Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial

Rebecca L Ashby, Rhian Gabe, Shehzad Ali, Una Adderley, J Martin Bland, Nicky A Cullum, Jo C Dumville, Cynthia P Iglesias, Arthur R Kang'ombe, Marta O Soares, Nikki C Stubbs, David J Torgerson

Summary

Background Drawbacks exist with the standard treatment (four-layer compression bandages) for venous leg ulcers. We have therefore compared the clinical effectiveness and cost-effectiveness of two-layer compression hosiery with the four-layer bandage for the treatment of such ulcers.

Methods We undertook this pragmatic, open, randomised controlled trial with two parallel groups in 34 centres in England and Northern Ireland. The centres were community nurse teams or services, family doctor practices, leg ulcer clinics, tissue viability clinics or services, and wound clinics. Participants were aged 18 years or older with a venous leg ulcer and an ankle brachial pressure index of at least 0·8, and were tolerant of high compression. We randomly allocated participants (1:1) to receive two-layer compression hosiery or a four-layer bandage, using a remote randomisation service and prevalidated computer randomisation program. Participants were stratified by ulcer duration and ulcer area with permuted blocks (block sizes four and six). The primary endpoint was time to ulcer healing, with a maximum follow-up of 12 months. Although participants and health-care providers were not masked to treatment allocation, the primary endpoint was measured by masked assessment of photographs. Primary analysis was intention to treat with Cox regression, with adjustment for ulcer area, ulcer duration, physical mobility, and centre. This trial is registered with the ISRCTN register, number ISRCTN49373072.

Findings We randomly allocated 457 participants to the two treatment groups: 230 to two-layer hosiery and 227 to the four-layer bandage, of whom 453 (230 hosiery and 223 bandage) contributed data for analysis. Median time to ulcer healing was 99 days (95% CI 84–126) in the hosiery group and 98 days (85–112) in the bandage group, and the proportion of ulcers healing was much the same in the two groups (70·9% hosiery and 70·4% bandage). More hosiery participants changed their allocated treatment (38·3% hosiery *vs* 27·0% bandage; p=0·02). 300 participants had 895 adverse events, of which 85 (9·5%) were classed as serious but unrelated to trial treatment.

Interpretation Two-layer compression hosiery is a viable alternative to the four-layer bandage—it is equally as effective at healing venous leg ulcers. However, a higher rate of treatment changes in participants in the hosiery group than in the bandage group suggests that hosiery might not be suitable for all patients.

Funding NIHR Health Technology Assessment programme (07/60/26).

Lancet 2014; 383: 871–79

Published Online
December 6, 2013
http://dx.doi.org/10.1016/S0140-6736(13)62368-5

See Comment page 850

Department of Health Sciences (R L Ashby PhD, R Gabe PhD, S Ali PhD, Prof J M Bland PhD, C P Iglesias PhD, Prof D J Torgerson PhD) **and Centre for Health Economics** (M O Soares MSc), **University of York, York, UK; School of Healthcare, University of Leeds, Leeds, UK** (U Adderley PhD); **School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK** (Prof N A Cullum PhD, J C Dumville PhD); **Liverpool School of Tropical Medicine, Liverpool, UK** (A R Kang'ombe MSc); **and Leeds Community Healthcare Trust, Leeds, UK** (N C Stubbs MSc)

Correspondence to:
Dr Jo Dumville, School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, M13 9PL, UK
jo.dumville@manchester.ac.uk

Introduction

Venous leg ulcers are open chronic wounds that occur within the gaiter region of the leg (from below the ankle, up to mid-calf) and are a consequence of venous insufficiency.[1] They typically present as repeated cycles of ulceration, healing, and recurrence. Such ulcers can take weeks or months to heal,[1–3] and 12-month recurrence rates are between 18% and 28%.[4,5] They are painful, malodorous, prone to infection, and severely affect patients' mobility and quality of life.[6,7]

Compression is an effective and recommended treatment for venous leg ulcers, which works by application of graduated pressure to the leg (highest at the ankle, decreasing to the knee), which improves venous return and reduces reflux.[8,9] In a systematic review, O'Meara and colleagues[10] concluded that multicomponent systems delivering high compression (defined as 40 mm Hg of compression at the ankle) were the most effective treatment for such ulcers.

The four-layer multicomponent compression bandage system (four-layer bandage) is regarded as the gold standard compression system to treat venous leg ulceration.[5,11] However, some drawbacks are associated with this treatment. The amount of compression delivered might be compromised by poor application technique, bandages can slip and need reapplication, and the bulky nature can reduce ankle or leg mobility, which creates difficulties in wearing of shoes and causes discomfort.[12,13]

Two-layer compression hosiery systems (two-layer hosiery) have recently been marketed for the treatment of venous leg ulcers. They are designed to deliver 40 mm Hg of compression at the ankle when both

layers—understocking and overstocking—are worn together. Two-layer hosiery is less bulky than the four-layer bandage and can be worn more easily with shoes, which might enhance ankle or leg mobility and patient adherence. Patients with sufficient mobility and dexterity can also remove and reapply two-layer hosiery, which encourages self-management and could reduce costs.[14,15]

Little evidence exists from randomised controlled trials about the effectiveness of two-layer hosiery for ulcer healing,[15–18] and no previous trials have compared two-layer hosiery with the four-layer bandage. Finlayson and colleagues[19] did a randomised controlled trial of hosiery (in which one layer delivered 35 mm Hg compression instead of the two layers delivering 35–40 mm Hg in VenUS IV) compared with the four-layer bandage and reported that the bandage group had a healing rate twice that of the hosiery group—a significant finding.

In VenUS IV, we aimed to compare the clinical effectiveness and cost-effectiveness of two-layer hosiery with the four-layer bandage. We also assessed ulcer recurrence because hosiery is recommended as a maintenance treatment post-healing to prevent recurrence.[9] We postulated that participants allocated to hosiery would have less ulcer recurrence than those allocated to the four-layer bandage, because they would be accustomed to wearing hosiery.

Methods

Study design and participants

We undertook a pragmatic, multicentre, two group, randomised controlled trial in 34 centres in England and Northern Ireland. We recruited participants from community nursing and tissue viability teams or services, family doctor practices, community and outpatient leg ulcer clinics, and wound clinics. Patients were eligible for inclusion if they had at least one venous leg ulcer (defined as any break in the skin that had either been present for longer than 6 weeks or occurred in a person with a history of venous leg ulceration). Ulcers were judged purely venous if no other cause was suspected. The ulcer was required to be venous in appearance (ie, moist, shallow, and of an irregular shape) and to lie wholly or partly within the gaiter region of the leg. Eligible participants were at least 18 years old and had to have an ankle brachial pressure index of at least 0·8 (measured within the previous 3 months), and to be able and willing to tolerate high compression. We excluded patients who had a pressure index greater than 1·20 (measured within the previous 3 months), were unable to receive high compression on the basis of nurses' clinical judgment or local guidelines, had wound exudate levels that precluded the use of hosiery, did not provide informed consent, were participating in another study assessing leg ulcer treatments, had known allergy to trial product(s), had gross leg oedema, had been recruited previously into this trial, or for another reason according to the clinical judgment of the treating nurse.

This trial was reviewed and approved by the Northern and Yorkshire Research Ethics Committee (09/H0903/25) and all participants gave informed consent. Because of the low-risk nature of this trial (both treatments being assessed were already being used routinely in clinical practice), we did not judge it necessary to have a separate Data Monitoring and Ethics Committee to oversee the trial. Instead, unmasked adverse events data, details of patients no longer receiving randomised treatments, and details of post-randomised exclusions were presented by the trial coordinator (RLA) and trial statisticians (RG, JMB) to independent members of the Trial Steering Committee (chair [Ian Chetter], independent clinician [Brenda King], and independent statistician [Jenny Freeman]) before Trial Steering Committee meetings. This decision was ratified by the study sponsors (National Institute for Health Research Health Technology Assessment programme) and minutes of these meetings were sent to the sponsors. We obtained research governance approval for all centres.

Randomisation and masking

We randomly allocated eligible participants to treatment groups by an independent remote telephone or online randomisation service based at the Trials Unit, University of York (York, UK). Randomisation was done with a prevalidated computer program and participants were stratified by ulcer duration (≤6 months or >6 months) and ulcer area (≤5 cm² and >5 cm², based on assessment of a wound tracing on a measurement grid made at baseline) with permuted blocks (block sizes four and six), because these criteria are known predictors of ulcer healing.[20] We could not mask participants or nurses to the allocated treatment.

Procedures

We recorded participants' personal and clinical details at baseline. We calculated body-mass index (BMI) as weight divided by height.[21] The largest eligible ulcer was designated the reference ulcer and the leg in which it occurred the reference leg. We recorded reference ulcer duration and time since first venous leg ulcer. We took a tracing of the reference ulcer with a wound measurement grid (P12 version 2, ConvaTec, Middlesex, UK) and calculated ulcer area (in cm²) with computer software (MouseEyes, version 3.1[22]). Nurses recorded participants' physical mobility, ankle mobility of the reference leg, treatment preference, and details of present treatments for leg ulcer.

Participants in the control group received the four-layer bandage (hereafter referred to as the bandage). The type of four-layer bandage system was not specified, but it had to deliver 40 mm Hg of compression at the ankle. Participants in the intervention group received two-layer hosiery (hereafter referred to as hosiery) in the form of a two-layer kit consisting of an understocking and an overstocking. When worn together, the two layers were required to deliver 35–40 mm Hg of compression at the ankle.

Participants were treated by their usual nurse and were given their allocated treatment within usual UK NHS settings and timescales. Participants received their treatment until they were no longer able to continue doing so and were changed to a different treatment that replaced the allocated trial treatment (designated the non-trial treatment), or until their reference leg healed and treatment was no longer needed, or until they were lost to follow-up, or until they died.

The primary endpoint was time to healing of the reference ulcer. We defined healing as complete epithelial cover in the absence of a scab (eschar) with no dressing needed. When the treating nurse judged the reference ulcer healed, a digital photograph was taken of the healed site and thereafter once per week for 4 weeks. Two assessors undertook central, independent, masked assessment of the photographs for healing and date, with a third assessor resolving disagreements.

Secondary endpoints were unmasked outcome assessment, unmasked measurement of time to healing of the reference leg, health-related quality of life, resource use, treatment change, adverse events, and ulcer recurrence. Health-related quality of life and resource use were measured at baseline and every 3 months thereafter by participant self-completion of the SF-12 and EQ-5D survey; participants also provided details of consultations they had with NHS health-care professionals. Nurses recorded when a participant changed from their allocated treatment and moved to a non-trial treatment and the reason why. We used this information to assess participant treatment change. After the reference leg healed, nurses assessed ulcer recurrence on a monthly basis. Participants were monitored for serious and non-serious adverse events throughout the trial, which were recorded as they occurred by the treating nurse. Adverse events were classified as serious (death, life-threatening or

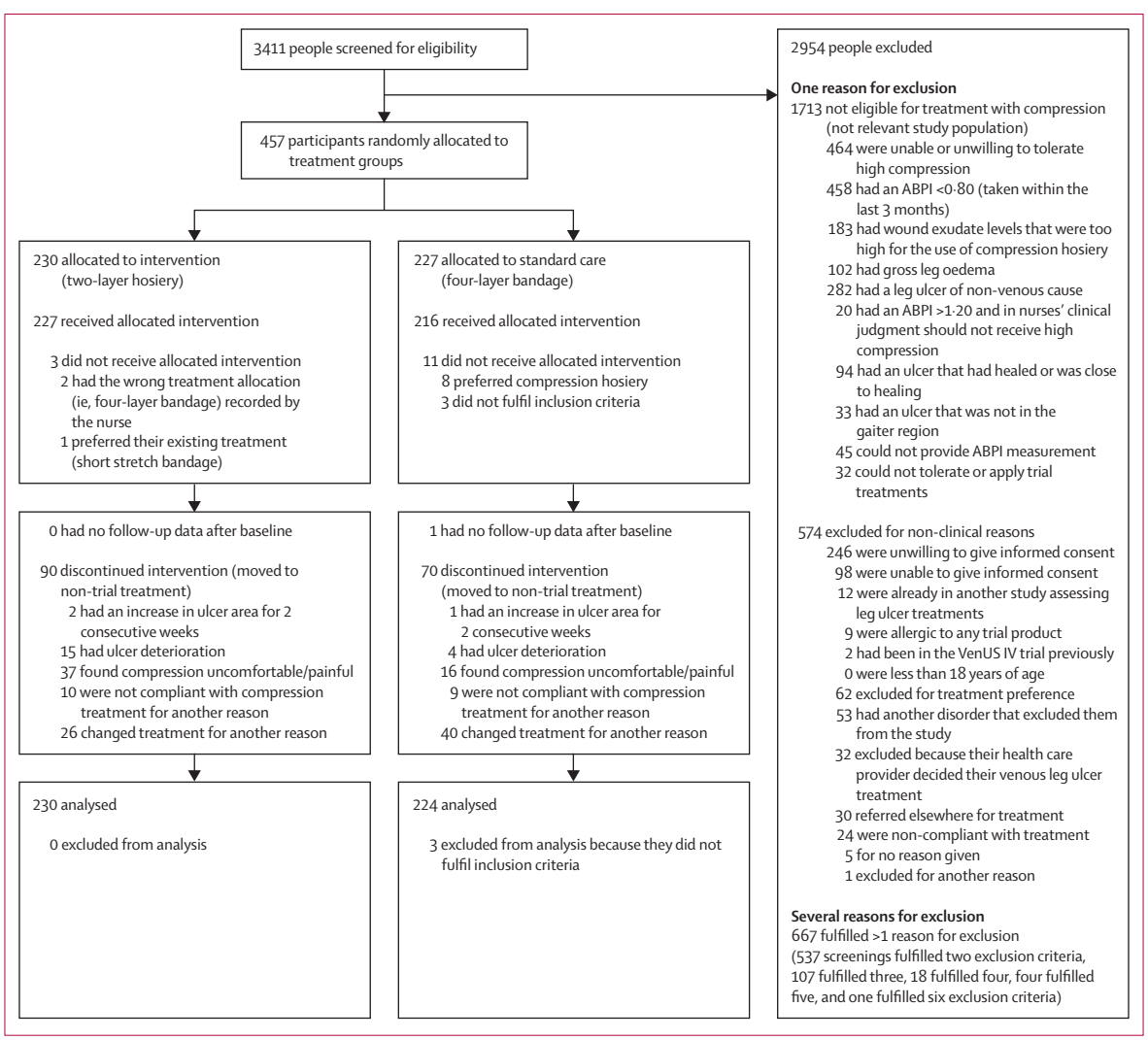

Figure 1: **Trial profile**
ABPI=ankle brachial pressure index.

limb-threatening event, admission to hospital, prolonged hospital stay, persistent or significant disability or incapacity, or other medically important situation) or non-serious (all other adverse events).

Recruitment began on Oct 1, 2009, and planned participant follow-up was 12 months. However, because of an extension of the recruitment phase until Feb 29, 2012, participants recruited during the final 12 months were followed up for between 4 and 12 months. Participant follow-up ended on June 30, 2012. Participants left the trial if they withdrew consent, were lost to follow-up, or died.

	Hosiery group (n=230)	Bandage group (n=224)	Overall (n=454)
Male participants	117 (51%)	113 (50%)	230 (51%)
Age (years)	68·3 (15·1)	68·9 (13·8)	68·6 (14·5)
BMI (kg/m²)	30·9 (7·9)	31·2 (8·0)	31·0 (8·0)
Missing	3 (1%)	3 (1%)	6 (1%)
Mobility			
Walks freely	139 (61%)	150 (67%)	289 (64%)
Walks with difficulty	89 (39%)	71 (32%)	160 (35%)
Immobile	1 (<1%)	3 (1%)	4 (1%)
Ulcer characteristics			
Ulcer area (cm²)	4·1 (1·6–8·7)	3·7 (1·6–8·2)	3·9 (1·6–8·7)
Missing	1 (<1%)	0	1 (<1%)
Ulcer duration (months)	4·0 (3·0–12·0)	4·0 (2·0–9·0)	4·0 (2·0–11·0)
Missing	1 (<1%)	2 (1%)	3 (1%)
Time since first ulcer (months)	36·0 (4·0–120·0)	36·0 (4·5–120·0)	36·0 (4·0–120·0)
Missing	3 (1%)	4 (2%)	7 (2%)
Total ulcers on reference leg	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Reference leg			
Left	135 (59%)	121 (54%)	256 (56%)
Right	95 (41%)	103 (46%)	198 (44%)
Ankle mobility of reference leg			
Full range of ankle motion	159 (69%)	154 (69%)	313 (69%)
Reduced range of ankle motion	65 (28%)	67 (30%)	132 (30%)
Ankle fixed	6 (3%)	3 (1%)	9 (2%)
Ankle brachial pressure index			
Ankle brachial pressure index of reference leg	1·1 (0·1)	1·1 (0·1)	1·1 (0·1)
Missing	3 (1%)	9 (4%)	12 (3%)
Patient treatment preference			
Hosiery	108 (47%)	112 (51%)	220 (49%)
Bandage	29 (13%)	29 (13%)	58 (13%)
No preference	91 (40%)	80 (36%)	171 (38%)
Present treatments*			
Bandage	119 (52%)	102 (46%)	221 (49%)
Short-stretch bandage	15 (6%)	14 (6%)	29 (6%)
Hosiery	18 (7%)	13 (6%)	31 (7%)
Other compression bandage	31 (14%)	38 (17%)	69 (15%)
Not receiving compression	37 (16%)	41 (18%)	78 (17%)
Other treatment	5 (2%)	8 (4%)	13 (3%)

Data are n (%), mean (SD), or median (IQR). "Missing" indicates the number of patients with missing data listed if data are missing for continuous variables. For the categorical variables, differences between the group n and the variable n are due to missing data. *Not mutually exclusive.

Table 1: **Baseline characteristics**

Statistical analysis

A power calculation based on VenUS I[5] suggested that 400 participants with a median survival in the bandage group of 100 days and follow-up of 12 months would provide 90% power to detect an increase in median time to healing of 41 days and a decrease in the hazard ratio (HR) for healing to 0·72, or a decrease in median time to healing of 72 days and an increase in the HR to 1·42. With the assumption of 10% attrition and a further inflation by 10% to account for potential centre effects, these estimates gave a final sample size of 489 participants.

We did analyses following the principles of intention to treat and we used STATA (version 12.0) for all analyses. Measures of risk, such as HR, are presented with 95% CIs. Statistical tests were two-sided with a significance level of 0·05.

We measured time to healing of the reference ulcer in days from randomisation. We investigated differences in healing rates with a Kaplan-Meier plot and, for the primary analysis, we estimated HRs with the Cox model (HR>1 favours hosiery), adjusted by ulcer area, ulcer duration, and participant mobility[5,23] with testing for inclusion of shared centre frailty effects.[24–26] We assessed the proportional hazards assumption through inspection of log–log plots and with Grambsch's and Therneau's test using Schoenfeld residuals.[27]

We scored SF-12 questionnaires with the QualityMetric Health Outcomes Scoring Software 2.0[28] and we summarised the physical and mental component summary scores by treatment group at each timepoint. We analysed the association between physical or mental component summary scores and treatment over time with a linear mixed model,[29,30] adjusted by ulcer area, ulcer duration, timepoint, centre, and participant mobility. We tested for an interaction between treatment and time for inclusion in these models.

We investigated treatment change by group in terms of the proportion of participants changing from their allocated treatment to non-trial treatment before healing. We analysed differences in rate of treatment change by trial group in post-hoc analyses with Cox regression, adjusted for age and by whether or not a participant had a non-serious adverse event.

We compared with a χ^2 test adverse events by treatment group as the number of participants who had at least one event and the number of events per participant with a zero-inflated random effects negative binomial regression model, adjusted for baseline ulcer area, ulcer duration, participant mobility, and centre. We analysed non-serious and serious adverse events separately.

We presented the proportion of participants who had recurrence of an ulcer on a previously healed reference leg by treatment group. We analysed time to recurrence with the Cox model, using the same adjustments as the primary outcome analysis.

We also did a within-trial cost-utility analysis from the perspective of the UK NHS and Personal Social Services[31]

for which the time horizon was 12 months; therefore, neither costs nor health benefits (quality-adjusted life-years) were discounted. We calculated individual patient cost as the product of ulcer-related resources used and the relevant unit costs. Elements of resource use measured were use of allocated trial compression treatments, use of non-trial compression treatments (where applicable), and health-care consultations (visits to or from health-care providers for ulcer-related reasons).

For the economic analysis, we used the quality-adjusted life-year as the measure of health benefit, and the EQ-5D[32,33] as the health state descriptor measure, with data gathered at baseline and quarterly up to 12 months. We estimated quality-adjusted life-years with time-weighted averages of the utility scores measured at the beginning and end of each quarterly interval in the study time horizon.[34] We estimated the differences in costs and quality-adjusted life-years between trial groups with use of separate inverse probability-weighted linear mixed models, with adjustments for baseline covariates: (log of) ulcer area, (log of) ulcer duration, participant mobility level, baseline utility (for quality-adjusted life-year regression), and centre treated as a random effect. We measured uncertainty about these estimates (ie, CIs for the difference in costs and effects) with non-parametric bootstrap.[34] To assess incremental cost-utility, we compared the mean difference in costs between trial groups with the mean difference in quality-adjusted life-years.

To explore decision uncertainty, we used the joint distribution of the bootstrapped pairs of mean costs and mean outcomes to assess the probability of the intervention being cost effective, at specific values of willingness to pay per quality-adjusted life-year. The cost-effectiveness acceptability curve[35] plots this information for a range of willingness to pay values.

This trial is registered as ISRCTN49373072.

Role of the funding source

The sponsor of the study was non-commercial and, although it managed the grant application process and monitored the study, had no direct role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author has full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Nov 1, 2009, and Feb 28, 2012, we screened 3411 people, and randomly allocated 457 participants to hosiery (230) and the bandage (227). We excluded three participants after randomisation, so 454 (230 hosiery and 224 bandage) participants contributed data to the analyses (figure 1). Table 1 shows the baseline characteristics of the participants.

We recorded no evidence of a difference in reference ulcer healing rates between the hosiery and bandage groups (figure 2). Median time to healing was 99 days (95% CI 84–126) for the hosiery group and 98 days (85–112) for the bandage group. The proportion of ulcers healing was similar by trial group (163/230 [71%] hosiery and 157/223 [70%] bandage). After adjustment for ulcer area,

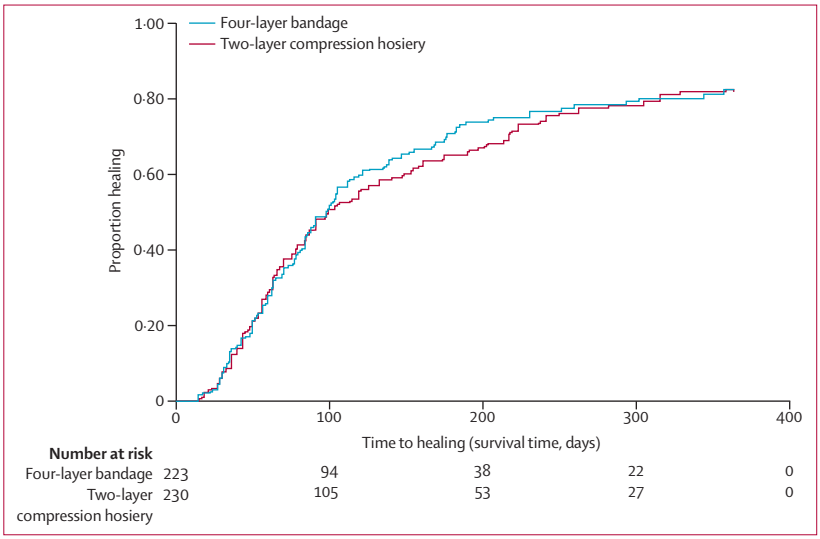

Figure 2: **Kaplan-Meier plot of time to healing (masked) by treatment group**

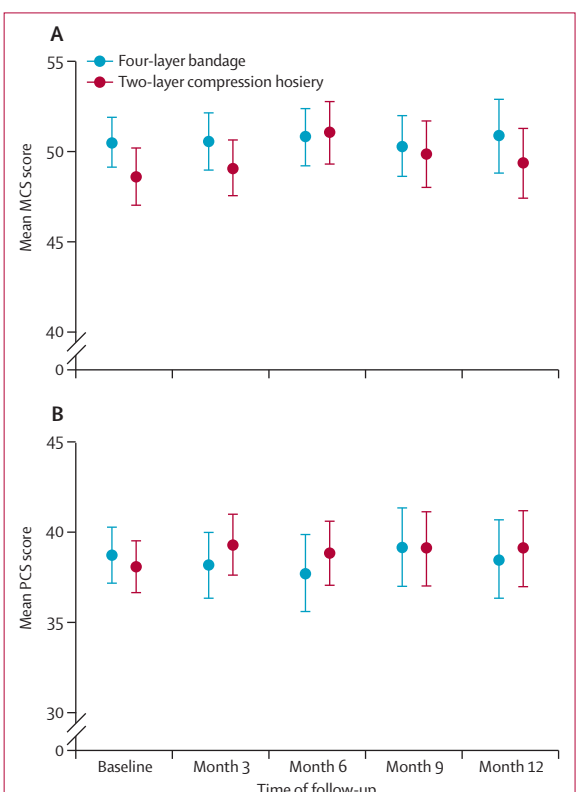

Figure 3: **SF-12 mental component summary and physical component scores over time according to treatment group (mean and 95% CI)**
Error bars are 95% CIs. MCS=mental component summary. PCS=physical component summary.

duration, and mobility with shared centre frailty effects, the HR was 0·99 (95% CI 0·79–1·25, p=0·96).

We also assessed the time to healing of the reference ulcer with use of unmasked outcome data (with healing dates as reported by unmasked nurses). Again, we noted no evidence of a treatment effect for two-layer hosiery compared with the four-layer bandage in this adjusted model, with a HR of 0·91 (0·73–1·12; data not shown).

Figure 3 shows mental and physical component summary scores over time. We recorded no evidence of a difference in mental component summary score by treatment over 12 months. For the physical component summary score, a transient effect occurred at 3 months, with a significant interaction of treatment with time (p=0·018)—patients allocated to hosiery had a higher physical component summary score than those assigned to bandage (suggesting better physical health), after adjustment for ulcer area, ulcer duration, participant mobility, centre, and timepoint.

In total, 150 of 454 (33%) participants changed to a non-trial treatment before their ulcers healed, and more did so in the hosiery group (88/230 [38%]) than in the bandage group (62/224 [28%]; p=0·02; table 2). Our findings show a higher rate of treatment change in the hosiery group (HR 1·59, 95% CI 1·14–2·21; p=0·005), in older patients (1·02, 1·00–1·03; p=0·003), and in those who had at least one non-serious adverse event (1·75, 1·18–2·59; p=0·005).

See Online for appendix

	Hosiery group (n=230)	Bandage group (n=224)	Overall (n=454)
Treatment change	88 (38%)	62 (28%)	150 (33%)
Reason for change			
Increase in ulcer area	2 (2%)	1 (2%)	3 (2%)
Ulcer deterioration	15 (17%)	4 (7%)	19 (13%)
Compression uncomfortable	37 (42%)	15 (24%)	52 (35%)
Participant not adherent	10 (11%)	8 (13%)	18 (12%)
Other	24 (27%)	34 (55%)	58 (39%)

Table 2: **Change from allocated trial treatment to non-trial treatment for each group**

	Hosiery group (n=230)	Bandage group (n=224)	Overall (n=454)
Participants with a serious adverse event	33 (14%)	33 (15%)	66 (15%)
Total number of serious adverse events	43	42	85
Participants with a non-serious adverse event	154 (67%)	130 (58%)	284 (63%)
Total number of non-serious adverse events	463	347	810

Data are n (%) or n.

Table 3: **Summary of serious and non-serious adverse events, by group**

	Mean annual cost, £ (95% CI)†	Mean quality-adjusted life-years (95% CI)†
Hosiery group	1492·9 (1187·3 to 1954·3)	0·685 (0·665 to 0·716)
Bandage group	1795·3 (1559·7 to 2185·0)	0·651 (0·619 to 0·682)
Difference between groups	−302·4 (−697·6 to 96·2)	0·034 (−0·001 to 0·078)

£1=US$1·62. *Adjusted for ulcer duration (logarithmic), ulcer area (logarithmic), participant mobility, and centre. Participant mobility was defined as dichotomous variable (ie, walk freely *vs* walk with difficulty or immobile). Centre has been adjusted for by a multilevel model, with centre used as a random effect. †95% CIs are bias corrected.

Table 4: **Adjusted* annual costs and quality-adjusted life-years**

In the hosiery group, 24 of 167 (14%) participants had ulcer recurrence compared with 41 of 176 (23%) in the bandage group. The rate of recurrence was greater with bandage than with hosiery (HR 0·56, 95% CI 0·33–0·94; p=0·026).

In the economic analysis, after adjustment for baseline covariates (as described previously), the average mean costs were about £300 (£1=US$1·62) lower per participant per year in the hosiery group than in the bandage group (appendix p 1 and table 4). This difference was mainly caused by more frequent nurse consultations in the bandage group than in the hosiery group. Other types of resource use were similar between the two groups (appendix p 2). After adjustment for ulcer area, ulcer duration, participant mobility, and centre, patients in the hosiery group had, on average, slightly more quality-adjusted life-years than those in the bandage group (table 4).

These findings suggest that hosiery is a dominant treatment—that is, on average it results in higher quality-adjusted life-years and lower costs than do bandages. The joint distribution of mean costs and mean quality-adjusted life-years shows that hosiery is very likely to be both more effective and less costly than bandages, with a roughly 95% probability of hosiery being cost effective at the commonly used thresholds of £20 000–£30 000 in the UK[36] (figure 4).

Discussion

We recorded no evidence of a difference in healing rates between participants allocated to receive hosiery or bandage. The HR for healing was 0·99 (95% CI 0·79–1·25), meaning that the hazard (ie, chance) of healing, at any specific timepoint, was almost the same in the two groups. The 95% CI indicates that hosiery might reduce the chance of healing by as much as 21% or increase it by as much as 25%.

The higher number of changes to non-trial treatment in the hosiery group than in the bandage group was unexpected. We had predicted that hosiery might be more tolerable because it is less bulky and can be worn with ordinary shoes; its effectiveness also relies less on

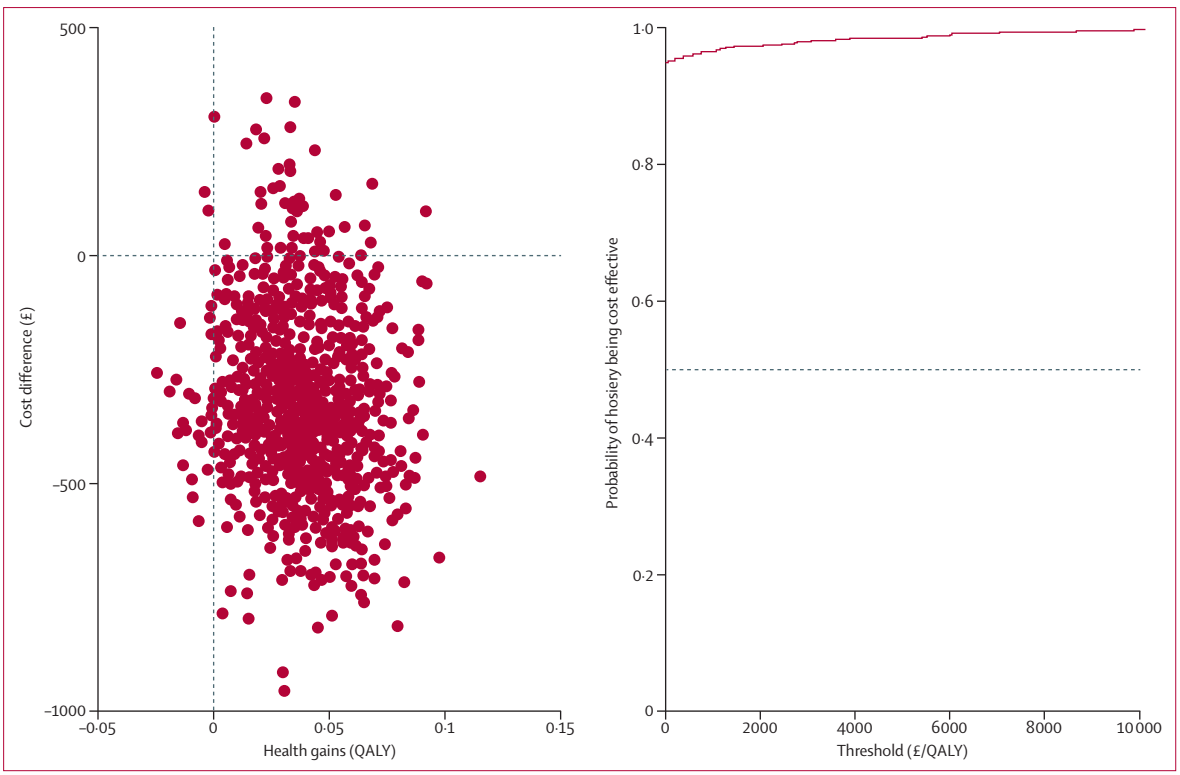

Figure 4: **Cost-effectiveness plane and acceptability curve for cost per QALY analysis**
QALY=quality-adjusted life-years.

applicator skill than does that of bandages. Instead, our results suggest that participants had more complaints about discomfort with hosiery, which led many participants in this group to change to another treatment. A systematic review of compression hosiery for the prevention of venous leg ulcer recurrence showed reduced compliance rates in patients wearing high-compression hosiery compared with those who wore moderate-compression hosiery post-healing.[37] However, the continuing use of compression stockings in people with a history of venous leg ulcers can be low.[38,39] For example, Jull and colleagues[39] reported that in a cohort of participants with a healed venous leg ulcer, only 52% (67/129) were wearing maintenance hosiery most days in the first 6 months after ulcer healing. They suggest that patient belief that wearing of stockings was worthwhile was a key factor in predicting continuing use of maintenance compression.

We postulated a priori that participants who become used to wearing hosiery as an ulcer treatment would be more likely to wear it as a maintenance treatment after healing and therefore reduce their risk of ulcer recurrence.[37] Although we did not assess which treatments were used after ulcers had healed on the reference leg, we did note a significant reduction in recurrence in people allocated to hosiery, which might support our hypothesis. We acknowledge that the assessment of recurrence was not masked in this study and that this analysis was not of the population as randomised but rather of those who healed. Additionally, we did not gather data for specific surgical interventions received in each group that might have affected recurrence—rates of venous surgery are generally low in this population and we do not have any reason to believe that receipt of such surgery would have been affected by the type of compression treatment allocated.

In terms of value for money, we noted that, on average, treatment of participants allocated to hosiery cost the NHS less than it did for those allocated to bandages, and these participants had marginally more quality-adjusted life-years than those in the bandage group. An analysis of the decision uncertainty associated with these results indicated that, compared with the bandage, hosiery is highly likely to be cost effective.

Thus, our results indicate that two-layer hosiery is as effective as the four-layer bandage for healing of venous leg ulcers and is more cost effective, probably because of fewer nurse consultations and improved self-management. Hosiery was also associated with a reduced chance of ulcer recurrence after healing.

Few data exist about how widely compression hosiery is used as a treatment for open leg ulcers in the UK (panel). In total, only 6·5% of participants in this study had been treated with hosiery before they entered the

Panel: Research in context

Systematic review

Five published randomised controlled trials have compared compression hosiery (minimum of 25 mm Hg compression at the ankle) with compression bandaging for treatment of venous leg ulcers. Four of these trials compared compression hosiery with the short-stretch bandage and one compared compression hosiery with the four-layer bandage. None of these trials assessed the new two-layer hosiery systems. Of the four randomised controlled trials that compared hosiery with the short-stretch bandage, three were identified as being at high risk of bias and one at an unclear risk of bias. A random effects model suggested that, on average, more ulcers healed with compression hosiery than with the short-stretch bandage (RR 1·66, 95% CI 1·07–2·58). The randomised controlled trial that compared compression hosiery (one class 3 compression stocking) with the four-layer bandage included 103 participants with venous leg ulcers. The adjusted hazard ratio (four-layer bandage *vs* compression hosiery) was 2·1 (95% CI 1·4–4·3), which favoured the four-layer bandage.

Interpretation

The results of VenUS IV suggest that two-layer hosiery that delivers 40 mm Hg pressure at the ankle is an effective alternative to the four-layer compression bandage. Two-layer hosiery has the additional benefit of reducing recurrence rates and being more cost effective. Although two-layer hosiery is not suitable for all patients (eg, those who are unable to apply or remove it), it offers some advantages over the four-layer bandage, including a reduction in the average number of nurse consultations needed and lower ulcer recurrence.

trial (compared with 49% who had been treated with a compression bandage). If we accept this figure as indicative of present UK practice, increased use of hosiery as a treatment is likely to result in substantial savings for the NHS and improved quality of life for people with venous ulcers.

Contributors

NAC, JMB, JCD, MS, CPI, UA, NS, and DJT contributed to the design of the trial, grant application, and trial protocol. JCD was chief investigator of the trial when it started and NAC took over as chief investigator while JCD was on maternity leave. RLA was trial coordinator. All authors were members of the trial management group, which was chaired by NAC and JCD, and oversaw the conduct of the trial. RG did the statistical analyses and JMB oversaw the conduct of these analyses. ARK wrote the statistical analysis plan. SA did the trial-based cost-effectiveness analysis and MOS oversaw and advised on all elements of the cost-effectiveness work. UA and NS gave clinical input and advice during the trial. DJT provided advice about trial conduct. All authors participated in data interpretation and in reporting the results. All authors helped to write the final report, provided comments, and have seen and approved the final version.

Trial steering committee members

This trial was overseen by the trial steering committee, which monitored trial progress in terms of recruitment, adverse events, problems arising, participant withdrawals, data quality, post-randomisation exclusions, and number of participants not receiving their allocated trial treatment. The independent trial steering committee members were: Prof Ian Chetter (Chair), Dr Jenny Freeman (external member), Brenda King (external member), John Hopper (patient representative), and Doreen Hopper (patient representative). Other members (past and present) were: Una Adderley, Shehzad Ali, Rebecca Ashby, Jacqui Ashton, Martin Bland, Sue Collins, Ben Cross, Nicky Cullum, Jo Dumville, Rhian Gabe, Pedro Saramago, Cynthia Iglesias, Arthur Kang'ombe, Marta Soares, Nikki Stubbs, David Torgerson, Jude Watson, Anne Witherow, and Gillian Worthy.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 07/60/26) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, the NHS, or the Department of Health. We thank all the participants who took part in this trial; the Principal Investigators, research nurses, and health care professionals who screened and recruited patients into the study, gathered trial data, and ensured the success of the trial; John Hopper and Doreen Hopper for acting as patient representatives; Sue Collins, who checked clinical data received for completeness and posted out questionnaires to study participants; Gemma Hancock and Angie Oswald, who did the masked outcome assessment of healing of ulcer photographs; Catherine Arundel, who measured the area of baseline ulcer tracings; and Hannah Buckley, who helped with the SF-12 analyses.

References

1 Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol* 2001; **44:** 401–21.
2 Abbade LP, Lastória S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. *Int J Dermatol* 2005; **44:** 449–56.
3 Maggisano R, Harrison AW. The venous system. Ontario: University of Toronto, 2004.
4 Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet* 2004; **363:** 1854–59.
5 Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, the VenUS Team. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. *Health Technol Assess* 2004; **8:** 1–105.
6 Hickie S, Ross S, Bond C. A survey of the management of leg ulcers in primary care settings in Scotland. *J Clin Nurs* 1998; **7:** 45–50.
7 Laing W. Chronic venous diseases of the leg. London: Office of Health Economics, 1992.
8 Royal College of Nursing. The nursing management of venous leg ulcers. London: Royal College of Nursing, 2006.
9 Scottish Intercollegiate Guidelines Network. Management of chronic venous leg ulcers—a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network, 2010.
10 O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2012; **1:** CD000265.
11 O'Meara S, Tierney J, Cullum N, et al. Four-layer compression bandage compared with short-stretch bandage for venous leg ulcers: a meta-analysis of randomised controlled trials using individual patient data (IPD). 17th Annual Meeting of the European Tissue Repair Society; Southampton, UK; Sept 26–28, 2007.
12 Adderley U, Thompson C. A study of the factors influencing how frequently district nurses re-apply compression bandaging. *J Wound Care* 2007; **16:** 217–21.
13 Meyer FJ, McGuinness CL, Lagattolla NR, Eastham D, Burnand KG. Randomized clinical trial of three-layer paste and four-layer bandages for venous leg ulcers. *Br J Surg* 2003; **90:** 934–40.
14 Scottish Intercollegiate Guidelines Network. The care of patients with chronic leg ulcer. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network, 1998.
15 Jünger M, Wollina U, Kohnen R, Rabe E. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. *Curr Med Res Opin* 2004; **20:** 1613–23.
16 Polignano R, Guarnera G, Bonadeo P. Evaluation of SurePress Comfort: a new compression system for the management of venous leg ulcers. *J Wound Care* 2004; **13:** 387–91.
17 Mariani F, Mattaliano V, Mosti G, et al. The treatment of venous leg ulcers with a specifically designed compression stocking kit. *Phlebologie* 2008; **37:** 191–97.
18 Taradaj J, Franek A, Brzezinska-Wcislo L, Blaszczak E, Polak A. Randomized trial of medical compression stockings versus two-layer short-stretch badaging in the management of venous leg ulcers. *Phlebologie* 2009; **38:** 157–63.

19 Finlayson KJ, Courtney MD, Gibb MA, O'Brien JA, Parker CN, Edwards HE. The effectiveness of a four-layer compression bandage system in comparison to Class 3 compression hosiery on healing and quality of life for patients with venous leg ulcers: a randomised controlled trial. *Int Wound J* 2012; published online June 21. DOI:10.1111/j.1742-481X.2012.01033.x.

20 Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 1999; **135:** 920–26.

21 WHO. BMI Classification. 2012. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed Nov 22, 2013).

22 Taylor RJ. 'Mouseyes': an aid to wound measurement using a computer. *J Wound Care* 1997; **6:** 123–26.

23 Dumville JC, Worthy G, Bland JM, et al, and the VenUS II team. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. *BMJ* 2009; **338:** b773.

24 Collett D. Modelling survival data in medical research. London: Chapman and Hall/CRC, 2003.

25 Cox D. Analysis of survival data. London: Chapman and Hall/CRC, 1984.

26 Kalbfleisch J, Prentice R. The statistical analysis of failure time date. New York: Wiley, 2002.

27 Schoenfeld D. Partial residuals for the proportional hazards model. *Biometrika* 1982; **69:** 51–55.

28 Saris-Baglama R, Dewey C, Chisholm G, Plumb E, Kosinki M, Bjorner J. QualityMetric Health Outcomes Scoring Software 2.0. Washington: QualityMetric Incorporated, 2007.

29 Fitzmaurice G, Laird N, Ware J. Applied longitudinal analysis. New Jersey: Wiley, 2004.

30 Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. New York: Springer-Verlag, 2000.

31 National Institute for Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Clinical Excellence, 2008.

32 Kind P. The EuroQol instrument: an index of health-related quality of life. In: Spilker B, ed. Quality of life and pharmacoeconomics in clinical trials. New York: Lippincott-Raven, 1996.

33 Brazier J. Measuring and valuing health benefits for economic evaluation. New York: Oxford University Press, 2007.

34 Glick H. Economic evaluation in clinical trials. Oxford: Oxford University Press, 2007.

35 Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004; **13:** 405–15.

36 McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics* 2008; **26:** 733–44.

37 Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev* 2012; **8:** CD002303.

38 Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. *Ann Vasc Surg* 2007; **21:** 790–95.

39 Jull AB, Mitchell N, Arroll J, et al. Factors influencing concordance with compression stockings after venous leg ulcer healing. *J Wound Care* 2004; **13:** 90–92.