An Examination of PROGUIDE® in Compression Therapy (EXPECT):

A multi-centre randomised non-inferiority trial of two compression systems in the treatment of venous leg ulcers

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Abstract

Background

Compression therapy is the gold standard treatment for venous leg ulcers. The aim was to determine whether the compression bandage PROGUIDE was non-inferior to an established bandaging system, PROFORE, in the treatment of ulceration.

Design

Multi-centre, prospective, randomised, stratified non-inferiority trial.

Methods

Patients were randomised to receive treatment with either the PROFORE or PROGUIDE bandage system. The primary outcome was the proportion of patients attaining full closure of limb ulceration by 24 weeks. A non-inferiority margin of the lower limit of the 95% CI being greater than -15% was specified. Secondary outcomes relating to bandage performance and patient endpoints were also measured.

Results

Of 303 patients with venous leg ulcers, 153 were randomised to PROGUIDE and 150 to PROFORE. At 24 weeks, full closure occurred in 92 (60.1%), the ulcer remained open in 24 (15.7%) and 37 (24.2%) were discontinued. With PROFORE full ulcer closure occurred in 102 (68.0%), 27 (18.0%) had open ulcers and 21 (14%) were discontinued. In the full analysis (intention to treat) population, this corresponded to a difference in ulcer closure of –7.9% (95% CI: –19.1 to 3.4%), P=0.17.

Results for secondary outcomes were in favour of PROFORE for comfort (odds of an 'uncomfortable' or 'very uncomfortable' bandage being reported ($p<0.001$) but showed no significant difference between the two bandage systems in terms of other outcomes.

Conclusions

The results did not meet the non-inferiority criterion of the lower limit of the 95% CI being greater than -15%, in either the full analysis or the per protocol population. This study has not demonstrated the non-inferiority of PROGUIDE compared to PROFORE.

Introduction

Background

Chronic venous leg ulceration is a common problem in clinical practice. Compression therapy is recognized as the gold standard of treatment of choice for this patient group [1]. Many different types of compression bandage system are commercially available, including short-stretch or inelastic bandages, elastic single layer bandages, tubular compression bandages, and multi-layer elastic and inelastic compression systems [2, 3].

The application of graduated external compression can help to improve venous function by reducing venous reflux leading to improvements in ambulatory venous hypertension which is the common pathway to venous ulceration. Patients present with a range of venous abnormalities including varicose veins that may be primary in development or occur secondary to deep vein thrombosis. Post-phlebitic syndrome is an important precursor to ulceration. Exacerbating factors include a loss of calf muscle function and chronic immobility and obesity [4].

The financial burden of managing patients with a wound was assessed during 2012/2013 and estimated at £2.2 million with 66% of the financial burden falling to community nursing services and general practitioners in the UK [5]. The main cost of £1.94 million was attributed to leg ulcers (projected number 731,000). When factoring the cost of co-morbidities for this group the cost increased to 5 .3 billion or 4% of the public health expenditure at the time. This is similar in magnitude to the treatment of obesity. Despite this 39% (0.9 million wounds) remained unhealed with the cost per patient ranging from £1719 to £5976. The costs drivers were related to non- healing and the presence of diabetes and nutritional deficiency. Effective compression is the mainstay of treatment and requires effective compression systems proven to be clinically and cost effective. There is an urgent

requirement to evaluate compression systems that are being developed and used in clinical and provide evidence of clinical and cost effectiveness. Recent research undertaken in the UK has confirmed that venous ulceration remains a large problem within primary care with the median duration of unhealed ulceration over 5 years despite access to compression therapy and national guidelines [6,7].

There is much debate about what constitutes an ideal compression system and difficulties in the standardisation of terms used to describe these systems. [8] The sub-bandage pressure (the pressure applied at the skin interface), generated by a compression bandages are proportional to the tensional force that exists in the bandage following extension. Bandages based on Lycra exhibit steep force extension curves so that the pressure generated varies greatly with the variations in the extensions applied to the bandages [9,10]. As the pressure within the veins of a standing subject is largely hydrostatic, the level of external pressure necessary to counteract this effect in the case of leg ulcers is lesser at the proximal end of the limb than at the distal end, as the hydrostatic head is effectively reduced. For this reason, theoretically, the external pressure from compression bandages is generally applied in a graduated fashion, with the highest pressure exerted at the ankle. However more recent research has challenged whether the concept of a graduation is the most effective approach with some evidence to support that the application of a higher pressure at mid- calf than at the ankle may improve venous function compared to the traditional gradient [11].

If a compression bandage is applied inappropriately tightly, there is the potential to cause tissue damage to the patient's limb; if applied too loosely, the efficacy of the bandage will be reduced. There is a lack of consensus regarding the optimal degree of pressure required

for ulcer healing [12]. In practice, the optimum pressure will probably vary according to many factors, including the severity of the condition, as well as both the height and limb size of the patient. More recently, consensus has suggested that in addition to the pressures applied on application, other factors such as the degree of stiffness are important. Stiffness is characterized by two terms: resting pressure (the pressure at the bandage interface with the skin when the patient is at rest) and working pressure (the pressure when the patient stands or extends their calf muscle during walking). Stiff systems can produce high peaks in amplitude pressure (walking pressure) when the patient stands and walks, due to changes in the calf muscle [13]. Systems such as PROFORE constitute stiff systems due to the combination of materials applied in layers and the use of cohesive materials. Advanced polymer technology (VARI-STRETCH®, Smith & Nephew, Hull, UK) was used to develop a system with a wide range of bandage extensions (30% to 70%). This system was developed to try to standardise the levels of compression applied and prevent excessive pressure being applied through over extension of powerful two-layer elastic systems. Such a polymer was incorporated into the two-layer compression bandaging system PROGUIDE® (Smith & Nephew, Hull, UK).

The pressure profiles of the new PROGUIDE® bandages were extensively examined during its development. This included laboratory-based testing as well as measurement of interface pressures with volunteers without venous disease. The four-layer bandaging system PROFORE® , for which extensive evidence has already been reported was chosen as the comparator in this study and the pressure profile of this system has been well defined . [1,2] The study undertaken in this paper is an example of how long it may take a lead investigator to organise findings from a study that does not report a favourable outcome and is of limited benefit to the sponsor. Despite this fact, negative outcomes in research

must always reach the research and clinical community to avoid the bias towards only reporting those with a positive outcome.,

Objectives

- The primary objective was to assess the performance of the PROGUIDE compression bandaging system, compared with that of PROFORE, in terms of closure of limb ulceration following 24 weeks treatment. The hypothesis was that the new bandage system would produce similar healing potential to the control arm of the study and would also address the issues of pain with compression due to excessive levels of compression being applied with single layer high powered bandage systems
- Secondary objectives were to compare the performance of the two bandage systems in terms of ulcer pain, control of limb oedema (change in ankle circumference), ulcer recurrence, patient comfort, management of exudate, bandage slippage (requirement for unscheduled bandage changes), and appearance of surrounding skin.

Methods

Study approvals

Ethical approval was obtained from Independent ethics committees of all centres. The trial was performed in accordance with the guidelines for international research including the Declaration of Helsinki [(14).]

Trial design

This was a multi-centre, prospective, randomised, stratified non-inferiority trial. The objective of a non-inferiority trial is to compare a novel treatment under evaluation with an established treatment, with a view of demonstrating that it is not clinically inferior with regards to a specified endpoint, known as the non-inferiority limit. If a 95% confidence interval for the difference between treatments is achieved it indicates that it lies above or

below this boundary value (in a favourable direction), then non-inferiority is deemed to have been established.

Changes to trial design

No changes were made to the methods following trial commencement.

Participants

Patients were recruited between July 2001 and August 2002 from 22 centres in the UK, Eire, Germany, Australia and the USA. In-patients, outpatients and primary based patients with lower limb ulceration were considered for this trial.

Inclusion criteria

Patients were recruited who were ≥18 years old; had an Ankle Brachial Pressure Index measured by Doppler ultrasound ≥0.8; had a venous leg ulcer of area between 1 cm^2 and 25 cm^2, with the ulcer located between the knee and ankle (at the level of, and including, the lateral and medial malleolus) and showing the typical appearance of venous ulceration (e.g. with lipodermatosclerosis), without exposure of the muscle, tendon or bone; had venous disease confirmed in the reference limb (e.g. by Duplex Ultrasound, Photo Plethysmography (PPG) or Doppler assessment of reflux); had current ulceration on the reference limb and that had been present for less than five years prior to the initial screening visit.

The inclusion of patients with ulcer duration of less than five years and baseline ulcer area of between 1 cm^2 and 25cm^2 was intended to maximise the likelihood of ulcer healing within 24 weeks, based on established independent risk factors for leg ulcer healing [13].

Exclusion criteria

Patients were excluded who may have been of child-bearing potential (not male, not having had a hysterectomy, and/or not post-menopausal as indicated by a two year menstruation-free interval); had ankle circumference of <18cm or >32cm (since PROGUIDE bandages are not designed to cover this range of ankle sizes); had an ulcer area >25 cm^2; were bed-bound; had ulcers that were deemed by the investigator to be caused by a medical condition other than venous insufficiency; had clinically-defined active cellulitis and were receiving systemic antibiotics (although, once their infection had been treated, the patient could enter the trial if they fulfilled all other criteria); had participated in this trial previously (i.e. had been randomised to treatment); had any condition(s) which seriously compromised the patient's ability to complete this study, or had a documented history of poor compliance with medical treatment.

Informed consent

Patients were recruited who understood the aims and objectives of the trial, were willing to participate in the trial, could comply with the weekly follow-up regimen, and had read the IRB/IEC approved patient information sheet and signed the consent form before screening procedures were undertaken. The trial patient information sheet and consent documentation were shared with 5 patients to ensure clarity of language during the study development stage.

Interventions

Prior to trial commencement, staff at all study sites were trained in the use of both bandage systems to ensure consistency of application. This included carrying out standardized site initiation visits and practice with both bandage systems and a video left for the site.

Measurement of interface pressure measurement was not used as the trial was undertaken before this was recommended or feasible in clinical trials.

At initial assessment, details were recorded regarding patients' demographic characteristics, medical history, concomitant medications, and ulceration details. This included confirming the venous pathology objectively through venous investigations (Duplex scan, Photoplethsmography (PPG) or Doppler ultrasound) rather than relying purely on the clinical evaluation of skin changes such as erythema and lipodermatoslerosis. In addition. data on the mobility status of the patient was recorded. Arterial disease was excluded by recording an ankle brachial pressure index (ABPI). Details of the ankle circumference were taken for all participants.

Bandages were applied according to manufacturers' instructions and all sites were trained intensively in both systems. Training was carried out by the study investigators and included following stages: video of both bandage systems, demonstration of the bandage application followed by a practice session, assessment of competence of all participating staff who would be applying the bandages by the study investigator in each site.

Ankle circumference was measured and use to select the correct bandage application. Bandages were changed at weekly intervals but more frequently if required for issues such as exudate and comfort and this was recorded. Extra wound contact layers, purely designed to manage exudate, as well as padding layers from each bandage kit, were available to use if required. No other types of dressings were permitted on the ulcerated area.

Once the ulcerated area had remained healed (defined as complete epithelialisation) for two consecutive weeks, the patient was withdrawn from treatment and asked to return at

four-weekly intervals to monitor recurrence. Recurrence was defined as any re-opening of the ulcer after complete healing (including transient breaks in the epithelium, breaks requiring re-bandaging, or sustained breaks). During this four- week follow-up period, the patient was treated as per the standard practice of the centre, using compression hosiery measuring (20-30 mmHg) which was considered best practice for prevention of ulcer recurrence at this time and ensured that patients could manage to apply and remove the garment effectively.

Any adverse events, defined as any undesirable clinical occurrence in a subject whether it was considered device-related or not, reported spontaneously by the patient or in response to questioning or observation by the investigator, were recorded.

Outcomes

The primary outcome variable was the proportion of patients attaining full closure of limb ulceration by week 24. Area of ulceration was measured at weekly intervals by tracing the ulcer and counting the squares, including part squares, within the traced area. Ulcer closure was defined as full epithelialisation and no scab present on all reference limb ulceration. Outcomes were assessed solely in terms of ulcer healing; no adjustment was made for area or duration of ulceration.

Secondary outcomes

The following patient endpoints were assessed:

- Ulcer pain in the first four weeks of treatment was measured weekly using a four-point scale (‘none’/‘mild’/’moderate’/’severe’).
- *A*ppearance of surrounding skin in the first four weeks of treatment (‘normal’ / ‘dry eczema’ / ‘wet eczema’ / ‘macerated’ / ‘excoriated’ / ‘other’).

- Control of limb oedema at the ankle circumference (1 cm above the tibial malleolus) at each weekly assessment. Volume measurement of the whole limb using serial circumference measures to calculate the volume of a truncated cone was not deemed necessary in this study.
- Patient ratings of bandage comfort in the first four weeks of treatment ('very comfortable'/'comfortable' /'uncomfortable'/'very uncomfortable')
- Exudate management at each weekly assessment (clinician ratings of whether there was exudate strikethrough ('yes'/'no')).
- Bandage slippage/requirement for unscheduled bandage changes at each weekly assessment (clinician ratings of whether bandage in place from toes to knee ('yes'/'no').

Changes to outcomes

No changes were made to trial outcomes after the trial commenced.

Sample size

The sample size calculation was conducted in nQuery Advisor 4.0. A sample size of 144 in each bandage system group was required to ensure that the lower limit of the two-tailed 95% confidence interval, for the true difference (PROGUIDE - PROFORE) in the proportion of patients whose reference limb had healed by week 24, lay above -0.15, which was the non-inferiority criterion. This corresponded to the confidence interval for the difference in two binomial proportions, with 90% power, and assumed that the percentage of patients that healed by week 24 was 81% for patients on both bandaging systems.

The target sample was 300 patients (150 in each bandage system group), allowing for 4% of patients being lost to follow-up.

Interim analyses

An interim analysis was performed on the first 140 patients recruited into the study. This interim review was performed in accordance with the analysis plan for the full patient data.

Randomisation

Sequence generation of random allocation to the treatment was performed by an independent statistician. Eligible patients were assigned a sequential patient number from the study register. Patients were randomised to either PROFORE or PROGUIDE by means of centre staff opening an opaque sealed envelope that was marked with the patient number. Each group was stratified according to area of largest ulcer (>1cm^2 and ≤ 10 cm^2, or >10 cm^2 and < 25cm^2). Only one limb was selected for the study. Patients with bilateral ulceration were randomised to one treatment only and received this on both limbs. The 'reference limb' was taken as the leg with the largest ulcer within the range of 1cm^2 to 25cm^2.

Blinding

Blinding was not possible in this study, since the two investigational products were visually different. However, statistical analysis was carried out blinded to group allocation, by persons who had not had contact with study participants.

Statistical analysis

Two populations were defined for the analysis:

1. Full analysis set – all patients who had completed the initial baseline assessment (also known as the intention to treat (ITT) analysis population).

2. Per protocol population – all patients who satisfactorily complied with the assigned treatment and had no major protocol violations.

Patients who withdrew prior to completion of the study were assigned the worst- case healing outcome (not healed by 24 weeks), as defined in the protocol. While the 24 week

outcome in these participants is unknown, it is reasonable to suggest that those who fail to complete a trial are more likely to be treatment failures over the relatively short 24 week follow up. The proportion of patients attaining ulcer closure by week 24 for both treatment groups, and the associated 95% confidence interval for the difference, were estimated. Non-inferiority of PROGUIDE was deemed to have been established if the lower limit of the 95% confidence interval for the difference between treatment means (wound closure rates) lay above -15%. That is, non-inferiority for PROGUIDE would be demonstrated if it were shown beyond reasonable doubt that no fewer than 15% fewer patients using this system, compared with patients using PROFORE, had healed by week 24 of treatment.

Alternatively, there would need to be at least 97.5% confidence that no fewer than 15% fewer patients had healed on PROGUIDE than on PROFORE by week weeks.

An accelerated failure time model was fitted to assess differences in the time to ulcer healing between PROGUIDE and PROFORE.

A multivariate analysis was conducted, whereby recruitment centre, baseline reference limb ulcer area and duration of current ulceration were included in the model. Other baseline covariates were assessed for inclusion in the model using a forward selection procedure with p=0.10 for parameter entry to the model. Inclusion of baseline covariates in the final model adjusts for any imbalances in the distribution of baseline variables between treatment groups and 95% confidence intervals were presented for each of the parameter estimates from the above analyses.

A three-level random effects logistic regression model was used to analyse differences between the two bandage systems for patient comfort ratings, exudate management, bandage slippage/requirement for unscheduled bandage changes, and appearance of surrounding skin.

A three-level ordered logistic regression was used to assess differences between the two bandage systems in the cumulative odds of reports of mild, moderate and severe pain during the preceding week.

A three-level ordered logistic regression was used to assess differences in patient ankle circumference between bandage systems during weeks 1 to 4.

Appropriate parametric and non-parametric summary statistics were calculated. Analysis of the data was performed using SAS Version 8.2, Proc StatXact Version 4 and MLWin version 1.10. All significance tests were two-sided. *P* values were calculated to a 5% level of significance, and 95% confidence intervals were generated where appropriate.

Results

Participants

Three hundred and three patients were randomized to receive treatment. 153 were allocated to PROGUIDE and 150 to PROFORE. Patients were recruited between July 2001 and August 2002. The final follow-up assessment was completed in February 2003.

Baseline data

All patients taking part in the study were treated as outpatients. Baseline characteristics of patients randomised to treatment are shown in Table 1. The mean patient age was 68 years (SD13.4), and 174 (57%) were female with other demographic characteristics comparable across the treatment groups.

[Table 1]

Baseline reference limb details are given in Table 2, and baseline reference limb details in Table 3.

[Table 2]

The two groups were generally well matched for ulcer characteristics. Median ulcer area was 4.1cm^2 for PROGUIDE patients and 3.1cm^2 for PROFORE patients. Median duration of the current episode of ulceration was 4.3 months for PROGUIDE patients and 5.0 months for PROFORE patients.

[Table 3]

Participant flow

Flow of participants through each stage is shown in Figure 1 and reasons for discontinuation or withdrawal are given in Table 4.

[Figure 1]

A total of 58 (19%) patients withdrew prior to healing or before the end of the 24-week period of treatment, 37 (24%) from the PROGUIDE treatment group and 21 (14%) from the PROFORE treatment group. The main reasons given for withdrawal were patient request or reports of adverse events.

[Table 4].

The odds of a patient withdrawing early were significantly greater for PROGUIDE than for PROFORE (p = 0.027), with an odds ratio of 1.97 (95% CI: 1.08 to 3.59).

Outcomes and estimation

Ulcer healing

Of the 153 randomised to PROGUIDE full closure occurred in 92 (60.1%), the ulcer remained open in 24 (15.7%) and 37 (24.2%) were discontinued. Of the 150 participants randomised to PROFORE full ulcer closure occurred in 102 (68.0%), 27 (18.0%) had open ulcers and 21 (14%) were discontinued. In the full analysis (intention to treat) population, this corresponded to a difference in ulcer closure of –7.9% (95% CI: –19.1 to 3.4%), P=0.17.

Results were similar for the per protocol population, which consisted of 253 (83.5%) of the 303 randomized patients. For this population, the number of patients who experienced complete ulcer closure over the 24 weeks of treatment was 84/131 (64.1%) for PROGUIDE and 89/122 (73.0%) for PROFORE. There was no significant difference between the groups in terms of the proportions attaining ulcer closure (p = 0.163), with a treatment difference of -8.8% (95% CI: -21.0% to 3.5%).

Although the differences in healing rates for the bandages were not statistically significant, the non-inferiority criterion of a lower confidence interval greater than -15% was not met in either the full analysis set or the per protocol population. Thus, it was not demonstrated that PROGUIDE was non-inferior to PROFORE in this study.

The median time to healing was 95 days for PROGUIDE compared with 71 days for PROFORE system. In order to adjust for the effect of those who discontinued treatment, an accelerated failure time model (AFT) was used. This indicated a time to heal ratio of 1.16 (95%CI 0.97 to 1.40) in favour of Profore, but which again failed to achieve a standard level of statistical significance (p=0.110), Figure 2.

Similar results to the full set analysis were obtained from the per protocol analysis, with no significant difference in time to healing between the two groups (p=0.107), and time to heal ratio 1.17 (95% CI: 0.97 to 1.42).

<u>Covariates related to ulcer healing</u>

Factors found to be significantly related to ulcer healing (see Figures 3 and 4) were:

- baseline ulcer area (p <0.001; time to heal ratio 1.05; 95% CI: 1.03 to 1.07), equating to a 5% longer healing time for each 1cm^2 increase in baseline ulcer area)

- duration of current ulceration (p <0.001; time to heal ratio 1.02 (95% CI: 1.01 to 1.03), equating to a 2% longer healing time for every month increase in ulcer duration)
- baseline ankle circumference (p=0.008; time to heal ratio 0.94 (95% CI: 0.91 to 0.99), equating to a 6% longer healing time for every 1cm decrease in baseline ankle circumference)
- baseline ulcer exudation (p=0.031; time to heal ratio 1.18 (95% CI: 1.01 to 1.37), equating to an 18% longer healing time as level of exudate increases by one point on the four- point scale)

Other factors found to be related to ulcer healing were patient sex (p<0.001), history of stroke (p<0.001) and history of osteoarthritis (p=0.026). Although there was significant evidence that the time to healing differed between treatment centres (p=<0.001), there was no evidence of an interaction between treatment effect and centre.

Secondary outcomes

Bandage performance

Bandage comfort

There was significant evidence of a greater odds (p<0.001) of an 'uncomfortable'/'very uncomfortable' bandage being reported by PROGUIDE patients compared to PROFORE, with an odds ratio of 2.64 (95% CI: 1.63 to 4.28). Both groups, however, had 'comfortable'/'very comfortable' ratings above 80%.

Exudate management

There was no evidence of a difference between the two groups in terms of exudate strike through (p=0.474), with an occurrence of 20% for both bandage systems.

Bandage changes and bandage slippage

There was no evidence of a difference in the odds of an unscheduled bandage change between the two bandage groups (p=0.130), with 25% of bandages being changed between assessments for PROGUIDE patients, and 22% being changed for PROFORE over the 24-week study period.

During the first four weeks of treatment, 77% of PROGUIDE and 86% of PROFORE bandages were recorded as being 'in place' (i.e. from toes to knee). The odds ratio of the difference was 0.53 (95%CI 0.33 to 0.86) in favour of Profore (p<0.001). However, the requirement for a bandage to be reapplied due to slippage was rare (4% for PROGUIDE and 2% for PROFORE).

Patient endpoints

Ulcer pain

There was no significant difference in the number of patients rating their ulcer pain as 'severe' in the two treatment groups (7% for PROGUIDE and 5% for PROFORE (p=0.898), with an odds ratio of 0.97 (95% CI: 0.59 to 1.59)).

Skin condition

There was marginal evidence of a greater odds (p=0.059) of abnormal appearance of surrounding skin in the PROGUIDE group compared to PROFORE, with an odds ratio of 1.66 (95% CI: 0.98 to 2.80).

Ankle circumference (control of limb oedema)

The mean percentage change in ankle circumference in the first four weeks of treatment was -3.4% (range -20.3% to 17.5%) for PROGUIDE and -3.0% (range -21.9% to 9.1%) for PROFORE. There was no evidence of a difference (p=0.379) in ankle circumference on

PROGUIDE compared to PROFORE, with an estimated difference of -0.10cm ((95% CI: -0.32 to 0.12cm).

Adverse events

There was a significantly greater likelihood of reporting one or more adverse in the PROGUIDE group (120/153 (78%)) than in the PROFORE group (95/150 (64%)) (p=0.006) (Table 5). This was chiefly due to the greater incidence of device-related adverse events in the PROGUIDE group (28% of adverse events device-related) than the PROFORE group (11% of adverse events device-related) (p<0.001). Most adverse events occurred early in the study and were due to pain or discomfort in the reference limb.

Discussion

There have been relatively few innovations in the field of compression therapy during the last decades. The same treatments such as Profore have been used for over 30 years and are still the standard practice in many hospitals and clinics worldwide. Even though compression therapy has been available for a long time, only recently have well-designed trials begun to be performed. The efficacy of many compression devices commonly used in clinical practice have not yet been fully evaluated.

While the healing rates in this study for both compression groups were broadly similar to previous studies, the higher rate of adverse events in the intervention group would indicate that the new system does not address the primary aim of the study which was to introduce a simplified bandage system that in addition to healing ulceration also prevented the recognised problem of pain that is associated with compression applied with too high a

level of compression. However, a randomised controlled trial and economic analysis of four-layer bandaging when compared to a usual system of care showed a significant difference in healing rates with 54% healing rate at three months with four-layer bandages (Profore) compared to only 34% in the control group (P=0.006). However, the control group did not standardise the compression used which may have influenced the healing rates [15]. There is no way to determine whether the selection of compression by public health nurses was appropriate or that the level of compression was consistent. The Profore system has been shown to be able to sustain pressure levels over time and this is thought to be a major feature of its effectiveness [12].

Clinical and cost effectiveness was assessed in a study of 453 participants comparing compression hosiery and four- layer bandaging. The median time to healing was similar in both groups (70.9%), however, a higher rate of treatment changes was required in the hosiery group compared to the bandage arm, probably due to the difficulties of control of exudate. The study reported marginally more quality of life adjusted life-years in the hosiery group ([16]. A trial comparing intermittent pneumatic compression, compression hosiery and an inelastic system found that the healing rates were lowest in the inelastic compression group [17]. However, the numbers in each group within the study are small and must therefore be interpreted with caution. Four-layer bandaging (Profore) was compared to inelastic systems and showed a reduction in the mean healing time of 10.9 days with Profore and a corresponding reduction in cost of £227.32. Systematic reviews of compression in venous ulcer healing support that four- layer bandaging is associated with a shorter healing time and improved cost effectiveness [1.]

Despite the reported clinical evidence there are great difficulties in interpreting the results from clinical trials and outcome studies due to the wide variation in clinical practice. In this study the introduction of a new compression system may have led to lower healing rates due to unfamiliarity. The use of many centres in such clinical trials may also influence the outcomes overall with compression studies showing a variation in healing rates by site and in different countries. The subtleties of the routine use and early application of compression therapy for venous ulcer healing are important in maximising health outcomes. The evidence suggests that despite the availability of compression it has not been consistently adopted internationally even when the evidence is provided.

Limitations of the study

The study hypothesis that a new bandage with use of materials that prevented high pressure application were not supported with higher rates of pain and adverse events in the PROGUIDE group. It can be hypothesised that this was due to high pressure in the PROGUIDE bandage despite the claims that high level pressure was not a feature of the compression materials. Patients reported higher level of pain that led to the higher reporting of adverse events in this group compared to PROGUIDE. Following the interim analysis all sites were contacted and retrained on the application of PROGUIDE to try and prevent over extension of the bandage. This probably led to a reduction in the pain reported PROGUIDE adverse events that occurred later in the trial.

EXPECT is the first known trial to investigate the efficacy of the VARI-STRETCH technology used in the PROGUIDE bandaging system. The healing rates at 24 weeks for the full analysis set were 60.1% for PROGUIDE and 68.0% for PROFORE. The healing rates for PROFORE were lower than those in other studies which may reflect the slightly greater chronicity of

wounds in the current study (median 5 months duration, maximum 4 years), compared to (median 6 weeks duration, maximum 2 years).

Baseline factors related to ulcer healing were similar to those reported in other studies of compression bandage treatment. In the present study, whilst initial and follow-up training in the use of both bandage systems was provided, PROGUIDE had not previously been used routinely at any of the study sites and this may have influenced the results.

Previous published trials of compression bandaging systems have demonstrated similar overall withdrawal rates to those encountered in this study (9-10, 20-21), however the withdrawal rate for PROGUIDE in this study (24%) was somewhat higher than for PROFORE (14%). This may again have been partly due to staff inexperience in using this new bandage and may have been a factor affecting the overall wound closure rates in the PROGUIDE group. The types of adverse events reported in this study included leg pain, ulcer breakdown, skin problems, and infections, and were similar to those experienced in previous trials of compression bandaging (9, 17, 18). Overall, adverse events, particularly those assessed to be device-related, were significantly more likely to be reported by PROGUIDE patients than PROFORE patients. However, a notable decrease in adverse events in the PROGUIDE group was recorded after the application technique of the two-layer system had been re-emphasized (the requirement being not to over-extend the bandage at the ankle and foot), and users had become more familiar with the new bandage system.

Clearly, an inherent difficulty in conducting studies of this type is that blinding is not possible. In future trials of compression bandaging, interface pressure measurement will become a required standard in assessing the performance of bandaging systems. This may

assist in interpretation of the adverse events encountered during such trials in which high pressure causing pain may influence patient withdrawal.

Despite investment on solutions to overcome some of the inherent difficulties of compression therapy that relate to issues such as pain, positive outcomes are not always achieved, as is evident in this study. The product (PROGUIDE) was withdrawn from production after the trial and this has in part, contributed to the delay in publication. It raises the great importance of continuing to develop and evaluate new compression systems through rigorous research. The study demonstrates the complexity and cost of running such projects. The differences in healing rates between centres is in part likely to be related to the familiarity with standard practice compared to new products and not to patient characteristics alone. This is a challenge for all clinical trials of medical devices in which blinding of the intervention cannot be achieved.

Conclusion

The primary objective of the trial was to determine whether the compression bandaging system PROGUIDE was non-inferior to an established bandaging system, PROFORE, in the treatment of limb ulceration. Results showed that wound closure rates were lower for PROGUIDE (61%) than for PROFORE (68%), with a difference between treatment means of -7.9% (95% CI: -19.1% to 3.4%). The non-inferiority criterion of a lower confidence interval greater than -15% was not met, either in the full analysis set or the per protocol population, and thus non-inferiority of PROGUIDE was not established. Adverse events, particularly device-related adverse events, were significantly more likely to be reported by PROGUIDE patients then by PROFORE patients. The problems identified associated with PROGUIDE in this study led to its withdrawal from clinical practice. This study reinforces the need to

conduct rigorous clinical trials on the plethora of compression materials used to treat venous ulceration to determine clinical effectiveness and the profile of adverse events that may influence the patient experience and adherence.

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References

1. O'Meara S, Cullum N, Nelson E.A., Dumville J.C. (2012) Compression for venous leg ulcers. *Cochrane Database of Systematic Reviews*. Issue 11. Article CD000265, doi: 10.1002/14651858.CD000265.pub3.

2. European Wound Management Association. (2003) Understanding compression therapy. MEP Ltd. London, UK.

3. Kunimoto B, Cooling M, Gulliver W, Houghton P, Orsted H, Sibbald R.G. (2001) Best practices for the prevention and treatment of venous leg ulcers. *Ostomy Wound Management.* 47 (2), pp34-46, 48-50.

4. Margolis D.J., Berlin J.A., Strom B.L. (2000) Which venous leg ulcers will heal with limb compression bandages? *American Journal of Medicine*. 109(1), pp15-19.

5. Guest J.F., Ayoub N, McIlwraith T. (2015) Health economic burden that wounds impose on the National Health Service in the UK. *British Medical Journal Open.* 5(12), pp e009283.

6. Moffatt C.J., Franks P.J., Doherty D.C., Martin R, Blewett R, Ross F. (2004) Prevalence of leg ulceration in a London population. *QJM: An International Journal of Medicine*. 97(7), pp431–437. https://doi.org/10.1093/qjmed/hch075.

7. Wounds UK Consensus. (2013) Guidelines for practice: Optimising venous leg ulcer services in a changing NHS. London: Wounds UK.

8. Thomas S, Fram P. (2003) Laboratory-based evaluation of a compression-bandaging system. *Nursing Times*. 99(40), pp24-28.

9. Thomas S. (2000) Measuring sub-bandage pressure. *Journal of Wound Care*. 9(10), pp491-492.

10. Melhuish J.M., Clark M, Williams R, Harding K.G. (2000) The physics of sub-bandage pressure measurement. *Journal of Wound Care*. 9(7), pp308-310.

11. International Lymphoedema Framework (2006) Best practice for the management of lymphoedema. MEP Ltd. London.

12. Williams C. (1996) Profore four-layer bandage system. *British Journal of Nursing*. 5(17), pp1075-1076, 1078.

13. Partsch H. (2005) *Dermatologic Surgery.* The static stiffness index: a simple method to assess the elastic property of compression material in vivo. 31(6), pp625-630.

14. World Medical Association (2013) Declaration of Helsinki - ethical principles for human research.

15. Polignano R, Bonadeo P, Gasbarro S, Allegra C. (2004) A randomised controlled study of four-layer compression versus Unna's Boot for venous ulcers. Journal of Wound Care. 13(1), pp21-24.

16. Torra i Bou J.E., Rueda López J, Blanco Blanco J, Torres Ballester J, Toda Lloret L. (2003) [Venous ulcers. Multilayer compression system or crepe bandage? Comparative study on effectiveness, cost, and impact on quality of life]. Revista de Enfermeria. 26(6), pp59-66.

17. Moffatt C.J., McCullagh L, O'Connor T, Doherty D.C., Hourican C, Stevens J, et al. (2003) Randomised trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration. *Wound Repair and Regeneration*. 11(3), pp166-171.

18. Ukat A, Konig M, Vanscheidt W, Munter K.C. (2003) Short-stretch versus multilayer compression for venous leg ulcers: a comparison of healing rates. Journal of Wound Care. 12(4), pp139-143.

19. Partsch H, Damstra R.J., Tazelaar D.J., Schuller-Petrovic S, Velders A.J., de Rooij M.J., et al. (2001) Multicentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. *Vasa*. 30(2), pp108-113.

20. Gupta A.K., Koven J.D., Lester R, Shear N.H., Sauder D.N. (2000) Open-label study to evaluate the healing rate and safety of the Profore Extra Four-Layer Bandage System in patients with venous leg ulceration. *Journal of Cutaneous Medicine and Surgery*. 4(1), pp8-11.

21. Carr L, Philips Z, Posnett J. (1999) Comparative cost-effectiveness of four-layer bandaging in the treatment of venous leg ulceration. Journal of Wound Care. 8(5), pp243-248.

Tables and Figures

Table 1: Baseline characteristics of patients randomised to treatment

	PROGUIDE n = 153	**PROFORE n = 150**	**Total n = 303**
Sex			
Male	64 (42%)	65 (43%)	129 (43%)
Female	89 (58%)	85 (57%)	174 (57%)
Age			
Mean	67.6	68.3	68.0
SD	13.0	13.9	13.4
Patient mobility			
Walks unaided	122 (80%)	120 (80%)	242 (80%)
Walks with aid	31 (20%)	29 (19%)	60 (20%)
Chair bound	0	1 (<1%)	1 (<1%)
Ulceration of leg			
Left	72 (47%)	68 (45%)	140 (46%)
Right	64 (42%)	66 (44%)	130 (43%)
Both	17 (11%)	16 (11%)	33 (11%)

Table 2: Baseline reference limb details

	PROGUIDE n = 153	PROFORE n = 150	Total n = 303
Leg			
Left	80 (52%)	74 (49%)	154 (51%)
Right	73 (48%)	76 (51%)	149 (49%)
Number of ulcers			
1	92 (63%)	94 (64%)	186 (63%)
2	33 (22%)	32 (22%)	65 (22%)
3	18 (12%)	12 (8%)	30 (10%)
4	2 (1%)	5 (3%)	7 (2%)
5	2 (1%)	4 (3%)	6 (2%)
Ankle circumference			
18-22 cm	23 (15%)	29 (19%)	52 (17%)
>22-28 cm	116 (76%)	107 (71%)	223 (74%)
>28-32 cm	14 (9%)	14 (9%)	28 (9%)
Arterial Function (Ankle Brachial Pressure Index)			
Mean	1.1	1.1	1.1
SD	0.2	0.2	0.2
Ankle mobility			
Full	122 (80%)	121 (81%)	243 (80%)
Limited	28 (18%)	29 (19%)	57 (19%)
Fixed	3 (2%)	0	3 (<1%)
Venous disease confirmed by:			
Duplex scan	57 (37%)	59 (39%)	116 (38%)
PPG	41 (27%)	37 (25%)	78 (26%)
Doppler	50 (33%)	50 (33%)	100 (33%)
Other	5 (3%)	4 (3%)	9 (3%)

Table 3: Baseline reference ulcer details

	PROGUIDE n = 153	PROFORE n = 150	Total n = 303
Ulcer Area (cm^2)			
Mean	6.6	5.8	6.2
Median	4.1	3.1	3.4
SD	7.0	6.4	6.7
Minimum	0.7	0.2	0.2
Maximum	45.4	26.8	45.4
N	152	148	300
Duration since first ulceration appeared (months)			
Mean	96.8	111.4	104.0
Median	46.2	48.0	47.8
SD	127.4	158.4	143.6
Minimum	0.4	0.4	0.4
Maximum	700.6	724.7	724.7
N	149	147	296
Number of times since ulceration healed and recurred			
Mean	3.1	3.2	3.1
Median	2.0	1.0	1.0
SD	6.4	5.1	5.8
Minimum	0.0	0.0	0.0
Maximum	60.0	30.0	60
N	143	139	282
Number of patients with previous ulceration	98 (64%)	89 (59%)	

	PROGUIDE n = 153	PROFORE n = 150	Total n = 303
Duration of current ulceration (months)			
Mean	9.4	8.4	8.9
Median	4.3	5.0	4.7
SD	12.5	10.0	11.3
Minimum	0.3	0.1	0.1
Maximum	62.5	49.7	62.5
N	152	149	301

Table 4: Reasons for discontinuation or withdrawal

	PROGUIDE	PROFORE	Total
Reason for discontinuation			
Complete healing of reference limb	93 (61%)	102 (68%)	195 (64%)
End of study period (24 weeks)	23 (15%)	27 (18%)	50 (17%)
Patient withdrawn	37 (24%)	21 (14%)	58 (19%)
N	153 (100%)	150 (100%)	303 (100%)
Reason for withdrawal			
Missed > 2 consecutive visits	2 (5%)	1 (4%)	3 (5%)
Lack of response	0	2 (8%)	2 (3%)
Patients own request	18 (46%)	12 (48%)	30 (47%)
Patient lost to follow-up	0	0	0
Poor performance of bandage system	2 (5%)	2 (8%)	4 (6%)
Adverse event	15 (38%)	6 (24%)	21 (33%)
Other	2 (5%)	2 (8%)	4 (6%)
n*	39 (100%)	25 (100%)	64 (100%)

* Six patients withdrawn from study for multiple reasons

Table 5: Device related adverse events

		PROGUIDE n=153	**PROFORE n=150**
Number of Adverse Events (of any type)		295	267
Number of device-related Adverse Events	Severe	2 (2.4%)	1 (3.6%)
	Non-severe	80 (97.6%)	27 (96.4%)
	Total	82 (28%)	28 (11%)
Number of patients reporting at least one Adverse Event (of any type)		120/153 (78%)	96/150 (64%)
Number of patients reporting at least one device-related Adverse Event		59/153 (39%)	22/150 (15%)

Figure 1: CONSORT flow diagram

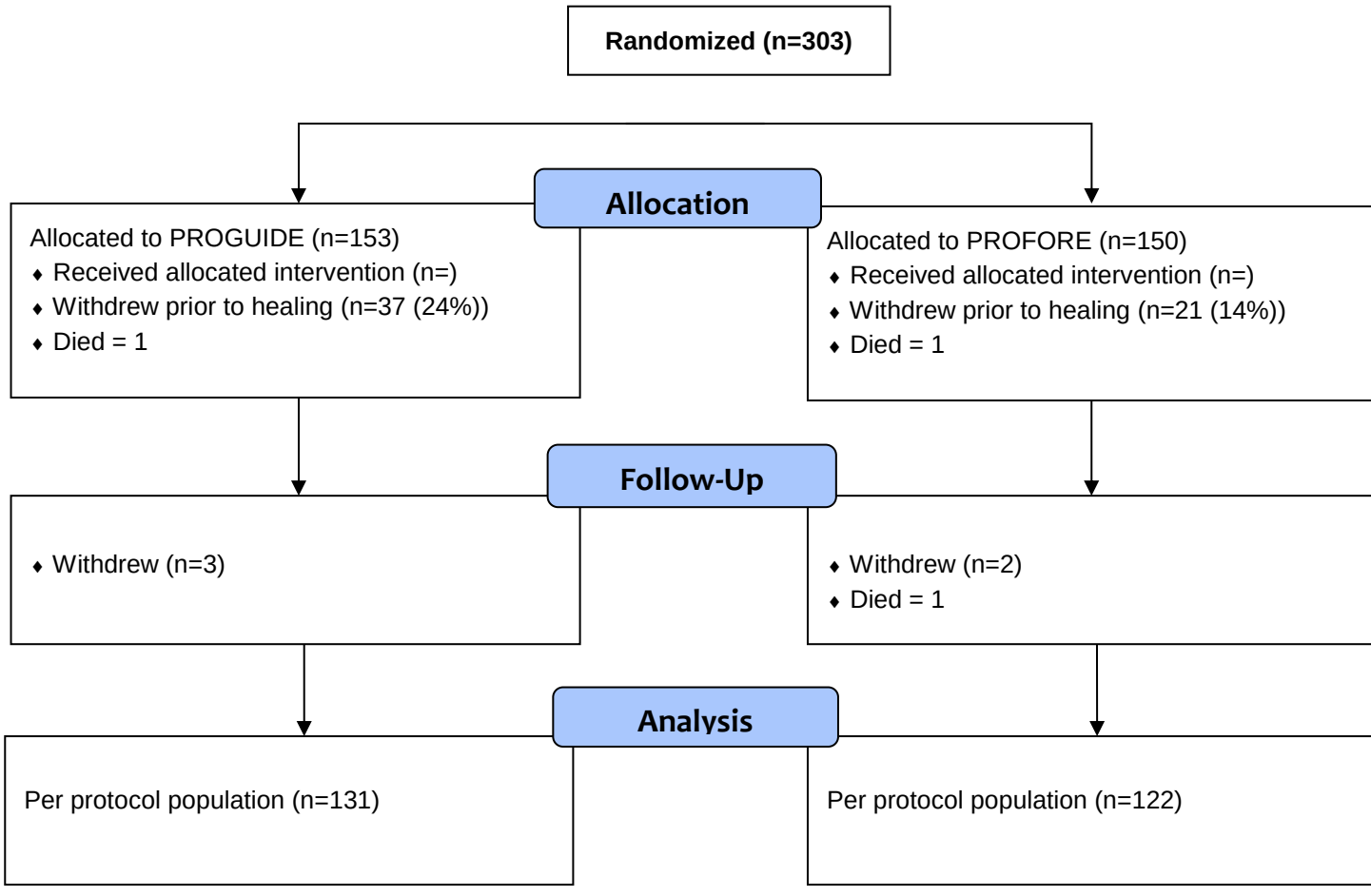

Figure 2: Kaplan-Meier plot of probability of healing (ITT) against time (by treatment group)

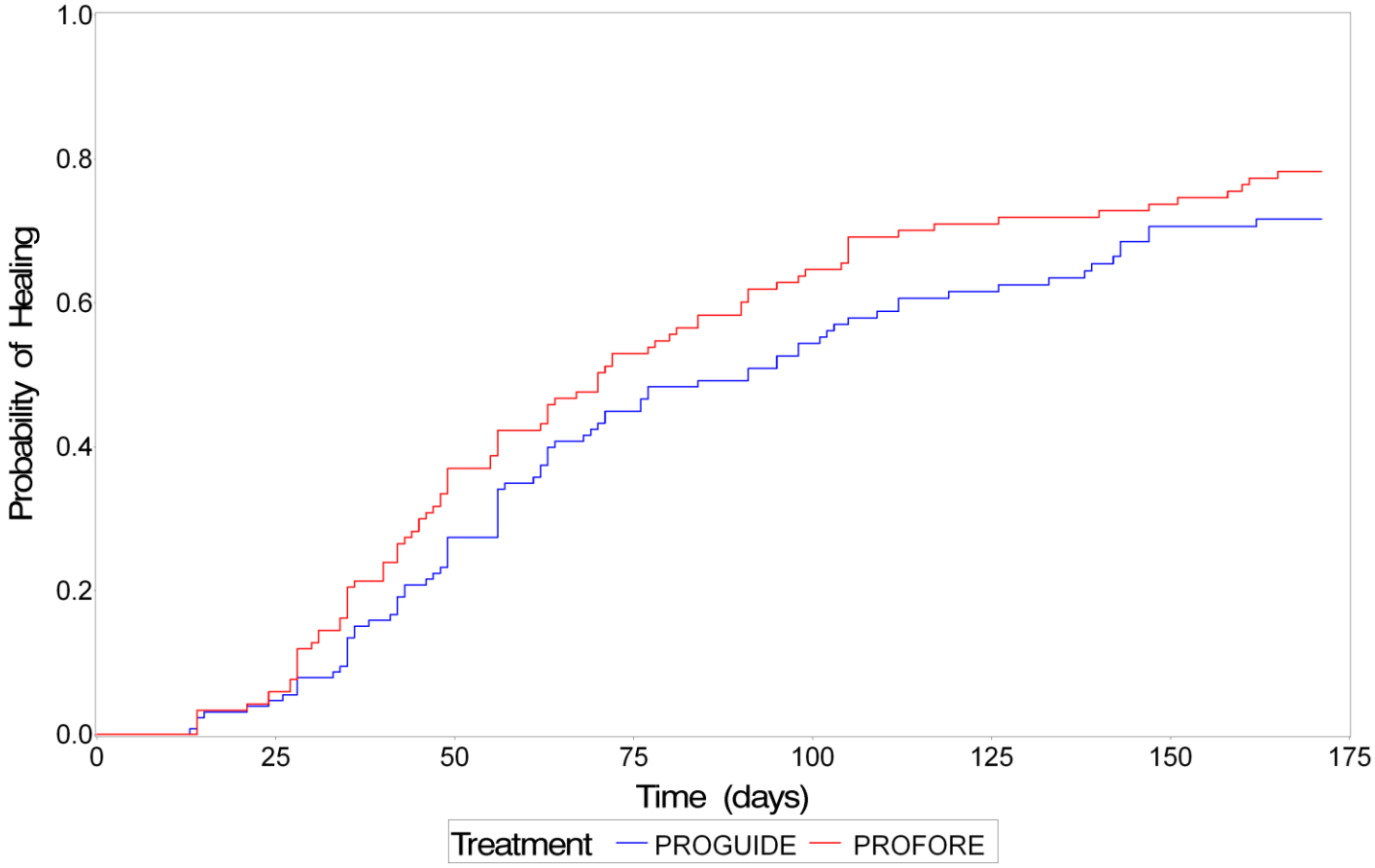

Figure 3: Kaplan-Meier plot of probability of healing (ITT) against time (by baseline ulcer area)

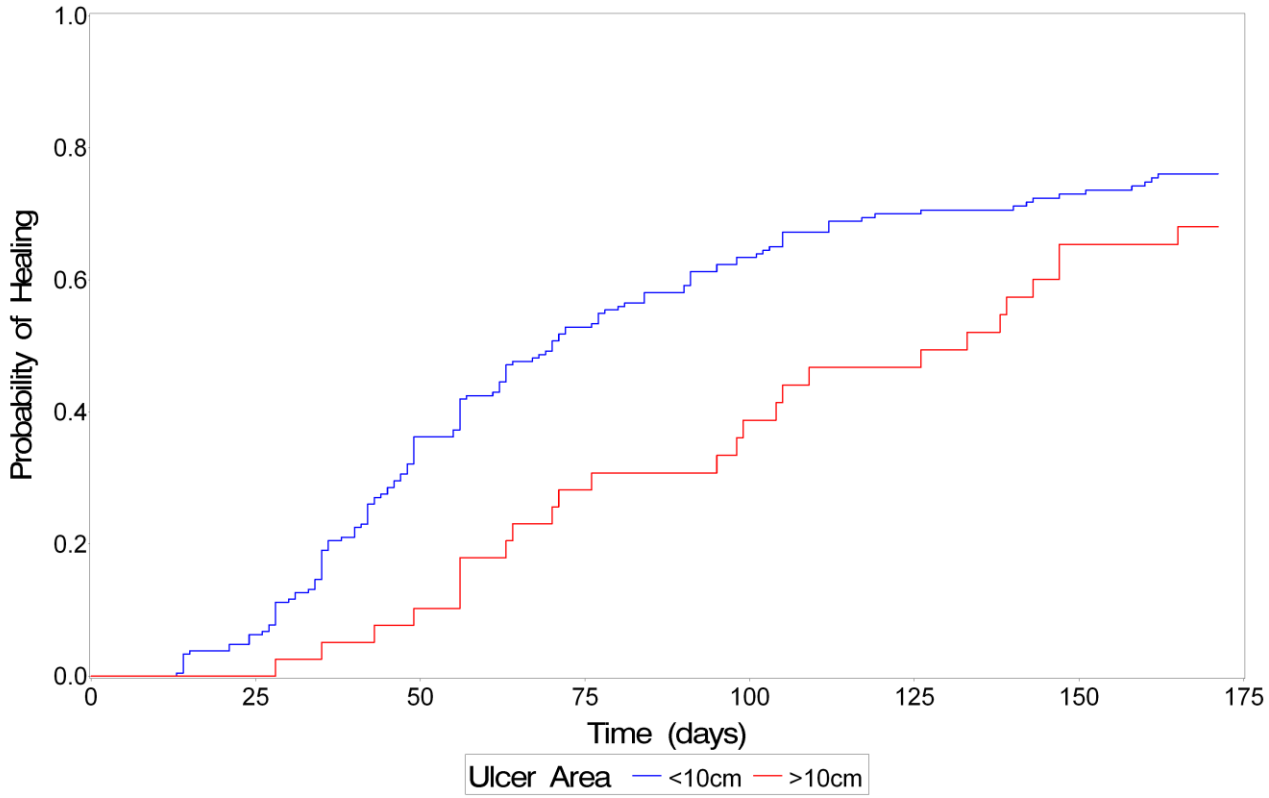

Figure 4: Kaplan-Meier plot of probability of healing (ITT) against time by (duration of current ulceration)