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Compression stockings to prevent the post-thrombotic syndrome (PTS)

Introduction:

Compression after deep vein thrombosis (DVT) has a long tradition in the initial treatment of symptoms and oedema and also in the prevention of PTS. Without compression a PTS may develop in more than 60 % of the patients. This high incidence can be significantly reduced by wearing compression stockings. In the TULIPA registry, the incidence of PTS in patients without venous disease before index DVT was 24.5 % after 3 years of follow-up. One year after DVT, 78.5% of the patients were still wearing compression stockings.[1]

In the recent ACCP guidelines for diagnosis and treatment of DVT, the use of compression stockings is recommended:[2]

> **4.1 In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**
> Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful.
>
> **4.2.1 In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).**

Recently, the publication of the SOX trial in the Lancet (Kahn et al, 2014) led to a controversial discussion, as the negative outcome of the study seems to show no benefit of compression in the prevention of the PTS, in patients with an initial DVT. In this context, the most important clinical studies related to the use of compression to prevent PTS, are presented and commented in this issue of the Compression Bulletin.

Summary:

Wearing compression stockings after deep vein thrombosis (DVT), with the goal to prevent post-thrombotic syndrome (PTS), is still a very good recommendation and should not be abandoned. It is an open question how much pressure a stocking must have to prevent signs and symptoms of a PTS. Even compression stockings with a low ankle pressure should not be considered as true «placebo stockings» because they are able to reduce symptoms and edema.
Using the Villalta scale, the Ginsberg's scale or other criteria alone to identify PTS events in patients after a first event of DVT may overestimate the true incidence of PTS.
Patients with a previous history of chronic venous insufficiency, for instance due to varicose veins, may already have had a positive score or venous ulcers prior to the first PTS event after a first DVT. All scores in use are not specific for PTS and need additional anamnestic and clinical assessments, for instance by CEAP classification, to clearly identify a new PTS event in patients that experienced a first DVT.

[1] *Hach-Wunderle V, Bauersachs R, Gerlach H-E, Eberle S, Schellong S, Riess H, Carnarius H, Rabe E: Post-thrombotic syndrome 3 years after deep venous thrombosis in the Thrombosis and Pulmonary Embolism in Out-Patients (TULIPA) PLUS Registry; Journal of Vascular Surgery: Venous and Lymphatic Disorders 2013;1: 5-12*

[2] *Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR: Antithrombotic Therapy for VTE Disease Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.Chest 2012;141(2_suppl):419S-494S. doi:10.1378/chest.11-2301*

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Hach-Wunderle V, Bauersachs R, Gerlach H-E, Eberle S, Schellong S, Riess H, Carnarius H, Rabe E

Post-thrombotic syndrome 3 years after deep vein thrombosis in the thrombosis and pulmonary embolism in out-patients (TULIPA) PLUS Registry

JVS: Venous and Lymphatic Disorders 2013;1:5-12

Aim
The aim of the study was to assess the incidence of post-thrombotic syndrome (PTS) in out-patients three years after a first episode of deep vein thrombosis (DVT) and without previously reported history of DVT prior to the index event, varicose veins, or chronic venous insufficiency (CVI) independent of PTS.

Methods
This was a prospective registry with a 3-year follow-up after an initial DVT in ambulatory patients. At the follow-up, 310 out of 1,388 patients with an index DVT from the TULIPA cohort were available for a clinical follow-up investigation. Of these, patients with a personal history of DVT prior to the index DVT, as well as patients with varicose veins and/or CVI at study entry (n = 154) or a missing Villalta score (n = 21) were excluded, resulting in a population of 135 patients.

Results
PTS with a score of ≥ 5 points 3 years after the index event was detected in 24.5 % Patients (n = 33/135), including 17.0 % (n = 23) with mild, 6.0 % with moderate (n = 8) and 1.5 % (n = 2) with severe cases of PTS. There were no patients with venous ulcers. In a multivariate analysis, age (1.05; 1.01 - 1.09) and calf swelling ≥ 3cm larger than the asymptomatic leg (2.94; 1.20 - 7.20) were predictive for a PTS. 78.5 % of the patients at the 1-year follow-up and 46.7 % of the patients at the 3-year follow-up used compression therapy. In patients with varicose veins, CVI, or DVT before index thrombosis, a Villalta score indicating PTS was present in 45 % of this subpopulation.

Conclusion
This prospective survey demonstrates a low incidence rate of PTS (24.5 %), three years after a first DVT in patients with no pre-existing DVT, varicose veins, or CVI. Patients showed a high adherence rate to compression therapy within the first 3 years of follow-up. Age and marked calf swelling were independent predictors of a PTS.

Comment of the editors
These results indicate that the Villalta scale is not specific for a PTS. About 45 % of the follow-up patients that had previously reported DVT, varicose veins, or CVI before the index DVT, had a present PTS as indicated by a Villalta Score. Patients with previously reported DVT, varicose veins or CVI may develop similar symptoms as those used to indicate a PTS by the Villalta scale, which might lead to an overestimation of the incidence of PTS.

Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW

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

Lancet 1997;349:759-62

Aim
The aim of the study was to assess the incidence rate of post-thrombotic syndrome (PTS) after a first episode of deep vein thrombosis (DVT) and to investigate the preventive effect of an immediate application of a sized-to-fit graded compression stocking.

Methods
Patients with a first episode of venogram-proven proximal DVT were randomly assigned to either no stockings (the control group) or sized-to-fit graded compression stockings for at least 2 years. PTS was assessed with a standard scoring system that combined clinical characteristics and objective leg measurements. Patients were followed up every 3 months during the first 2 years, and every 6 months thereafter for at least 5 years. The primary outcome measure was the cumulative incidence of mild-to-moderate PTS .

Results
44 of 315 consecutive out-patients considered for inclusion did not meet the inclusion criteria and 77 did not consent to take part. 194 patients were therefore randomly assigned either to the compression stockings group (n = 96) or the no stockings group (n = 98). The median follow-up was 76 months (range 60-96) in both groups. Mild-to-moderate PTS, defined as a score ≥ 3 plus at least one clinical sign, occurred in 19 patients (20 %) in the stocking group and in 46 (47 %) control-group patients ($p < 0.001$). Severe PTS (score ≥ 4) developed in 11 patients (11 %) in the stocking group, compared with 23 patients (23 %) in the control group ($p < 0.001$). In both groups, most cases of PTS occurred within 24 months of the acute thrombotic event.

Conclusion
About 70 % of patients in the no stockings group developed mild-to-moderate or severe PTS within 2 years. A sized-to-fit compression stocking helped to reduce the incident rate by about 50 %.

Comment of the editors
This was the first prospective randomized study showing a reduction of the PTS incidence rate by wearing of compression stockings. The patients started wearing compression stockings 2-3 weeks after initial diagnosis of DVT. The incidence of PTS could be reduced from 70 % to 31 % by wearing of compression stockings. The results of this study were confirmed by Prandoni (2004) and form the basis for the recommendation to use compression after DVT in most of the national and international DVT guidelines.

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Prandoni P, Lensing AWA, Prins MH, Frulla M, Marchiori A, Bernardi E, Tormene D, Mosena L, Pagnan A, Girolami A

Below-knee elastic compression stockings to prevent the post-thrombotic syndrome

Ann Intern Med 2004;141:249-56

Aim
The aim of the study was to evaluate the efficacy of elastic compression stockings for the prevention of the post-thrombotic syndrome (PTS) in patients with proximal deep vein thrombosis (DVT).

Methods
Before discharge from the hospital, 180 consecutive patients with a first episode of symptomatic proximal DVT and receiving conventional anticoagulant treatment, were randomly assigned to wear or not to wear elastic below-knee compression stockings for two years (30-40 mmHg at the ankle), with a follow-up period of 3 years.
The patients were examined at 3 and 6 months after the index event and thereafter every 6 months until the end of the follow-up period. The presence and severity of PTS was assessed by use of a standardized score, that takes account of subjective symptoms and objective signs. The assessments were performed by investigators who were unaware of the treatment allocation.

Results
44 out of 90 patients (49 %) in the control group and 23 out of 90 patients (26 %) in the stocking group developed PTS. All but one event developed in the first two years. The hazard ratio for PTS in the stocking group compared with the control group was 0.49 (CI 0.29-0.84, P = 0.011). These findings suggest that 4.3 patients need to be treated with medical compression stockings to prevent one additional case of PTS.

Conclusion
Wearing of medical below-knee compression stockings for two years after proximal DVT can reduce the overall incidence rate of the PTS by 50 %.

Comment of the editors
The results of this study are in full agreement with the trial of Brandjes et al (Lancet 1997;349:759-62). Based on these randomized controlled trials, prescription of medical compression stockings should not be withheld to patients after DVT. The authors recommend that stockings must be applied quickly, since venous hypertension and valve damage occur soon after a thrombotic episode. In fact, compression was started in the Prandoni study in average one week after the acute event. It may be hypothesized that immediate compression and walking could have even further improved the positive outcome.

Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR et al - SOX trial investigators

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

Lancet 2014;383:880-8

Aim
The aim of the study was to assess the efficacy of elastic compression stockings (ECS) compared with placebo stockings for the prevention of the post-thrombotic syndrome (PTS).

Methods
This was a multicenter randomized placebo-controlled trial of active versus placebo ECS used for 2 years to prevent PTS after a first proximal deep vein thrombosis (DVT). Between 2004 and 2010, 806 patients from 24 centers in Canada and the USA were enrolled. Patients were randomly assigned to receive either knee high, 30-40 mmHg compression stockings or «placebo stockings» with an identical appearance, but less than 5 mmHg compression at the ankle. Stockings were shipped to the patient by courier directly after the randomization took place. Stockings were applied within 2 weeks of DVT diagnosis and were replaced every 6 months, the treatment period was 2 years. Follow-up visits occurred at 1, 6, 12, 18, and 24 months. The primary endpoint was the cumulative incidence of PTS (from 6 to 24 months follow-up), diagnosed by Ginsberg's criteria (leg pain and swelling of ≥ 1 month duration). Secondary endpoints were the cumulative incidence and severity of PTS assessed by Villalta criteria, the presence of leg ulcers, objectively confirmed recurrent venous thromboembolism (VTE), death, adverse events, venous valvular reflux at the level of the popliteal vein (present or absent at 12 months visit), and quality of life.

Results
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 using the Ginsberg-criteria. There were no between-group differences in the cumulative incidence of PTS defined with Villalta criteria, distribution of PTS, severity category and the rate of ipsilateral leg ulcer. Venous valvular reflux at 12 months was also similar.
There were no differences in generic and disease-specific quality of life results. Use of study stockings at each visit was similar between the groups. Results were similar in a pre-specified per-protocol analysis of patients who reported «frequent use» of stockings (wearing stockings at least 3-days per week).

Conclusion
The findings of the study showed that ECS did not reduce the incidence of PTS at two years in patients after a first proximal DVT, compared to patients wearing placebo stockings. The authors interpretation of the study results was, that the findings do not support routine wearing of ECS after DVT.

Comment of the editors
The results of the present study contradict those of previous findings from randomized trials and meta-analyses and this led to a controversial discussion that was published recently in the Lancet (Vol. 284;129-131; July 12, 2014). Not all questions of the experts could be fully answered in this article, and therefore some of the open discussion points are worth to be highlighted here again, as they might have led to a potential over reporting of PTS in the active ESC treatment group and in consequence to the negative outcome of the study:

- One point of discussion is the time point of compression therapy initiation. Although elastic stocking use was initiated earlier than in the two previously described clinical trials of Brandjes (1997) and Prandoni (2004), it might be expected, that an faster start of compression therapy would have influenced the outcome of the study in favour of the active ESC. An initiation of compression therapy in the acute phase of DVT, where it has a proven, positive effect on pain and swelling reduction, would directly affect the diagnosis of PTS, using the Ginsberg's criteria of ipsilateral pain and swelling. In addition, no information is available at which time point the patients have started to wear the stockings after they have been sent to them by courier.

- Another important point is the question about expected compliance differences between the two treatment groups. It is most likely, that even under the best possible blinding conditions, differences in patients convenience (e.g. how easy can the stocking be put on, temperature sensitivity, etc), will negatively influence the compliance rate of patients that are allocated to the active ECS with 30-40 mmHg. It seems clear, that a high compliance to treatment has a major effect on the outcome of such a study and therefore, non-compliance to the active ECS (not wearing the stockings for whatever reason) might explain the trials null result. The approach to rely on patient self-reported compliance might not have been sufficient to ensure that treatment differences are fully recognized. One possible approach could have been to use unblinded study personnel to assess compliance (e.g. check stockings at study visits) and to properly instruct patients on how to wear the ECS, they were allocated to.

- Further to this, compliance to study treatment was defined as «wearing the stockings at three or more days per week». This definition may be much too low and the authors did not provide information about how many hours per day the patients used the stockings. It should be taken into consideration that the main effect of compression is to successfully reduce oedema and symptoms and signs of chronic venous insufficiency which can only be expected, when the compression stockings are on the leg. A patient that was wearing the stockings for only 3 days, might have experienced relief of oedema, feeling of heaviness or pain over this period of three days, but it can be expected that the symptoms would have appeared again on the other days of the week. Asking this patient if swelling and symptoms were present during the week, the answer might have been most probably «yes» – this even if the symptoms had disappeared on the days when the stockings were worn.

- Unclear remains the answer whether a placebo ECS can be described as a «true» placebo. In a previous study (H Partsch 2004) it could be shown that also «placebo stockings» exerting a pressure of <10 mm Hg had a significant effect concerning oedema prevention. Hypothetically, even a small compression effect in combination with the above mentioned points (late initiation of compression therapy and non-compliance in the active ECS group), might have let to the observed outcome of the study by reducing the difference of the effectivity between the two treatment arms.

- As nicely demonstrated in the study of Hach-Wunderle et al. (2013), the rate of PTS in patients with a first DVT, as assessed by the Villalta score, is generally low if the patients are mobilized with compression stockings immediately after starting with anticoagulation. Pre-existing DVT, varicose vein and chronic venous insufficiency often lead to an over-reporting of PTS. The high rate of PTS (Villalta criteria) and leg ulcers reported in both treatment groups after a first episode of DVT, might be an indication that patients with previously reported DVT, varicose veins or CVI had reported similar symptoms as those used to indicate PTS in the Villalta scale.

Based on above mentioned considerations and discussion, the authors conclusion, that routine wearing of ECS after DVT does not prevent PTS is possibly too restrictive and might unjustifiedly lead to the loss of a valuable and affordable therapy option for patients after a first episode of DVT. The current evidence continuous to support the use of compression after DVT for at least 6 months and to adjust the future management to the signs and symptoms at this time. Answers to the open questions might be provided in future clinical trials.