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Associations among patient, treatment, or wound-level factors and venous leg ulcer healing: wound characteristics are the key factors in determining healing outcomes

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Abstract

Chronic venous leg ulcers are challenging to heal and often recur. This has a significant impact on older individual health and is a financial burden on health care resources. This study aimed to identify factors associated with the healing of venous leg ulcers via secondary examination of data from a previously published prospective randomised controlled trial of elastic and inelastic compression systems. The data from the 45 patients who finished the trial was reanalysed for a hypothesis generating study. Larger ulcers, higher exudate levels, larger calf circumferences, and longer ulcer duration at baseline were associated with lack of healing at 12 weeks. There was some evidence that NSAID use was associated with an increased likelihood of non-healing (unadjusted OR for healing, 0.13, 95% CI (0.02, 0.70)). There was no evidence that other variables, including gender and BMI, were associated with healing. The key risk factors for wound healing are largely wound based or inherent to wound development, as these were found to be the factors with the strongest associations in the analysis. Future research should address how and why these factors are associated with wound healing over a longer time frame, and explore how NSAIDs may affect wound healing outcomes.

Introduction

Venous leg ulcers (VLUs) are of increasing concern to healthcare systems worldwide, as the rate appears to be increasing in line with an ageing population.(1) In Australia, VLUs are the most common clinical wound seen in community practice(2), continue to be an under-recognised issue, and have been identified as a growing silent epidemic.(3) The best available evidence reports VLUs affect around 1% of the population and about 3% of those over 80 years old in Western countries.(4) The incidence of venous leg ulceration has been reported as 1.5 to 3.0 in 1,000 in people aged 65 and increases with age to 20 in 1,000 in people aged over 80 years.(1) The burden and cost of VLU is expected to rise dramatically due to the ageing population,(5, 6) increasing incidence of diabetes(7), chronic cardiovascular disease, and obesity.(8, 9) Furthermore, VLUs follow a pattern of prolonged healing and ulcer recurrence, with some research reporting a recurrence rate of up to 70% within 3 months.(10-12) Due to underlying aetiology, VLU healing is commonly protracted, with 30% remaining unhealed after six months.(13) Because every day that a VLU is present doubles the cost of treatment (14), and increases the risk of infection (15), understanding what factors aid or inhibit healing is needed to promote healing. The reduction in health services costs as a result of timelier healing has been calculated at AUD1.2 billion in recent economic modelling estimates.(16, 17)

A number of studies (10, 13) have identified some key factors that inhibit or promote wound healing. Broadly, these factors fall under three categories. The first, patient characteristics, relates to the issues a patient presents with upon arriving for treatment. These characteristics include age (18), gender (19), smoker status (20, 21), calf circumference(22),

and BMI.(23) The second, wound characteristics, relate to the quality of the wound itself, including wound depth and duration (22), wound bed granulation tissue (24), surrounding skin characteristics (25), and exudate level.(19) The third relates to current medical interventions/ health behaviours. As people with diagnosed VLUs often have comorbid conditions, it is likely they will be taking associated medications e.g. anti-coagulants, anti-rheumatics, and aspirin.(26, 27) However, no recent prospective study to date has examined all these factors in one sample to understand what matters most to wound healing. We sought to examine how patient, wound, and treatment factors are related to wound healing in a prospective study.

Key factors affecting VLU healing time: evidence summary

At time of writing, clinical observation is the key method by which a wound is assessed as "difficult to heal".(2, 4) While risk assessment tools do exist, none are currently incorporated in clinical practice guidelines. This is likely due to the poor quality of evidence currently available (10, 13), and a lack of consistency on what defines VLU healing.(28, 29)

A number of patient level characteristics have been identified by previous studies as important in increasing VLU healing times.(30) Primarily, advanced age, male gender, history of ulcers, diabetes, BMI, calf circumference, smoker status, and having a history of at least one previous venous leg ulcer have been considered as risk factors for prolonged time to healing (19), compression adherence and as a result, smaller calf circumference, was associated with healing. However, a systematic review highlighted that of these factors, only having a history of at least one previous venous leg ulcer was a consistently identified risk factor, while age only had inconsistent or varying evidence.(13)

Wound characteristics, such as wound depth, granulation tissue type, and exudate level have also been identified as important factors which may affect VLU healing.(19, 22, 24, 25) One prospective study (N=189) reported >2cm wound depth (was the only wound characteristic that increased time to healing, while ulcer size (<20cm), shorter ulcer duration (<12 months), and epithelialisation on >10% of the ulcer surface lead to improved healing outcomes.(22) Larger ulcers have been reported to predicted longer time to healing, although exudate composition did not significantly predict wound healing time.(19) However, as outlined by Parker et al. (13), the way exudate levels are measured varies considerably (31, 32), therefore making it difficult to make clear judgements as to what specific wound characteristics impact on VLU healing outcomes.

Ongoing treatment characteristics such as the patient's health behaviours and medical interventions by clinicians (33) (beyond direct surgical VLU intervention) may also affect VLU healing. Most individuals with VLUs have concurrent comorbidities(29), such as diabetes and high blood pressure (34), or report significant pain from the VLU, and are often on drugs like aspirin, anti-coagulants, and anti-inflammatories.(26, 27, 35) Recent research reports there is only low quality evidence that aspirin reduces time to heal.(36) Similarly, low quality evidence reports anti-coagulants (37) and anti-inflammatories (38) such as non-steroidal anti-inflammatories (NSAIDs), may reduce time to healing. Furthermore, best practice guidelines to treat people with VLUs recommend compression therapy (39-41), although patient adherence to compression may cast some doubt on these findings.(33) The lack of high quality evidence makes it difficult for clinicians to understand which factors such

as patient characteristics, wound characteristics, and on-going treatments in VLU wound healing may predict time to healing.(13, 42)

Research gap and present study

Knowledge of key factors to optimise VLU healing are needed for healthcare professionals to ensure high quality assessments and treatment (43) based on individual patients. As VLUs are challenging and expensive to treat, understanding what factors protect or promote healing in a risk assessment would be useful for clinicians in initial assessments. The aim of this study was to identify which factors are associated with wound healing in a secondary analysis of a Randomised Controlled Trial (RCT), in order to generate research questions and hypotheses for future research.(44) This study measured wound characteristics, patient characteristics, and concurrent treatments, and how these may relate to VLU wound healing. It was hypothesized that larger calf circumference, larger ulcer size, and longer ulcer duration would lead to decreased odds of wound healing, while compression adherence would lead to increased odds of healing. However, this study also assessed other factors, including age, BMI, gender, smoking, anaemia, diabetes, osteoarthritis, hypertension, NSAID use, ulcer depth, wound exudate level, Margolis index (45), surrounding skin, and compression adherence.(44, 46) As the relationship between these factors and VLU healing has been inconsistent, no predictions were made in regards to their relationship with VLU healing.

Materials and Methods

Participants and setting:

This secondary analysis was based on a multi-centre, parallel-group, randomized controlled trial, which was conducted in four specialist wound clinics on the use of tubular bandages for VLUs.(44) Participants (N=45) were recruited between February 2009 and January 2011 from hospital outpatient wound clinics in metropolitan settings in Victoria and Queensland, Australia. Eligible participants were aged over 18 years, ambulant, capable of giving informed consent, and of attending weekly clinics. The VLU had to 1) have been confirmed by clinical assessment; 2) have been present for at least 4 weeks; 3) have an area 1 to 20 cm2 as measured by digital planimetry; 4) have an ankle brachial pressure index of 0.8 mmHg; and 5) with an ankle circumference of between 20 to 30 cm. Patients were ineligible if they were participating in another clinical trial, had evidence of severe liver disease, cardiac disease, chronic pulmonary disease, clinically suspected deep vein thrombosis, a medical condition likely to require systemic corticosteroids during the study period, were suffering from severe depression or psychiatric illness, or if they had suspected thrombophlebitis. Patient characteristics are listed in Table 1, reproduced from the original study.(44) These participants were older (over 60), mostly white (Caucasian), and overweight, fitting the demographic profile of the average person with a VLU.(47) There were no non-completers nor missing data, as all those recruited completed the trial in full. The study was approved by all host universities and health agencies.

Outcome measures:

The primary outcome measure was whether or not the wound healed by week 12 (end of study treatment). Wound size was measured every week with Visitrak, an acetate wound tracing wound measurement system. This was also confirmed by photographing the target

ulcer. The Visitrak system has been shown to provide accurate and reliable measurement of wound area.(48) End of treatment was defined as the visit at which the ulcer healed or week 12, whichever came first. Complete healing was defined as 100% epithelialization or skin closure without exudate.

Statistical analysis

The study conceived was hypothesis-generating and explorative. As such, a power calculation of sample size was not performed. All analyses were according to treatment group. Continuous variables were analysed with descriptive statistics (e.g., mean, median, standard deviation). Categorical variables were analysed by using frequency tables with numbers and percentages of patients. All statistical hypotheses were two-sided. Due to subgroup analyses, retrospective evaluation, and multiple comparisons, the statistical results presented should be regarded as exploratory and hypothesis generating. The p-values and CI have not been adjusted for multiple comparisons and should only be considered as descriptive measures of the strength of association.

Since randomisation occurred after the baseline measures were taken, it cannot be a confounder of the relationships, hence it does not need to be included to estimate the relationship between characteristics and outcome. As for the choice of variables entered into the multivariable analysis, these were selected as potential confounders of the characteristic-outcome relationships.

The statistical analysis considered the 29 variables recorded at baseline listed in Table 2 across four categories: patient demographics (age, sex, race, body mass index, ankle mobility, calf circumference, percentage reduction from base to week 4 and ankle circumference),

medical history and comorbid conditions (anaemia, diabetes, hypertension, history of DVT, history of hip surgery, hypertension, osteoarthritis, smoking status and history of venous surgery), patient drugs (anticoagulants, anti-platelets, anti-rheumatics, aspirin, corticosteroids and NSAIDs) and wound characteristics (ulcer depth at baseline, exudate level, granulation percentage, ulcer duration, ulcer size, Margolis index, ankle brachial pressure index, compression adherence. Continuous variables were descriptively summarized using medians with 25th and 75th percentiles, and categorical factors were reported using percentages. Univariate logistic regression models were used to identify baseline factors that were associated with healing.

Previous studies have demonstrated that initial wound size and duration are risk factors for non-healing.(22) Furthermore, the percentage reduction in wound size from baseline is known to be associated with healing outcome.(22) Thus, a two-predictor logistic model was fitted to investigate the effect of percentage reduction from baseline to week 4 and Margolis Index on the healing of ulcers when included in the model jointly. The variable percentage reduction from baseline to week 4 is a continuous variable. The Margolis index is a prognostic score for VLU healing based on categorisations of the ulcer area and duration (45). It is a binary variable with three factors based on ulcer size and duration given by ulcer $\leq$5cm and $\leq$ 6 months (baseline category), ulcer >5cm or >6 months and ulcer >5cm and >6 months.

From the results of univariate logistic models, it was noted that ulcer durations and sizes are important for healing outcomes. Thus, the association between ulcer healing and each clinical variable after adjusting for ulcer duration and size was studied using three-predictor

logistic regression models. Ulcer duration is a binary variable with two factors of ≤ 6 months and > 6 months. Ulcer size is also a binary variable with two categories of ≤ 5 cm and > 5 cm.

Results

Summaries of each characteristic for participants with healed and unhealed wounds are presented in Table 2 as the number and percentage for categorical variables, and as medians, lower and upper quartiles for continuous variables. The number of participants with missing values of the characteristics are shown. Univariate logistic regression models were fit to estimate the odds of healing venous leg ulcers and results are presented as odds ratios with 95% confidence intervals and p-values. Looking purely at statistical significance is not the best approach, particularly for a dataset of this size. As such, we avoid making statements based only on the p-value associated with a statistic; instead, we have discussed the clinical importance of our findings in light of the statistical results. This aligns with current recommendations from the American Statistical Association on the use and interpretation of p-values.(49)

The importance of individual factors was tested using the univariate logistic regression model. According to Table 2, none of the patient characteristics appeared to be important predictors. With regard to the ongoing treatments, NSAIDs are associated with ulcer healing outcome (OR=0.13, 95%CI=(0.02, 0.70)). Moreover, in these univariate models, several wound characteristics were associated with ulcer healing: Margolis index for ulcer size higher than 5cm and prolonged for more than 6 months (OR=0.13, 95%CI=(0.02, 0.70)), ulcer duration higher than 6 months (OR=0.03, 95%CI=(<0.01, 0.21)), ulcer size exceeding 5 cm

(OR=0.19, 95%CI=(0.05, 0.71)), calf circumference (OR=1.16, 95%CI=(1.02, 1.33)), percentage reduction from base to week 4 (OR=1.05, 95%CI=(1.02, 1.08)), granulation percentage over 50% (OR=3.67, 95%CI=(0.85, 15.84)) and the minimal exudate level (OR=28.00, 95%CI=(1.99, 394.40)).

The importance of Margolis index and percentage reduction in wound size was investigated using a multivariable logistic regression model and the results are described in Table 3. When adjusting for potential confounders of the outcome-exposure relationship, a change in the estimate of the effect should be expected. According to the model, the odds of healing was reduced for a Margolis index of associated with an ulcer that had persisted for >6 months and was larger than 5cm relative to an ulcer that was <6months old and less than 5 cm (OR=0.03, 95%CI=(<0.01, 0.78)) and increased for each percentage point reduction in wound size from baseline to week 4 (OR=1.04, 95%CI=(0.99, 1.09); Table 3). In other words, wounds older than 6 months and larger than $5cm^2$ are less likely to heal and the higher the percentage of wound size reduction from base to week 4, the greater the odds of the wound healing by 12 weeks. From the results presented in Table 2, we demonstrated that ulcer duration and size are two of the strongest predictors of healing. Using multivariable logistic regression, we evaluated the effect of the predictor variables on whether a patient would heal, adjusted for ulcer duration and size (results shown in last two columns of Table 2). According to the model, NSAIDS and calf circumference are significant in ulcer healing (OR=0.05, 95%CI=(<0.01, 1.35) and OR=1.32, 95%CI=(1.00, 1.74), respectively), once adjusted for ulcer duration and size.

Discussion:

Understanding what factors predict or impede wound healing time is critical to ensure positive outcomes for patients with VLUs. The aim of this study was to identify what factors (i.e., wound characteristics, patient characteristics, and concurrent treatments) are associated with wound healing by 12 weeks in a secondary analysis of RCT data in order to generate new research questions and hypotheses for further study. In doing so, we provide novel directions for further research.

As hypothesized, larger calf circumference, larger ulcers, and longer ulcer duration were associated with lower odds of wound healing. Smaller ulcer duration and size were strongly associated with increased odds of healing. This is consistent with previous evidence showing that with compression treatment, ulcer size and ulcer duration are particularly strong factors that appear to increase healing outcomes.(22, 50) We recommend that people with VLUs should be referred to specialist wound clinic consultants by primary care clinicians within three months of treatment to ensure early intervention to optimise healing outcomes, as per the clinical practice guidelines in Australia.(51)

Contrary to our hypothesis, we found no evidence that ABPI index or compression adherence were associated with improved healing outcomes. Compression adherence and ABPI indices have been the focus of the VLU literature (39-41), although we would recommend ABPI measurement needs to be assessed in conjunction with other risk factors.

An unexpected finding was NSAID use was possibly associated with lower odds of healing, while minimal exudate levels were associated with increased odds of healing. This finding may be spurious due to the small sample size with short follow up, but the finding is plausible in the context of previous research. This is especially true as these factors of

exudate levels and NSAID use likely interact (52), but further research on the use of NSAIDs and exudate levels is warranted. Recent evidence has shown that there is a possibility that NSAID use negatively affects skin healing capabilities, as a rat based study has shown that NSAIDs can negatively affect fibroblast cells critical for new skin formation.(52) A recent meta-analysis showed that non-selective NSAIDs inhibit wound healing in animal models, although the quality of the evidence on whether or not NSAIDs affect wound healing in humans is generally poor.(53) As NSAIDs are often used in conjunction with other treatments (54) and higher levels of exudate are generally considered an indication of inflammation (22), this suggests that careful consideration of anti-inflammatory agents with assessment of exudate levels may need to be incorporated in risk assessments.

This study did not provide evidence of associations between wound healing and patient characteristics. There was no evidence that patient characteristics (age, male gender, diabetes, BMI, and smoker status) were associated with improved healing outcomes. These data suggest patient characteristics that are directly relevant to initially developing an ulcer may have a more indirect relationship with wound healing.

Our findings suggest poorer wound characteristics tended to result in longer wound healing times. Meanwhile, patient characteristics did not appear to have strong associations with the odds of wound healing. Finally, our findings did not provide evidence that concurrent treatments were associated with healing, or in the case of NSAIDs, were associated with decreased odds of wound healing. Together, these findings cautiously suggest that clinicians should focus on wound characteristics when predicting healing, and should be careful with the administration of NSAIDs, as it may hinder healing.(52)

A few key limitations are worth noting for this research. This study tested a large number of hypotheses with a small sample size. This may increase the risks of detecting spurious associations and may fail to detect evidence of true relationships. Furthermore, due to the smaller sample size, our analysis could not assess moderating or mediating effects between variables, which may have limited our ability to understand the effect of NSAIDs. Another issue was the follow up time; in the space of three months, it may not have been possible to detect long-term differences. Future research should address this by using an international prospective sample of sufficient size to detect moderation/mediational relationships, and use a longer follow up time. Despite these issues, this research indicates that wound characteristics are the most important part of understanding wound healing, adding to previous findings in this space.

Conclusion

This prospective study has identified evidence that larger ulcers, longer ulcer duration, and larger calf circumference associated with decreased odds of wound healing, while presenting some evidence that NSAID use might negatively affect wound healing. Furthermore, this study found minimal exudate levels was associated with increased odds of healing. There was no association between wound healing and patient characteristics, which requires further exploration. This paper found wound factors are the key variables related to wound healing outcomes. Future research with a larger sample is needed to assess some of the factors highlighted in this study to understand other factors that may be associated with VLU healing.

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Tables

Table 1: Demographic and clinical characteristics of the 45 participants at baseline assessment

	N=45
Age in years, mean (SD)	75.05 (12.26)
Male gender, *n* (%)	23 (51.1%)
Caucasian ethnicity, *n* (%)	45 (95.5%)
BMI groups, *n* (%)	
<20	3 (6.6%)
20–24	6 (13.3%)
24–29	9 (20%)
30+	25 (55.6%)
Risk status, *n* (%)	
Never smoked	25 (55.6%)
Former smoker (<10 years ago)	6 (13.3%)
Former smoker (>10 years ago)	11 (24.4%)
Current smoker	3 (6.6%)
Normal range of ankle mobility *n* (%)	
Full range	38 (84.4%)
Reduced	7 (15.6%)
Ankle circumference (cm2)	
Median (range)	24 (20, 29)
Mean (SD)	23.9 (2.6)
Calf circumference (cm2)	
Median (range)	37 (27, 50)
Mean (SD)	37.9 (6.0)
Ankle brachial pressure index	
Median (range)	1.2 (0.8, 1.6)
Mean (SD)	1.2 (0.17)
Ulcer location (R : L)	22:23
Ulcer area (cm2)	
Median (range)	6 (1.2, 19.8)
Mean (SD)	7 (5.7)
Ulcer duration (months)	7.6
Margolis index	
(0) ulcer size <5 cm2 and <6 months, *n* (%)	16 (35.6%)
(1) ulcer size >5 cm2 or >6 months, *n* (%)	16 (35.6%
(2) ulcer size >5 cm2 and >6 months, *n* (%)	13(28.9%)

Table 2: Odds ratios for healing of venous leg ulcers. Unadjusted odds ratios are the results for univariate logistic regression model and adjusted odds ratios are the results obtained from

three-predictor logistic regression model. Summaries presented as medians (lower quartile, upper quartile).

Characteristic	No. miss.	Wound unhealed n(%)	Wound healed n(%)	Unadjusted		Adjusted	
				Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Ongoing treatments							
Anticoagulants	0						
No		14 (42.4)	19 (57.6)				
Yes		4 (33.3)	8 (66.7)	1.47 (0.37, 5.88)	0.58	2.43 (0.19, 29.99)	0.49
Anti-platelets	0						
No		16 (37.2)	27 (62.8)				
Yes		2 (100.0)	0 (0.0)	1		1	
Anti-rheumatics	1						
No		13 (36.1)	23 (63.9)				
Yes		4 (50.0)	4 (50.0)	0.57 (0.12, 2.65)	0.47	0.78 (0.05, 11.12)	0.85
Aspirin	0						
No		11 (35.5)	20 (64.5)				
Yes		7 (50.0)	7 (50.0)	0.55 (0.15, 1.98)	0.36	0.41 (0.05, 3.21)	0.39
Corticosteroids	0						
No		18 (41.9)	25 (58.1)				
Yes		0 (0.0)	2 (100.0)	1		1	
NSAIDs	0						
No		11 (30.6)	25 (69.4)				
Yes		7 (77.8)	2 (22.2)	0.13 (0.02, 0.70)	0.018	0.05 (<0.01, 1.35)	0.076
Wound characteristics							
Ulcer depth at baseline	0						
Grade II		10 (34.5)	19 (65.5)				
Grade III		8 (50.0)	8 (50.0)	0.53 (0.15, 1.83)	0.31	0.89 (0.12, 6.93)	0.92
Exudate level	0						
Copious		4 (80.0)	1 (20.0)			1	
Medium		12 (50.0)	12 (50.0)	4.00 (0.39, 41.23)	0.24	0.18 (<0.01, 3.85)	0.28

Minimal		2 (12.5)	14 (87.5)	28.00 (1.99, 394.40)	0.014	28.00 (1.99, 394.40)	0.014
Granulation percentage	1						
<50%		15 (50.0)	15 (50.0)				
>50%		3 (21.4)	11 (78.6)	3.67 (0.85, 15.84)	0.082	7.08 (0.43, 117.81)	0.17
Ulcer duration	11						
≤ 6mo		2 (10.0)	18 (90.0)				
>6mo		11 (78.6)	3 (21.4)	0.03 (<0.01, 0.21)	<0.001		
Ulcer size	0						
≤5cm		5 (21.7)	18 (78.3)				
>5cm		13 (59.1)	9 (40.9)	0.19 (0.05, 0.71)	0.013		
Margolis index	11						
ulcer ≤5cm and ≤ 6mo		1 (7.7)	12 (92.3)				
ulcer >5cm or >6mo		4 (33.3)	8 (66.7)	0.17 (0.02, 1.78)	0.14	0.50 (0.02, 9.45)	0.64
ulcer >5cm and >6mo		8 (88.9)	1 (11.1)	0.01 (<0.01, 0.19)	0.002	0.09 (<0.01, 5.22)	0.25
Ankle brachial pressure index	1						
0.8-1		4 (44.4)	5 (55.6)				
1-1.2		4 (23.5)	13 (76.5)	2.60 (0.46, 14.63)	0.28	1.55 (0.07, 34.60)	0.78
>1.2		10 (55.6)	8 (44.4)	0.64 (0.13, 3.20)	0.59	1.11 (0.07, 17.58)	0.94
100% bandage compliance	0						
No		2 (22.2)	7 (77.8)				
Yes		16 (44.4)	20 (55.6)	0.36 (0.07, 1.96)	0.24	3.14 (0.18, 55.22)	0.43
Patient Characteristics							
Sex	0						
Female		8 (36.4)	14 (63.6)				
Male		10 (43.5)	13 (56.5)	0.74 (0.22, 2.46)	0.63	1.11(0.14, 8.57)	0.92

Current smoker	0						
No		17 (40.5)	25 (59.5)				
Yes		1 (33.3)	2 (66.7)	1.36 (0.11, 16.21)	0.81	1	
Anaemia	0						
No		17 (41.5)	24 (58.5)				
Yes		1 (25.0)	3 (75.0)	2.12 (0.20, 22.21)	0.53	0.11(<0.01, 2.82)	0.19
Diabetes	0						
No		15 (38.5)	24 (61.5)				
Yes		3 (50.0)	3 (50.0)	0.62 (0.11, 3.51)	0.59	0.68 (0.04, 10.51)	0.78
History of DVT	1						
No		12 (40.0)	18 (60.0)				
Yes		5 (35.7)	9 (64.3)	1.20 (0.32, 4.47)	0.79	3.60 (0.28, 47.06)	0.33
History of hip surgery	0						
No		14 (40.0)	21 (60.0)				
Yes		4 (40.0)	6 (60.0)	1.00 (0.24, 4.20)	1.00	0.28 (0.02, 4.34)	0.37
Hypertension	0						
No		9 (52.9)	8 (47.1)				
Yes		9 (32.1)	19 (67.9)	2.38 (0.69, 8.20)	0.17	1.68 (0.22, 12.86)	0.62
Osteoarthritis	0						
No		12 (46.2)	14 (53.8)				
Yes		6 (31.6)	13 (68.4)	1.86 (0.54, 6.40)	0.33	0.26 (0.02, 3.09)	0.29
History of venous surgery	0						
No		14 (43.8)	18 (56.3)				
Yes		4 (30.8)	9 (69.2)	1.75 (0.44, 6.88)	0.42	0.18 (0.01, 3.09)	0.24
Ankle mobility	0						
Full mobility		15 (39.5)	23 (60.5)				
Reduced mobility		3 (42.9)	4 (57.1)	0.87 (0.17, 4.45)	0.87	3.34 (0.13, 85.92)	0.47
Age (yrs)	0	80.3 (63.8, 86.3) *	76.3 (63.0, 83.9) *	0.99 (0.95, 1.04)	0.81	0.91 (0.81, 1.04)	0.16

BMI	2	28.0 (24.0, 32.4) *	31.0 (27.1, 38.6) *	1.07 (0.99, 1.16)	0.11	1.11 (0.95, 1.30)	0.17
Ankle Circ.	2	23.0 (21.0, 25.0) *	24.5 (23.0, 26.0) *	1.21 (0.93, 1.58)	0.15	1.54 (0.89, 2.66)	0.12
Calf Circ.	2	35.0 (33.0, 38.0) *	38.0 (36.0, 44.0) *	1.16 (1.02, 1.33)	0.028	1.32 (1.00, 1.74)	0.048
% reduction from base to week 4	8	16.7 (9.1, 33.3) *	85.9 (51.1, 95.8) *	1.05 (1.02, 1.08)	<0.001	1.09 (0.95, 1.25)	0.22

Table 2: Odds ratios of healing for two-predictor logistic regression model containing both Margolis index and percentage reduction from baseline to week 4.

	Odds Ratio (95% CI)	p-value
Margolis index		
ulcer >5cm or >6mo	1.01 (0.40,25.00)	0.995
ulcer >5cm and >6mo	0.03(<0.01, 0.78)	0.035
Percentage reduction from base to week 4	1.04 (0.99, 1,09)	0.069

Table 1: Demographic and clinical characteristics of the 45 participants at baseline assessment

	N=45
Age in years, mean (SD)	75.05 (12.26)
Male gender, *n* (%)	23 (51.1%)
Caucasian ethnicity, *n* (%)	45 (95.5%)
BMI groups, *n* (%)	
<20	3 (6.6%)
20–24	6 (13.3%)
24–29	9 (20%)
30+	25 (55.6%)
Risk status, *n* (%)	
Never smoked	25 (55.6%)
Former smoker (<10 years ago)	6 (13.3%)
Former smoker (>10 years ago)	11 (24.4%)
Current smoker	3 (6.6%)
Normal range of ankle mobility *n* (%)	
Full range	38 (84.4%)
Reduced	7 (15.6%)
Ankle circumference (cm2)	
Median (range)	24 (20, 29)
Mean (SD)	23.9 (2.6)
Calf circumference (cm2)	
Median (range)	37 (27, 50)
Mean (SD)	37.9 (6.0)
Ankle brachial pressure index	
Median (range)	1.2 (0.8, 1.6)
Mean (SD)	1.2 (0.17)
Ulcer location (R : L)	22:23
Ulcer area (cm2)	
Median (range)	6 (1.2, 19.8)
Mean (SD)	7 (5.7)
Ulcer duration (months)	7.6
Margolis index	
(0) ulcer size <5 cm2 and <6 months, *n* (%)	16 (35.6%)
(1) ulcer size >5 cm2 or >6 months, *n* (%)	16 (35.6%
(2) ulcer size >5 cm2 and >6 months, *n* (%)	13(28.9%)

Table 2: Odds ratios for healing of venous leg ulcers. Unadjusted odds ratios are the results for univariate logistic regression model and adjusted odds ratios are the results obtained from three-predictor logistic regression model. Summaries presented as medians (lower quartile, upper quartile).

Characteristic	No. miss.	Wound unhealed n(%)	Wound healed n(%)	Unadjusted		Adjusted	
				Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Ongoing treatments							
Anticoagulants	0						
No		14 (42.4)	19 (57.6)				
Yes		4 (33.3)	8 (66.7)	1.47 (0.37, 5.88)	0.58	2.43 (0.19, 29.99)	0.49
Anti-platelets	0						
No		16 (37.2)	27 (62.8)				
Yes		2 (100.0)	0 (0.0)	1		1	
Anti-rheumatics	1						
No		13 (36.1)	23 (63.9)				
Yes		4 (50.0)	4 (50.0)	0.57 (0.12, 2.65)	0.47	0.78 (0.05, 11.12)	0.85
Aspirin	0						
No		11 (35.5)	20 (64.5)				
Yes		7 (50.0)	7 (50.0)	0.55 (0.15, 1.98)	0.36	0.41 (0.05, 3.21)	0.39
Corticosteroids	0						
No		18 (41.9)	25 (58.1)				
Yes		0 (0.0)	2 (100.0)	1		1	
NSAIDs	0						
No		11 (30.6)	25 (69.4)				
Yes		7 (77.8)	2 (22.2)	0.13 (0.02, 0.70)	0.018	0.05 (<0.01, 1.35)	0.076
Wound characteristics							
Ulcer depth at baseline	0						
Grade II		10 (34.5)	19 (65.5)				
Grade III		8 (50.0)	8 (50.0)	0.53 (0.15, 1.83)	0.31	0.89 (0.12, 6.93)	0.92
Exudate level	0						
Copious		4 (80.0)	1 (20.0)			1	

Medium		12 (50.0)	12 (50.0)	4.00 (0.39, 41.23)	0.24	0.18 (<0.01, 3.85)	0.28
Minimal		2 (12.5)	14 (87.5)	28.00 (1.99, 394.40)	0.014	28.00 (1.99, 394.40)	0.014
Granulation percentage	1						
<50%		15 (50.0)	15 (50.0)				
>50%		3 (21.4)	11 (78.6)	3.67 (0.85, 15.84)	0.082	7.08 (0.43, 117.81)	0.17
Ulcer duration	11						
≤ 6mo		2 (10.0)	18 (90.0)				
>6mo		11 (78.6)	3 (21.4)	0.03 (<0.01, 0.21)	<0.001		
Ulcer size	0						
≤5cm		5 (21.7)	18 (78.3)				
>5cm		13 (59.1)	9 (40.9)	0.19 (0.05, 0.71)	0.013		
Margolis index	11						
ulcer ≤5cm and ≤ 6mo		1 (7.7)	12 (92.3)				
ulcer >5cm or >6mo		4 (33.3)	8 (66.7)	0.17 (0.02, 1.78)	0.14	0.50 (0.02, 9.45)	0.64
ulcer >5cm and >6mo		8 (88.9)	1 (11.1)	0.01 (<0.01, 0.19)	0.002	0.09 (<0.01, 5.22)	0.25
Ankle brachial pressure index	1						
0.8-1		4 (44.4)	5 (55.6)				
1-1.2		4 (23.5)	13 (76.5)	2.60 (0.46, 14.63)	0.28	1.55 (0.07, 34.60)	0.78
>1.2		10 (55.6)	8 (44.4)	0.64 (0.13, 3.20)	0.59	1.11 (0.07, 17.58)	0.94
100% bandage compliance	0						
No		2 (22.2)	7 (77.8)				
Yes		16 (44.4)	20 (55.6)	0.36 (0.07, 1.96)	0.24	3.14 (0.18, 55.22)	0.43
Patient Characteristics							
Sex	0						
Female		8 (36.4)	14 (63.6)				

Male		10 (43.5)	13 (56.5)	0.74 (0.22, 2.46)	0.63	1.11(0.14, 8.57)	0.92
Current smoker	0						
No		17 (40.5)	25 (59.5)				
Yes		1 (33.3)	2 (66.7)	1.36 (0.11, 16.21)	0.81	1	
Anaemia	0						
No		17 (41.5)	24 (58.5)				
Yes		1 (25.0)	3 (75.0)	2.12 (0.20, 22.21)	0.53	0.11(<0.01, 2.82)	0.19
Diabetes	0						
No		15 (38.5)	24 (61.5)				
Yes		3 (50.0)	3 (50.0)	0.62 (0.11, 3.51)	0.59	0.68 (0.04, 10.51)	0.78
History of DVT	1						
No		12 (40.0)	18 (60.0)				
Yes		5 (35.7)	9 (64.3)	1.20 (0.32, 4.47)	0.79	3.60 (0.28, 47.06)	0.33
History of hip surgery	0						
No		14 (40.0)	21 (60.0)				
Yes		4 (40.0)	6 (60.0)	1.00 (0.24, 4.20)	1.00	0.28 (0.02, 4.34)	0.37
Hypertension	0						
No		9 (52.9)	8 (47.1)				
Yes		9 (32.1)	19 (67.9)	2.38 (0.69, 8.20)	0.17	1.68 (0.22, 12.86)	0.62
Osteoarthritis	0						
No		12 (46.2)	14 (53.8)				
Yes		6 (31.6)	13 (68.4)	1.86 (0.54, 6.40)	0.33	0.26 (0.02, 3.09)	0.29
History of venous surgery	0						
No		14 (43.8)	18 (56.3)				
Yes		4 (30.8)	9 (69.2)	1.75 (0.44, 6.88)	0.42	0.18 (0.01, 3.09)	0.24
Ankle mobility	0						
Full mobility		15 (39.5)	23 (60.5)				
Reduced mobility		3 (42.9)	4 (57.1)	0.87 (0.17, 4.45)	0.87	3.34 (0.13, 85.92)	0.47

Age (yrs)	0	80.3 (63.8, 86.3) *	76.3 (63.0, 83.9) *	0.99 (0.95, 1.04)	0.81	0.91 (0.81, 1.04)	0.16
BMI	2	28.0 (24.0, 32.4) *	31.0 (27.1, 38.6) *	1.07 (0.99, 1.16)	0.11	1.11 (0.95, 1.30)	0.17
Ankle Circ.	2	23.0 (21.0, 25.0) *	24.5 (23.0, 26.0) *	1.21 (0.93, 1.58)	0.15	1.54 (0.89, 2.66)	0.12
Calf Circ.	2	35.0 (33.0, 38.0) *	38.0 (36.0, 44.0) *	1.16 (1.02, 1.33)	0.028	1.32 (1.00, 1.74)	0.048
% reduction from base to week 4	8	16.7 (9.1, 33.3) *	85.9 (51.1, 95.8) *	1.05 (1.02, 1.08)	<0.001	1.09 (0.95, 1.25)	0.22

*Denotes Range

Table 3: Odds ratios of healing for two-predictor logistic regression model containing both Margolis index and percentage reduction from baseline to week 4.

	Odds Ratio (95% CI)	p-value
Margolis index		
ulcer >5cm or >6mo	1.01 (0.40,25.00)	0.995
ulcer >5cm and >6mo	0.03(<0.01, 0.78)	0.035
Percentage reduction from base to week 4	1.04 (0.99, 1,09)	0.069

Table 1: Demographic and clinical characteristics of the 45 participants at baseline assessment

	N=45
Age in years, mean (SD)	75.05 (12.26)
Male gender, *n* (%)	23 (51.1%)
Caucasian ethnicity, *n* (%)	45 (95.5%)
BMI groups, *n* (%)	
<20	3 (6.6%)
20–24	6 (13.3%)
24–29	9 (20%)
30+	25 (55.6%)
Risk status, *n* (%)	
Never smoked	25 (55.6%)
Former smoker (<10 years ago)	6 (13.3%)
Former smoker (>10 years ago)	11 (24.4%)
Current smoker	3 (6.6%)
Normal range of ankle mobility *n* (%)	
Full range	38 (84.4%)
Reduced	7 (15.6%)
Ankle circumference (cm2)	
Median (range)	24 (20, 29)
Mean (SD)	23.9 (2.6)
Calf circumference (cm2)	
Median (range)	37 (27, 50)
Mean (SD)	37.9 (6.0)
Ankle brachial pressure index	
Median (range)	1.2 (0.8, 1.6)
Mean (SD)	1.2 (0.17)
Ulcer location (R : L)	22:23
Ulcer area (cm2)	
Median (range)	6 (1.2, 19.8)
Mean (SD)	7 (5.7)
Ulcer duration (months)	7.6
Margolis index	
(0) ulcer size <5 cm2 and <6 months, *n* (%)	16 (35.6%)
(1) ulcer size >5 cm2 or >6 months, *n* (%)	16 (35.6%
(2) ulcer size >5 cm2 and >6 months, *n* (%)	13(28.9%)

Table 2: Odds ratios for healing of venous leg ulcers. Unadjusted odds ratios are the results for univariate logistic regression model and adjusted odds ratios are the results obtained from three-predictor logistic regression model. Summaries presented as medians (lower quartile, upper quartile).

Characteristic	No. miss.	Wound unhealed n(%)	Wound healed n(%)	Unadjusted		Adjusted	
				Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Ongoing treatments							
Anticoagulants	0						
No		14 (42.4)	19 (57.6)				
Yes		4 (33.3)	8 (66.7)	1.47 (0.37, 5.88)	0.58	2.43 (0.19, 29.99)	0.49
Anti-platelets	0						
No		16 (37.2)	27 (62.8)				
Yes		2 (100.0)	0 (0.0)	1		1	
Anti-rheumatics	1						
No		13 (36.1)	23 (63.9)				
Yes		4 (50.0)	4 (50.0)	0.57 (0.12, 2.65)	0.47	0.78 (0.05, 11.12)	0.85
Aspirin	0						
No		11 (35.5)	20 (64.5)				
Yes		7 (50.0)	7 (50.0)	0.55 (0.15, 1.98)	0.36	0.41 (0.05, 3.21)	0.39
Corticosteroids	0						
No		18 (41.9)	25 (58.1)				
Yes		0 (0.0)	2 (100.0)	1		1	
NSAIDs	0						
No		11 (30.6)	25 (69.4)				
Yes		7 (77.8)	2 (22.2)	0.13 (0.02, 0.70)	0.018	0.05 (<0.01, 1.35)	0.076
Wound characteristics							
Ulcer depth at baseline	0						
Grade II		10 (34.5)	19 (65.5)				
Grade III		8 (50.0)	8 (50.0)	0.53 (0.15, 1.83)	0.31	0.89 (0.12, 6.93)	0.92
Exudate level	0						
Copious		4 (80.0)	1 (20.0)			1	
Medium		12 (50.0)	12 (50.0)	4.00 (0.39, 41.23)	0.24	0.18 (<0.01, 3.85)	0.28
Minimal		2 (12.5)	14 (87.5)	28.00 (1.99, 394.40)	0.014	28.00 (1.99, 394.40)	0.014
Granulation percentage	1						
<50%		15 (50.0)	15 (50.0)				

>50%		3 (21.4)	11 (78.6)	3.67 (0.85, 15.84)	0.082	7.08 (0.43, 117.81)	0.17
Ulcer duration	11						
≤ 6mo		2 (10.0)	18 (90.0)				
>6mo		11 (78.6)	3 (21.4)	0.03 (<0.01, 0.21)	<0.001		
Ulcer size	0						
≤5cm		5 (21.7)	18 (78.3)				
>5cm		13 (59.1)	9 (40.9)	0.19 (0.05, 0.71)	0.013		
Margolis index	11						
ulcer ≤5cm and ≤ 6mo		1 (7.7)	12 (92.3)				
ulcer >5cm or >6mo		4 (33.3)	8 (66.7)	0.17 (0.02, 1.78)	0.14	0.50 (0.02, 9.45)	0.64
ulcer >5cm and >6mo		8 (88.9)	1 (11.1)	0.01 (<0.01, 0.19)	0.002	0.09 (<0.01, 5.22)	0.25
Ankle brachial pressure index	1						
0.8-1		4 (44.4)	5 (55.6)				
1-1.2		4 (23.5)	13 (76.5)	2.60 (0.46, 14.63)	0.28	1.55 (0.07, 34.60)	0.78
>1.2		10 (55.6)	8 (44.4)	0.64 (0.13, 3.20)	0.59	1.11 (0.07, 17.58)	0.94
100% bandage compliance	0						
No		2 (22.2)	7 (77.8)				
Yes		16 (44.4)	20 (55.6)	0.36 (0.07, 1.96)	0.24	3.14 (0.18, 55.22)	0.43
Patient Characteristics							
Sex	0						
Female		8 (36.4)	14 (63.6)				
Male		10 (43.5)	13 (56.5)	0.74 (0.22, 2.46)	0.63	1.11(0.14, 8.57)	0.92
Current smoker	0						
No		17 (40.5)	25 (59.5)				
Yes		1 (33.3)	2 (66.7)	1.36 (0.11, 16.21)	0.81	1	
Anaemia	0						
No		17 (41.5)	24 (58.5)				
Yes		1 (25.0)	3 (75.0)	2.12 (0.20, 22.21)	0.53	0.11(<0.01, 2.82)	0.19
Diabetes	0						
No		15 (38.5)	24 (61.5)				

Yes		3 (50.0)	3 (50.0)	0.62 (0.11, 3.51)	0.59	0.68 (0.04, 10.51)	0.78
History of DVT	1						
No		12 (40.0)	18 (60.0)				
Yes		5 (35.7)	9 (64.3)	1.20 (0.32, 4.47)	0.79	3.60 (0.28, 47.06)	0.33
History of hip surgery	0						
No		14 (40.0)	21 (60.0)				
Yes		4 (40.0)	6 (60.0)	1.00 (0.24, 4.20)	1.00	0.28 (0.02, 4.34)	0.37
Hypertension	0						
No		9 (52.9)	8 (47.1)				
Yes		9 (32.1)	19 (67.9)	2.38 (0.69, 8.20)	0.17	1.68 (0.22, 12.86)	0.62
Osteoarthritis	0						
No		12 (46.2)	14 (53.8)				
Yes		6 (31.6)	13 (68.4)	1.86 (0.54, 6.40)	0.33	0.26 (0.02, 3.09)	0.29
History of venous surgery	0						
No		14 (43.8)	18 (56.3)				
Yes		4 (30.8)	9 (69.2)	1.75 (0.44, 6.88)	0.42	0.18 (0.01, 3.09)	0.24
Ankle mobility	0						
Full mobility		15 (39.5)	23 (60.5)				
Reduced mobility		3 (42.9)	4 (57.1)	0.87 (0.17, 4.45)	0.87	3.34 (0.13, 85.92)	0.47
Age (yrs)	0	80.3 (63.8, 86.3) *	76.3 (63.0, 83.9) *	0.99 (0.95, 1.04)	0.81	0.91 (0.81, 1.04)	0.16
BMI	2	28.0 (24.0, 32.4) *	31.0 (27.1, 38.6) *	1.07 (0.99, 1.16)	0.11	1.11 (0.95, 1.30)	0.17
Ankle Circ.	2	23.0 (21.0, 25.0) *	24.5 (23.0, 26.0) *	1.21 (0.93, 1.58)	0.15	1.54 (0.89, 2.66)	0.12
Calf Circ.	2	35.0 (33.0, 38.0) *	38.0 (36.0, 44.0) *	1.16 (1.02, 1.33)	0.028	1.32 (1.00, 1.74)	0.048
% reduction from base to week 4	8	16.7 (9.1, 33.3) *	85.9 (51.1, 95.8) *	1.05 (1.02, 1.08)	<0.001	1.09 (0.95, 1.25)	0.22

*Denotes Range

Table 3: Odds ratios of healing for two-predictor logistic regression model containing both Margolis index and percentage reduction from baseline to week 4.

	Odds Ratio (95% CI)	p-value
Margolis index		
ulcer >5cm or >6mo	1.01 (0.40,25.00)	0.995
ulcer >5cm and >6mo	0.03(<0.01, 0.78)	0.035
Percentage reduction from base to week 4	1.04 (0.99, 1,09)	0.069