

Review Article

Review on the value of graduated elastic compression stockings after deep vein thrombosis

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Summary

Graduated elastic compression stockings (GECS) are commonly used in the primary prevention of deep vein thrombosis (DVT); however, their role in preventing recurrent DVT and also post-thrombotic syndrome is less well established. The aim of this review was to investigate the effect of GECS after DVT. A literature search was performed by two independent searchers in order to identify randomised controlled trials on the effect of GECS in preventing recurrent DVT and post-thrombotic syndrome. Four randomised trials, including 537 patients, were identified. Two of the studies demonstrated that below-knee GECS significantly reduced post-thrombotic syndrome during follow-up, while a smaller study showed equivocal results. GECS reduced the incidence of post-thrombotic syndrome from 54%

to 25.2% [relative risk (RR) 0.47, 95% confidence interval (CI) 0.36–0.61] with the number needed to treat (NNT) being 4 (95% CI 2.7–5.0). The rate of recurrent asymptomatic DVT was also significantly reduced by GECS (RR 0.20, 95% CI 0.06–0.64; NNT 5); the reduction in symptomatic DVT was not significant (RR 0.79, 95% CI 0.50–1.26; NNT 34). In conclusion, there is level Ia evidence to suggest that GECS can significantly reduce the incidence of post-thrombotic syndrome (PTS) after DVT, and therefore these should be routinely prescribed. The evidence for recurrent DVT is less conclusive. Further research is needed towards standardising PTS diagnostic criteria and evaluating more effective preventive measures after DVT.

Keywords

Graduated elastic compression stockings, recurrent deep vein thrombosis, venous thromboembolism, post-thrombotic syndrome, prevention

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Introduction

Despite advances in the prophylaxis and treatment of deep vein thrombosis (DVT), the incidence of the disease and its acute complications remain high, especially in high-risk populations. Long-term sequelae, such as the post-thrombotic syndrome (also known as post-phlebotic syndrome) (PTS) are common (1).

Graduated elastic compression stockings (GECS) have been recommended after the acute phase of DVT for long-term prevention of PTS (2, 3). Their effectiveness has been attributed to improvement of venous haemodynamics (4–6).

GECS are widely used to prevent primary DVT, but their use after acute DVT is less popular. This review focused on the role of GECS in preventing recurrent venous thromboembolism and PTS after DVT.

Patients and methods

Search method

Two of the authors (SKK and SSD) independently conducted a literature search, using the following key words in PubMed search (MEDLINE database, National Library of Medicine of the USA from 1954 to April 2006 inclusive): venous thromboembolism, deep vein/venous thrombosis, post thrombotic syndrome and stockings, post-phlebotic syndrome and stockings. The aim was to identify randomised controlled trials investigating the role of GECS in preventing recurrent DVT and PTS. The ISI Web of Knowledge proceedings (1990–2006) and Current Contents were also searched using the same key words. This was followed by a manual search of the full text of the relevant abstracts to identify additional studies. Unpublished data (e.g. from the stocking companies and the authors of the included studies) were not included.

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Table 1: Study characteristics.

Study	Study type	Number of patients enrolled	Interval between DVT and enrolment	Inclusion criteria		Compression pressure (ankle)	Control group	Follow-up (mean or median) in months
				DVT site	Clinical status			
Belcaro, 1993 ⁷	RCT	116	7 months	N/R	Following 6 months anticoagulation	N/R	No stockings	36
Brandjes, 1997 ⁸	RCT	194	2–3 weeks	Proximal	Post acute phase of DVT	40 mmHg	No stockings	76
Ginsberg, 2001 ⁹	Double-blind RCT	47	12 months	Proximal	Asymptomatic venous reflux	20–30 mmHg	Placebo stockings	57
Prandoni, 2004 ¹⁰	RCT	180	300 5–10 days	Proximal	Post acute phase of DVT	30–40 mmHg	No stockings	50.5 (GECS) 47.5 (control)

DVT = deep vein thrombosis, RCT = randomised controlled trial, N/R = not reported, GERandomiseCS = graduated elastic compression stockings.

Statistics

Raw data (number of patients who developed an end-point in the intervention and control groups) were extracted from the articles included in the manuscript, and added before data analysis. MedCalc for Windows (version 4.20.021, Mariakerke, Belgium) was used to calculate the relative risk (RR), ratio of the event rate in the two study groups, and confidence intervals (CI). GraphPad QuickCalcs (<http://www.graphpad.com>, GraphPad Software, Inc, San Diego, CA, USA) was used to calculate number needed to treat (NNT) in order to prevent one negative outcome (the reciprocal of the difference between the event rate in the two groups, also known as absolute risk reduction, multiplied by 100).

The Comprehensive Meta-Analysis program (version 2.2.023, Biostat, Englewood, NJ, USA) was used to calculate the Cochran Q (chi-square and p value) and inconsistency (I^2) statistics that evaluate the heterogeneity of the included studies. A non-significant p value for the Cochran Q statistic indicates that the included studies are homogeneous. An I^2 value of 0% indicates no heterogeneity, while larger values are consistent with increasing heterogeneity.

Table 2: Clinical scale for post-thrombotic syndrome (PTS) (11).

Symptoms	Signs
Cramps	Pretibial oedema
Pruritus	Induration of the skin
Pain	Hyperpigmentation
Heaviness	New venous ectasia
Paraesthesia	Redness
	Pain during calf compression

Severity of symptoms is rated from 0 (not present or minimal) to 3 (re). A total score of 15 or more on two consecutive visits or the presence of a venous ulcer indicated severe PTS. A total score of 5 to 14 on two consecutive visits indicated mild PTS. The presence of a venous ulcer of the lower limb was recorded. In patients with bilateral thrombosis, the higher score was used.

Results

Four randomised controlled trials on the effect of GECS on prevention of recurrent venous thromboembolism or PTS were identified (7–10) (Table 1); only two reported both end-points (8, 10). The total number of patients enrolled was 537. Three studies provided power calculations *a priori* (8–10). One study did not specify the extent of DVT (7); the other three only included patients with proximal DVT (8–10). All studies included patients with symptomatic DVT (7–10), but one also included asymptomatic DVT found on routine venography after major orthopaedic surgery (9). The diagnosis of the original DVT was made by ultrasound (7, 10) or venography (8, 9). The risk profile of included patients was not provided in detail in any of these studies. All of them excluded patients who had DVT in the past. Only one study categorised patients according to the presence of temporary or permanent risk factor, in order to determine the duration of anticoagulation (10); however, randomisation to GECS or not was not stratified accordingly (10). Subgroup analysis was also not provided.

The interval between DVT and enrolment to each of the studies varied, ranging from 5–10 days to 12 months. Selection criteria among the studies also varied significantly. Two studies recruited patients in the early phase following acute DVT (8, 10), the others (7, 9) randomised patients at seven and 12 months following the DVT, respectively. The end-points of the latter studies were also different. One examined recurrent DVT (7) and the other (9) PTS in patients with asymptomatic venous reflux. Only one of the studies examined the effect of GECS on prevention of both symptomatic and asymptomatic DVT (7). Different diagnostic tests were employed to detect recurrent symptomatic DVT, including ultrasound, venography, and I^{125} -labelled fibrinogen scan, and the definition of PTS was not consistent in the three studies; two of them (8, 10) used a previously validated scoring system (Table 2) (11), the third study (9) defined PTS as the presence of chronic pain and leg swelling at least six months after DVT. One study distinguished severe from mild-to-moderate PTS (8).

Follow-up varied between the studies, ranging from 36–76 months. Three of the studies included patients with proximal DVT (8–10), whereas in the fourth study (7) the site of DVT was

Table 3: Effect of GECS on recurrent DVT and PTS rates in patients with a first episode of DVT. A) Effect of GECS on recurrent DVT rates in patients with a first episode of DVT. Event rate is expressed as percentage (%), followed by the corresponding number of patients with event/total number of patients. B) Effect of GECS on recurrent PTS rate in patients with a first episode of DVT. Event rate is expressed as percentage (%), followed by the corresponding number of patients with event/total number of patients.

A)								
Study	Recurrent symptomatic DVT				Recurrent asymptomatic DVT			
	Control	GECS	RR (95% CI)	NNT (95% CI)	Control	GECS	RR (95% CI)	NNT (95% CI)
Belcaro, 1993 ⁷	17.5% (11/63)	3.8% (2/53)	0.22 (0.05–0.93)		28.6% (18/63)	5.7% (3/53)	0.20 (0.06–0.64)	
Brandjes, 1997 ⁸	13.3% (13/98)	14.6% (14/96)	1.1 (0.55–2.21)					
Ginsberg, 2001 ⁹								
Prandoni, 2004 ¹⁰	14.4% (13/90)	13.3% (12/90)	0.92 (0.45–1.91)					
Total	14.7% (37/251)	11.7% (28/239)	0.79 (0.50–1.26)	34 (N/A)	28.6% (18/63)	5.7% (3/53)	0.20 (0.06–0.64)	5 (2.8–9.9)

GECS, graduated elastic compression stockings; DVT, deep vein thrombosis; N/A, not applicable; RR, relative risk; CI, confidence interval; NNT, number need to treat (calculated for the pooled data only).

not reported. The compression profile of the GECS was not reported in one study (7), while in the rest, compression ranged from 20–40 mmHg at ankle level. GECS were used in all four studies (7–10). Only one of the studies was double-blind (9), using placebo stockings in the control group. Blinding was ensured by the use of control stockings (9) and/or by asking the patient to remove the stockings before the assessment (8–10); assessors were unaware of patient group. Duration of compression was at least two years in all studies.

Prevention of recurrent DVT

Three studies (7, 8, 10) evaluated whether GECS prevented recurrent symptomatic venous thromboembolism (Table 3A and Fig. 1A). One demonstrated a significant reduction of DVT from 17.5% (11/63) in the control group to 3.8% (2/53) in the intervention group (RR 0.22, 95% CI 0.05–0.93) (7), while the other two (8, 10) did not reach statistical significance. The calculated total RR was not significant, 0.79 (95% CI 0.50–1.26); NNT was 34. Heterogeneity of the three studies was not significant (Q statistic 3.94, $p=0.14$), but inconsistency was moderately large (I^2 was 49.2%).

Only one study assessed the effect of GECS in preventing recurrent *asymptomatic* DVT using ultrasound imaging (7). The results were in favour of GECS (RR: 0.20, 95% CI 0.06–0.64) with an incidence of recurrent asymptomatic DVT of 28.6% (18/63) in the control group compared to 5.7% (3/53) in the GECS group. The NNT was 5 (95% CI 2.8–9.9).

Prevention of PTS

Prevention of PTS was investigated in three studies (8–10), and two of them showed a significant reduction compared to controls (8, 10); the third study (9) was smaller, probably underpowered and also recruited patients 12 months after the acute phase of DVT (Table 3B and Fig. 1B). GECS significantly reduced the incidence of both mild-to-moderate PTS from 46.9% (46/98) in

B)				
Study	PTS			
	Control	GECS	RR (95% CI)	NNT (95% CI)
Brandjes, 1997 ⁸	70.4% (69/98)	31.3% (30/96)	0.44 (0.32–0.61)	
Ginsberg, 2001 ⁹	4.3% (1/23)	0% (0/24)	N/A	
Prandoni, 2004 ¹⁰	48.9% (44/90)	25.6% (23/90)	0.52 (0.35–0.79)	
Total	54.0% (114/211)	25.2% (53/210)	0.47 (0.36–0.61)	4 (2.7–5.0)

GECS, graduated elastic compression stockings; PTS, post-thrombotic syndrome; DVT, deep vein thrombosis; N/A, not applicable; RR, relative risk; CI, confidence interval; NNT, number need to treat (calculated for the pooled data only).

the control group to 19.8% (19/96) in the GECS group (RR 0.42, 95% CI 0.27–0.66) and severe PTS from 23.5% (23/98) in the control group to 11.5% (11/96) in the GECS group (RR 0.49, 95% CI 0.25–0.95) (8). The pooled incidence of PTS was decreased from 54% in the control group to 25.2% in the GECS group (RR 0.47, 95% CI 0.36–0.61); NNT was 4 (95% CI 2.7–5.0). When the smaller study was excluded, the NNT remained unchanged (4, 95% CI 2.4–4.5). The two studies that showed the benefit of GECS in PTS prevention used GECS that exerted at least 30 mmHg at the ankle (8, 10). Heterogeneity and inconsistency of the three studies was not significant (Q statistic was 0.434, $p=0.805$ and I^2 was 0%).

Compliance was around 93% in the two studies that reported on this issue (8, 10). The main reasons for not using GECS were discomfort and itching (10). Ischaemic complications were not reported.

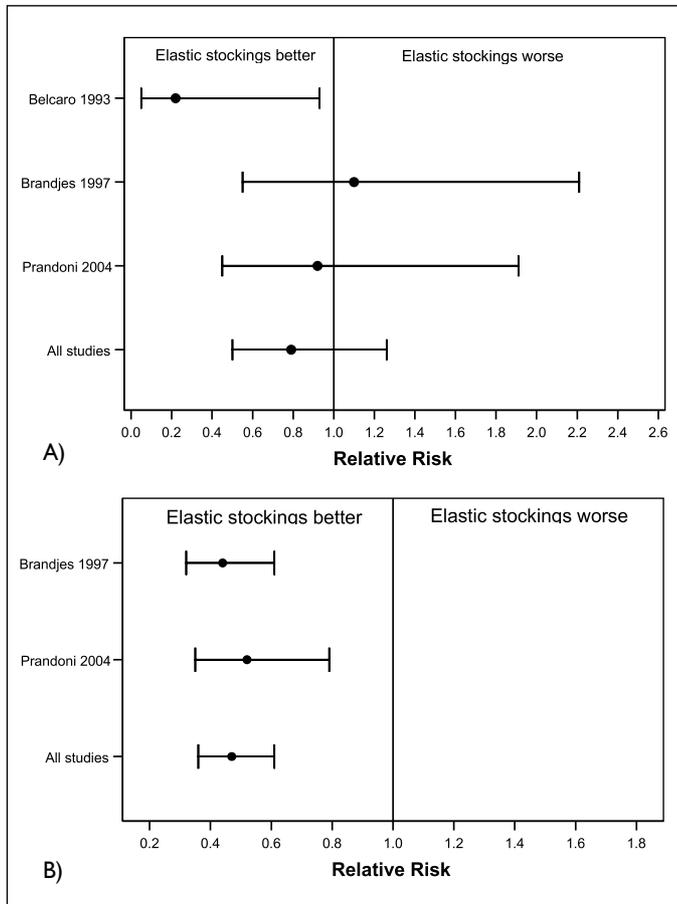


Figure 1: A) Effect of graduated elastic compression stockings (GECS) in reducing recurrent deep vein thrombosis (DVT) incidence. Results for each study and all three studies combined are shown as relative risks (RR) and 95% confidence intervals (CI). **B) Effect of GECS in reducing post-thrombotic syndrome (PTS) incidence.** Results for each study and all three studies combined are shown as RR and 95% CI.

Discussion

The usefulness of GECS in patients with DVT was studied in the present review; their effect on recurrent DVT and PTS being the main study end-points. Homogeneous results on prevention of PTS, but not recurrent DVT, were found. The multifactorial nature of DVT could explain, at least in part, this discrepancy (12).

PTS

PTS is characterised by pain, heaviness and swelling of the affected leg, aggravated by standing or walking. Without any preventive measures, PTS can complicate proximal DVT in approximately 60% (8, 10). Severe PTS occurs in 25% (8) and results in skin and subcutaneous tissue changes, including leg ulceration. This review provided level Ia evidence (randomised studies with homogeneity) that GECS can reduce the incidence of PTS, by approximately 50%; accordingly GECS should be prescribed in all DVT patients with no contraindications for

compression. The routine use of GECS is further supported by the small NNT, i.e. four patients should wear GECS to prevent one case of PTS. Early use of GECS is important since no benefit was found when these were used one year after the acute phase of DVT (9). There are various diagnostic criteria and scoring methods in evaluating the presence and severity of PTS (11, 13, 14). A poor correlation between the Villalta (11) and Ginsberg scales (9) in estimating PTS has been recently reported (15), and the use of different diagnostic systems could explain not only the negative results of one of the included studies (9) but also the wide range of PTS incidence and prevalence in the literature. The Ginsberg measure required the presence of both oedema and pain to set the diagnosis of PTS; therefore, it is more rigid than the Villalta score (9) and identifies more severe disease (15). The disagreement between different scores stresses the need for future research focused on validation and standardisation of diagnostic criteria for PTS to improve the clinical diagnosis of PTS and also allow comparison between different studies (15). However, in the present review all studies were randomised; this compensates not only the effect of the different scoring systems used for PTS evaluation but also the effect of the selection criteria.

The current cost for a pair of GECS class 3 (pressure 25–35 mmHg) varies from £10.44 (ready-made, off-the-self GECS) to £21.42 (made-to-measure GECS) (16). Assuming that a new pair would be needed every six months for two years, total treatment cost for two years would be £41.76 for most patients and £85.68 for those few patients that need made-to-measure GECS. Taking into account the NNT of four and the fact that less than 3% of all patients would need made-to-measure GECS based on previous data (17), the cost to prevent one PTS would be approximately £167, excluding any additional costs for repeat prescription, consultation and the cost of recurrent DVT or PTS. However, a comprehensive health economic analysis is beyond the scope of this review.

Recurrent DVT

Although GECS are effective in primary prevention of DVT (18, 19), there is no compelling evidence supporting the use of GECS in preventing recurrent symptomatic DVT. The reason for this discrepancy is unclear, but different patient population or selection criteria might be responsible and explain the marginal heterogeneity and inconsistency found on statistical analysis. Difficulty in diagnosing recurrent DVT in patients with PTS has also been suggested (20). DVT is a multicausal disease (12) and different response to GECS might be the case. Future studies could address this issue by including patients at higher risk for DVT, like those with permanent risk factors. The single study that has shown decrease in *asymptomatic* recurrent DVT provided level Ib evidence (7). More studies are needed to confirm this finding and upgrade this evidence. As recently shown, patients with PTS are at an almost three-fold increased risk of developing recurrent DVT (RR 2.6) (20).

Mechanism of action

GECS reduce venous hypertension, the amount of both venous reflux and venous volume and improve calf muscle pump function and ambulatory venous pressure in patients with established venous insufficiency (4–6). This results in improvement of ve-

nous symptoms, decreased oedema and prevention of skin breakdown and leg ulceration. Although these mechanisms explain the role of GECS in treating complicated varicose veins and PTS (3, 9), a similar mode of action could be postulated in the studies included in the current manuscript. Furthermore, as one of the studies (7) showed, prevention of recurrent asymptomatic DVT by GECS could prevent deterioration of the anatomical extent of the disease; this might be responsible, at least in part, for their clinical effectiveness in preventing PTS. Unfortunately follow-up examinations with ultrasound or venography are not available in any of the three studies in which PTS was the main end-point (8–10). A recent study showed that the incidence of venous reflux was similar in patients with or without PTS (54.6% and 44%, respectively; $p=0.12$) (15).

GECS

All studies used below-knee GECS. Although compliance is probably better with below-knee GECS compared to full-length GECS, the latter offer additional haemodynamic benefit and could be more effective in PTS prevention. The duration of GECS use was two years in the two largest studies (8, 10), and, therefore, GECS use could be recommended in all patients, at least for this time interval. Compression profile seems to be an important determinant of stocking effectiveness. GECS that exert an ankle pressure less than 30 mmHg were not effective (9); this could be the result of incomplete vein compression (21). However, it remains unknown if very high pressure, i.e. 50

mmHg would be effective without increasing the risk of ischaemic complications (22).

Conclusions

The current review provides further evidence supporting the recommendations of a recent consensus statement (23) and a Cochrane review (24) which both suggested the routine use of GECS following DVT for prevention of PTS. We extended the analysis to evaluate the effect of GECS on recurrent DVT (symptomatic and asymptomatic). A non-significant RR reduction (RRR) in recurrent asymptomatic DVT of 21% and a significant RRR in recurrent asymptomatic DVT of 80% (in one study) were noted. The NNT with GECS to prevent one negative outcome was also calculated; this number is 34 for recurrent symptomatic DVT, 5 for asymptomatic recurrent DVT and 4 for PTS.

There is level Ia evidence (25) to suggest that GECS can significantly reduce the incidence of PTS, and should, therefore, be routinely prescribed to patients after proximal DVT. The evidence for recurrent DVT is less conclusive. Further research is also needed towards validating and standardising PTS diagnostic criteria and evaluating more effective preventive measures after DVT.

Abbreviations

CI, confidence interval; DVT, deep vein thrombosis; GECS, graduated elastic compression stockings; NNT, number needed to treat; PTS, post-thrombotic syndrome; RR, relative risk.

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