# Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration

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A multicenter prospective randomized clinical trial was undertaken to compare a generic four-layer bandage system with a cohesive short-stretch system (Actico, Activa Healthcare) in the management of venous leg ulceration. Both systems are designed to produce sufficient pressure to counteract venous hypertension. Patients in leg ulcer services with leg ulceration were screened for inclusion in this trial. Patients with arterial disease (ankle brachial pressure index < 0.8) and causes of ulceration other than venous disease were excluded. For patients with bilateral ulceration, the limb with the larger area of ulceration was studied. Patients were randomized to receive either type of compression bandage and simultaneously randomized to one of two foam dressings that were changed weekly unless more frequent changes were clinically required. In all, 156 patients met entry criteria and were randomized from the 12 clinical centers with median (range) ulcer size of 4.33 (0.33–123.10) $cm^2$. Analysis revealed that after 24 weeks a total of 111 (71%) of patients had complete ulcer closure, 32 (21%) had withdrawn from the trial, 12 (8%) remained with open ulceration, and one patient had died. Of the 74 patients randomized to the four-layer bandage, 51(69%) had ulcer closure on treatment compared with 60/82 (73%) on the cohesive short-stretch system. Intention-to-treat analysis produced a hazard ratio for healing of 1.08 (95 percent CI 0.63–1.85, $p = 0.79$). Withdrawal rates were similar between groups (15, 20% four-layer bandage; 17, 21% cohesive short-stretch system). Ulcer closure rates for patients treated with the cohesive short-stretch system were similar to those for patients managed by the four-layer bandage system in this trial. **(WOUND REP REG 2004;12:157–162)**

The mainstay of the treatment of patients with venous ulceration is compression bandaging. The four-layer bandage (4LB) system has been shown to provide adequate sustained compression and high healing rates, both in observational studies[1–3] and in randomized clinical trials of therapies.[4,5] However, the Cochrane systematic review of compression therapy indicated that while effective compression heals venous ulcers, the evidence for bandage regimens healing most ulcers is still lacking.[6] Information on the effectiveness of short-stretch bandaging is less clear, although the Cochrane Review has identified five studies that compare multilayer high compression with inelastic (short-stretch) regimens.[7–11] The meta-analysis of four of these trials indicated a small benefit of healing using

| | |
|---|---|
| 4LB | Four-layer bandage |
| ABPI | Ankle brachial pressure index |
| CSSB | Cohesive short-stretch bandage |
| ITT | Intention-to-treat |

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multilayer bandaging with relative risk 1.10 (95 percent CI 0.78–1.55), which did not achieve statistical significance. More recently, a larger study ($n = 112$) has been published that shows a benefit of short-stretch bandaging over multilayer, with a difference in healing of 11 percent over 16 weeks, although again this failed to achieve a standard level of statistical significance.[12] Short-stretch bandaging is used extensively in mainland Europe, and there are a number of centers in the United Kingdom that have adopted this method as their treatment of choice.

The aim of this trial was to compare two systems of high-compression bandaging, a generic 4LB system and a two-layer cohesive short-stretch bandage (CSSB) system (Actico; Activa Healthcare, Burton on Trent, UK), in the management of patients with venous ulceration. In addition, a subgroup analysis was undertaken in patients with impaired mobility.

## MATERIALS AND METHODS

Ours was a 12-center prospective randomized stratified parallel groups open factorial trial comparing 4LB with CSSB in the management of venous leg ulceration. Patients were stratified according to the estimated size of their ulcer at entry (greater than or less than 10 $cm^2$). Patients were randomized to a bandage system and one of two foam dressings (Allevyn, Smith & Nephew, Hull, UK or Mepilex, Molnlycke Health Care, Göteborg, Sweden) using a factorial design. Randomization took place following consent and eligibility checks by means of opening sealed envelopes in sequential order. At each center there were two randomization lists, one for patients with a total area of ulceration on the reference limb of $\leq 10$ $cm^2$, and one with total area > 10 $cm^2$. Separate randomization lists were used in all centers. The 4LB system was adapted according to the patient's limb circumference, in line with previous recommendations.[4] Ankle circumference was measured at the initial assessment and following 1 week of bandaging to allow for reduction in circumference following compression. This study was approved by the multicenter research ethics committee (MREC) for Wales and ratified by all local research ethics committees covering each of the 12 clinical centers.

### Exclusion criteria

Patients within each of the clinical centers were considered for the trial provided that they were at least 18 years of age. Both genders were included, all suitable males, and females providing that they were not pregnant. Patients were considered to have venous ulceration if they had signs and symptoms of venous disease and an ankle brachial pressure index (ABPI) of greater or equal to 0.8. Photoplethysmography was undertaken to confirm a diagnosis of venous ulceration, but this took place postrandomization, and as such was not an entry requirement. Minimum ulcer duration was set at 2 weeks. Initially, a maximum ulcer duration was set at 24 weeks, but following slow recruitment a trial amendment was made to increase this to 52 weeks. Patients were provided with an information sheet, and encouraged to discuss any queries or uncertainties with the research nurse. Following this consultation, the patient was asked to provide written informed consent. Causes of ulceration other than venous disease based on their clinical presentation were also excluded, as were patients with active cellulitis who were receiving systemic antibiotics, and those with dry nonexuding wounds (an entry criterion for the dressing part of the trial). Patients who had previously entered the trial were not re-entered if they developed a new area of ulceration.

### Reference limb

Patients with bilateral ulceration were randomized to one bandage system and one dressing only whenever this was clinically indicated. The reference limb was considered the one with the largest estimated area of ulceration at entry. Information was collected on the contra-lateral limb, although this was not used in the principal analysis.

Randomization was performed at a ratio of 1 : 1 between the 4LB and CSSB systems and between the two dressing types, after stratification for ulcer area. Estimation of ulcer size was undertaken by the nurses by comparing the ulcer with a template of known area (10 $cm^2$). This allowed for stratification prior to the formal area measurement.

### Patients

All patients within the clinical services were considered for entry, whether they were receiving care within the service or were newly presenting, provided they fulfilled the patient entry criteria. A patient entry log was completed for all patients considered for the trial, together with reasons for noninclusion.

### Treatment regimen

The standard regimen was to wash the limb using an emollient dissolved in tap water, debride the wound, and apply a simple hypoallergenic cream to hydrate the skin. The centers were requested to use their normal routine with regard to debridement. This was normally simple mechanical debridement to remove slough and other dead tissue. Because the trial was factorial in design, the selection of a primary dressing was on the basis of the randomization procedure. Patients were randomized to receive one of two foam dressings (Allevyn, Smith & Nephew or Mepilex, Molnlycke

Health Care AS). The limb was then rebandaged using the randomized bandage system. The 4LB used was similar to that used in the original Charing Cross system and included the following bandages: Flexiban (Activa Healthcare), Setocrepe and Elset (SSL, Oldham, UK), and Coban (3M, Loughborough, UK). The CCSB used an underlayer (Flexiban, Activa Healthcare) in combination with the cohesive bandage Actico (Activa Healthcare). All bandages were applied according to the manufacturers' instructions. Re-dressing and rebandaging were undertaken weekly unless required more frequently on clinical grounds.

### Sample size

The original study sample size was estimated at 200 patients (100 patients in each group), assuming a healing rate of 80 percent, with reasonable clinical improvement estimated as 15 percent (90% power and level of significance of 5%). The trial amendment that changed the maximum ulcer duration entry criterion from 24 to 52 weeks also altered the sample size estimate. It was expected to reduce the baseline-healing rate from 80 percent down to 70 percent with a corresponding increase in sample size of 240 (120 in each group). Logistical difficulties occurred during the trial requiring the recruitment period to be extended from 1 year to 2 years, with a cutoff set during January 2002. The inclusion of 159 (156 evaluable) patients by that time was taken as the trial population. This reduced the power of the study from 90 percent down to 81 percent.

### End points and statistical analyses

The duration of the trial was for 24 weeks or until closure of all areas of ulceration on the reference limb. In cases where the original ulcer closed but a new area developed on the same limb while the original ulcer was still present, the limb was considered to be open until this new area of ulceration had also closed. If patients withdrew from their randomized treatment, they continued to be followed up to the 24-week limit. The definition of ulcer closure was the point at which complete epithelialization of the reference limb occurred, irrespective of the time to its subsequent breakdown. Patients with ulcer closure were provided with class II compression hosiery (Activa Healthcare) and continued to be followed up until 24 weeks. The principal analysis was by proportional hazards survival analysis performed on an intention-to-treat (ITT) basis. Baseline measures were assessed for relationships with ulcer closure. Covariates included in the principal analysis were trial center, dressing used, and ulcer size (according to stratification). Potential interaction between dressing and bandage systems was evaluated by including the interaction covariate in the main hazards model.

Patients remained in the trial until complete ulcer closure or until the patient had received 24 weeks of treatment. Patients who withdrew from the randomized treatment were allocated to an alternative treatment and continued to be followed up until closure or until they had reached 24 weeks. The analysis based on ITT meant that patients remained in their original randomized groups, irrespective of subsequent treatments applied. All adverse incidents were detailed on an adverse incident form and reasons for withdrawal were ascertained wherever possible.

While subgroup analysis is not generally recommended in clinical trials, an analysis was undertaken in this trial to examine the effectiveness of the different bandage systems in patients with a mobility deficit. This is due to the widely held belief that short-stretch regimens perform poorly in this patient group due to the need for an active calf muscle pump to reverse venous hypertension, although recently this belief has been challenged.[13]

## RESULTS

A total of 159 patients were entered into the trial, of whom three did not achieve prerandomization selection criteria. Using published guidelines,[14] these three were excluded, two due to significant arterial disease (ABPI < 0.8) and one who had not given informed consent and who withdrew at 1 week. The remainder made up the trial population.

### Screening and group randomization

Each center was required to screen patients for the trial, however, it was apparent that some centers were prescreening patients for inclusion. In these centers the recruitment log consisted of just those patients who were randomized. Of the 12 centers, five screened all their patients for inclusion (Table 1). In these centers, 40 percent were recruited into the trial, the most frequently cited reasons for noninclusion of patients being too long ulcer duration (11.4%) and significant arterial disease (10.4%).

Seventy-four patients were randomized to 4LB and 82 to CSSB. The randomized groups were also well matched for dressing type with 52.7 percent of patients randomized to 4LB also receiving Allevyn compared with 51.2 percent randomized to CSSB also on Allevyn (Table 2). The groups were well matched for age, gender, medical history, and ulcer characteristics. While the measurement of venous disease was not an entry criterion, we did undertake photoplethysmography in those who were able and willing to take part. Of the 101 who fulfilled these criteria, 96 (95.0%) had demonstrable venous incompetence. The other 5 (5.0%), had clinical evidence of venous disease, but a

**Table 1.** Patient screening logs for five centers

| Randomized | Reason for not randomized | N | percent |
|---|---|---|---|
| Yes | | 80 | 39.8 |
| No | | 121 | 60.2 |
| | Long ulcer duration | 23 | 11.4 |
| | Arterial disease | 21 | 10.4 |
| | No ulcer/other skin condition | 18 | 9.0 |
| | Nonvenous ulcer | 13 | 6.5 |
| | Patient refusal | 11 | 5.5 |
| | Noncompliance | 11 | 5.5 |
| | Nearly healed/dry ulcer | 8 | 4.0 |
| | Infection | 4 | 2.0 |
| | Doing well on current treatment | 3 | 1.5 |
| | Unable to tolerate compression | 3 | 1.5 |
| | Could not provide informed consent | 2 | 1.0 |
| | Allergic to trial products | 2 | 1.0 |
| | Patient out of area | 1 | 0.5 |
| | Other health condition | 1 | 0.5 |

normal refilling time (>25 seconds). Seventy-seven (76.2%) patients had evidence of deep vein disease (< 25 seconds with calf tourniquet), with just 19 (18.8%) having isolated superficial venous disease that was corrected by application of either above- or below-knee tourniquet.

### Ulcer closure

Overall healing rates were high in this trial. In total 111 (71.2%) patients healed on randomized bandage treatment. Of the remainder, 11 were unhealed after 24 weeks on treatment, one patient died, and 33 (21.2%) withdrew from randomized bandage treatment. The "on treatment" outcomes were similar between groups, with 51/74 (68.9%) ulcer closure on 4LB compared with 60/82 (73.2%) on CSSB (Table 3). The "intention-to-treat" analysis was similar to that "on treatment" with 59/74 (79.7%) healing in patients randomized to 4LB compared with 62/82 (75.6%) randomized to CSSB. Cumulative healing rates given by the Kaplan-Meier curves showed 56 percent healing at 12 weeks in both randomized groups (Figure 1). After 24 weeks, this had risen to 85 percent in the 4LB group compared with 83 percent on CSSB. The hazard ratio for healing was slightly in favor of Actico (hazard ratio = 1.08, 95 percent CI 0.63–1.85), after adjustment for the covariates, but this did not achieve a standard level of statistical significance ($p = 0.79$).

Of the total group, 18 (24.3%) patients randomized to 4LB had a mobility deficit compared with 14 (17.1%) patients randomized to CSSB. The Kaplan-Meier curve is given in Figure 2, which also indicates the hazard ratio for healing was 1.35 95 percent CI 0.60–3.03 in favor of the CSSB. This indicates that there was little evidence to suggest that the CSSB was any less effective in these patients than when using the 4LB.

**Table 2.** Baseline patient characteristics in 156 patients, given by randomized group

| Parameter | 4LB group | CSSB group |
|---|---|---|
| n | 74 | 82 |
| Sex: male | 27 (36.5%) | 34 (41.5%) |
| female | 47 (63.5%) | 48 (58.5%) |
| Age-mean (SD) | 67.5 (14.3) | 70.9 (13.4) |
| Ulcer size | | |
| $\leq 10$ cm$^2$ | 59 (79.7%) | 67 (81.7%) |
| $> 10$ cm$^2$ | 15 (20.3%) | 15 (18.3%) |
| – median (range) ulcer size | 5.0 (0.3–115.8) | 3.5 (0.5–123.1) |
| Ulcer duration | 8 (2–40) | 8 (2–40) |
| – median (range) weeks | | |
| Previous ulceration | 29 (39.2%) | 28 (34.6%) |
| ABPI | 1.14 (0.80–2.00) | 1.11 (0.8–1.45) |
| – median (range) | | |
| Hypertension | 23 (31.1%) | 28 (34.6%) |
| Deep vein thrombosis | 14 (18.9%) | 8 (9.8%) |
| Diabetes | 2 (2.7%) | 7 (8.5%) |
| Rheumatoid arthritis | 3 (4.1%) | 5 (6.1%) |
| Mobility | | |
| Chair/bed | 0 (0) | 1 (1.2%) |
| Walk with aid | 18 (24.3%) | 14 (17.1%) |
| Walk freely | 56 (75.7%) | 67 (81.7%) |
| Limb mobility | | |
| Fully mobile | 54 (74.0%) | 73 (89.0%) |
| Limited | 17 (23.3%) | 26 (16.8%) |
| Fixed | 2 (2.7%) | 0 (0) |

**Table 3.** Outcome at 24 weeks in 156 patients randomized to treatment group

| Outcome | 4LB group | SSB group |
|---|---|---|
| n | 74 | 82 |
| Ulcer closure | 51 (68.9%) | 60 (73.2%) |
| Open at 24 weeks | 6 (8.1%) | 5 (6.1%) |
| Withdrawal | 16 (21.6%) | 17 (20.7%) |
| Reasons | | |
| Adverse event | 7 | 6 |
| Patient request | 2 | 2 |
| Moved/lost to follow-up | 6 | 9 |
| Dressing related withdrawal | 1 | 0 |

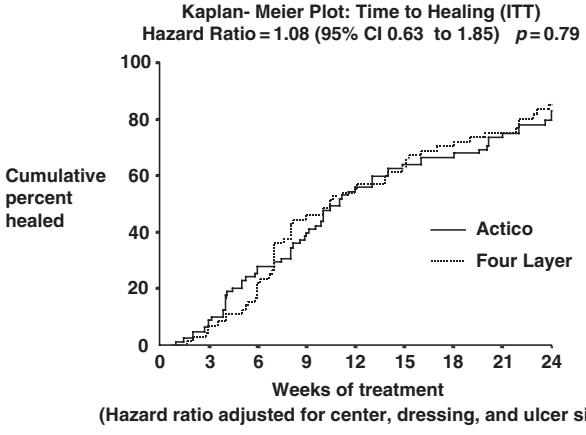


**FIGURE 1.** Kaplan-Meier plot for ulcer healing in patients randomized to Actico ($n = 82$) and 4LB ($n = 74$) analyzed on an ITT basis. Hazard ratio given after adjustment for covariates of trial center, ulcer size, and wound dressing.

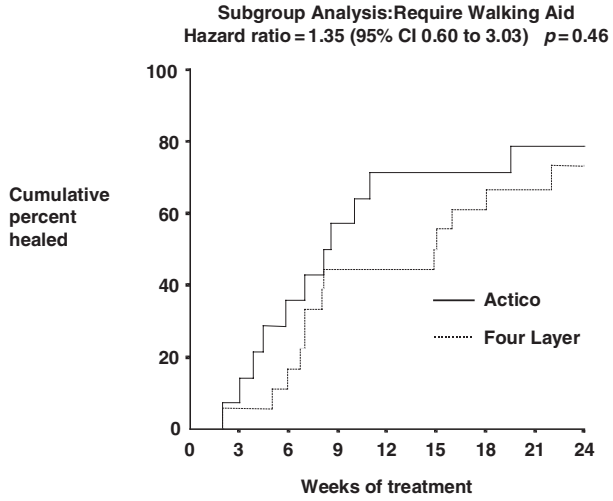


**FIGURE 2.** Kaplan-Meier plot for ulcer healing in patients with a mobility deficit randomized to Actico ($n = 14$) and 4LB ($n = 18$) analyzed on an ITT basis.

### *Trial discontinuation*

Table 3 also gives the treatment discontinuation during follow-up in the 156 patients. It shows that 16 (21.6%) patients on 4LB withdrew from their randomized bandage treatment compared with 17 (20.7%) on CSSB. Wound deterioration and bandage-related withdrawals occurred in seven patients on 4LB compared with six on CSSB, of which four (three on 4LB, one on CSSB) were considered to be due to infection. Peri-ulcer skin maceration was given as a reason in four cases (two in each group).

In all, 45 patients experienced 66 adverse events, 23 (30 events) on 4LB and 22 (36 events) on CSSB (Table 4). Of the 21 that were possibly or definitely related to the bandage, discontinuation occurred in seven patients on 4LB and six on CSSB.

**Table 4.** Adverse events categorized by randomization group

| Parameter | 4LB group | SSB group |
|---|---|---|
| Patients | 23 (31.1%) | 22 (26.8%) |
| Events | 30 | 36 |
| Related to bandage | | |
| No | 18 | 27 |
| Possible | 6 | 2 |
| Definite | 6 | 7 |
| Effect on study course (definite and possible) | | |
| None | 5 | 3 |
| Discontinued | 7 | 6 |
| Device-related adverse incidents (all causes given) | | |
| n | 12 | 9 |
| Tissue damage/new ulcer | 2 | 3 |
| Eczema/reaction to bandage | 2 | 2 |
| Pain | 2 | 2 |
| Maceration | 2 | 2 |
| Other | 4 | 0 |

## *DISCUSSION*

This trial was designed to evaluate whether CSSB was associated with improved ulcer closure compared with a 4LB system. It has shown that based on ITT analysis there is no evidence that either bandage is superior over a 24-week follow-up. It has shown that patients tolerated the CSSB in a similar way to those patients on 4LB with similar proportions withdrawing from treatment. Moreover, there was no evidence to suggest that patients with a mobility deficit experienced poorer healing on CSSB compared with patients on 4LB.

The 4LB was originally designed for use within an outpatient environment,[1] and work has since shown that it can be equally effective in other clinical areas, particularly dedicated leg ulcer clinics.[2,3] The results of the present trial are similar to those findings, indicating that patients with ulcers present for less than 1 year can achieve good closure when using either the 4LB or CSSB bandage systems. Other trials have shown similar rates using similar entry criteria,[4,5] although patients with more chronic ulceration have experienced lower closure rates.[15] This may be explained by differences in factors such as more chronic, larger ulceration. The present trial has confirmed that it is possible to achieve high healing rates in patients using a systematic approach to patient care and has shown that the rate of healing is similar between the two different bandage regimens. It would appear that both regimens are equally well tolerated in these patients.

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## *APPENDIX*

In addition to the authors, the following centers and nursing staff contributed patients to this trial:

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