Prevention of recurrence of venous ulceration: Randomized controlled trial of class 2 and class 3 elastic compression

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Objective: **To compare venous ulcer recurrence and compliance with two strengths of compression hosiery.**
Methods: **This study was a randomized controlled trial with a 5-year follow-up. The setting was the leg ulcer clinics of a teaching and a district general hospital in Scotland, United Kingdom. Patients were 300 outpatients with recently healed venous ulcers, with no significant arterial disease, rheumatoid disease, or diabetes mellitus. Interventions were fitting and supply of class 2 or class 3 compression hosiery. Four-monthly refitting by trained orthotists and surveillance by specialist nurses were performed. The main outcome measures were recurrence of leg ulceration and compliance with treatment.**
Results: **Thirty-six percent (107/300) of patients had recurrent leg ulceration by 5 years. Recurrence occurred in 59 (39%) of 151 class 2 elastic compression cases and in 48 (32%) of class 3 compression cases. One hundred six patients did not comply with their randomized compression class, 63 (42%) in class 3 and 43 (28%) in class 2. The difference in recurrence is not statistically significant, but our estimate of the effectiveness of class 3 hosiery is diluted by the lower compliance rate in this group. Restricted ankle movement and four or more previous ulcers were associated with a higher risk of recurrence.**
Conclusions: **There was no evidence of a difference in recurrence rates at the classic level of significance (5%), but the lowest recurrence rates were seen in people who wore the highest degree of compression. Therefore, patients should wear the highest level of compression that is comfortable. (J Vasc Surg 2006;44:803-8.)**

Recurrence of chronic leg ulceration is common. In the Lothian and Forth Valley Leg Ulcer Study,[1] multiple recurrences were documented in 67% of ulcerated legs, the remaining 33% never having healed their first ulcer. Externally applied compression in the form of bandages or stockings is the mainstay of the treatment of venous ulcers.[2] This is supported by a systematic review of trials of compression[3] and by physiological studies that have confirmed increased femoral vein velocity,[4,5] increased venous pressure,[6] increased subcutaneous blood flow,[4,7] increased total blood flow,[7,8] and prolongation of venous refilling time.[9] Compression hosiery is also advised after leg ulcer healing, but the optimal grade of compression required to prevent recurrence is not known.[7,10] There may well be a trade-off between compliance, thought to be higher with lower levels of compression, and effectiveness, because higher compression is often recommended. The highest compression hosiery available in the United Kingdom (class 3 compression) may be associated with poor compliance, particularly in the elderly; therefore, any advantage of high compression over moderate compression may be compromised by poor compliance. There are no published trials comparing the effectiveness or compliance with different grades of compression hosiery. This randomized controlled trial was designed to investigate the ulcer recurrence rate and patient compliance associated with moderate-compression (class 2) or high-compression (class 3) hosiery.

METHODS

Population. Three hundred patients with newly healed venous leg ulcers defined by clinical, Doppler, or duplex criteria were recruited into this randomized controlled trial over 2 years. Only people considered suitable for compression hosiery were eligible. After written consent was obtained, their lower limbs were examined by hand-held Doppler scan to determine the nature and extent of venous disease.[11] The range of ankle movement was recorded: 80° to 100° was classified as normal, fixed was defined as 10° or less, and restricted was defined as anything falling between these extreme ranges. Patients who were diabetic, who had an ankle-brachial pressure index of less than 0.8, or who had seropositive rheumatoid arthritis were excluded. Any pre-existing leg swelling was first reduced by elevation. Patients were then measured and fitted for compression hosiery and given verbal and written information on the care of their legs.

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Interventions. Patients received either class 2 (moderate compression; 18-24 mm Hg at the ankle) or class 3 (high compression: 25-35 mm Hg at the ankle) graduated compression hosiery (knee or thigh length; Jobst (BSN Medical, Hull, UK) or Medi (Medi, Hereford, UK), depending on the year of recruitment). The stockings were prescribed and dispensed in the National Health Service hospital clinic. Attendance at the clinic was free of charge, and transport was arranged if necessary. National Health Service prescription hosiery was free to people with a low income or of pension age (60 or 65 years). Charges for other patients were £4 to £6 (US$6-$10) per stocking. Follow-up appointments were arranged every 4 months for examination of the leg, continued education on skin care, and remeasurement and supply of hosiery. Patients were given a hotline telephone number to contact a leg ulcer nurse in the event of any problem.

Randomization. Allocation to the two groups was by a telephone randomization service in the hospital. This was designed to conceal the allocation (moderate or high compression) from the research nurse enrolling the patient into the trial until the point of randomization, to reduce selection bias. Nurses, orthotists, and patients were aware of the group to which patients were allocated immediately after randomization.

Sample size. An a priori sample size calculation, assuming that ulcer recurrence was 40% in one group and that a 15% difference in reulceration rates was clinically important, indicated that 150 people were required in each group to detect this difference at the conventional 5% level of significance (80% power).

Outcomes. The primary outcome was ulceration, defined as a skin break in the same leg that failed to heal after 6 weeks' treatment with high-compression bandaging and simple low-adherent dressings. Skin breaks that resolved within 6 weeks were also recorded, and a secondary analysis examined the relationship between the level of compression and the outcome "all skin breaks." Ulceration on the reference limb (the limb with the recently healed ulcer at recruitment) anywhere between the malleoli and the knee was considered as a recurrence. We decided not to restrict the definition of recurrence to those occurring at or near the site of the original ulcer because the intervention acts on the entire lower limb. Furthermore, ulceration anywhere on the limb heralds the start of ulcer treatment (weekly visits, compression bandages, dressings, and so on) and is the outcome of most relevance to clinicians and patients.

Compliant patients were defined as those who wore the allocated class of hosiery throughout the study; the remainder were noncompliant. Research nurses assessed compliance at each visit by both questioning and observation. Both the limb and the hosiery were inspected for signs that the hosiery had been worn (hosiery paler and less tight than initially; limb not edematous).

The follow-up period was 5 years. The patient continued to attend if a change in strength of stocking was required or after reulceration.

Table I. Baseline characteristics

Variable	*Stocking allocation*		
	Class 2 (n = 151)	*Class 3 (n = 149)*	*Total*
Mean age, y (SD)	65.1 (12.9)	63.6 (11.4)	300
Age (y)			
<30	1	4	5
30 to <40	2	3	5
40 to <50	14	10	24
50 to <60	37	26	63
60 to <70	49	51	100
70 to <80	36	44	80
≥80	10	13	23
Sex			
Male	59	66	125
Female	92	83	175
Ulcer location (side)			
Right	69	67	136
Left	82	82	164
Recent ulcer duration			
<6 mo	112	118	230
6-11 mo	18	14	32
1-2 y	14	13	27
≥3 y	5	3	8
Missing data	2	1	3
Years since first ulcer			
<5	76	64	140
5 to <10	19	17	36
≥10	55	68	123
Missing data	1	0	1
No. ulcer episodes			
1	50	45	95
2-3	54	41	95
≥4	46	62	108
Missing data	1	1	2
Leg fracture			
Yes/no	20/128	17/131	37/259
Previous DVT			
Yes/no	28/121	35/112	63/233
Severe lipodermatosclerosis			
Yes/no	52/147	48/148	100/295
Ankle movements			
Full	118	114	232
Equinus	8	8	16
Fixed	3	4	7
Missing data	4	2	6
Popliteal DV Doppler			
Nonpatent	0	1	1
Patent + competent	90	95	185
Patent + incompetent	54	47	101
Missing data	7	6	13

DV, deep vein.

Analysis. Our primary analysis compared time to reulceration on an intention-to-treat basis, ie, people were analyzed according to the groups to which they were allocated rather than the compression they were wearing at the point of recurrence. Analysis of time to recurrence was performed by using standard methods for survival data (Kaplan-Meier curves and Cox proportional hazards model). Observations were censored at the time of death or loss to follow-up. A secondary analysis investigated the recurrence rates by considering the compression systems that the patient

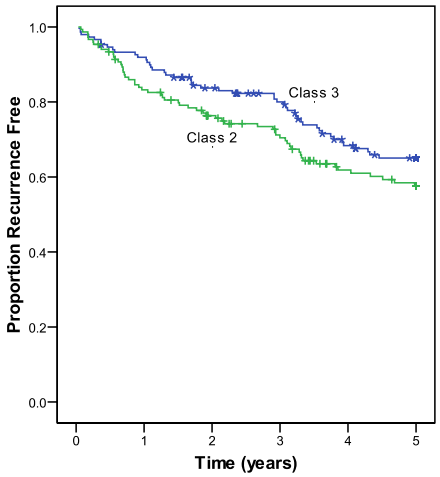

Fig 1. Survival curve showing time to recurrence in Class 2 and Class 3 hosiery.

was wearing at the time by applying a Cox proportional hazards model with a time-dependent covariate.

The ethics committees at both hospitals approved the protocol.

RESULTS

The two treatment groups were comparable in terms of age, sex, ulcer location, and leg ulcer and general medical history (Table I). One hundred fifty-one patients were randomized to class 2 and 149 to class 3 compression hosiery. Fifty participants did not complete the 5-year follow-up for the following reasons: death (n = 36), moving elsewhere (n = 9), refusal (n = 2), untraceability (n = 2), or illness (n = 1). One hundred seven ulcers recurred: 48 (32%) in the class 3 group and 59 (39%) in class 2. A total of 126 people reported a skin break, and in 107 people these were still open at 6 weeks and, hence, were classified as ulcers. Figure 1 presents a Kaplan-Meier curve of time to reulceration. The difference between the two treatment groups was not statistically significant (Cox proportional hazards model; $P = .14$). The Cox proportional hazards model accounts for imbalances in the distribution of risk factors at baseline, which happens when modest numbers of patients are randomized, such as the higher proportion of people with more than three previous ulcers in the class 3 group than the class 2 group. A secondary analysis including all skin breaks as the end point showed similar results (Cox proportional hazards model; $P = .13$).

The associations of potential risk factors for recurrence with ulcer outcome, other than level of compression, are shown in Table II. The only variables showing a statistically significant univariate association with reulceration, using a Cox proportional hazards model, were duration of history of leg ulcers ($P = .03$), number of previous episodes of leg ulcer ($P < .001$), lipodermatosclerosis ($P = .04$), restricted ankle movements ($P = .004$), and ankle-brachial pressure index ($P = .03$).

One hundred six patients did not comply with their randomized compression class, 63 (42%) in class 3 and 43 (28%) in class 2. Of these, eight patients (three in class 3 and five in class 2) stopped wearing compression altogether, whereas the others changed their compression, usually to a lower grade. We recorded the time at which noncompliance commenced, permitting the application of a Cox proportional hazards model with a time-dependent covariate to indicate continued wearing of the randomized stocking. The results from a model including this time-dependent covariate, together with the risk factors that remained statistically significant in a multivariable model, are summarized in Table III. Patients who continued to use class 3 stockings had the lowest risk of reulceration, but this risk was not statistically significantly different from the remainder of patients in both class 2 and class 3 (hazard ratio for hazard reulceration, 1.4; 95% confidence interval, 0.9-2.1).

Multiple previous episodes of leg ulceration was a significant risk factor ($P = .002$), with more than three episodes being associated with an approximate doubling of risk. Risk of reulceration was also approximately doubled if there was less than full ankle movement ($P = .005$). After allowance for these factors, no other potential risk factor was statistically significant at the 5% level. The people at highest risk were those with limited ankle movement and more than three previous ulcers, because 68% of this group experienced recurrence within 5 years, in comparison with a 26% recurrence rate when patients had both a full ankle motion and only one previous ulcer (Table IV).

DISCUSSION

Leg ulcers commonly recur after healing.[1,12] Healing therefore represents an opportunity for secondary prevention, either by conservative measures or venous surgery. It is logical to offer newly healed patients professionally fitted graduated compression, because although it is known that superficial venous surgery reduces the risk of recurrence,[13] surgery will not be appropriate for all patients, and a minority will refuse or be unsuitable for surgery.[13] Franks et al[14] found that noncompliance with compression is associated with an increased risk of recurrence, but there are no studies comparing recurrence in moderate and high compression to determine whether any potential decrease in compliance associated with higher compression is offset by reduced recurrence rates.

The precise mechanism of action of compression therapy is unknown. Certainly swelling is inhibited, although the significance of edema in the etiology of leg ulceration is not clear. Graduated compression is known to enhance venous function,[5,7] and the approximation of valve leaflets by the external compression has been suggested as a possible factor.[15,16]

This study reports a high recurrence rate (36% over 5 years) despite close surveillance and care by leg ulcer specialist nursing staff and dedicated orthotists. This may be partly explained by the patient population that requires referral to such specialist clinics, or it may reflect the relatively full follow-up and the longest period of any study of

Table II. Risk factors for recurrence

Variable	*Major recurrence*		
	No	*Yes*	*Total*
Sex			
Male	75/125 (60%)	50/125 (40%)	125
Female	118/175 (67%)	57/175 (33%)	175
Age (y)			
<60	63 (65%)	34 (35%)	97
60 to <70	67 (67%)	33 (33%)	100
≥70	63 (61%)	40 (39%)	103
Arthritis			
No	147 (66%)	77 (34%)	224
Osteoarthritis	38 (64%)	21 (36%)	59
Rheumatoid	1 (25%)	3 (75%)	4
Other	4 (57%)	3 (43%)	7
No. episodes			
1	69 (73%)	26 (27%)	95
2-3	70 (74%)	25 (26%)	95
≥4	53 (49%)	55 (51%)	108
Years since first ulcer			
<5	100 (71%)	40 (29%)	140
5 to <10	24 (67%)	12 (33%)	36
≥10	68 (55%)	55 (45%)	123
No. years since first ulcer, mean (SD)	9.1 (11.0)	13.9 (13.7)	
ABPI			
<1.0	47 (63%)	28 (37%)	75
1.0 to <1.2	41 (52%)	38 (48%)	79
1.2 to <1.4	69 (69%)	31 (31%)	100
≥1.4	34 (77%)	10 (23%)	44
Mean ABPI (SD)	1.2 (0.22)	1.1 (0.17)	
Long saphenous incompetence			
None	52 (59%)	36 (41%)	88
Clinical	24 (67%)	12 (33%)	36
Doppler	28 (80%)	7 (20%)	35
Both	83 (64%)	47 (36%)	130
Short saphenous incompetence			
None	111 (61%)	70 (39%)	181
Clinical	3 (33%)	6 (67%)	9
Doppler	28 (78%)	8 (22%)	36
Both	38 (68%)	18 (32%)	56
Lipodermatosclerosis			
None	19 (70%)	8 (30%)	27
Mild	116 (69%)	52 (31%)	168
Severe	56 (56%)	44 (44%)	100
Ankle movements			
Full	163 (70%)	69 (30%)	232
Plantigrade	18 (46%)	21 (54%)	39
Equinus	8 (50%)	8 (50%)	16
Fixed	2 (29%)	5 (71%)	7

Data are n (%) unless otherwise noted. The following variables were not included in the table because they had no association with recurrence: side of ulceration, recent ulcer duration, body mass index, history of deep vein thrombosis, sclerotherapy, vascular surgery, being a smoker, or having allergies.
ABPI, Ankle-brachial pressure index.

leg ulcer recurrence, to our knowledge. However, this study has identified that recurrence is more likely with more previous ulcers, poor ankle movement, lipodermatosclerosis, and an ankle-brachial pressure index of between 0.8 and 1.0, rather than more than 1.0. These factors identify patients at an increased risk of recurrence and may allow clinicians to identify patients in greatest need of assessment for venous surgery or intensive support to wear high-compression hosiery. Perhaps the role of conservative management alone in the prevention of leg ulcer recurrence needs to be reviewed, because recurrence rates are high with this approach.

This study did not find a strong relationship between the absence of venous insufficiency and reulceration, and this might seem to contradict the findings of the ESCHAR (Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration) study.[13] Our findings may be due to chance or to the low power of our study to find differences in reulceration rates between subgroups.

Table III. Results of Cox proportional hazards model and hazard ratios for ulcer recurrence

Risk factor	*Hazard ratio*	*95% Confidence interval*	P *value*
Stocking (time dependent)			.13
Trial class 3	1		
Other	1.40	0.91-2.14	
No. episodes			.002
1	1		
2-3	0.78	0.45-1.36	
≥4	1.79	1.10-2.91	
Ankle movement			.005
Full	1		
Restricted	1.86	1.21-2.86	

A previous randomized controlled trial in 153 people identified the effectiveness of compression in the prevention of venous ulceration (21% recurred at 6 months with compression vs 46% without; relative risk (RR), 0.46; 95% confidence interval, 0.28-0.76),[17] but the relative benefit of high vs moderate compression has not previously been studied, to our knowledge. In our trial, there was no statistically significant difference in recurrence rates, but fewer people experienced recurrence with high compression, although not at the conventional levels of statistical significance. It is important to note that this trial does not demonstrate equivalence in recurrence rates in moderate and high compression. The hazard ratio and confidence interval demonstrate that the clinical effects of choosing class 2 rather than class 3 compression are consistent with a range of outcomes, ranging from a 9% reduction to a doubling of the hazard of recurrence. Recently, it has been argued by Claxton et al[18] that, for health care decision making, traditional rules of inference whereby evidence is accumulated until the *P* value is less than a prespecified value (usually .05) are irrelevant because clinicians are faced with decisions that need to be made immediately—they cannot delay their decisions until sufficient research evidence becomes available. They argue that decisions should be based on the mean net benefit, irrespective of whether traditional levels of statistical significance are reached. Using this approach, this trial suggests that high-compression hosiery (class 3) is the preferred treatment, because it is more likely to be effective than moderate compression.

The potential relationship between compression levels and effectiveness is indirectly supported by the research on venous ulcer healing. Cullum et al[3] found that high-compression systems healed more ulcers than low or moderate compression. This trial supports the premise that high-compression therapy is more effective for addressing chronic venous insufficiency than moderate compression and that patients should wear the highest level of compression tolerable. Although our trial is large in comparison with other trials in venous ulceration (only two venous ulcer trials, to our knowledge, have recruited more participants: those of Nelson et al[19] and Barwell et al[13]), it did not have sufficient power to detect, as statistically significant, a moderate difference in effectiveness (39% vs 32% recurrence rate at 5 years), and there were no previous trial data on which to base a sample size calculation at the start of the trial; therefore, we used an estimate. Nevertheless, a 7% difference in recurrence rates at 5 years would mean that 1 additional ulcer would be prevented for every 15 people treated with class 3 rather than class 2 hosiery. In the United Kingdom, the clinical preference is for class 2 hosiery, and, hence, nurses may demand a large difference in effectiveness to justify the increased support and assistance in application and removal for people to wear a higher grade (class 3). The original sample size calculation, in which the reulceration rates were estimated at 40% and 25%, would yield a number needed to treat of 7, whereas our results found the number needed to treat to prevent 1 additional reulceration to be 15 over 5 years. Qualitative work to illuminate the barriers to clinicians and patients using high compression might be useful.

This study has several important strengths. It recruited a large population of people representative of those receiving community care for venous ulceration and followed them up for 5 years. Experienced research nurses followed patients up to monitor use of the compression hosiery, standard protocols were followed to treat skin breaks, and the hotline allowed patients to report skin breaks promptly, meaning that data on recurrence are reliable. The trial addressed a question of clinical importance and used outcome measures likely to be of relevance to decision makers. Our analyses were conducted on an intention-to-treat basis to assess the likely real effect of the interventions on recurrence rates and to maintain the comparability of the two groups from randomization.

The limitations of the trial include the lack of any validated methods for assessing compliance with compression therapy (in contrast to methods for assessing compliance with smoking cessation, for example). We considered validating the compliance data by visiting patients at home, unannounced, but considered this intrusive, labor intensive, and unlikely to be passed by an ethics committee.

We used telephone allocation in preference to sealed sequentially numbered envelopes because these are open to subversion to reduce selection bias. During the trial follow-up, however, we were informed that on at least one occasion the allocation concealment was not maintained by the telephone service because both the leg ulcer clinic and the telephone service were extremely busy; therefore, the allocations for two patients were supplied "in order to save time." Discussion with the clinic nurses reassured us that the order of recruitment to the trial was not affected by this error, but it highlights the need for vigilance in trial allocation systems. We were unable to characterize the venous insufficiency for every patient in this trial by using Duplex imaging as a result of funding and staff resource limitations, but experienced surgeons recorded the presence of venous insufficiency by using handheld Doppler scanning. The association of venous insufficiency and the risk of recurrence was a secondary aim of this study, and, given that the trial is randomized, then the two groups are likely to have

Table IV. Recurrence rates with previous episodes of ulceration and ankle movement

	Previous episodes of ulceration			
Ankle movement	*1*	*2 or 3*	*≥4*	*Total*
Full	22/84 (26%)	17/75 (23%)	30/72 (42%)	69/232 (30%)
Restricted	4/10 (40%)	7/18 (39%)	23/34 (68%)	34/62 (55%)
Total	26/95 (27%)	25/95 (26%)	55/108 (51%)	107/300 (36%)

Missing values means that the column totals do not always agree, but values were calculated with the maximum amount of data available.

had similar distributions of venous insufficiency and obstruction.

Our trial is the first trial, to our knowledge, to address this important clinical question and provides the basis for further research into the relative benefits of high or moderate compression. The recurrence rates in our trial also set a benchmark for future studies.

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AUTHOR CONTRIBUTIONS

Conception and design: DRH, RJP, BG, DB, CVR
Analysis and interpretation: EAN, DRH, RJP, BG, DB, CVR
Data collection: EAN, BG, DB
Writing the article: EAN, DRH, RJP, CVR
Critical revision of the article: BG, DB
Final approval of the article: EAN, DRH, RJP, BG, DB, CVR
Statistical analysis: RJP
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Overall responsibility: EAN

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