CLINICAL RESEARCH STUDY

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Venous Compression for Prevention of Postthrombotic Syndrome: A Meta-analysis

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ABSTRACT

PURPOSE: To determine the effectiveness of venous compression stockings or compression bandages on the reduction of postthrombotic syndrome in patients with deep venous thrombosis.

METHODS: We attempted to identify all published trials in all languages identified by PubMed through June 2009. Meta-analysis was performed.

RESULTS: Based on 5 randomized trials of patients with deep venous thrombosis comparing treatment with venous compression to controls, mild-to-moderate postthrombotic syndrome occurred in 64 of 296 (22%) treated with venous compression, compared with 106 of 284 (37%) in controls (relative risk = 0.52). Severe postthrombotic syndrome occurred in 14 of 296 (5%) treated, compared with 33 of 284 (12%) controls (relative risk = 0.38). Any postthrombotic syndrome occurred in 89 of 338 (26%) treated, compared with 150 of 324 (46%) controls (relative risk = 0.54).

CONCLUSION: Venous compression reduced the incidence of postthrombotic syndrome, particularly severe postthrombotic syndrome. Venous compression in patients with deep venous thrombosis would seem to be indicated for this purpose. There was, however, wide variation in the type of stockings used, time interval from diagnosis to application of stockings, and duration of treatment. Further investigation, therefore, is needed.

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KEYWORDS: Deep venous thrombosis; Postthrombotic syndrome; Venous compression stockings

The reported incidence of postthrombotic syndrome after symptomatic deep venous thrombosis varies widely and depends on the severity of the postthrombotic syndrome. Some reported that by the end of 1 month, among 347 patients with deep venous thrombosis, 34% developed mild postthrombotic syndrome, 10% moderate, and 4% severe.[1] Among patients with deep venous thrombosis who did not wear compression stockings, 20% to 82% developed postthrombotic syndrome of any severity.[2-6]

Deep venous obstruction, calf muscle dysfunction, and venous reflux are contributing factors to the postthrombotic syndrome.[7] Venous hypertension developing due to venous reflux results in increased capillary filtration, leading to edema in the lower leg and skin changes, including dermatitis, lipodermatosclerosis, and white skin atrophy.[8] Local tissue hypoxia is associated with venous ulcers.[9] Disturbed microcirculation, perhaps due to precapillary fibrin cuffs, has been speculated to lead to a decrease of cutaneous oxygen concentration, contributing to spontaneous breakdown of the skin, but secondary hypoxia has not been demonstrated.[7]

It has become common practice to prescribe graduated compression stockings for patients with deep venous thrombosis, particularly proximal deep venous thrombosis, to prevent postthrombotic syndrome.[10,11] Review in the clini-

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cal guideline by Kearon et al[11] led them to conclude that graduated compression stockings were beneficial for the prevention of postthrombotic syndrome, although a randomized trial by Ginsberg et al[3] showed no benefit. A meta-analysis by Kolbach et al[8] that included 3 randomized trials showed an overall benefit of compression stockings in the prevention of any postthrombotic syndrome and of severe postthrombotic syndrome. A meta-analysis by Giannoukas et al[12] that included 4 randomized trials also showed an overall benefit of compression stockings in the reduction of any postthrombotic syndrome. Because of the potential importance of graduated compression stockings in the prevention of postthrombotic syndrome, we updated the literature review on this subject and performed a meta-analysis to include a randomized trial since the previous meta-analyses by Kolbach et al[8] and Giannoukas et al.[12]

CLINICAL SIGNIFICANCE

- Mild-to-moderate postthrombotic syndrome occurs in 37% of patients with deep venous thrombosis, and severe occurs in 12%.
- Venous compression, usually with below-knee compression stockings, reduced the incidence of mild postthrombotic syndrome to 22%, and severe to 5%.
- Venous compression stockings are effective in reducing the incidence of postthrombotic syndrome in patients with deep venous thrombosis.

METHODS

Study Identification

We attempted to identify all published trials in all languages that used compression stockings to prevent the postthrombotic syndrome. Studies were identified by searching PubMed through June 2009. Key words in the literature search were: "postthrombotic syndrome" combined with "prevention," "elastic stockings," or "compression therapy." We augmented our searches by manually reviewing the reference lists of all original articles and all review articles. This was done by 2 of the authors, working separately. Each study was evaluated for inclusion by at least 2 authors.

Studies were included if they met all of the following criteria: patients were randomized for comparison between treatment with compression stockings or compression bandages and no compression treatment; anticoagulant therapy was the same in compression therapy groups and the no-stocking groups; the diagnosis of deep venous thrombosis was made on the basis of objective tests; raw data were presented in sufficient detail to permit calculations of the incidence of postthrombotic syndrome.

The literature search identified 257 citations. Among these, 64 were unrelated to postthrombotic syndrome, 69 were reviews or a guideline, 84 were related to prophylaxis or treatment without specific investigation of compression stockings, 23 were related to the pathophysiology and diagnosis of postthrombotic syndrome, 10 were case series or case reports, and 2 described methods of ongoing investigations. Complete versions of the articles were obtained if, from the title or abstract, they satisfied the inclusion criteria. Five randomized trials evaluated the effects of graduated compression stockings or compression bandages on the prevention of postthrombotic syndrome, and these were included.

Definitions of mild-to-moderate and severe postthrombotic syndrome used by Brandjes et al,[2] Partsch et al,[4] and Prandoni et al[5] were based on the Villalta scoring system,[13] which was summarized by Kahn and Ginsberg.[14] In the Villalta scoring system, a score of 5-14 indicated mild-to-moderate postthrombotic syndrome, and a score of $\geq$15 indicated severe. Aschwanden et al[6] used the Clinical-Etiology-Anatomic-Pathophysiologic (CEAP) scoring system,[15] also summarized by Kahn and Ginsberg.[14] Aschwanden et al[6] excluded from their results those with the lowest scores of 0-3. We interpreted a CEAP score of C4 (skin changes, pigmentation, eczema, lipodermatosclerosis) to indicate mild-to-moderate postthrombotic syndrome, and a CEAP score of C5 (skin changes with healed ulcer) and C6 (skin changes with active ulcer) to indicate severe postthrombotic syndrome. Ginsberg et al[3] did not quantify severity.

Statistical Methods

Meta-analysis was performed using the Metan procedure of Stata, release 8.0 (StataCorp LP, College Station, Tex). Summary effects for the outcomes were calculated by using the fixed-effects model. The random-effects model produced similar results. We considered a probability of $P < .05$ to be statistically significant for all statistical tests.

RESULTS

Age and sex of the patients in the 5 included trials are shown in Table 1. Among 338 treated patients, below-knee stockings were used in 308 (91%) patients, thigh-length stockings in 17 (5%), and thigh bandages in 13 (4%).[2-6] Characteristics of the stockings, time interval between diagnosis of deep venous thrombosis and application of stockings, duration of stocking use, duration of follow-up, the scoring system used, and the incidence of postthrombotic syndrome are shown in Table 2.

Among patients treated with venous compression, mild to moderate postthrombotic syndrome occurred in 64 of 296 (22%), compared with 106 of 284 (37%) in controls.[2-6] The relative risk of mild-to-moderate postthrombotic syndrome was 0.52 (95% confidence interval [CI], 0.40-0.67; $P < .001$) (Figure 1).

Table 1 Sex and Age of Included Patients

First Author (Reference)	Year	Sex		Mean Age (Years)	
		Control	Stockings	Stockings	Control
Brandjes[2]	1997	M = 55 F = 44	M = 54 F = 42	60	59
Ginsberg[3]	2001	M = 70 F = 90	M = 23 F = 19	46-62*	40-60*
Partsch[4]	2004	M = 7 F = 4	M = 16 F = 10	61-62	47
Prandoni[5]	2004	M = 35 F = 55	M = 42 F = 48	60	63
Aschwanden[6]	2008	M = 45 F = 40	M = 54 F = 30	64	64

*Ages differed in study groups.

Severe postthrombotic syndrome occurred in 14 of 296 (5%) patients treated with venous compression, compared with 33 of 284 (12%) controls.[2-6] The relative risk of severe postthrombotic syndrome, comparing stockings with no stockings, was 0.38 (95% CI, 0.22-0.68; $P = .001$) (Figure 2). Open lesions were found in 3 of 296 (1.0%) patients who used compression stockings and 9 of 284 (3.2%) controls. This difference was not significant.

Any postthrombotic syndrome occurred in 89 of 338 (26%) treated with compression stockings compared with 150 of 324 (46%) controls.[2-6] The relative risk of any postthrombotic syndrome was 0.54 (95% CI, 0.44-0.67; $P < .001$) (Figure 3).

Sensitivity analysis showed that the results for the outcomes of all episodes of postthrombotic syndrome, or cases of mild/moderate postthrombotic syndrome, were robust. Removal of individual studies did not alter our findings. The venous compression advantage was not lost for any of the outcomes when a single study was removed from the meta-analysis.

Statistical tests did not detect heterogeneity in risk ratio among studies for the outcomes of all episodes of postthrombotic syndrome, or cases of mild/moderate postthrombotic syndrome, or cases of severe postthrombotic syndrome.

DISCUSSION

The risk of postthrombotic syndrome, on average, was reduced 46% by venous compression, usually by below-knee compression stockings. Venous compression was more effective in reducing the incidence of severe postthrombotic syndrome (62% risk reduction) than mild-to-moderate postthrombotic syndrome (48% risk reduction). One investigation (Ginsberg et al)[3] showed little benefit. In this investigation, the control patients received stockings that were 1-2 sizes too large.[3] We speculate that the unfitted stockings may have had a beneficial effect despite being 1-2 sizes too large. Also, these investigators waited 1 year after the episode of acute deep venous thrombosis before randomizing for patients for compression stockings. Whether this delay contributed to the failure to show an effect of compression stockings is uncertain. Patients in the control group in this investigation had nearly the same incidence of postthrombotic syndrome (28%) as patients in the treatment groups in the investigations by Prandoni et al (26%) and Brandjes et al (31%).[2,3,5]

The time interval between diagnosis of acute deep venous thrombosis and the application of stockings, and the duration of application of compression stockings may have affected the results. The lowest relative risks for postthrombotic syndrome after the application of compression stockings were reported by Brandjes et al[2] (risk ratio 0.44) and by Prandoni et al[5] (risk ratio 0.52). These investigators applied stockings 2-3 weeks or within 5-10 days after the diagnosis of deep venous thrombosis, and compression stockings were worn for 2 or more years.[3,5] In contrast, Partsch et al[4] treated patients with compression therapy immediately, but only for 9 days, whereas control patients received no compression treatment for only 9 days.[4] Thereafter, half or more of both controls and treated patients wore compression stockings for 2 years. These investigators showed a risk ratio of .66 with treatment, suggesting that the early application of venous compression is important. Both Ginsberg et al[3] and Aschwanden et al[6] showed no statistically significantly lower risk ratio for skin changes in those who wore compression stockings. Aschwanden et al[6] started randomization to compression stockings 6 months after the diagnosis of deep venous thrombosis, and Ginsberg et al[3] waited 1 year before randomizing for treatment. This may have adversely affected the results.

In addition to differences in time to application of stockings, and duration of use, some used below-knee stockings,[2,5,6] thigh-length stockings,[4] or either.[3] Strength of stockings varied (Table 2).

There is no universal agreement on a definition of postthrombotic syndrome.[3] All definitions, however, include chronic complaints of the legs following deep venous thrombosis.[8] Symptoms may include pain, heaviness, pruritus, and paresthesia, and signs may include pretibial edema, erythema, induration, hyperpigmentation, new venous ectasia, pain during calf compression, and ulceration.[8] Definitions of severity differ,[3,13,15] and certain definitions, of necessity, are arbitrary.[15] The International Society on Thrombosis and Haemostasis recommended the Villalta scale as a standard scale for severity of postthrombotic-syndrome.[16] We used the definition of severity in the Villalta system when that system was used by the investigators. In the only study that used the CEAP scoring system,[6] we defined severe as showing healed or active ulcer. This corresponded to "severe" by the Villalta system, in which presence of ulcer was considered severe. Because of correspondence of the scoring systems for "severe," we do not believe that differences in the scoring methods affected the results of the meta-analysis.

The investigation by Aschwanden et al[6] excluded patients with the mildest signs, telangiectasias, reticular veins, malleolar flare (C1 classification), varicose veins (C2 clas-

Table 2 Stocking Characteristics, Study Protocol, and Results

First Author, Year	Group	Patients (n)	Stocking Pressure (mm Hg)	Stocking Length and Type	Interval Diagnosis to Stocking	Stocking Duration (Years)	Follow-up (Years)	Scoring System	Mild/ Moderate	Severe	Total
Brandjes[2] 1997	Control	98					≥5	Villalta-Prandoni Scale*	46/98 (47)	23/98 (23)	69/98 (70)
	Stocking	96	40 at ankle 36 at lower calf 21 at upper calf	GCS below knee	2-3 weeks	≥2	≥5		19/96 (20)	11/96 (11)	30/96 (31)
Ginsberg[3] 2001	Control	40	Stockings 1-2 sizes too large	Below knee or thigh (1-2 sizes too large)			1.8-4.9	‡			11/40 (28)
	Stocking	42	20-30 below knee, n = 24 30-40 below knee, n = 14 30-40 thigh, n = 4	ECS below knee, n = 38 ECS thigh length, n = 4	1 year	1.4-4.6	1.4-4.6				11/42 (26)
Partsch[4] 2004	Control	11			No stockings for 9 days	Bed rest 9 days, no stockings in all, then stockings in 8/11 (73%) × 2 years	2	Villalta-Prandoni Scale*	9/11 (82)	0/11 (0)	9/11 (82)
	Stocking	26	30-40	Thigh length ECS (n = 13) or gauze-zinc oxide and calamine impregnated bandage on lower leg and firm thigh adhesive bandage (n = 13)	Immediate	9 days stockings or Unna boot in all, then stockings in 13/26 (50%) × 2 years	2		14/26 (54)	0/26 (0)	14/26 (54)
Prandoni[5] 2004	Control	90					3-5	Villalta-Prandoni Scale*	34/90 (38)	10/90 (11)	44/90 (49)
	Stocking	90	30-40 at ankle	GSC below knee	5-10 days	2	3-5		20/90 (22)	3/90 (3)	23/90 (26)
Aschwanden[6] 2008	Control	85					2.9	CEAP Classification†	17/85 (20)	0/85 (0)	17/85 (20)
	Stocking	84	26.3-36.1 at ankle	CS below knee	6 months	3.2	3.2		11/84 (13)	0/84 (0)	11/84 (13)

GCS = graduate compression stockings; ECS = elastic compression stockings; CS = compression stockings.
*Villalta-Prandoni Scale.[13]
†CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) Classification.[15]
‡Typical pain plus swelling (≥1 month duration) occurring ≥6 months after acute deep venous thrombosis.[3]

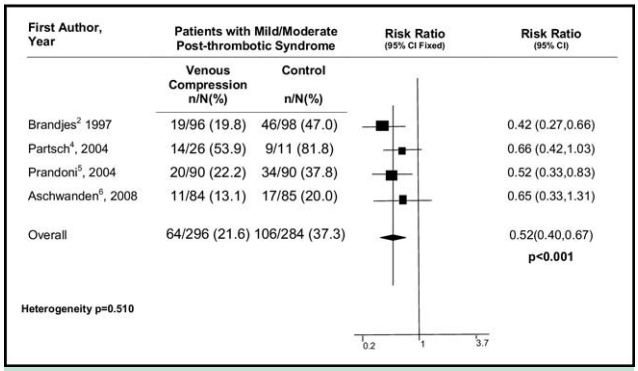

Figure 1 Proportional effects of venous compression on prevention of mild-to-moderate postthrombotic syndrome. Overall relative risk with venous compression was 0.52 (P <.001). Black squares = point estimates (with area proportional to number of events) and horizontal lines = 95% confidence interval (CI) for observed effects in different subgroups; diamonds = point estimate and 95% CI for overall effects, with proportional reductions indicated alongside; long vertical line = hazard ratio of 1.0 (ie, no effect of treatment), and shorter vertical line = observed overall effect.

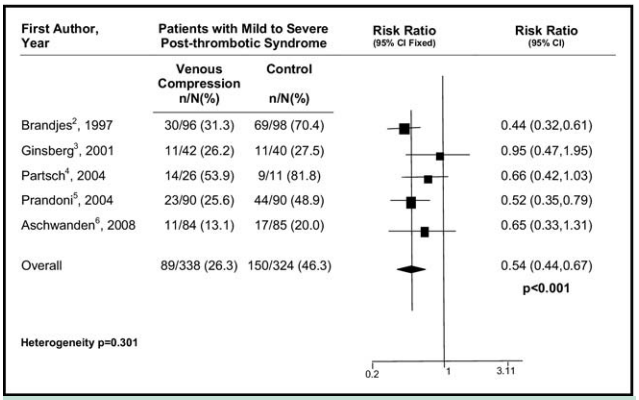

Figure 3 Proportional effects of venous compression on prevention of mild to-severe postthrombotic syndrome. Overall relative risk with venous compression was 0.54 (P <.001). Black squares = point estimates (with area proportional to number of events) and horizontal lines = 95% confidence interval (CI) for observed effects in different subgroups; diamonds = point estimate and 95% CI for overall effects, with proportional reductions indicated alongside; long vertical line = hazard ratio of 1.0 (ie, no effect of treatment), and shorter vertical line = observed overall effect.

sification), and edema with no skin changes (C3 classification).[6] They showed no statistically significant reduction of postthrombotic syndrome (CEAP score 4 or greater). However, they showed fewer symptoms in those treated with stockings.

A strength of this meta-analysis is that all included investigations were randomized. A weakness is that investigators used different methods of vein compression, different time intervals from diagnosis to application of stockings, different durations of treatment, different methods for quantifying severity of postthrombotic syndrome, and different definitions of control groups. Even with these differences, however, investigators showed a benefit of venous compression. In view of the importance of the postthrombotic syndrome, the potential benefit of compression stockings, and variability of the methods employed by previous investigators, a randomized, double-blind multicenter clinical trial (the SOX Trial) of 800 patients followed for 2 years is ongoing.[17]

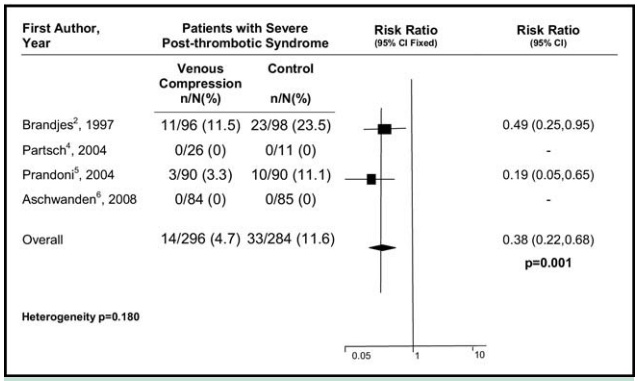

Figure 2 Proportional effects of venous compression on prevention of severe postthrombotic syndrome. Overall relative risk with venous compression was 0.38 (P <.001). Black squares = point estimates (with area proportional to number of events) and horizontal lines = 95% confidence interval (CI) for observed effects in different subgroups; diamonds = point estimate and 95% CI for overall effects, with proportional reductions indicated alongside; long vertical line = hazard ratio of 1.0 (ie, no effect of treatment), and shorter vertical line = observed overall effect.

In conclusion, venous compression was effective in reducing the incidence of postthrombotic syndrome, particularly severe postthrombotic syndrome. Use of venous compression in patients with deep venous thrombosis would seem to be indicated for this purpose. However, there was wide variability in the methods employed by the various investigators. Further investigation, therefore, is needed.

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