

# Compression Bulletin 28

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## **Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome**

Compression stocking use alone showed similar efficacy to CLT in the treatment of established PTS. Additional components of the complex lymphedema therapy, consisting of skin care, compression device use, manual lymphatic drainage and exercises, did not improve the results further. In consequence treatment with graduated compression stockings is indicated in patients suffering from PTS.

## **Clinical and cost-effectiveness of compression hosiery versus compression bandages in the treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomized controlled trial**

The treatment of venous leg ulcers with two-layer compression hosiery is more cost-efficient and as effective as the current standard of treatment with four-layer bandages.

### **Congresses:**

<b>21<sup>th</sup> Bonn Vein Days</b>	Bonn, Germany	February 20 – 21, 2015
<b>27<sup>th</sup> American Venous Forum (AVF)</b>	Palm Springs, USA	February 25 – 27, 2015
<b>ICC Meeting</b>	London, UK	May 14, 2015
<b>16<sup>th</sup> European Venous Forum (EVF)</b>	St Petersburg, Russia	July 01 – 04, 2015
<b>UIP Chapter Meeting</b>	Seoul, Korea	August 27 – 29, 2015

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Kahn SR, Shapiro S, Ducruet T, Wells PS, Rodger MA, Kovacs MJ et al

## Graduated compression stockings to treat acute leg pain associated with proximal DVT. A randomized controlled trial.

*Thrombosis and Haemostasis 2014; 28:112(6). [Epub ahead of print]*

### Aim

The aim of this sub analysis was to establish whether elastic compression stockings (ECS) vs placebo ECS were effective in reducing leg pain in patients with acute DVT using data from the SOX trial (1).

### Methods

The SOX trial was a randomized, placebo-controlled trial of active ECS (knee-length, 30-40 mmHg) vs placebo ECS (knee-length, < 5 mm Hg) in the prevention of postthrombotic syndrome in patients with proximal DVT. Patients were advised to wear the stocking during the day for 2 years. Patients, physicians and study personnel were blinded to treatment allocation. Patients were assessed for leg pain severity as a secondary outcome at baseline, 14, 30 and 60 days post randomization using an 11-point scale (0-10 where 10 is worst possible pain). A subgroup of patients who reported daily use of their stockings at one month were also analysed.

### Results

409 patients received active ECS whilst 394 received placebo ECS. 60.1 % of patients were male with a mean age of 55.1 years. Mean time from DVT diagnosis to randomisation was 4.7 days. Proximal DVT was diagnosed in

iliac vein in 11.6% patients, common femoral vein in 26.9%, femoral vein in 31.3% and popliteal vein in 30.3%. Mean pain scores were reduced at each assessment for both active and placebo ECS groups, from 5.18 at baseline to 1.39 at 60 days in active ECS patients and from 5.38 to 1.13 in placebo ECS patients. No significant differences were found between groups at any stage of follow-up. Similar results were found in the subgroup reporting daily use of the stockings at 30 days.

### Conclusion

No evidence was found for the increased reduction of leg pain with the use of ECS vs placebo ECS in patients with proximal DVT. However, the first follow-up at 14 days means that a difference between groups before this time point, in the acute phase of DVT, cannot be evaluated.

### Comment of the editors

This paper presents a secondary analysis of the SOX trial (1), concentrating on potential effects of compression stockings regarding "acute leg pain" associated with proximal DVT. As a matter of fact, compression started only 2-3 weeks after the acute stage of DVT so that a potential positive effect of compression in the acute stage cannot be ruled out.

(Randomization took place 4-5 days after diagnosis and then the individually fitting stockings had to be manufactured and sent by mail to the patients, which means that compression started at a stage when acute leg pain had subsided).

This is very different from a previous Austrian study quoted by the authors in which compression and walking was initiated as soon as the diagnosis of DVT was established and anticoagulant therapy was started (2). In this trial a modified Lowenberg test was used assessing the pain level under an increasing calf squeeze by a sphygmomanometer on both legs in addition to the visual analogue scale (VAS) in order to differentiate pain during walking and rest. Not only an immediate reduction of leg swelling, but also of pain during walking and rest could be demonstrated after compression was applied, in contrast to a bed-rest-group without compression, showing a much slower regression of pain and edema.

In the SOX trial the pain level on the 11-point VAS scale was between 5.0 and 5.4 at "baseline", obviously the time of randomization about 5 days after diagnosis, which corresponds nicely to the values of the Austrian study seen in the bed rest group without compression after 5 days. However this finding

neglects the much more intense pain when the patient presents himself in the acute stage of DVT.

Pain during walking and swelling as the leading symptoms of acute DVT are the main reasons why patients are searching medical advice. In this initial stage patients are usually gratefully impressed to experience an immediate relief of swelling and pain by compression. This positive experience is also the reason for a better compliance when patients are advised to apply compression for longer time periods to prevent PTS. Patients like in the SOX trial, who did not experience the positive effect of compression on pain and edema and who's ECS treatment was started only weeks after the acute DVT will certainly be less compliant to continue compression (3).

It had been shown that the quality of an exact anticoagulation in the first days of acute DVT has an important implication on the late outcome (4). This seems also to be true for good compression reducing the symptoms of vein wall inflammation. It was also shown that the presence of residual venous symptoms and signs one month after DVT are strongly predictive of subsequent PTS (5). Reducing the acute symptoms and maintaining the improved outcome by ongoing compression may therefore

prevent the patients from prolonged phases of pain and swelling which characterize PTS. To verify this, future studies evaluating the potential role of adjunctive compression therapy in DVT need to start immediately as soon treatment is initiated.

Compression of the leg in acute DVT enable patients to walk better and has therefore become one main recommendation in addition to effective anticoagulation in managing such patients at home (6).

1. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, Tagalakis V, Houweling AH, Ducruet T, Holcroft C, Johri M, Solymoss S, Miron MJ, Yeo E, Smith R, Schulman S, Kassis J, Kearon C, Chagnon I, Wong T, Demers C, Hanmiah R, Kaatz S, Selby R, Rathbun S, Desmarais S, Opatrny L, Ortel TL, Ginsberg JS; SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014 Mar 8;383(9920):880-8.
2. Blättler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. *Int Angiol*. 2003 Dec;22(4):393-400.

3. Labropoulos N, Gasparis AP, Caprini JA, Partsch H. Compression stockings to prevent post-thrombotic syndrome. *Lancet*. 2014 Jul 12;384(9938):129-30.
4. Hull RD, Pineo GF. Heparin and low-molecular-weight heparin therapy for venous thromboembolism: will unfractionated heparin survive? *Semin Thromb Hemost*. 2004 Feb;30 Suppl 1:11-23.
5. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Lamping DL, Johri M, Ginsberg JS. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008 Nov 8;149(10):698-707.
6. Hach-Wunderle V, Bauersachs R, Gerlach H, Eberle S, Schellong S, Riess H, Carnarius H, Rabe E. Postthrombotic syndrome 3 years after deep venous thrombosis in the Thrombosis and Pulmonary Embolism in Out-Patients (TULIPA) PLUS Registry. *J Vasc Surg: Venous and Lym Dis* 2013;1:5-12.

Franzeck UK, Schalch I, Jäger KA, Schneider E, Grimm J, Bollinger A

## Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich Study)

*Circulation* 1996;93:74-79

### Aim

The aim of this study was to provide long-term analysis of postthrombotic syndrome in low-risk patients after acute deep vein thrombosis (DVT). No previous prospective studies have reported beyond 10 years.

### Methods

Patients with no previous history of DVT, pulmonary embolism (PE) and hypercoagulable state whose symptoms did not exceed 5 days were classed as low risk for adverse clinical events and therefore included in the study. Clinical and haemodynamic assessment was performed on admission, 3 months, 6 months and at 1 year. Follow up visits were then performed annually until the 5<sup>th</sup> year, with a final visit in the 12<sup>th</sup> year. All patients received heparin followed by oral anticoagulants. Thigh or calf compression stockings of compression class III were fitted for each patient and the importance of compression therapy reiterated at each visit.

### Results

58 patients were enrolled in the study with a complete follow-up obtained in 39 (8 women, 31 men). 13 of these had calf thromboses, and 26 had multilevel and/or proximal thromboses. Mean follow-up time was 11.6 years. The mortality rate during the study was 14%, including 2 PEs. Recurrent thrombosis occurred in 24% of the initial 58 patients.

After 12 years 64% of the 39 patients had normal clinical findings, 28% had mild chronic venous insufficiency (CVI) stage I and 5% had moderate CVI stage II. Severe CVI stage III was reported in only 1 patient.

Compliance with compression therapy at 12 years was greater in patients with multilevel or proximal thrombotic disease than those with isolated calf vein thromboses, 54% vs 23% ( $p < 0.01$ ). All patients with multilevel or proximal thromboses who used regular compression therapy (defined as use of stocking during the day for on average at least 5 days a week) had only mild or no postthrombotic symptoms at 12 years. These compliant patients also showed no relevant trophic skin lesions. The venous ulcer recorded during the study was in a patient who used stockings only occasionally.

### Conclusion

This study reports a low incidence of moderate and severe postthrombotic syndromes after acute lower limb DVT, particularly in patients with calf vein thrombosis. However, the adverse clinical event rate is high, including two fatal PEs. The benefits of regular compression therapy were clear in patients with multilevel or proximal thromboses who showed only mild or no postthrombotic symptoms at 12 years.

### Comment of the editors

This is a historical land mark publication describing clinical signs and functional parameters concerning outflow resistance up to 12 years after acute thrombosis of the lower extremity.

At the time the investigation was carried out the incidence of a PTS was generally overestimated. The reported outcome of this study that 62% of the patients did not develop a PTS defined by clinical signs is comparable with newer data based on the diagnosis made by the Villalta scale.

All investigated patients suffered from a first episode of phlebographically clearly defined deep vein thrombosis and patients with preexistent signs of chronic venous insufficiency were excluded. The authors emphasized that all the skin changes developed between the second and fourth years, and that thereafter no

significant alterations in clinical status occurred. Only 1 patient developed a venous ulcer after the 4-year visit.

This is very different from the recently published SOX-trial in which venous ulcers have been observed already one month after a first episode deep vein thrombosis<sup>1</sup>. It is extremely unlikely that these ulcers developed on normal skin without previous venous damage. Unfortunately in the SOX trial any clinical characterization of the enrolled patients is missing, both at baseline and at follow-up visits.

Although this was not the aim of their investigation Franzeck et al. underline in their publication some arguments favoring wearing of compression stockings in connection with careful instructions on the importance of daily compression

therapy. They state: "All patients who used regular compression therapy had only mild or no postthrombotic symptoms after 12 years. No relevant trophic skin lesions were present in these highly compliant patients, whereas the only venous ulcer observed in this study developed in a patient who used compression stockings only occasionally. Two additional patients with poor compliance showed marked trophic changes of the lower leg skin."

One consequence from Franzeck's study which is also endorsed by later publications, is the fact that compression is beneficial especially in the first one or two years after DVT and that beyond this period a continuation of compression therapy may be limited to those patients with a clear benefit.

1. Kahn SR, Shapiro S, Wells PS, et al. SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomized placebo-controlled trial. *Lancet*. 2014 Mar 8;383(9920):880-8.

Holmes CE, Bambace NM, Lewis P, Callas PW, Cushman M

## Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome

*Vascular Medicine* 2014;19(1):42-48

### Aim

The aim of the study was to compare the efficacy of graduated compression stockings alone with complex lymphedema therapy (CLT) in patients with clinically established post-thrombotic syndrome (PTS).

### Methods

Patients with a history of ipsilateral DVT and clinical diagnosis of PTS of the lower extremity were randomized to receive CLT or a 30–40 mmHg graduated compression stocking. CLT consisted of skin care, compression stocking and device use, manual lymphatic drainage and exercises. The primary outcomes were changes in PTS at 1 and 3 months follow-up as assessed by the Villalta score. Changes in disease-specific quality of life were also recorded using the VEINES-QOL questionnaire. Investigators remained blind to treatment allocation throughout the study.

### Results

31 patients were randomized to the study and data analysed on an intention-to-treat basis. 11 patients discontinued therapy or were lost to follow-up, including 4 cases of new DVT and 4 CLT patients who cited travel and time constraints. Compliance to stocking use was high in both groups at 1 and 3 months. Patients in both treatment arms were assessed as having moderate PTS at base-

line, with a mean Villalta score of 9.9 in the CLT group and 10.9 in the stockings only group. Severity of PTS decreased at 1 month, an effect that was maintained at 3 months follow-up for both patient groups. The average score at 3 months indicated an improvement to mild PTS, 7.6 points for CLT patients ( $p = 0.05$ ) and 7.7 points for stockings only ( $p = 0.03$ ). No significant difference was found between treatment groups. No impact on quality of life was seen for either treatment group.

When patients were analysed based on compression stocking use prior to study entry, those who had not used stockings in the previous 7 days derived a greater benefit from either intervention, with a decrease in PTS score of -8.8 points in non-users vs -1.5 in users ( $p = 0.07$ ). A trend towards improvement of quality of life was also seen in the group who had not used stockings prior to enrolment. Analysis of the patients with the highest PTS score at baseline showed a greater improvement with either treatment compared with those with less severe disease.

### Conclusion

Compression stocking use alone showed similar efficacy to CLT in the treatment of established PTS, with an improvement from moderate to mild PTS over a period of 3 months.

### Comment of the editors

This study demonstrates the significant improvement of PTS by wearing 30-40 mmHg graduated compression stockings. Despite the controverse discussion wether PTS itself can be prevented by compression stockings the results show clearly that treatment of PTS is possible with compression. This effect becomes very clear when previous compression users where compared to non-users. Those who had not used stockings in the previous 7 days decreased in Villalta PTS score by 8.8 points compared to users with 1.5 points ( $p = 0.07$ ). Interestingly additional components of CTD, consisting of skin care, compression device use, manual lymphatic drainage and exercises, did not improve the results further. In consequence treatment with graduated compression stockings is indicated in patients suffering from PTS.

Ashby RL, Gabe R, Ali S, Adderley U, Bland JM, Cullum NA et al

# Clinical and cost-effectiveness of compression hosiery versus compression bandages in the treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial

*Lancet* 2014;383:871-79

## Aim

The aim of the study was to compare the clinical and cost-effectiveness of two-layer compression hosiery with a four-layer bandage in the treatment of venous leg ulcers.

## Methods

VenUS IV was an open, randomized controlled trial of compression hosiery vs four-layer bandage in the treatment of venous leg ulcers. Patients were eligible for inclusion if they had at least one venous leg ulcer, an ankle brachial pressure index  $\geq 0.8$  and were able to tolerate high compression. The four-layer bandage was required to deliver 40 mmHg of compression at the ankle while the two-layer hosiery delivered 35-40 mmHg. Primary endpoint was time to healing of the reference ulcer, with maximum follow-up of 12 months. Secondary endpoints included health-related quality of life, resource use, treatment change, adverse events and ulcer recurrence.

## Results

457 patients were randomized to treatment, with 230 in the hosiery group and 224 in the bandage group available for intention-to-treat analysis. No difference in the time to healing was found between groups. Median time to healing was 99 days for patients using hosiery and 98 days for those using the bandage.

The proportion of healed ulcers was also similar, 71% and 70% for hosiery and bandage groups, respectively. However, the recurrence of ulcers was less in the hosiery group (14%) than the bandage patients (23%). Treatment change was more frequent in the hosiery group than bandage users, 38% vs 28%, respectively, with a higher proportion of patients reporting the compression to be uncomfortable.

Economic analysis suggests an average mean cost of £300 less per patient per year in the hosiery group than the bandage group, mainly due to reduced number of nurse consultations. The hosiery patients also had slightly more quality-adjusted life-years than the bandage patients.

## Conclusion

Two-layer compression hosiery is as effective as the current standard of a four-layer bandage for the treatment of venous leg ulcers. The hosiery was also associated with a reduced risk of ulcer recurrence and was found to be more cost-effective.

## Comment of the editors

Venous leg ulcers (VLU) are associated with pain, loss of quality of life and high costs for the health system and for the patients.<sup>1</sup> In the last decade two-layer compression stockings were introduced

in VLU treatment as an alternative to compression bandages. The benefit may be a better standardization of the compression and less need for help by health professionals in performing the bandaging.

This big prospective randomized study compared 230 VLU patients using two-layer hosiery (35-40 mmHg at the ankle) with 224 VLU patients using a four-layer-bandage system (40 mmHg at the ankle). In the intention-to-treat analysis the authors could demonstrate that time-to-healing and healing rate were not statistically different in the two groups. In addition using compression hosiery led to cost reduction of £300 per patient and year, due to reduced number of nurse consultations. This makes compression hosiery more cost effective compared to bandages.

In consequence two-layer compression stockings should be considered as a standard option for treatment of VLU if this seems applicable from the ulcer conditions.

<sup>1</sup> Purwins S, Herberger K, Debus ES, Rustenbach SJ, Pelzer P, Rabe E, Schäfer E, Stadler R, Augustin M. Cost-of-illness of chronic leg ulcers in Germany. *Int Wound J*. 2010 Apr;7(2):97-102.

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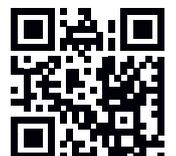
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