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# Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke

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Received 11 April 2000

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## Summary

Graded compression stockings are commonly used to prevent deep-vein thrombosis (DVT) after stroke, but their efficacy in this setting has not been evaluated. Extrapolation of effectiveness from trials in patients undergoing elective surgery may be inappropriate. We undertook a randomized, controlled trial, with blinded data review, in a University hospital Acute Stroke Unit. Patients were allocated to graded compression stockings or to standard care alone. DVT incidence was determined at baseline and at day  $7 \pm 2$  by colour-flow Doppler ultrasound. Ninety-eight patients with acute, immobilizing stroke were randomized; 97 had full outcome data. One patient had clinically manifest

DVT, and no patient had pulmonary thromboembolism. DVT was detected in 7/65 patients allocated stockings, and 7/32 controls (odds ratio 0.43, 95% CI 0.14–1.36); DVT involving femoral veins was detected in 3/65 and 2/32. In the first week after stroke, radiologically-detected DVT remains common, but is usually clinically silent. Proximal DVT is less common. Graded compression stockings produced a reduction in DVT incidence comparable to that in other patient groups, but the reduction was not statistically significant, and the magnitude of effect size requires confirmation. There is greater doubt over efficacy in early prevention of proximal DVT.

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## Introduction

Around half of all deaths in the first month after acute stroke result from secondary complications of immobility rather than from brain injury.<sup>1</sup> Venous thromboembolic disease, manifested as deep-vein thrombosis (DVT) and subsequent pulmonary thromboembolism (PTE), is an important secondary complication since it is potentially preventable. Although improvements in delivery of routine stroke care such as early mobilization and rehydration might be expected to reduce DVT incidence, the continued need for effective prevention is emphasized by the results of large trials such as the International Stroke trial (IST),<sup>2</sup> where PTE accounted for death in 3.6% of patients randomized. However, large trials of both unfractionated and low-molecular-mass heparins<sup>2-4</sup> commenced in the acute phase of stroke have found

bleeding risks to negate or even outweigh any reduction in PTE incidence. Although in the low-dose heparin subgroup in the IST (assigned unfractionated heparin 5000U b.d.) there was no increase in bleeding risk, routine anticoagulant prophylaxis in the acute phase of stroke is not recommended in the UK at the time when DVT risk is greatest.

In a systematic review of 12 randomized controlled trials in surgical patients, graded compression stockings reduced the incidence of peri-operative DVT by 68%.<sup>5</sup> Although these findings have resulted in recommendations that stockings be used for DVT prophylaxis after stroke (e.g. by the Scottish Intercollegiate Guidelines Network),<sup>6</sup> these guidelines acknowledge the absence of controlled trials in stroke. Continuing uncertainty is reflected in recent

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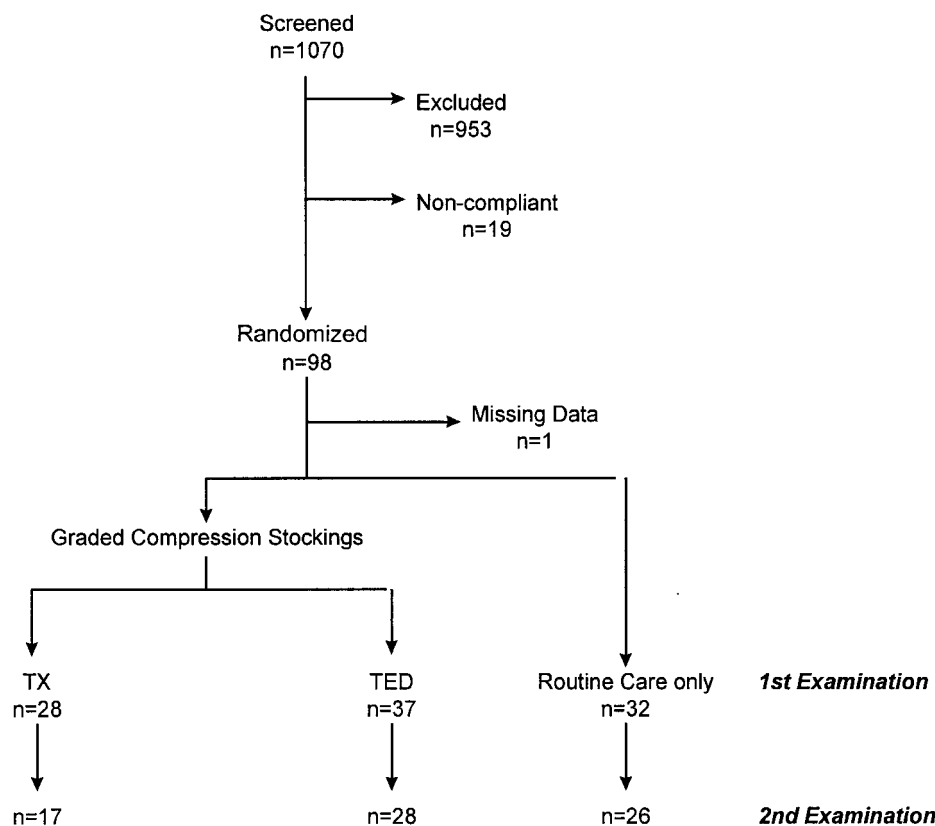


Figure 1. Screening process.

survey findings that only 46% of UK stroke physicians believe stockings to be effective.<sup>7</sup> Stroke patients are usually hospitalized many hours after onset of immobility, commonly have comorbidities that exacerbate DVT risk, and frequently have impaired comprehension or orientation that limits compliance with stockings. Although inexpensive, stockings occupy considerable nursing time if applied correctly. In contrast, surgical populations are generally fitter, better able to comply with treatment, and use stockings before being immobilized.

We considered it uncertain whether extrapolation of stocking use from predominantly primary prevention (surgical) to a secondary prevention (stroke) setting was justified, and therefore undertook a randomized controlled trial of graded compression stockings for DVT prevention in immobile patients after acute stroke.

## Methods

The study was approved by the hospital Ethics Committee. Informed consent was sought from all patients eligible for the study, or, if incapable of giving consent, assent was obtained from their next of kin. The study was conducted in an Acute Stroke Unit with a catchment population of approximately

226 000, admitting any patient within 72 h of stroke onset, irrespective of age or clinical condition.

Standard care includes computed tomographic (CT) or magnetic resonance imaging of brain soon after admission, aspirin for all ischaemic strokes, intravenous fluids for those unable to swallow, and early mobilization (generally within 24 h of admission). Stroke type was characterized by the Oxfordshire Community Stroke Project (OCSP) Classification,<sup>8</sup> and neurological deficit by the National Institutes of Health Stroke Scale (NIHSS).<sup>9,10</sup>

Patients with clinically diagnosed acute stroke who were not independently ambulant within 24 h of admission, and had leg weakness of NIHSS  $\geq 1$  (unable to maintain straight-leg raising against gravity for 5 s) were eligible. Patients with coma, life-threatening intercurrent illness, critical lower-limb ischaemia, or severe dermatological conditions were excluded. Patients were randomized (using computer-generated random numbers in sealed envelopes) to standard care or standard care plus full length stockings of either Kendall TED (TED group) or Brevett TX (TX group) brands, adjusted individually for patients' size, and applied by nursing staff according to manufacturers' recommendations.

Colour flow Doppler ultrasound examinations were done by a single observer using an Acuson

**Table 1** Exclusion reasons

Cause	<i>n</i>
Mobile (or discharged)	537
Amputee	12
Consent refused or unobtainable	77
Coma or poor prognosis	66
Peripheral vascular disease	4
Dermatological (incl. MRSA)	19
Non-stroke diagnosis	20
Other clinical trial	59
Technical or administrative	17
Stockings already in use	34
Other*	108

\*The principal reason for exclusion in this category was randomization to another clinical trial.

128 with motion discrimination software, and all examinations were videotaped for blinded independent review. The calves and thighs of both legs were examined prior to application of stockings, and again at day 7 ( $\pm 2$  days).

Power calculations assumed 50% DVT incidence,<sup>11</sup> and 50% relative risk reduction with stockings, a magnitude of effect in line with systematic review in other conditions. The study had 80% power to detect this difference at 5% significance with 100 patients randomized in a 2:1 ratio of

stockings to standard treatment. Treatment effects were expressed as an odds ratio, and absolute risk reduction as number needed to treat (NNT) for benefit with 95% CIs. Non-significant absolute risk reductions therefore result in CIs for NNT that overlap infinity.<sup>12</sup>

## Results

From April 1995 to December 1997, 1070 patients were screened. Ninety-eight were recruited to the study. Reasons for non-recruitment were recorded (Figure 1 and Table 1). Demography and stroke characteristics are shown in Table 2.

One patient had clinically manifest DVT during the study period.

Femoral and popliteal vessels were examined in 98% of patients at the initial examination, with external iliac vessels being visualized in 40%. The examination was repeated in 73% of femoral and popliteal vessels, and in 29% of external iliac vessels. There was no significant difference in the numbers of dropouts during the study period (11 in TX group; 8 in TED; 6 in routine care;  $p=0.16$ ,  $\chi^2$  test). Seven patients died between the first and second examinations. Three patients were intolerant of stockings, and a further four patients withdrew for unstated reasons in the stocking group; in addition, there

**Table 2** Demography and stroke characteristics of patients studied

	Group				<i>p</i>
	TX	TED	Routine	All	
Total ( <i>n</i> )	28	37	32	97	
Mean age (years)	73	76	76	76	0.42
Mean mass (kg)	62	70	68	67	0.60
<i>OCSP</i>					
TACS	9	9	11	29	
PACS	7	13	11	31	
LACS	6	10	5	21	
POCS	4	2	2	8	
<i>Risk factors</i>					
Hypertension	15	14	14	43	0.52
Ischaemic heart disease	9	11	9	29	0.99
Previous stroke or TIA	10	8	9	27	0.35
Smoker	10	9	9	28	0.39
Diabetes	2	3	3	8	0.32
DVT or PTE	1	3	0	4	0.38
Family history	1	0	0	1	0.48
<i>Waterlow score</i>					
Median [interquartile]	16 [12–21]	17 [13–22]	18 [14–22]	17 [13–21.5]	
<i>NIHSS</i>					
Median [interquartile]	11 [7–24]	10 [6–20]	14 [5–24]	11 [6–22]	

OCSP, Oxfordshire Community Stroke Project classification; TACS, total anterior circulation stroke; PACS, partial anterior circulation stroke; LACS, lacunar stroke; POCS, posterior circulation stroke; NIHSS, National Institutes of Health Stroke Scale.

**Table 3** Outcome during study period

Group	TX	TED	Routine	All
Total	28	37	32	107
Home	4	3	3	10
Medical wards	4	12	10	26
Stroke rehabilitation	12	19	15	46
Died	7	2	4	13

were two protocol violations in that stockings in the TX group were not worn as intended. Since no significant differences in compliance or tolerability were found, TX and TED groups were combined for analyses of efficacy.

At initial examination, DVT was detected in 3/32 control and 6/65 stocking patients ( $p=0.98$ ,  $\chi^2$ ). At follow-up examination, DVT was detected in 5/26 control and 3/45 stocking patients ( $p=0.08$ ,  $\chi^2$ ). Overall, DVT was detected within the first 7 days after stroke in seven patients in each group, representing a non-significant reduction in DVT incidence with stockings (odds ratio 0.43, 95% CI 0.14–1.36; NNT for benefit 9, 95% CI 5–(–13)). DVT involving proximal veins was detected in two control and three stocking patients (odds ratio 0.74, 95% CI 0.12–4.64). The absolute risk of proximal DVT was 6.25% in controls and 4.6% in stocking-allocated patients (absolute risk reduction 1.65%, NNT for benefit 61 [95% CI 18–(–4)]). Using a combined end-point of confirmed DVT or death before the second examination, 15/65 and 10/32 patients were affected, giving an OR of 0.66 (0.26–1.70).

Of the eight DVTs detected at day 5–9, five were new DVTs not evident on initial examination. Six patients with DVTs on initial examination were unavailable for follow-up scans (three proximal and three distal DVTs; two standard care and four stocking). Four of the five new DVTs seen on day 5–9 occurred in the standard care group, and one in the stocking group. The majority of DVTs at first examination (6/9) and day 5–9 (6/8) were confined to popliteal veins. Femoral veins were involved in only five patients, three being present at first examination, and two at day 5–9 (one each in stocking and standard care groups). One patient with proximal DVT at day 5–9 had isolated ipsilateral popliteal DVT at initial examination: this patient was in the stocking group.

## Discussion

Although important because potentially preventable, the true magnitude of venous thromboembolic disease after stroke is difficult to ascertain. The first systematic study of DVT incidence in the acute

phase of stroke was conducted over 20 years ago,<sup>11,13</sup> using <sup>125</sup>I-fibrinogen scintigraphy, a technique highly sensitive to thrombus formation. DVT incidence was 53% in the first 10 days after stroke, with 9% subsequently suffering PTE. Subsequent studies using the <sup>125</sup>I-fibrinogen method reported DVT incidence from 20–50%.<sup>14–16</sup> Colour flow Doppler ultrasound has high sensitivity (95–98%) and specificity (up to 100%) when compared to contrast venography,<sup>17,18</sup> and the incidence of 22% in our control group is comparable to that in the placebo arm of the most recent of the studies using scintigraphy.<sup>16</sup> Method of DVT detection is therefore probably not the main factor giving rise to uncertainty over incidence. Unfortunately, the higher incidence assumed in our original sample size calculations proved to be incorrect. Studies vary widely with respect to the population studied, timing of assessments, and application of diagnostic tests. Clinical recognition of PTE is notoriously poor, as few as 21% of post-mortem cases being suspected in one recent study.<sup>19</sup> The reported 14-day incidence of PTE in the International Stroke Trial of 0.8%,<sup>3</sup> and in the Trial of Org10172 in Acute Stroke Treatment (TOAST) of 0.6%,<sup>4</sup> are in marked contrast to the 5.6% incidence in the placebo group of the Fraxiparine in Ischaemic Stroke Study (FISS-bis),<sup>2</sup> and suggest strongly that reliance on clinical suspicion remains routine even in trial settings.

These problems confound any attempt to determine whether advances in care delivery to acute stroke patients such as more widespread use of aspirin, early mobilization, and rehydration might have effected a reduction in DVT incidence over time, as we hypothesized. The potential magnitude of the problem, and the failure of net benefit from routine early heparin treatment, both emphasize the importance of ascertaining the effectiveness or otherwise of graded compression stockings in the specific setting of stroke.

Our study confirms that DVT remains common in immobile acute stroke patients (22% of control patients within the first 9 days), but clinical manifestations of DVT are rare (1/14, or 7%). Most DVTs (9/14, 64%) were present on initial assessment, i.e. within 24 h of hospital admission. Our results indicate reduced risk of early DVT with graded compression stockings over and above standard management, but the small numbers in the study are reflected in wide confidence intervals and lack of statistical significance, and are further confounded by a higher than anticipated drop-out rate before the second examination. However, the odds ratio of 0.43 is comparable to values obtained in a systematic review of compression stockings for DVT prevention across a range of patient groups, most studies being conducted in patients undergoing surgical procedures (G Ferris *et al.*, personal communication). The more

conservative estimate taking death before second examination as an additional end-point still produces an odds ratio of 0.66, compatible with a worthwhile reduction.

Proximal DVT is thought to be most clinically relevant, since associated with high risk of pulmonary embolism. Most DVTs at first examination (6/9) and day 5–9 (6/8) were confined to popliteal veins. Femoral veins were involved in only five patients, and in only one case could convincing evidence of propagation of distal thrombus within the study period be demonstrated, this occurring in a patient randomized to stockings. Our figures provide much less certainty regarding the efficacy of stockings for proximal DVT prevention. Further, the lower absolute risk of proximal as opposed to distal DVT means that many more patients would need to be treated to prevent a single clinically relevant end-point (NNT of 61 to prevent a proximal DVT versus NNT of 9 for any DVT). Considerable nursing time may therefore be devoted to a strategy of limited effectiveness. However, if all proximal DVTs are consequent to propagation of distal thrombus, then longer follow-up of patients than we were able to undertake in this study may reveal considerably greater risk of proximal DVT, and therefore leaves open the possibility of a more favourable absolute risk reduction with stockings. Since stockings are relatively inexpensive and have few complications, routine use may be justifiable. On the other hand, a high proportion of patients with early immobility (as we found) are either discharged mobile, or die, within the early stages after stroke, and this will be likely to dilute any benefit from stockings. Risk assessment scales such as the Waterlow score were not predictive of DVT risk in this study, and alternative means of effective targeting of stockings to maximize benefit would undoubtedly help.

Ultimately, however, radiologically-defined DVT incidence is a surrogate measure. The influence of stocking use on outcomes of direct clinical relevance is a more important question. A trial to demonstrate efficacy of stockings with respect to reduction of fatal or non-fatal PTE or symptomatic DVT would need to be very large: around 750 patients per group assuming a 30-day likelihood of 5% for the combined end-point, and a relative risk reduction in line with that observed in this study. Variability in reported PTE incidence in recent studies emphasizes the major efforts that would be required for case ascertainment and diagnostic investigation.

This study provides some evidence in favour of graded compression stockings for DVT prevention in stroke patients, with an effect broadly in line with that evident from systematic review of studies in other clinical conditions. Ideally, this should be confirmed in a larger population. Additional clarifica-

tion of effect size with respect to proximal DVT prevention may be beneficial to permit comparison with other demands on nursing time in the acute phase of stroke, and there is a need for trials to address the relevance of stocking design (e.g. length, different manufacturers) to outcomes.

## Acknowledgements

This study was funded by the Stroke Association (UK). Karen Shields carried out all ultrasound scans and Iain Sim assisted with data collection and processing. Manufacturers of graded compression stockings were not involved in any part of this study, and have not been made aware of the results except via open dissemination at scientific meetings. The authors are grateful to Gill Ferris and colleagues for sharing data from the systematic review of venous thromboprophylaxis.

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