of strategies to reduce unblinding to 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 blinding of assessors.[31] Most patients, research nurses and site investigators remained unaware of treatment allocation. While partial unblinding may have occurred in the active stocking group, as 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 results differ from those of two previous randomized trials that showed substantial benefit of 30-40 mm Hg ECS to prevent PTS after proximal DVT.[10, 11] Both studies were open label, single center and smaller than our study. In Brandjes' study of 194 patients randomized to wear a made-to-measure 40 mm Hg knee-length ECS for at least two years vs. no stocking, mild-to-moderate PTS (assessed using a Villalta-like scale) occurred in 20% vs. 47% of patients and severe PTS occurred in 11% vs. 23% of patients.[10] In Prandoni's study of 180 patients randomized to wear 'off the rack' 30-40 mm Hg knee length ECS for two years vs. no stocking, PTS (assessed using Villalta's scale, with positive criteria required on at least two consecutive visits) occurred in 25% vs. 49% of patients and severe PTS occurred in 4% vs. 12% of patients.[11] In both of the above studies, stockings were replaced every six months, as in our study. The lower rates of PTS in the treatment groups than the control groups in these studies could be due, at least in part, to their open-label design. While both of the previous trials were assessor-blinded, assessment of PTS is based on both patient-reported symptoms and clinician assessed-signs. As apparent benefits of a treatment may 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 two studies. The characteristics of patients in our trial (e.g. age, sex distribution, DVT risk factors, anatomical extent of DVT, duration of anticoagulation) were similar to those of the previous studies. Compliance with ECS may have been greater in the two previous trials than in our study, but due to differences in how frequency of use was measured and reported in the three studies, this is uncertain. Differences may relate to the particular brand of active ECS used in our study, but we

believe this is unlikely as 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, as 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 two previous trials that reported benefit of stockings.[10, 11]

We believe that our results are generalizable 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 two previous ECS trials[10, 11] as well as to published cohorts and population-based studies of patients with DVT.[2, 33]

Our findings that ECS initiated at the time of acute DVT do not prevent PTS are consistent with a small randomized trial that initiated ECS one year after proximal DVT and found no difference in rates of PTS compared to wearing a sham stocking that was 1-2 sizes too large.[15] Similarly, in patients with proximal DVT who wore ECS for 6 months and were then randomized to stopping stockings or using them for an additional 18 months, there was no difference in rates of PTS at 2 years.[34] While these and our results suggest that ECS may not influence the natural history of PTS development after DVT, whether compression stockings may be of benefit to improve symptoms of established PTS or of acute DVT warrants evaluation in future studies.

In conclusion, we found that wearing ECS for two years after a first proximal DVT did not prevent PTS, reduce the severity of PTS when it occurred, reduce recurrent VTE, improve quality of life, or reduce venous valvular reflux. Thus, our results do not support routine wearing of ECS after DVT.

Research in context

Systematic review:

At the time of applying for funding of the SOX Trial, in September 2003, we conducted a computer database search for individual trials and systematic reviews of the use of compression stockings initiated early after DVT diagnosis to prevent the post-thrombotic syndrome. 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 in which 194 patients with symptomatic proximal DVT were randomized to daily use of knee-length custom-made 40 mm Hg ECS, applied within 2-3 weeks of DVT diagnosis for at least 2 years, vs. no stocking. Use of stockings reduced the incidence of mild/moderate PTS from 47% to 20% and of severe PTS from 23% to 11%.[10] In 2004, after the SOX Trial began, Prandoni published the results of a trial of off-the-rack 30-40 mm Hg ECS used for two years to prevent PTS after a first episode of proximal DVT. Among 180 patients, those randomized to ECS had a 24·5% incidence of PTS, compared to 49·1% in controls.[11] Both of the above trials were single center, open-label studies. A new search of the 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 found that wearing 30-40 mm Hg graduated ECS did not reduce the incidence of PTS at two years in patients with a first proximal DVT, compared to wearing placebo stockings. Similarly, ECS did not influence the occurrence of venous ulcers, rate of recurrent VTE, 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.

Conflict of interest

None

Acknowledgements

Funding/Support: Funding for this study was provided by Canadian Institutes for Health Research (grant number MCT 63142, MOP 102610), with active and placebo stockings provided as in-kind support by Sigvaris Corp. Dr. Kahn is supported by a National Research Scientist award from the Fonds de recherche du Québec - Santé (FRQS). Dr. Rodger is supported by a Career Investigator award from the Heart and Stroke Foundation of Ontario and a Tier 1 Research Chair Award, Faculty of Medicine, University of Ottawa. Dr Kearon is supported by a Career Investigator award from the Heart and Stroke Foundation of Ontario. Dr. Ginsberg is supported by a Career Investigator award from the Heart and Stroke Foundation of Ontario and is a recipient of the David Braley and Nancy Gordon Chair for Investigation of Thromboembolic Diseases.

We gratefully acknowledge the contribution of the SOX Trial Central Trial Coordinators Tatiana Vydykhan, MSc (study start-up – Jan 2007), Hadia Shbaklo, PhD (Jan 2007 – May 2008) and Adrielle Houweling, MSc (May 2008 – present). We thank Monika Hudoba, Lindsay Young and Ria Giakoumakis of Sigvaris Corp, St. Laurent, QC, for their assistance with distribution of study stockings during the trial. We thank Russell Steele PhD, Department of Mathematics and Statistics, McGill University and Centre for Clinical Epidemiology, Jewish General Hospital for his suggestions on missing data analyses.

The following institutions, site investigators (in addition to those named as co-authors) and research coordinators participated in the SOX Trial (numbers in parentheses are the numbers of patients who were randomized). Canada: Jewish General Hospital, Montreal, QC — Dr. E. Lang, E. Shulikovsky (138); The Ottawa Hospital, Ottawa, ON — Dr. M. Forgie, C. Hilliker, V. Borsella, J. Chen, F. Hallé, A. Levac, R. Larose, C. Blais (131); London Health Sciences Centre, London, ON — Dr. A. Lazo-Langner, M. McLean, B. Morrow, R. Corpuz (66); Montreal General Hospital, Montreal, QC — B. St-Jacques, S. Finkenbine (56); Hôpital Notre-Dame, Montreal, QC — Dr. M. Dominquez, Dr. A. Roussin, Dr. F. Joyal, V. Daniel, S. Paris, D. Bélisle, D. Forand (52); Queen Elizabeth II Health Sciences Centre, Halifax, NS — B. Gallant, L. Gray, A. MacNeil (46); McMaster University Medical Center, Hamilton, ON — Dr. S. Bates, P. Stevens (46); Toronto General Hospital, Toronto, ON — Dr. B. Brien, Dr. A. McLeod, Dr. R. Wu, M. Dzyuba, S. Jenkins (39); Victoria Heart Institute Foundation, Victoria, BC —S. Sorensen, L. Reimer, N. Lounsbury (36); Hamilton Health Sciences–General, Hamilton, ON — Dr. J. Eikelboom, L. Rudd-Scott, M. Zondag, M. Robinson (34); Hôpital Maisonneuve-Rosemont, Montreal, QC — Dr. D.-T. Nguyen, D. Sylvestre, J. Trinh Lu, L. Chevalier (25); St. Mary's Hospital Center, Montreal, QC — K. Mendelew, K. McTavish, K. Nguyen (22); Juravinski Hospital, Hamilton Health Sciences, Hamilton, ON — Dr. P Gross, Dr. A. Lee, Dr. L.-A. Linkins, Dr. J. Weitz, T. Winkworth, M. Thompson, D. Donovan (21); Hôpital du Sacré-Coeur, Montreal, QC — Dr. M. Laurier, Dr. N. Routhier, Dr. A.-M. Mansour, Dr. M. Helou, Dr. G. Grégoire, C. Chagnon, C. Nadon (15); St. Boniface General Hospital, Winnipeg, MB — Dr. G Drobot, J. Arbez, S. Erikson-Nesmith (15); CHA Hôpital de l'Enfant-Jésus, Montreal, QC — Dr. R. Delage, Dr. C. Doyle, Dr. J. Morin, Dr. P.-F. Leblond, Dr. C. Petitclerc, Dr. G. Cantin, C. Jobin, Y. Hébert, J. Poulin (13); St. Joseph's Hospital, Hamilton, ON — Dr. J. Douketis, Dr. M

Crowther, Dr. W. Lim, T. Schnurr (12); Sunnybrook Hospital, Toronto, ON — Dr. R. Jay, Dr. W. Bartle, Dr. W. Geerts, F. Sealey, L. Kaus (10); Hôpital Pierre-Boucher, Montreal, QC — N. Fortin (4); Royal Victoria Hospital, Montreal, QC — K. Riches, C. Barber (3); Hamilton Health Sciences – Chedoke Division, Hamilton, ON — Dr. F. Spencer, T. Lyon, D. Magier, S. Robinson (2); United States: Henry Ford Hospital, Detroit, MI — H. Gikas, S. Ellsworth (11); Oklahoma University Health Sciences Center , Oklahoma City, OK — (8); Duke University Medical Center, Durham, NC — M. A. Gleim, S. Adams, C. Mette (1).

SOX Trial Coordinating Center: Center for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada; **Statistical analysis:** C. Holcroft, T. Ducruet, Center for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada; **Independent Adjudication Committee**: A. Hirsch, M. Blostein, Jewish General Hospital, Montreal, QC, Canada. **Data Safety Monitoring Board**: G. Raskob, S. Vesely, D. Thompson, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, United States; B. L. Davidson, Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle, Washington, United States.

Figure legends

Figure 1. Title: Flow of patients in the trial.

Legend: Three patients were determined to be ineligible to participate and were excluded from the analysis (active ECS: 1 patient had no DVT [did not receive study stockings]; placebo ECS: 1 patient had previous DVT [did not receive study stockings], 1 patient 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 center- the patient insisted on using the same type of stocking throughout the trial without knowing if it was active or placebo.

Figures 2a, 2b and 3: Of the 803 patients in the intention-to-treat analysis, 795 were included in the time-to-event analysis. The 8 patients (6, active stockings; 2, placebo stockings) who were not included are those for whom no follow up data were available after the baseline visit.

Figure 2a. Title: Cumulative incidence of the primary outcome (post-thrombotic syndrome, as per Ginsberg's criteria) in patients in the active and placebo stockings group.

Legend: The primary outcome was first assessed at the 6 month visit and each six months thereafter. Data from patients who withdrew consent or who were lost to follow-up were censored at the time of the last follow-up assessment. Patients who stopped study stockings but agreed to be followed were included in the intention-to-treat analysis. Cumulative incidence of PTS (at 750 days) was 14·2% in active ECS vs. 12·7% in placebo ECS (HR adjusted for centre 1·13; 95% CI 0·73-1·76; p=0·58).

Figure 2b. Title: Cumulative incidence of the post-thrombotic syndrome (Villalta criteria; secondary outcome) in patients in the active and placebo stockings group.

Legend: The secondary outcome, PTS diagnosed using Villalta's criteria, was first assessed at the 6 month visit and each six months thereafter. Data from patients who withdrew consent or who were lost to follow-up were censored at the time of the last follow-up assessment. Patients who stopped study stockings but agreed to be followed were included in the intention-to-treat analysis. 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 vs. 52·3% in placebo ECS (HR adjusted for centre 1·00; 95% CI 0·81-1·24; p=0·96).

Figure 3. Title: Analysis of pre-specified subgroups.

Legend: For all subgroup treatment effects, 95% confidence intervals overlapped each other and the null. Test of interaction p-value was p= 0·047 for sex, p=0·38 for age category, p=0·60 for body mass index category and p=0·55 for extent of DVT.

Figure 1. Flow of patients in the trial.

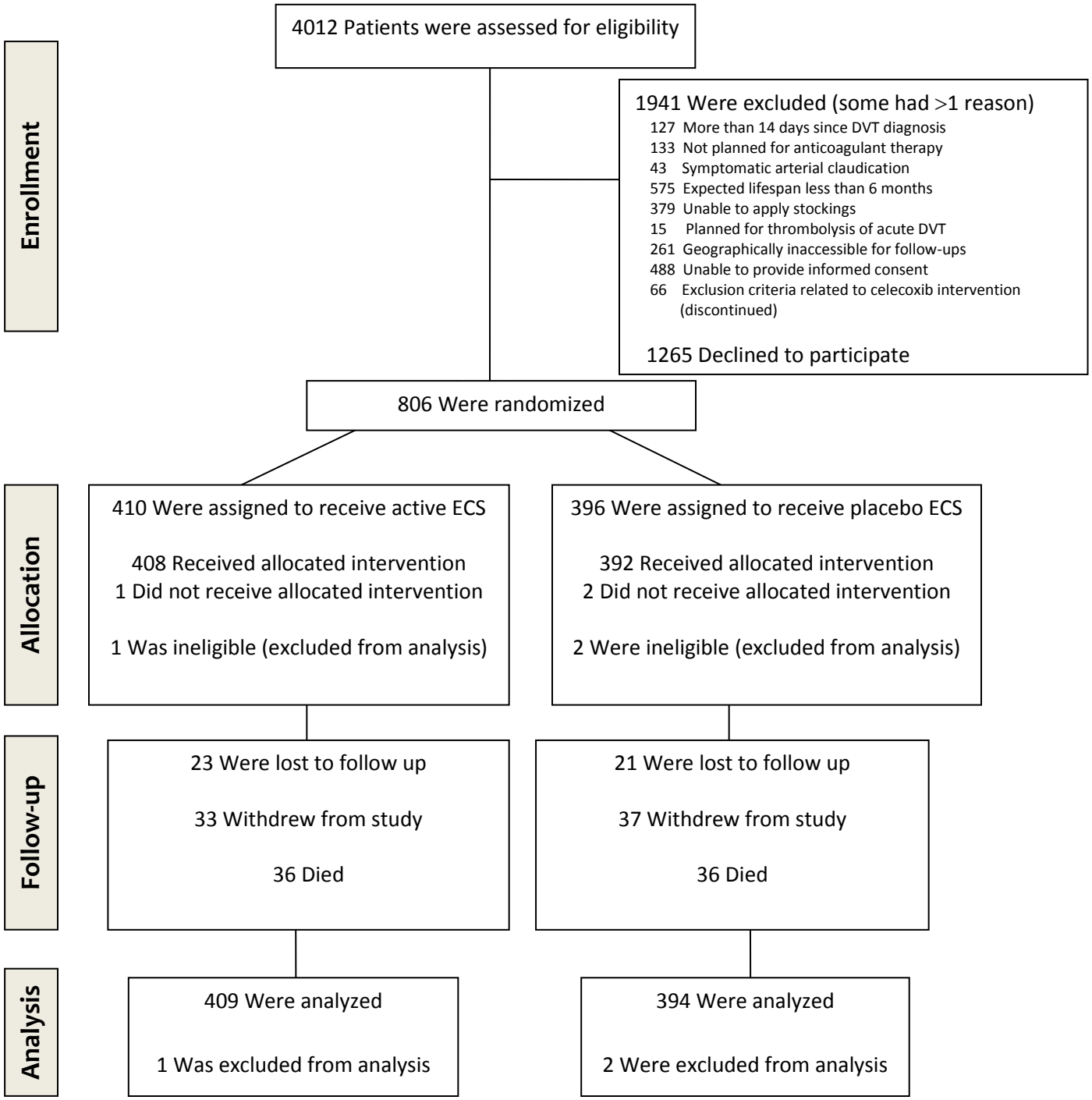

Figure 2a. Cumulative incidence of the post-thrombotic syndrome (primary outcome: Ginsberg's criteria) in patients in the active and placebo stockings groups.

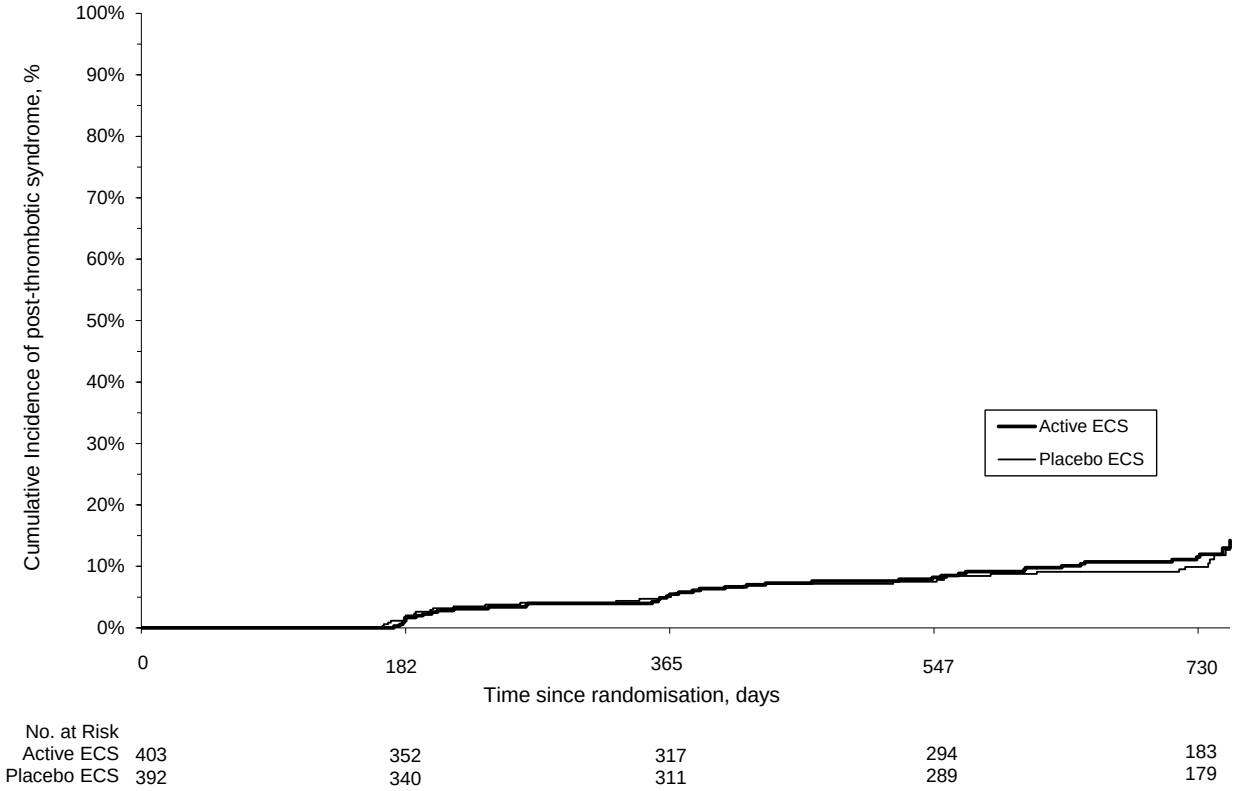

Figure 2b. Cumulative incidence of the post-thrombotic syndrome (Villalta's criteria) in patients in the active and placebo stockings groups.

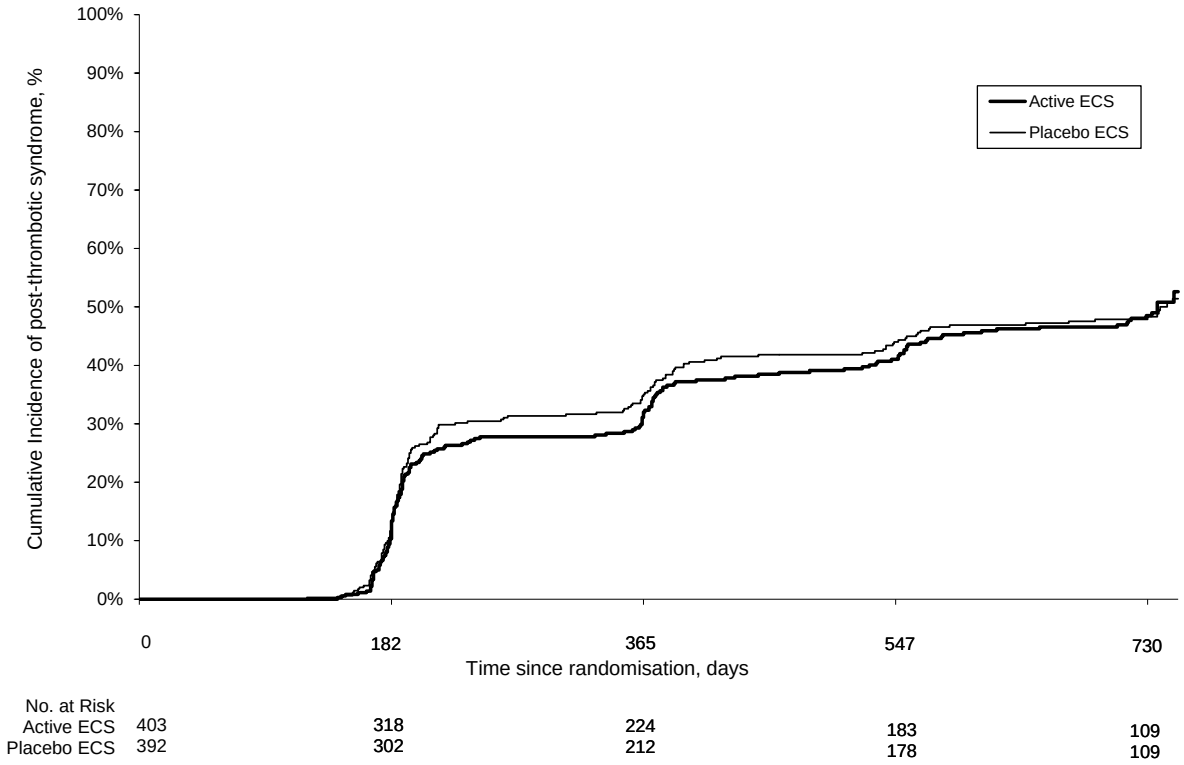

Figure 3. Analysis of prespecified subgroups

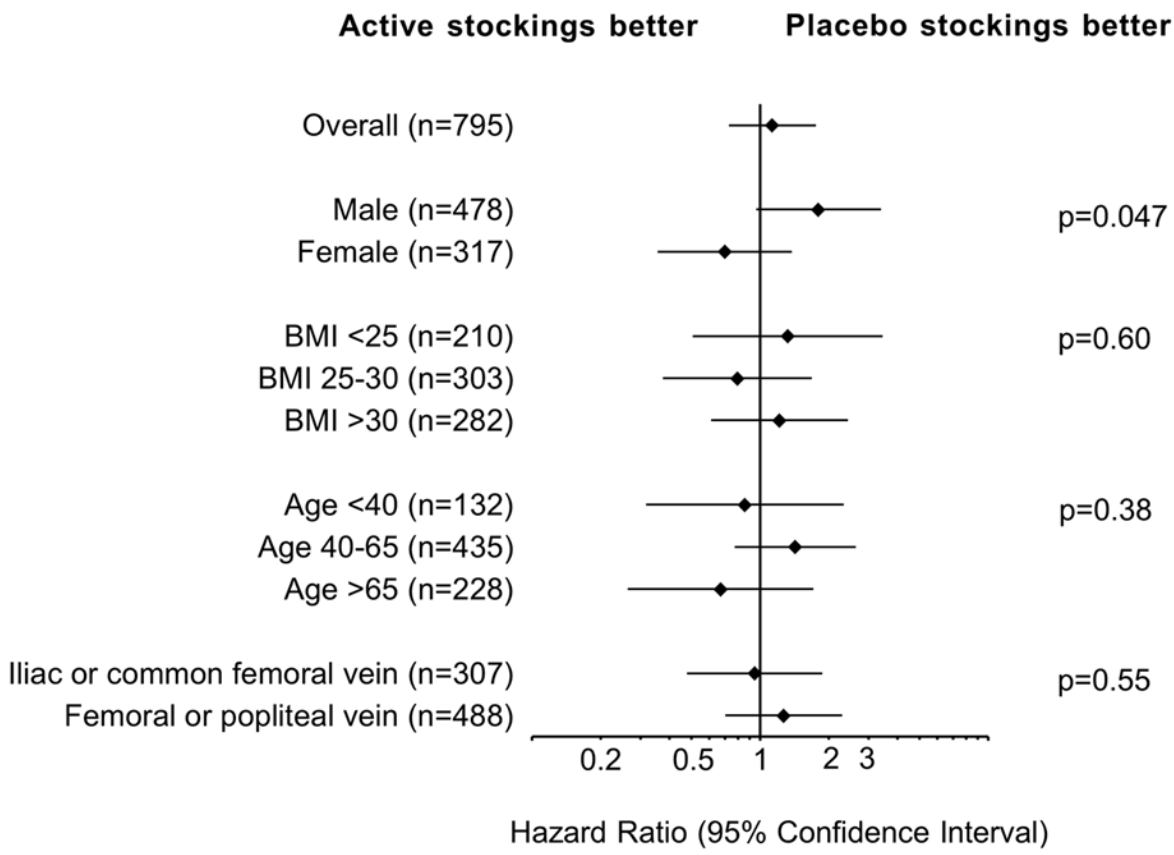

Table 1. Baseline characteristics

	No. (%)*	
	Active stockings (N=409)	**Placebo stockings (N =394)**
Age, mean (SD), 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)
Caucasian	371 (90·7)	354 (89·9)
Body mass index, mean (SD), kg/m^2	29·0 (6·1)	28·9 (6·1)
Days from DVT diagnosis to randomization, mean (SD)	4·8 (4·1)	4·6 (3·8)
Characteristics of deep venous thrombosis		
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 deep venous thrombosis ^		
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, last 3 months	77 (18·8)	64 (16·2)
Trauma, last 3 months	42 (10·3)	51 (12·9)
Immobilized in last month	67 (16·4)	61 (15·5)
Active cancer [+]	52 (12·7)	46 (11·7)
Pregnant, postpartum, oral contraceptives or hormonal replacement therapy[#]	37 (24·0)	55 (33·1)
Family history of venous thromboembolism	85 (20·8)	82 (20·8)
Deep venous thrombosis 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, median (IQR), days	8 (6, 11)	8 (6, 10)
Duration of warfarin, median (IQR), days	186 (113, 240)	180 (100, 214)
Duration of investigational anticoagulant[&], median (IQR), days	189 (183, 647)	205 (182, 546)
Duration of oral anticoagulation (warfarin or investigational), median (IQR), days	186 (113, 253)	182 (104, 220)

Abbreviations: SD, standard deviation; DVT, deep vein thrombosis; IQR, interquartile range.
[*] Unless otherwise indicated
[^] In the case of bilateral DVT, the leg with the most proximally extensive DVT was used as the index leg
[+] Diagnosed within last 6 months or treatment ongoing or 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) to standard anticoagulation

Table 2. Outcomes, by treatment group

	Active stockings (N =409)	Placebo stockings (N=394)	Hazard ratio [a] (95% CI)
Primary outcome			
Post-thrombotic syndrome (Ginsberg's criteria [b])			
N	44	37	
Cumulative incidence [c], %	14·2%	12·7%	1·13 (0·73, 1·76)
Secondary outcomes			
Post-thrombotic syndrome (Villalta's criteria [d])			
N	176	168	
Cumulative incidence [c], %	52·6%	52·3%	1·00 (0·81-1·24)
Villalta severity category [e]			
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 [f]	17 (4·2%) patients 17 ulcers	16 (4·1%) patients 17 ulcers	
Recurrent venous thromboembolism	33 (8·1%) patients 45 events (36 DVT, 9 PE)	38 (9·6%) patients 44 events (32 DVT, 12 PE)	

Recurrent ipsilateral DVT	16 (3·9%) patients 18 events	17 (4·3%) patients 17 events
Ipsilateral venous valvular reflux at 12 months [g]	120/291 (41·2%)	117/283 (41·3%)
Death [h]	36 (8·8%)	36 (9·1%)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
[a] Adjusted for centre. Of the 803 patients in the intention-to-treat analysis, 795 were included in the time-to-event analysis. The 8 patients (6, active stockings; 2, placebo stockings) who were not included are those for whom no follow up data were available after the baseline visit
[b] Pain and swelling of one 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]
[c] Cumulative incidence as of 750 days follow-up
[d] Villalta score ≥5 or ulcer at or after the 6 month visit [16, 18]
[e] 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].
[f] In active stockings group, 2 cases of leg ulcer were noted at the 1 month visit, 6 at the 6 month visit, 7 at the 12 month visit, and 2 at the 24 month visit. In the placebo stockings group, 5 cases of leg ulcer were noted at the 1 month visit, 7 at the 6 month visit, 2 at the 12 month visit, 2 at the 18 month visit and 1 at the 24 month visit.
[g] A total of 574 study patients underwent ultrasound assessment for venous valvular reflux at 12 months
[h] No deaths in either group were considered by investigators to be definitely or likely due to PE, or judged by adjudicators to be attributable (primary or contributing cause) to PE.

References

1. Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, et al. The Long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996; **125**(1): 1-7.

2. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. Ann Intern Med. 2008; **149**: 698-707.

3. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost. 2008; **6**(7): 1105-12.

4. van Korlaar I, Vossen C, Rosendaal F, Cameron L, Bovill E, Kaptein A. Quality of life in venous disease. Thromb Haemost. 2003; **90**(1): 27-35.

5. Guanella R, Ducruet T, Johri M, Miron MJ, Roussin A, Desmarais S, et al. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost. 2011; **9**(12): 2397-405.

6. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis. 2009; **28**(4): 465-76.

7. Kahn SR. How I treat postthrombotic syndrome. Blood. 2009; **114**(21): 4624-31.

8. Cohen JM, Akl EA, Kahn SR. Pharmacologic and compression therapies for postthrombotic syndrome: a systematic review of randomized controlled trials. Chest. 2012; **141**(2): 308-20.

9. Henke PK, Comerota AJ. An update on etiology, prevention, and therapy of postthrombotic syndrome. J Vasc Surg. 2011; **53**(2): 500-9.

10. Brandjes DPM, Buller HR, Heijboer H, Hulsman MV, de Rijk M, Jagt H. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997; **349**: 759-62.

11. Prandoni P, Lensing AWA, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med. 2004; **141**(4): 249-56.

12. Kahn SR, Elman E, Rodger MA, Wells PS. Use of elastic compression stockings after deep venous thrombosis: a comparison of practices and perceptions of thrombosis physicians and patients. Journal of Thrombosis and Haemostasis. 2003; **1**: 500-6.

13. Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. CMAJ. 2004; **171**(9): 1027-8.

14. Kahn SR, Shbaklo H, Shapiro S, Wells P, Kovacs M, Rodger M, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (The SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. BMC Cardiovascular Disorders. 2007; **7**(1): 21.

15. Ginsberg JS, Hirsh J, Julian J, Vander LM, Magier D, MacKinnon B, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med. 2001; **161**(17): 2105-9.

16. Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis. 1994; **24**(Suppl 1): 158a.

17. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. J Thromb Haemost. 2009; **7**: 884-8.

18. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost. 2009; **7**: 879-83.

19. Ginsberg JS, Shin A, Turpie AG, Hirsh J. Detection of previous proximal venous thrombosis with Doppler ultrasonography and photoplethysmography. Arch Intern Med. 1989; **149**(10): 2255-7.

20. Ginsberg JS, Caco CC, Brill-Edwards PA, Panju AA, Bona R, Demers CM, et al. Venous thrombosis in patients who have undergone major hip or knee surgery: detection with compression US and impedance plethysmography. Radiology. 1991; **181**(3): 651-4.

21. Ware JE, Kosinski MA, Keller SD. SF-36 physical and mental summary measures: A user's manual. Boston: The Health Institute, New England Medical Center. 1994.

22. Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. J Clin Epidemiol. 2006; **59**(10): 1049-56.

23. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluating outcomes in chronic venous disorders of the leg: Development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. J Vasc Surg. 2003; **37**(2): 410-9.

24. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Int Med. 2004; **164**: 17-26.

25. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics. 1982; **38**(1): 163-70.

26. Dupont WD, Plummer WD. PS power and sample size program available for free on the internet. Control Clin Trials. 1997; **18**(3): 274.

27. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med. 1994; **13**: 1341-52.

28. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res. 2011.

29. Kahn SR, Desmarais S, Ducruet T, Arsenault L, Ginsberg JS, and VSI. Comparison of performance of two clinical scales to diagnose the post-thrombotic syndrome: Correlation with patient-reported disease burden and valvular reflux. Journal of Thrombosis and Haemostasis. 2006; **4**: 907-8.

30. Enden T, Haig Y, Kløw N-E, Slagsvold C-E, Sandvik L, Ghanima W, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. The Lancet. 2012; **379**(9810): 31-8.

31. Hróbjartsson A, Thomsen ASS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ. 2013; **185**(4): E201-E11.

32. Price DD, Finniss DG, Benedetti F. A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. Annu Rev Psychol. 2008; **59**(1): 565-90.

33. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and Mortality from Venous Thromboembolism in a Real-World Population: The Q-VTE Study Cohort. The American Journal of Medicine. 2013.

34. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: A randomized controlled trial. J Vasc Surg. 2008; **47**(5): 1015-21.