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Elastic compression stockings for prevention of the post-thrombotic syndrome in patients with and without residual vein thrombosis and/or popliteal valve reflux

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Contributions

PP, AWAL and MHP designed the study; SV, RP and DT contributed patients, analysed and interpreted data; FN and MHP performed the statistical analysis; GP provided the administrative support; PP, AWAL and MHP drafted the manuscript; all authors critically wrote or revised the intellectual content of the manuscript, reviewed and/or commented on each draft, and approved the final version for submission.

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The efficacy of elastic compression stockings (ECS) for prevention of the post-thrombotic syndrome (PTS) arising after a proximal deep-vein thrombosis (DVT) is controversial.[1,2] Although most randomized studies showed a substantial reduction of PTS with the use of ECS,[3-5] the recent large SOX clinical trial that used sham stockings as comparator failed to confirm these findings.[6] Accordingly, most international guidelines do not longer recommend routine use of ECS for prevention of PTS.[1,7] However, they are still commonly prescribed in clinical practice.[8]

A recent systematic review showed that patients with DVT who at 6 weeks or later had either residual vein thrombosis (RVT) or popliteal valve reflux (PVR) had a higher risk of subsequent PTS than those without these findings.[9] As these ultrasound features are associated with longstanding venous hypertension that could be modified by compression therapy,[10] the early identification of RVT and PVR has the potential to identify a subgroup of patients who may still benefit from use of ECS.

In a prospective cohort study of 869 patients with a proximal DVT that was either unprovoked or associated with transient risk factors, we observed an increased risk of PTS in those with RVT.[11] Briefly, all patients received an initial treatment with unfractionated or low-molecular-weight heparin followed by vitamin K antagonists according to international guidelines with individual treatment durations (ranging between 3 and 24 months) based on patient's preferences and risk profile. Patients with recent (<2 years) ipsilateral DVT and those requiring indefinite anticoagulation were not eligible.[11] Patients were advised to wear ECS (30-40 mmHg at the ankle) for at least two years, and were followed-up for 3 years. They were instructed to report on a booklet the duration they wore the stocking, use of not permitted stockings, and occurrence of adverse effects impairing their use. At 3 months, an ultrasound assessment was done to document the presence of RVT (vein diameter under maximum compressibility >4 mm)[11] and PVR (retrograde flow through the popliteal valve after manual compression of the mid-thigh >0.5 seconds, which persisted after repeating the manoeuvre with a tourniquet).[12] The Villalta scale was used to assess the PTS development every six months. A score of 5 to 14 in two, even non-consecutive, assessments indicated non-severe PTS, while a score $\geq$15 or the presence of skin ulcer in a single assessment indicated severe PTS.[1,11,13]

Here we report the risk of PTS in relation to therapeutic adherence to ECS and presence of RVT, PVR or both in the 861 patients who survived at least six months. Two trained physicians who were unaware of other patient's details or study outcomes

assessed the adherence to ECS. Patients who used the ECS for ≥70% of daytime for the first year were considered adherent ('stockings' group). Patients who did not accept the advised ECS, discontinued ECS use during the first year, or used the ECS <70% of daytime were considered non-adherent ('non-stockings' group).

The main demographic and clinical characteristics of the two groups were compared using standard methods. The hazard ratio (HR) for the effect of ECS on PTS development in the whole population, as well as in patients with and without RVT and/or PVR was estimated using the proportional hazard Cox's regression model. Interaction terms were defined between RVT and ECS, and between PVR and ECS. A minimal significant model was achieved by a likelihood ratio-guided forward stepwise variables selection method. In each of the four subgroups of patients with or without RVT and/or PVR in the 'stockings' or 'non stockings' group, the cumulative incidence of PTS was estimated by the Kaplan-Meier method, tested by the log-rank test, and graphically represented by product-limit survival estimates by the final minimal significant model.

Of the 861 patients, 511 (59.3%) belonged to the 'stockings' group, and the remaining 350 (40.7%) to the 'non-stockings' group. The two groups had substantially comparable demographic and clinical characteristics (Table 1). RVT and/or PVR was detected in 539 patients (62.6%). Of these, RVT alone was found in 299 (55.5%), PVR alone in 115 (21.3%) patients, and the combination of RVT with PVR in 125 (23.2%).

PTS developed in 249 of the 539 patients (46.2%; severe in 35, 6.5%) with RVT and/or PVR, and in 90 of the 322 (28.0%; severe in 11, 3.4%) without RVT and/or PVR (HR, 2.18; 95% CI, 1.73-2.74). PTS developed in 162 of the 511 patients (31.7%; severe in 19, 3.7%) in the 'stockings' group, and in 177 of the 350 (50.6%; severe in 25, 7.1%) in the 'non-stockings' group (HR, 0.64; 95% CI, 0.51-0.79; p<0.001).

In patients with RVT and/or PVR, PTS developed in 114 of the 328 (34.8%) in the 'stockings' group (severe in 14, 4.3%), and in 135 of the 211 (64.0%) in the 'non-stockings' group (severe in 19, 9.0%), for HRs of all and severe PTS of 0.52 (95% CI, 0.41-0.66; p<0.001) and 0.41 (95% CI, 0.21-0.83; p=0.013), respectively. In patients without RVT and/or PVR, PTS developed in 48 of the 183 (26.2%) patients in the 'stockings' group (severe in 5, 2.7%), and 42 of the 139 (30.2%) patients in the non-stockings group (severe in 6, 4.3%), for HRs of all and severe PTS of 0.95 (95% CI, 0.62-1.44; p=0.80) and 0.59 (95% CI, 0.18-1.95; p=0.59), respectively (Table 2). In patients with RVT and/or PVR, the 36-month PTS-free survival figures were 35.2% (95% CI, 28.7-41.7) in the 'non-stockings' group, and 64.0% (95% CI, 58.7-69.3) in the 'stockings' group (P<0.001). In patients

without RVT and/or PVR, the respective figures were 69.3% (95% CI, 61.5-77.1) and 73.5% (95% CI, 67.0-78.0) respectively (P=0.43) (Figure 1).

Of utmost importance, while the interaction term for use of ECS and presence of RVT was highly significant (P<0.037), the term for use of ECS and presence of PVR was not (P=0.46).

Our study strongly suggests that in patients with proximal DVT, adequate use of ECS provides a clinically important reduction in any and severe PTS in patients with ultrasound evidence of RVT (with or without PVR) at 3 months, whereas in patients without RVT such an effect is absent. In a clinical context dominated by persistent uncertainty on the necessity for compression therapy to prevent PTS, our study has the potential to revive a stalled discussion.

Recently, a hypothesis-generating meta-analysis showed a more than two-fold higher incidence of PTS in patients with ultrasound evidence of RVT at least 6 weeks after the index DVT.[9] In patients with PVR, the incidence of PTS was also increased but only by one-third. In hindsight, this small increase could be easily explained by the confounding effect of RVT that can also occur in combination with PVR. Indeed, in our study 48% of patients with PVR had also RVT, but in the multivariate minimal-significant Cox's model, there was no independent effect of PVR on the incidence of PTS, as well as on the relative efficacy of adequate use of ECS.

Our observation is pathophysiologically plausible. Indeed, in the absence of longstanding vascular damage venous hypertension and subsequently PTS are unlikely to occur.[9,14] This is also consistent with the demonstration that PTS is unlikely to develop in individuals with a limited thrombotic burden and in those with isolated calf DVT.[1]

Our results are robust, as they are based on a prospective observation of patients with proximal DVT who were followed-up for up to three years.[11] Also, the assessment of the adequacy of use of ECS was done by physicians who were unaware of clinical outcomes or potential confounders. To minimize the effect of potential confounders, patients with recent ipsilateral DVT were excluded, as were patients with a short life expectancy and those requiring indefinite anticoagulation. The main limitation of our study is the lack of random allocation to ECS or no ECS. However, the two study groups were virtually comparable for demographic and clinical characteristics.

The clinical implication of our observations in combination with results of contemporary studies is that in patients without RVT at three months, ECS can be safely withheld as long as leg complaints have disappeared, ideally after completing the first six

months following the thrombotic episode.[15] However, there is still uncertainty in patients with substantial damage to their venous system, as demonstrated by the presence of RVT at three months. Hence, we believe that trials should be initiated to assess the effect of ECS in patients with proximal DVT and RVT. As our patients were instructed to use ECS from the beginning, and the likelihood of RVT at 3 months was substantial (>50%), we think that both in clinical practice and in further confirmatory studies ECS should be given as soon as possible after the acute DVT in all patients while awaiting the ultrasound test, which has the potential to help decide the subsequent approach.

In conclusions, our results show that the ultrasound assessment of RVT in patients with proximal DVT has the potential to identify those who are likely to benefit from the long-term use of ECS. While awaiting confirmation from properly randomised clinical trials, they are in our opinion plausible enough to inform the long-term management of patients with proximal DVT.

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Table 1. Demographic and clinical characteristics of the study patients, separately in the 'stockings' and 'non-stockings' groups

Characteristics	**Non ECS group** (N=350)	**ECS group** (N=511)	**p value**
Age, years,			
- mean ± SD	62.4 ± 16.5	58.1 ± 18.3	0.001
- median (range)	62 (15-91)	65.5 (18-89)	-
Males	163 (46.6)	252 (49.3)	0.429
Obesity	48 (13.7)	56 (11.0)	0.223
Unprovoked DVT	180 (51.4)	258 (50.5)	0.787
Previous VTE	52 (14.9)	51 (10.0)	0.030
Symptoms of PE	59 (16.9)	67 (13.1)	0.127
DVT location			
- common femoral vein ± popliteal vein	166 (47.4)	261 (51.1)	0.293
- popliteal vein only	184 (52.6)	250 (48.9)	
Vein abnormalities			
- RVT (alone or combined with PVR)	176 (50.3)	248 (48.5)	0.613
- PVR (alone or combined with RVT)	108 (30.9)	132 (25.8)	0.106
Recurrent DVT and/or PE			
- Overall	53 (15.1)	74 (14.5)	0.788
- Ipsilateral DVT	14 (4.0)	35 (6.8)	0.098
Deaths	21 (6.0)	36 (7.0)	0.545
Length of treatment, months			
- mean ± SD	5.1 ± 4.0	5.4 ± 4.1	0.207
- median (range)	3 (1-24)	3 (3-24)	-
Duration of follow-up, months			
- mean ± SD	34.0 ± 6.3	34.2 ± 5.9	0.670
- median (range)	36 (6-36)	36 (6-36)	-

ECS=elastic compression stockings; DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism; RVT=residual vein thrombosis; PVR=popliteal valve reflux; VTE=venous thromboembolism; TTR=time spent in the therapeutic warfarin range; SD=standard deviation

Numbers in parentheses indicate percentages unless otherwise specified

Table 2. Incidence of PTS in patients according to the use of compression elastic stockings and the presence of RVT and PVR.

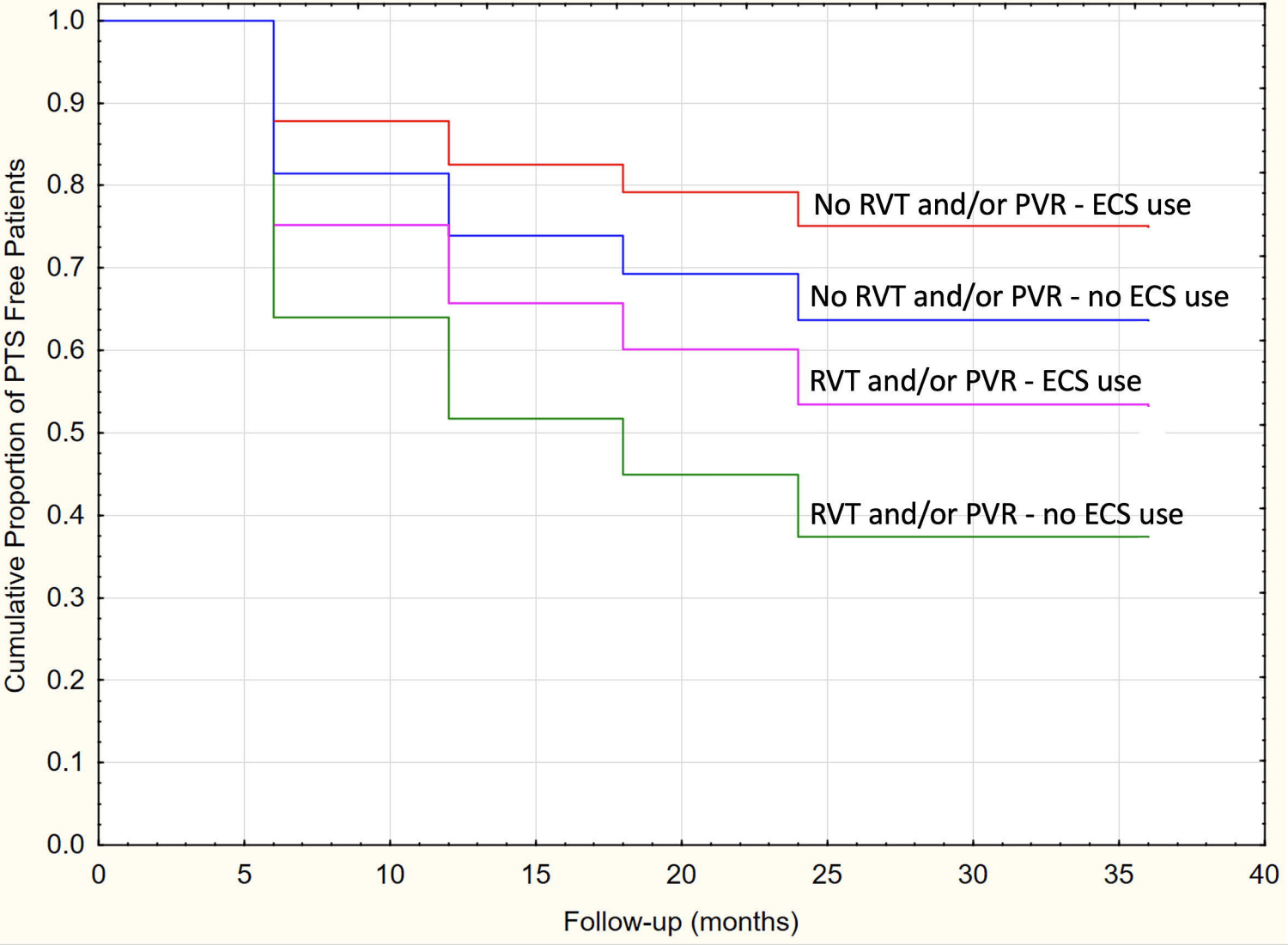
PTS	No RVT and/or PVR		RVT and/or PVR			PVR alone		RVT alone		RVT and PVR	
	No ECS (N=139)	ECS (N=183)	No ECS (N=211)	ECS (N=328)		No ECS (N=35)	ECS (N=80)	No ECS (N=103)	ECS (N=196)	No ECS (N=73)	ECS (N=52)
Mild and severe	42 (30.2)	48 (26.2)	135 (64.0)	114 (34.8)		10 (28.6)	18 (22.5)	70 (68.0)	68 (34.7)	55 (75.3)	28 (53.8)
P	0.430		0.001			0.488		0.001		0.001	
Severe alone	6 (4.3)	5 (2.7)	19 (9.0)	14 (4.3)		2 (5.7)	3 (3.8)	9 (8.7)	9 (4.6)	8 (11.0)	2 (3.8)
P	0.625		0.001			0.763		0.001		0.028	

PTS=post-thrombotic syndrome; ECS=elastic compression stockings; RVT=residual vein thrombosis; PVR=popliteal valve reflux

Legend and footnotes of Figure 1

Legend. Cumulative incidence of PTS-free patients in each of the four subgroups according to the presence of RVT and/or PVR and use of ECS

Footnotes. PTS=post-thrombotic syndrome; ECS=elastic compression stockings; RVT=residual vein thrombosis; PVR=popliteal valve reflux


Cumulative Proportion of PTS Free Patients
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
Follow-up (months)
No RVT and/or PVR - ECS use
No RVT and/or PVR - no ECS use
RVT and/or PVR - ECS use
RVT and/or PVR - no ECS use