Compression Bulletin 36

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One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial

The aim of this study was to establish whether stopping elastic compression stocking (ECS) use after 12 months was non-inferior to standard treatment of 24 months in preventing post-thrombotic syndrome (PTS) in patients with proximal deep vein thrombosis (DVT). Stopping compression therapy at 12 months was less effective than standard treatment over 24 months in preventing PTS.

Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial

The trial was designed to assess the safety and efficacy of individualized duration of compression therapy in preventing post-thrombotic syndrome compared with the standard duration of 24 months in patients with acute, proximal, deep vein thrombosis (DVT).

There was no difference between a standardized duration of 24 months and a individualized shorter treatment duration in the prevention of PTS. However, the expected benefit of a shorter treatment time on quality-of-life was not substantiated.

Clinical and economic impact of compression in the acute phase of deep vein thrombosis

The authors of this study investigated the impact of compression therapy in the acute phase of deep vein thrombosis (DVT) on the individual elements of, and total, Villalta score, health-related quality-of-life (HRQOL) and healthcare costs. While the study found multilayer bandaging to be slightly more effective than compression stockings, it was at significantly greater cost.

Compression therapy for prevention of post-thrombotic syndrome

This comprehensive review aimed to establish the relative effectiveness and rate of complications of compression therapy in order to prevent post-thrombotic syndrome (PTS) in patients with deep vein thrombosis (DVT). As a result of considerable differences between studies and lack of or unclear risk of blinding due to clinical assessment scores the authors downgraded the evidence from moderate to low-quality, highlighting the need for large, high-quality trials.

Congresses:

60th Annual Meeting of the German Society of Phlebology (DGP) September	Bielefeld, Germany	September 26 – 29, 2018
19th Annual Meeting of the Swiss Society for Vascular Diseases (USGG)	Lugano, Switzerland	October 24 – 26, 2018
32th Annual Meeting of the American College of Phlebology (ACP)	Nashville, Tennessee, USA	November 8 – 11, 2018

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Published under the auspices of the UIP since 2001
www.stemmerlibrary.com

Mol GC, van de Ree MA, Klok FA, Tegelberg MJAM, Sanders FBM, Koppen S, de Weerdt O, Koster T, Hovens MMC, Kaasjager HAH, Brouwer RE, Kragten E, Schaar CG, Spiering W, Arnold WP, Biesma DH, Huisman MV

One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial

BMJ 2016;353:i2691

Aim
This study aimed to establish whether stopping elastic compression stocking (ECS) use after 12 months was non-inferior to standard treatment of 24 months in preventing post-thrombotic syndrome (PTS) in patients with proximal deep vein thrombosis (DVT).

Methods
The OCTAVIA study was a randomised, controlled, single-blind, non-inferiority trial in eight centres in the Netherlands. Patients who had been diagnosed with DVT less than one year previously, had been prescribed graduated ECS class III (34-46 mmHg) and who had reported strict compliance (≥6 days a week) were randomised to either continue or cease ECS treatment at 12 months. Follow-up was performed at 3 months via telephone, and at 6 and 12 months at the clinic.

The primary endpoint was incidence of PTS at 24 months after DVT diagnosis defined as Villalta score ≥5 or presence of venous ulcer. Secondary endpoints included quality-of-life assessed using the VEINES-QOL/Sym questionnaire at baseline and 12 months.

Results
A total of 518 patients had data available for analysis; 262 patients continued ECS use and 256 discontinued therapy. During the 12-24 month period, 19.9% of patients who discontinued ECS and 13% who continued therapy developed PTS, giving an adjusted hazard ratio of 1.6 (95% CI 1.02-2.5). The majority of cases of PTS were classified as mild (Villalta score 5-9); 84% in the stop-ECS group and 91% in the continue group.

Quality-of-life measures did not significantly change from baseline to 12 months in either group, although there was a trend towards a decrease in the stop-ECS group compared with a positive trend in the continue group.

Following data collection it was discovered that 28% of patients had been prescribed a lower class of ECS than required by the protocol, 23-32 mmHg vs 34-46 mmHg. However, post-hoc analyses did not show any interaction of ECS grade with either primary or secondary endpoints.

Conclusions
In patients compliant with ECS use, cessation of therapy at 12 months was not non-inferior to standard treatment. The authors also suggest that continuing ECS beyond 24 months may be beneficial in preventing PTS in some patients and deserves further research.

Comments of the Editors
In previous studies wearing medical compression stockings (MCS) for a fixed duration of two years was able to reduce the incidence of post thrombotic syndrome (PTS) after proximal deep venous thrombosis (DVT) by 50% (Brandjes, Prandoni). As only a part of the DVT patients develop PTS it was discussed whether the duration of MCS prophylaxis could be shortened in so far asymptomatic patients. In the present study the authors compared 12 versus 24 months of MCS prophylaxis in a prospective randomized non-inferiority study. Only patients after proximal DVT, wearing MCS for one year and who had no PTS at inclusion, were randomized. After two years significantly, more patients who discontinued MCS developed PTS (19.9 versus 13%).

These results indicate that even asymptomatic patients 12 months after proximal DVT have a 20 % risk to develop PTS if MCS prevention is discontinued and that this incidence can be reduced to 13 %. These findings are in discordance with the results of the SOX trial where no difference in PTS incidence was found with or without MCS (Kahn). The main reason may be that the compliance in the SOX study was low with only 56 % of patients wearing their MCS for at least three days a week at the end of the follow-up period compared to a high compliance of 93 % in the patients in this study at one year after DVT at inclusion in the study and 84 % at the end of follow-up. The OCTAVIA trial excluded patients who had DVT and a history of MCS treatment before index DVT but this did not fully exclude patients with chronic venous disease like varicose veins. This may explain why one patient in the compression group developed a venous ulcer after the short time of two years after DVT.

In conclusion the results confirm the benefit of MCS for the prevention of PTS and propose a standard duration of MCS prophylaxis of two years. No data is available concerning the effect of MCS after this time in so far asymptomatic patients after proximal DVT.

Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759-62. doi:10.1016/S0140-6736(96)12215-7.

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Kahn SR, Shapiro S, Wells PS, et al. SOX trial investigators.
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ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, Mostard GJM, ten Wolde M, van den Heiligenberg SM, van Wissen S, van de Poel MHW, Villalta S, Serné EH, Otten H-M, Klappe EH, Bistervels IM, Lauw MN, Piersma-Wichers M, Prandoni P, Joore MA, Prins MH, ten Cate H, for the IDEAL DVT investigators

Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial

Lancet Haematology 2018;5:e25-33

Aim
The IDEAL DVT study aimed to assess the safety and efficacy of individualised duration of compression therapy in preventing post-thrombotic syndrome compared with the standard duration of 24 months in patients with acute, proximal, deep vein thrombosis (DVT).

Methods
This was a multicentre, randomised, single-blind, non-inferiority trial at centres in the Netherlands and Italy. Adults who had an acute, proximal thrombosis of the leg and had received appropriate treatment within the first 24 hours were randomised 1:1 to compression stocking treatment based on their Villalta score, or standard treatment of 24 months. Patients were excluded if they had undergone active thrombolysis, previous ipsilateral DVT, pre-existing severe venous insufficiency, or contraindications for compression therapy.

A custom-fitted, knee-length, graduated compression stocking class III (ankle pressure 30-40 mmHg) was prescribed for all patients. Patients were assessed for signs of post-thrombotic syndrome using the Villalta scale at 3, 6, 12 and 24 months. Adherence was measured via questionnaires and telephone contact. For patients receiving individualised treatment their Villalta score determined the duration of compression therapy:

- Therapy could be discontinued if Villalta score was ≤4 at both 3 and 6-month visits
- Therapy continued for 24 months if score was ≥5 at both 3 and 6-month visits
- Therapy continued for 6 months if score was ≥5 at 3-months but was ≤4 at 6-months. If the Villalta score was ≤ 4 again at 12-months, compression therapy was discontinued

Any anticoagulation medication was determined by the treating physician.

Results
Over a period of four years, 865 patients were enrolled; 437 were randomised to individualised treatment and 428 to standard duration. Baseline characteristics and anticoagulant therapy were similar between groups.

After 6 months, 55 % of patients were able to discontinue compression therapy, followed by another 11 % at 12 months. Of the 6 % who had compression use reinstated, 3 % required ongoing therapy due to persistent leg complaints, while 3 % only required a temporary return to treatment, (i.e. one week of treatment).

Post-thrombotic syndrome occurred in 29 % of patients in the individualised treatment group, and 28 % of the standard duration group (OR 1.06, 95 % CI, 0.78-1.44). The majority of these cases were identified at 6 months (21 % in both groups). The number of recurrent venous thromboembolic episodes was similar between groups.

Adherence to compression stocking use was high, with over 90 % of patients adherent after 3 months and almost 80 % at 24 months. Quality-of-life scores were similar, and significantly improved over time for both groups. No serious adverse events or deaths were related to treatment.

Conclusions
The duration of compression stocking treatment tailored to an individual was non-inferior to standard duration of 24 months in preventing post-thrombotic syndrome in patients with acute proximal DVT. However, the expected benefit of a shorter treatment time on quality-of-life was not substantiated. The authors suggest that the use of compression beyond 6 months in order to prevent mild post-thrombotic syndrome be assessed for cost-effectiveness.

Comments of the Editors
In this study the authors answered the question if the standard duration of medical compression stocking (MCS) prophylaxis can be safely shortened if the individual signs and symptoms of post-thrombotic syndrome (PTS) after proximal deep venous thrombosis (DVT) where taken into account after 3, 6 and 12 months. Patients with previous DVT or severe chronic venous insufficiency where excluded from the study. Compression was started immediately after DVT and switched to below-knee 30-40 mmHg MCS as soon as possible.

The results show that in approximately 50 % of the patients MCS prophylaxis could be stopped at 6 months without a higher incidence of PTS at 24 months compared to the ongoing MCS group. Only in a small part of the patients the decision of MCS discontinuation had to be revised when new symptoms developed. The overall PTS incidence at 24 months was almost identical with 29 and 28 %. In contrary to the SOX trial, challenging the usefulness of MCS for prevention of PTS after proximal DVT, adherence to therapy advice was much higher in the IDEAL study with more than 90 % after 3 months and almost 80 % at the last follow-up visit (Kahn). These good adherence values are like those reported in other trials that showed efficacy of compression therapy to prevent PTS (Brandjes, Prandoni, Mol). In contrary to the OCTAVIA study, with a comparison of 12 months and 24 months MCS prophylaxis in patients free of PTS, at 12 months the individualized access did not lead to higher incidence of PTS after 24 Months (Mol).

In conclusion, individualised duration of MCS prophylaxis resulted in a shortened treatment duration of only 6 months in more than 50 % of patients, and was safe and effective. In these cases patient´s comfort may have been improved and overall costs may have been reduced.

Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014; 383: 880–88.

Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759–62.

Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004; 141: 249–56.

Mol GC, van de Ree MA, Klok FA, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. BMJ 2016; 353: i2691.

Amin EE, Joore MA, ten Cate H, Meijer K, Tick LW, Middeldorp S, Mostard GJM, ten Wolde M, van den Heiligenberg SM, van Wissen S, van de Poel MHW, Villalta S, Serné EH, Otten H-M, Klappe EH, Prandoni P, ten Cate-Hoek AJ

Clinical and economic impact of compression in the acute phase of deep vein thrombosis

Journal of Thrombosis and Haemostasis 2018; Jun 1:epub ahead of print

Aim
This study aimed to assess the impact of compression therapy in the acute phase of deep vein thrombosis (DVT) on the individual elements of, and total, Villalta score, health-related quality-of-life (HRQOL) and healthcare costs.

Methods
This was a sub-study of the randomised, controlled, IDEAL DVT trial in the Netherlands and Italy. Patients received compression therapy as per the treatment centre protocol, either: thigh-high, short-stretch, multilayer compression bandaging applied by healthcare professionals, or; thigh-high compression stocking (35mmHg) or no compression, started within 24 hours of DVT diagnosis.

Villalta score was assessed at 3 months and included 5 patient-rated symptoms (pain, cramps, heaviness, paraesthesia and itching) and 6 physical items (pretibial oedema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia and redness). HRQOL was measured after one week and 3 months using the EQ-5D, SF-36 and VEINES-QoL questionnaires. Healthcare costs included GP visits (and transportation), general practice centre, specialist visit, use of painkillers, home care nursing demand, and cost of compression material.

Results
A total of 865 patients were enrolled in the IDEAL-study study, 668 of whom received compression: 48.5 % received multilayer bandaging and 29.6 % received compression stockings. 6 % of the stocking group switched to bandaging due to leg complaints.

Villalta score
Three months after acute DVT no significant difference was found between groups in the patient-rated elements of the Villalta scale. The mean total objective score, however, was significantly lower for patients with compression vs no compression (bandaging, 1.47; stockings, 1.59; no compression, 2.21; $p < 0.001$). When the compression groups were combined, significant differences in skin induration, hyperpigmentation, venectasia and pain upon calf compression were found compared with no compression.

Quality-of-life
In the acute phase of treatment, patients receiving stocking therapy had significantly higher EQ5D and VEINES-QoL scores vs the bandaging group. However, this difference was no longer significant at 3 months. No significant differences were found between the combined compression groups and no compression.

Healthcare costs
The mean total cost per patient was highest for the multilayer bandaging group (€ 417.08), compared with € 114.25 for the stocking group and € 105.86 for no compression. This difference was mainly due to the higher compression material and home care nursing costs associated with bandaging.

Conclusions
While the study found multilayer bandaging to be slightly more effective than compression stockings, it was at significantly greater cost. Therefore, the authors suggest the need to identify those patients most at risk of post-thrombotic syndrome, and thus greatest benefit, while stockings present the most cost-effective choice for unselected patients when initial compression therapy is required.

Comments of the Editors

Compression and immediate mobilisation of patients with acute deep vein thrombose has some tradition in the Netherlands and in German speaking countries, but up to now positive effects concerning a reduction of pain and swelling have been demonstrated in very few and small studies only. This retrospective sub analysis of data from the large IDEAL-study proves now that compression in the acute phase of DVT has clear advantages compared to no compression. Unfortunately, no clear parameters concerning pain and swelling in the acute phase of DVT were available in this retrospective analysis. Villalta scores after 3 months could be evaluated, compression groups had lower overall objective Villalta scores than the no compression group. Differences were mainly due to irreversible skin signs (induration, hyperpigmentation, venectasia) and pain on calf compression. Subjective and total Villalta scores were similar across groups. In the acute phase quality of life parameters showed better HRQOL for initial compression stockings. Although in the IDEAL study pre-existing signs of venous insufficiency were excluded, the incidence of irreversible signs of hyperpigmentation, ectasia and skin induration, could be reduced, significantly more pronounced in the group of patients who received multilayer bandaging, but at higher costs.

The use of Villalta scale alone may be a problem for the assessment of therapeutic effects since this is rather non-specific, both for PTS and for deep vein thrombosis. It may be assumed that Villalta score was already elevated in the acute stage as well, although patients with clinical signs of chronic venous insufficiency had been excluded.

Appelen D, van Loo E, Prins MH, Neumann MHAM, Kolbach DN

Compression therapy for prevention of post-thrombotic syndrome

Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD004174.

Aim
This review aimed to establish the relative effectiveness and rate of complications of compression therapy in order to prevent post-thrombotic syndrome (PTS) in patients with deep vein thrombosis (DVT).

Methods
In order to update a review published in 2003, randomised controlled trials evaluating compression therapy for the treatment of DVT were identified from the Cochrane Vascular Specialised Register and the Cochrane Central Register of Controlled Trials in 2017. All studies had to assess incidence of PTS, while secondary endpoints included venous thromboembolism (VTE), adverse events, quality-of-life and compliance.

Results
Ten randomised controlled trials were identified, with 5 suitable for inclusion in the meta-analysis; 3 compared elastic compression stockings (ECS, 30-40 mmHg) with no compression and 2 compared ECS (20-40 mmHg) with placebo stockings.

Overall, use of elastic compression stockings led to a clinically significant reduction in the total incidence of PTS (RR 0.62, 95 % CI: 0.38 to 1.01; P = 0.05), but no reduction in the incidence of severe PTS (RR 0.78, 95 % CI 0.53 to 1.15; P = 0.21) and no clear difference in DVT recurrence (RR 0.94, 95 % CI 0.69 to 1.28; P = 0.69).

Other key findings include:

- No difference between compression and no compression in the acute phase of DVT on the incidence of PTS (2 studies)
- No difference in PTS between thigh-length vs knee-length stockings (1 study)
- Use of ECS for 2 years was associated with a lower incidence of PTS than use for 12 months (1 study)
- A significant improvement in well-being and DVT-related quality-of-life with compression treatment vs bed rest ($p < 0.05$; 1 study)
- No difference in quality-of-life scores between compression and placebo (1 study)

Adverse events were poorly reported but included itching, erythema and other allergic reactions and no serious adverse events were recorded. Compliance to treatment was variable, but generally high.

Conclusions
Because of considerable differences between studies and lack of or unclear risk of blinding due to clinical assessment scores the authors downgraded the evidence from moderate to low-quality, highlighting the need for large, high-quality trials.

Comments of the Editors
This Cochrane review gives an admirable overview of the literature on the question if compression therapy can reduce postthrombotic syndrome, by carefully analysing the literature on this subject in a critical manner. However, due to the extraordinary methodological differences between the presented studies one should not expect clear information regarding a single clinical case. The main value of this critical meta-analysis is rather that it provides an excellent source of the existing literature on this subject, emphasizing points which need to be clarified in future studies.