State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings

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Background: **Current treatment modalities for chronic leg ulcers are time consuming, expensive, and only moderately successful. Recent data suggest that creating a subatmospheric pressure by vacuum-assisted closure (V.A.C., KCI Concepts, San Antonio, Texas) therapy supports the wound healing process.**

Methods: **The efficacy of vacuum-assisted closure in the treatment of chronic leg ulcers was prospectively studied in a randomized controlled trial in which 60 hospitalized patients with chronic leg ulcers were randomly assigned to either treatment by V.A.C. or therapy with conventional wound care techniques. The primary outcome measure was the time to complete healing (days). Statistical analysis was performed on the intention-to-treat basis.**

Results: **The median time to complete healing was 29 days (95% confidence interval [CI], 25.5 to 32.5) in the V.A.C. group compared with 45 days (95% CI, 36.2 to 53.8) in the control group ($P = .0001$). Further, wound bed preparation during V.A.C. therapy was also significantly shorter at 7 days (95% CI 5.7 to 8.3) than during conventional wound care at 17 days (95% CI, 10 to 24, $P = .005$). The costs of conventional wound care were higher than those of V.A.C. Both groups showed a significant increase in quality of life at the end of therapy and a significant decrease in pain scores at the end of follow-up.**

Conclusions: **V.A.C. therapy should be considered as the treatment of choice for chronic leg ulcers owing to its significant advantages in the time to complete healing and wound bed preparation time compared with conventional wound care. Particularly during the preparation stage, V.A.C. therapy appears to be superior to conventional wound care techniques. (J Vasc Surg 2006;44:1029-38.)**

Chronic leg ulcers (CLUs) affect approximately 1% of the adult population in developed countries.[1] The prevalence increases with age and is estimated to be 4% to 5% in the population aged ≥80 years.[1,2] The course and prognosis of patients with leg ulcers differs according to the underlying pathogenesis, which is venous disease in up to 80%.[2]

Several treatment modalities and protocols have been reported to date, all of them mainly focusing on ambulatory treatment of venous ulcers.[2-4] The cornerstones of these regimens are compression therapy and resolution of the cause.[2-5] It is broadly accepted now that ulcers should be débrided of necrotic and fibrous tissue to allow formation of granulation tissue, adequate epithelialization, and to decrease the chance of infection.[2-4,6] Apart from both surgical or chemical débridement, there is not much evidence for the use of special dressings underneath the compression bandages.[2-4,7-10]

By following the currently available protocols, about 50% of ulcers will heal ≤4 months, about 20% do not heal ≤2 years, and about 8% do not even heal after 5 years.[11,12] Furthermore, various studies reported a recurrence rate after wound healing with nonoperative techniques of up to 57% after 1 year.[13] Owing to these poor healing results, many patients will be admitted to the hospital for inpatient treatment.

Although the use of suction on wounds has been known since the late 1950s, it was not until 1993 that Fleischmann introduced vacuum sealing for soft-tissue damage in open fractures.[14,15] In 1995, Kinetic Concepts, Inc, San Antonio, Texas introduced into the US market a commercial system, V.A.C., for promoting vacuum-assisted closure. The V.A.C. system exerts a controlled, local subatmospheric pressure in the wound.[16]

Owing to our own promising retrospective preliminary data and the relative paucity of prospective randomized controlled trials, we started a randomized controlled trial to study the efficacy of V.A.C. in wound healing compared

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with standard wound dressings in hospitalized patients with recalcitrant CLU as defined in the inclusion criteria. We also evaluated the effect of V.A.C. therapy on recurrence rate, quality of life (QOL), pain, comfort, and costs of treatment.[17-19]

PATIENTS AND METHODS

Patients. The study was conducted in the Departments of Dermatology at the University Hospital Maastricht and the Atrium Medical Centre Heerlen, The Netherlands. All patients hospitalized with chronic venous, combined venous and arterial, or microangiopathic (arteriolosclerotic) leg ulcers of >6 months' duration were eligible for entry in the study after surgical treatment options had been exhausted and extensive ambulatory treatment (>6 months) in an outpatient clinic according to the Scottish Intercollegiate Guideline Network (SIGN) had failed.[20]

Duplex ultrasound scans of the deep and superficial venous system, an arterial work-up consisting of Doppler ultrasound scans, ankle-brachial pressure index (ABI), and transcutaneous oxygen pressure, as well as bacterial cultures were performed in all patients. In those with no apparent venous or macroangiopathic arterial insufficiency but with decreased transcutaneous oxygen pressure, biopsy specimens were taken to demonstrate microangiopathic (ie, arteriolosclerotic) changes. On the basis of these findings, patients were divided into groups: (1) those with chronic venous insufficiency of the deep or superficial system without an arterial incompetence, (2) those with combined arterial and venous insufficiency of the deep or superficial system (ABI, 0.60 to 0.85), or (3) arteriolosclerotic (Martorell's ulcer, biopsy proven) leg ulcers.

Before inclusion in the study, underlying venous and arterial insufficiency was dealt with, and patients underwent ambulatory conservative local treatment for at least 6 months. This consisted of ambulatory débridement whenever necessary, daily or weekly (whenever necessary) cleansing with tap water, and nonadherent wound dressings creating a controlled moist wound environment (SIGN guidelines). Because no wound infections were observed, no topical or systemic antibiotics were used.

Patients with venous or combined venous/arterial leg ulcers were treated with multilayer, short, stretch bandages. If the ulcer did not reduce in size after 6 months of ambulatory treatment, patients were hospitalized to add bed rest and skin grafting to their treatment and became eligible for entry in the study.

Patients meeting one of the exclusion criteria—ulcer chronicity <6 months duration, age >85 years old, the use of immune suppression, allergy to wound products, malignant or vasculitis origin, or ABI <0.60—were excluded from the study. In patients presenting with multiple ulcerations, the clinically most severe CLU, according to the staging system described by Falanga,[21] was included in the study.

Every patient was provided with trial information sheets and written informed consent was obtained. Full ethics approval from the respective local medical ethical committees was obtained, and the study was performed in accordance with guidelines set forth by the Declaration of Helsinki.[22]

Procedures. Hospitalized CLU patients were randomly assigned to the V.A.C. group or to the control group (standard wound care) by a computer program using random permuted blocks of eight. Randomization was carried out within three strata, one for each ulcer type: venous, combined venous/arterial, and arteriolosclerotic ulcers. Treatment allocation occurred through telephone calls to the coordinating center. In both study groups and both study centers, an initial necrosectomy was performed by sharp débridement under local anesthesia until pinpoint bleeding appeared.[6]

In patients assigned to treatment with V.A.C., polyurethane ether foam was applied to the wound during the preparation stage. This foam was appropriately trimmed to fit each individual wound. A noncollapsible drainage tube embedded in the foam was connected to the V.A.C. pump; thereafter, an airtight adhesive drape was applied on top of the foam, and a permanent negative pressure of 125 mm Hg was exerted. The tube drained the wound secretion into a collection canister. In this way, a previously open wound was temporarily converted into a controlled, closed, and moist wound. A wound was considered to be prepared when granulation tissue covered 100% of the surface and wound secretion was minimal.[21]

Transplantation of full-thickness punch skin grafts was then performed.[23] This autologous grafting, in which 4-mm superficial pieces of skin are normally taken from the thigh, was performed under local anaesthetic (Xylocaine 1%, AstraZeneca, Wilmington, Del). In conjunction with a punch graft, the skin is picked up using a rounded biopsy knife (Biopsy punch, Kai Medical Europe, Solingen, Germany) and cut off. The pieces of skin are placed on the ulcer, spaced 5-mm apart, and are covered with a nonadhesive dressing, such as polyvinylalcohol foam. After 4 days of continuous subatmospheric pressure, once all skin grafts attached well, standard wound care was continued using a nonadhesive dressing (Atrauman; Hartmann, Nijmegen, The Netherlands) and a multiple-layer compression bandage (Rosidal K; Lohmann & Rauscher, Rengsdorf, Germany), when possible, until complete healing.

Patients assigned to standard wound care received daily local wound care according to the SIGN guideline and compression therapy (especially patients with venous or combined venous/arterial ulcers) until complete healing.[20] Compression therapy consisted of double-layered, short, stretch bandages (Rosidal K,) applied from the toe to below the knee, creating a submalleolar pressure of 25 to 35 mm Hg. Two basic types of commercially available wound dressings were used in this study, including hydrogels (Nugel, Johnson & Johnson, Amersfoort, The Netherlands) and alginates (Sorbalgon, Hartmann, Paul Hartmann B.V., Nijmegen, The Netherlands). The choice of dressing mostly depended on the wound bed and the amount of exudate.[2-4,7]

Once 100% granulation was achieved and minimal wound secretion was seen, these patients also received punch skin-graft transplantation covered with a nonadhesive dressing (Atrauman) and compression therapy. The inner dressing was not be changed for 4 days.[7,21] Once all skin grafts had attached well, standard wound care was continued using a nonadhesive dressing (Atrauman) and a multilayer compression bandage (Rosidal K), when possible, until complete healing.

In both treatment groups, only toilet and basic hygiene mobility was permitted during the wound bed preparation and transplantation stage. After complete wound healing, community-grade elastic support stockings class 2 (Mediven 550, Medi Nederland B V, Breda, The Netherlands; or Eurostar, Varodem, Horn, The Netherlands) or 3 (Eurostar, Varodem, Horn, The Netherlands) were prescribed, depending on the cause of the ulcer.

Evaluation criteria. Because masking the interventions was not possible, patients were reviewed clinically by the same independent research physician and consultant dermatologist twice a week until wound closure. Thereafter, the same research physician prospectively monitored the patients at 3, 6, and 12 months after discharge. All participating clinicians completed standardized case record forms during their control visits, treatments, and follow-ups.

Two time spans in wound healing were distinguished: (1) the wound bed preparation, and (2) the time to complete healing. The stage for wound bed preparation was defined as the time between surgical débridement and application of the punch skin grafts. The time to complete healing, being the primary end point, was defined as the period between surgical débridement and 100% epithelialization (wound closure). Patients were only discharged after complete healing; therefore, length of hospital stay equalled total healing time. Secondary end points included (1) duration of the wound bed preparation, (2) percentage of ulcer recurrences $\leq$1 year after discharge, defined as an epithelial breakdown anywhere along or within the index leg ulcer region, and (3) skin-graft survival, defined as the percentage of successfully adhered skin grafts after 4 days of complete bed rest and local therapy. Furthermore, we compared between both experimental groups the QOL, pain scores, the total time needed for wound care until complete wound closure, and the costs per ulcer.

Quality of life and pain scores. Quality of life was measured at baseline and once a week during hospitalization using the EuroQol Derived Single Index (EQ-DSI). This index is a generic questionnaire consisting of five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.[24] Scoring of these parameters can be transformed into a single index of health status, with the highest score reflecting the best possible health status. During dressing changes, pain scores were derived using the Short Form-McGill Pain Questionnaire (SF-MPQ) and the Present Pain Intensity (PPI) score as adjectival pain scale, as previously reported.[25] The SF-MPQ is designed to provide quantitative measures of clinical pain. It consists of 15 descriptors of 11 sensory and four affective items, with a maximum response of three for each item (maximum possible sensory and affective score is 33 and 12, respectively). Pain intensity using the PPI score was recorded on a scale from 1 to 5, with 1, mild; 2, discomforting; 3, distressing; 4, horrible; and 5, excruciating.

Time consumption. The total time needed for wound care until total wound closure was based on empirical time registration by the attending dermatologist and the nurse who performed wound care. Both time spans were calculated in minutes.

Cost analysis. The total costs related to wound care for each ulcer included the salary for personnel and the material costs for wound care procedures until the moment of complete healing. Personnel costs for each procedure were based on empirical time registrations by the dermatologist and nurse who performed the wound care. Because we chose to keep patients hospitalized until complete healing was achieved, in contrast to normal clinical practice, we did not incorporate admission costs in the budget. Costs related to materials were based on actual cost prices as calculated by the financial department of the University Hospital Maastricht. The costs of both treatment modalities were calculated in dollars ($) for each ulcer.

Statistical analysis. Data from a retrospective study showed that the mean $\pm$ SD duration of the >90% wound closure period was 50 $\pm$ 12 days in standard would care vs 31$\pm$ 7 days in V.A.C.[17] To detect a minimal difference of 7 days in preparation time with a power of 95% (α = 5%), the number of patients required in each treatment-group was 30, as derived from sample-size calculations.

Results were analyzed on an intention-to-treat basis.[26] Time to complete healing (Fig 1), duration of wound bed preparation (Fig 2), and recurrence rates (Fig 3) were compared using the Kaplan-Meier survival analysis.[27] The log-rank test was used to test for statistically significant differences between the groups.[27] To adjust for small imbalances in the baseline distribution of relevant prognostic factors (Table I) to wound healing, multivariate analysis was performed using Cox's proportional hazards model (Table II).[13,28,29] The regression coefficient expresses the independent contribution of potential determinants to duration of cleaning and wound healing. Hazard ratios (HR) and their 95% confidence intervals (CI) are presented. $P <$ .05 was considered to be statistically significant.

Percentages were compared by the χ^2 test, and continuous variables were compared using the independent samples *t* test for normally distributed variables and the two-independent sample test for non-normally distributed variables. The paired *t* test was used to compare QOL scores before treatment and at the end of follow-up. All data were analyzed using the SPSS 11.0 software package (SPSS Inc, Chicago, Ill).

RESULTS

Recruitment. From May 2001 to May 2003, 71 patients with 85 CLUs were hospitalized and screened for

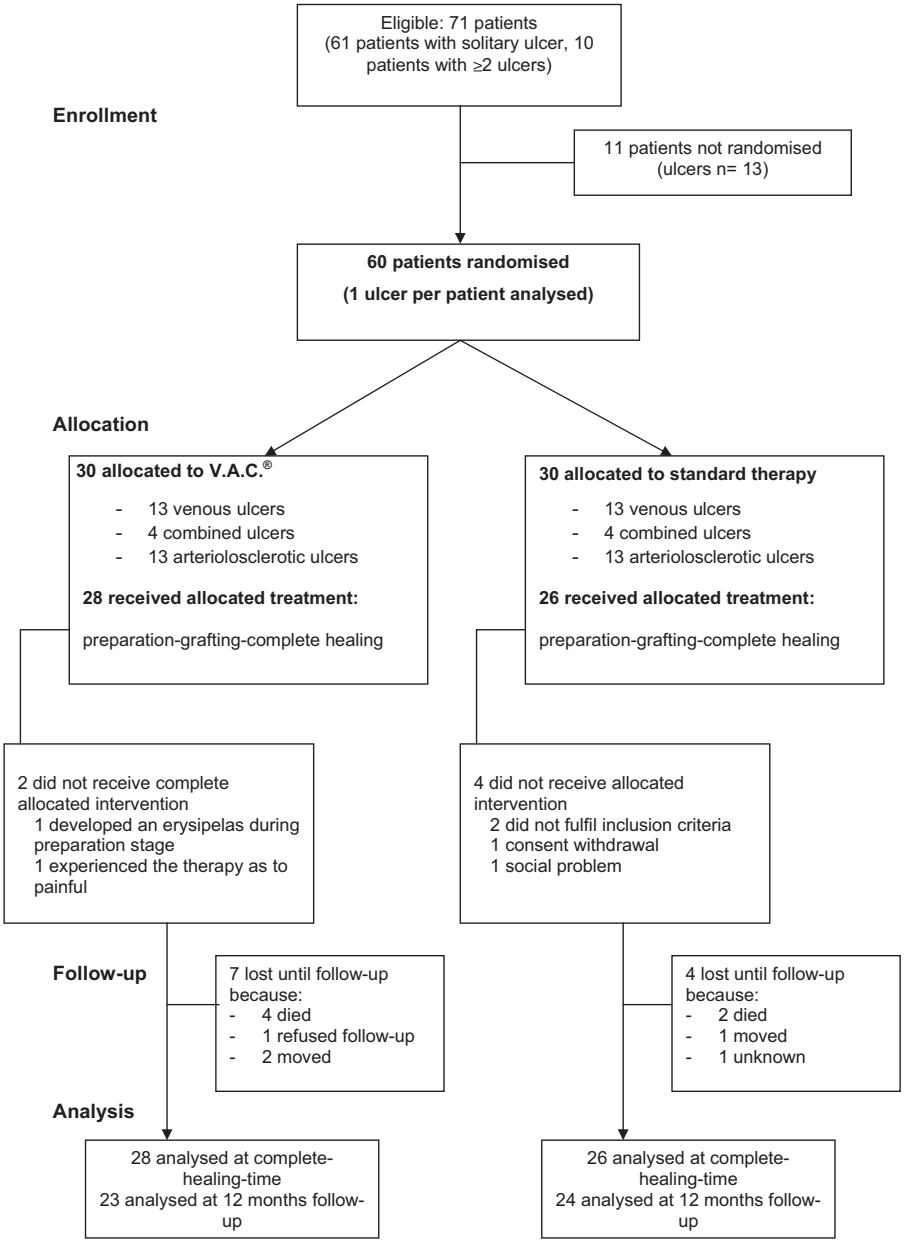

Fig 1. Time to complete healing (days) in the vacuum-assisted closure *(V.A.C.)* group compared with standard wound care.

inclusion (Fig 4). Eleven patients with 13 ulcers were not included because they were not interested in participating.

Protocol violations. Four randomized patients (n = 4 ulcers), two in the V.A.C. group and two in the control group, did not complete the protocol due to reasons mentioned in Fig 4. In addition, one patient switched from conventional to V.A.C. therapy after 8 weeks due to an unsatisfactory therapeutic outcome. Finally, during analysis it became apparent that two patients were falsely included because they had peripheral arterial disease. Still, the therapeutic outcome in these patients was analyzed according to the intention-to-treat principle.[26] During follow-up, seven V.A.C. patients and four controls were lost due to reasons outlined in Fig 1.

Patient and ulcer characteristics. Among the 60 patients, 51 had one ulcer, six had two ulcers, and three had three ulcers (n = 72 ulcers). All patients gave informed consent for inclusion in the study and were randomly allocated between the two treatment arms (Fig 4).

Patient and ulcer characteristics of both groups are shown in Table I. Although the median ulcer surface area was larger in the control group, no statistical differences were observed in common risk factors known to be associ-

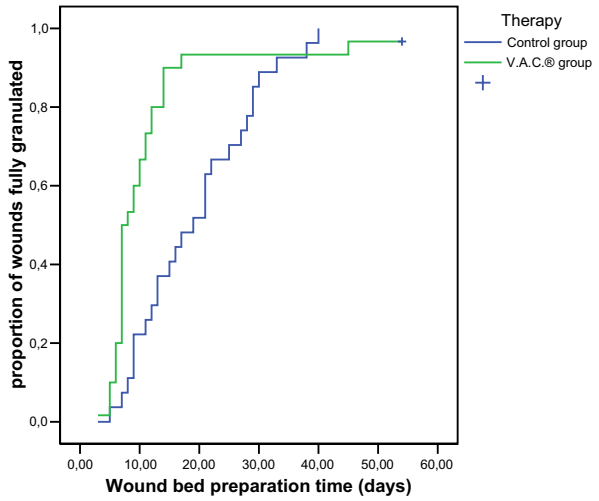

Fig 2. Wound bed preparation time (days) in the vacuum-assisted closure *(V.A.C.)* group compared with standard wound care.

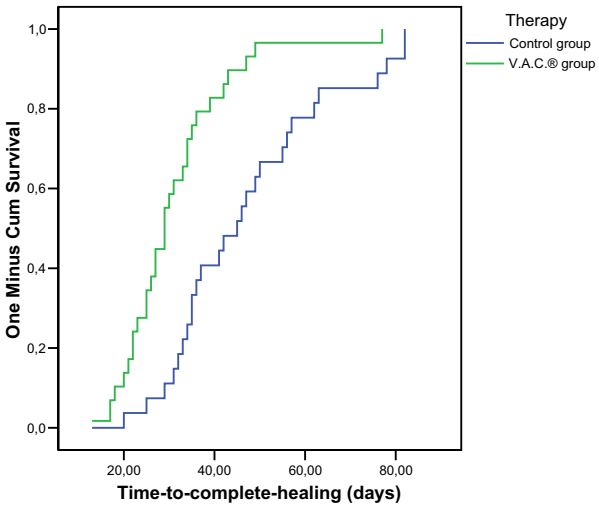

Fig 3. Recurrence rate (months) in the vacuum-assisted closure *(V.A.C.)* group compared with standard wound care.

ated with delayed ulcer healing or in demographic and clinical characteristics.[13,28,29]

Effectiveness of V.A.C. vs conventional wound care. Kaplan-Meier survival analysis showed that the time to complete healing was reduced in the V.A.C. group (P = .0001). The median total healing time was 29 days (95% CI, 25.5 to 32.5) in the V.A.C. group vs 45 days (95% CI, 36.2 to 53.8) in the control group. Ninety percent of the ulcers treated with V.A.C. healed within 43 days. At that point, only 48% of all ulcers in the control group had healed (Fig 1). As patients were only discharged after complete healing, length of hospital stay equalled total healing time. Only one ulcer failed to heal in both the control and V.A.C. treated groups, respectively.

V.A.C. therapy resulted in a significantly shorter wound bed preparation time (P = .005). The median preparation time was 7 days (95% CI, 5.7 to 8.3) in the V.A.C. group vs 17 days in the control group (95% CI, 10 to 24). Moreover, 90% of the ulcers treated with V.A.C. could be cleaned within 14 days. By contrast, only 37% of the ulcers in the control group could be cleaned within this time span (Fig 2).

Cox multivariate regression analysis (Table II) showed that that treatment by V.A.C. was still associated with significant faster time to complete healing (HR = 3.2; 95% CI, 1.7 to 6.2) and preparation time (HR = 2.4; 95% CI, 1.2 to 4.7) independently of small imbalances in prognostic factors (eg, the ulcer surface area) to wound healing between both study groups.

Secondary outcomes. Kaplan-Meier survival analysis (Fig 3, Table III) showed a median recurrence rate at month 4 (95% CI, 0.7 to 7.4) after the V.A.C. therapy vs month 2 (95% CI, 0.5 to 3.6) in the control group (P = .47). After 1-year follow-up (Table III), 52% (n = 12) of all healed V.A.C. ulcers relapsed compared with 42% (n = 10) in the control group (P = .47). All differences were not statistically significant.

The median percentage of successful skin grafts (Table III) differed significantly (P = .011) between the V.A.C. and control groups, with 83% ± 14% vs 70% ± 31%.

The total nursing time consumption (Table III) was significantly longer during standard wound care (386 ± 178 minutes) than during V.A.C. therapy (232 ± 267 minutes; P = .001). There were no significant differences (P = .937) between the V.A.C. and control groups with respect to time consumption for medical attention through the physician (177 ± 76 minutes vs 181 ± 91 minutes).

Quality of life. During the hospitalization period, 56 ulcers healed. Changes in QOL and in pain scores are presented in Table IV. The study groups showed significant increases in QOL at the end of therapy. During the first week, the QOL score was significantly lower in the V.A.C. group (P = .031); however, this difference had already disappeared in the second week, and during follow-up, life quality was similar in both groups.

With respect to pain scores, both groups showed a significant decrease at the end of follow-up, too. Comparison of pain scores revealed that the scores were initially similar during the first weeks of treatment. From week 5 onwards, however, PPI scores were significantly lower in the V.A.C. group.

Cost analysis. We have listed wound care costs in Table V. Costs for personnel were calculated on the basis of average fees for medical and nursing personnel adjusted for the clocked time spent by medical doctors and nurses with the patients. The total wound care costs for a hospitalized CLU were 25% to 30% lower for V.A.C. than for standard wound care (Mann-Whitney U test, P = .001). Because we chose to keep patients hospitalized until complete healing was achieved, in contrast to normal clinical practice, we did not incorporate admission costs in the cost analysis. Considering that length of hospital stay was significantly longer for patients with standard wound care, the

Table I. Demographic and clinical characteristics

	Treatment		
	*SWC (n = 30)**	*V.A.C. (n = 30)**	P
Male	7 (23)	7 (23)	NS
Female	23 (77)	23 (77)	
Age	72 (45-83)	74 (53-81)	NS†
Median ulcer chronicity at inclusion (months)	7 (6-12)	8 (6-24)	NS†
Median ulcer surface (length × width = cm^2)	43 (3-250)	33 (2-150)	NS†
Smoking	9 (30)	6 (21)	NS
Diabetes mellitus type II	5 (17)	5 (17)	NS
Immobility	13 (43)	12 (41)	NS
Hypertension	12 (40)	13 (45)	NS
No ulcer history	14 (47)	12 (40)	NS
Ulcer environment (0-4)‡	2 (0-4)	2 (0-4)	NS
Infection signs (*Pseudomonas aeruginosa*)	6 (20)	8 (28)	NS
Median ankle-brachial index (%)	100 (59-130)	100 (59-100)	NS†
Medication use			NS
Antibiotics	1 (3)	1 (4)	
Nonselective β-blockers	5 (17)	4 (15)	
ACE inhibitors	9 (30)	6 (23)	
Selective β_1-blockers	5 (17)	4 (15)	
Anticlotting therapy	7 (23)	10 (39)	
Ca^{2+} antagonists	4 (13)	1 (4)	
Ulcer type			
Venous origin	13 (43)	13 (43)	NS
CEAsP	7 (54)	9 (69)	
CEApP	6 (46)	3 (23)	
CEAdP	0	1 (8)	
Combined venous/arterial origin	4 (13)	4 (13)	NS
Arteriolosclerotic origin	13 (43)	13 (43)	NS

SWC, Standard wound care; *ACE,* angiotensin-converting enzyme inhibitors.
*Data are median (minimum-maximum) or number and (%) unless otherwise specified.
†Mann Whitney *U* test; χ^2 or Fisher exact as appropriate.
‡Ulcer environment (surrounding skin symptoms like petechiae, eczema, erythema, and/or maceration).

Table II. Hazard ratios with 95% confidence intervals for determinants of duration of wound-bed preparation and wound healing

	Wound bed preparation duration			*Wound healing duration*		
Variable	*HR*	*95% CI*	P	*HR*	*95% CI*	P
Ulcer area (cm^2)	0.56	0.29-1.09	0.09	0.5	0.25-1.01	0.058
Smoking	0.5	0.20-1.21	0.3	0.4	0.16-0.98	0.056
Infection signs	0.45	0.21-1.21	0.12	0.99	0.46-2.16	0.98
Ulcer history	1.08	0.61-1.91	0.79	0.93	0.50-1.71	0.8
Therapy	2.4	1.19-4.71	<.01*	3.22	1.66-6.21	<.000*
ACE inhibitors	1.9	0.57-2.07	0.8	0.95	0.49-1.82	0.88
Anticlotting therapy	1.03	0.53-2.01	0.92	0.69	0.35-1.38	0.3

HR, Hazard ratio; *CI,* confidence interval; *ACE,* angiotensin-converting enzyme inhibitor.
*Significant difference $P < .05$.

actual cost-efficiency of V.A.C. treatment would be even greater.

Complications. The complication rate was higher in the V.A.C. group (40%) compared with the control group (23%), but the difference was not statistically significant ($P = .17$). Table VI summarizes all adverse events.

DISCUSSION

Despite the development of modern diagnostic tools and remarkable therapeutic improvement, many CLUs do not heal satisfactorily in an outpatient clinic within a certain time period.[2-5,6-10,30] Furthermore, current treatment modalities are time consuming and expensive.[2] In this study, we used a prospective and comparative study model to evaluate the efficacy of V.A.C. treatment in recalcitrant CLUs treated in an inpatient facility compared with current standard therapeutic regimens. Our study shows that V.A.C. therapy results in a significant reduction of wound preparation time and the time to complete healing compared with common treatment modalities. Because ambu-

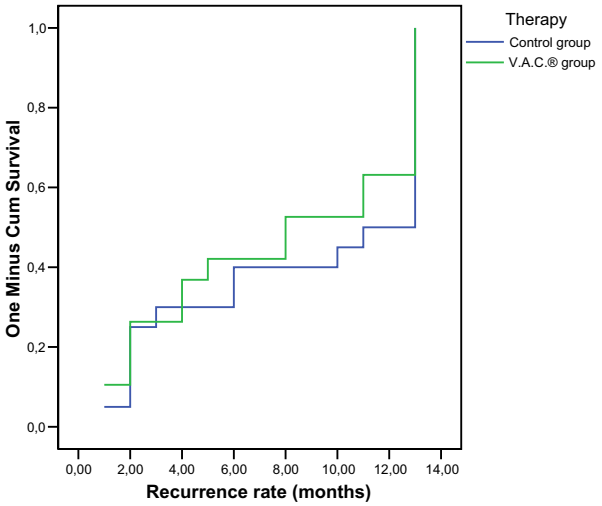

Fig 4. Trial profile. *V.A.C.*, Vacuum-assisted closure.

Table III. Secondary outcomes

	Conventional treatment	*V.A.C.*	P
Recurrence percentage (n)	42% (10)	52% (12)	.405*
Median recurrence moment (month)	2nd	4th	.47†
Median percentage skin graft survival (SD)‡	70% (31)	83% (14)	.011§
Median wound care time (SD)			
Nurse*	330 (178)	232 (267)	.001§
Physician	181 (91)	177 (76)	.937§

V.A.C., Vacuum-assisted closure.
*χ^2 test.
†Log-rank test.
‡Significant difference $P < .05$.
§Mann-Whitney *U* test.

latory V.A.C. pump units are available, this treatment might be offered on an outpatient basis. Providing that patients adhere strictly to the treatment protocol and trained wound care nurses are employed, the same efficacy may be reached in an outpatient setting.

Mouës et al[31] randomized patients with acute traumatic or infected wounds, pressure ulcers, and other chronic leg ulcers to V.A.C. vs standard wound care. They did not find any difference in wound bed preparation time; however, they did observe a significant reduction in wound area surface by V.A.C., implying a positive effect of V.A.C. on wound healing. Their failure to observe decreased wound bed preparation time may be related to inclusion of patients with acute infected or traumatic wounds.

For practical reasons, we subdivided the time to complete healing and distinguished the preparation phase and the overall complete healing time. Apparently, the greatest benefit of V.A.C. in our study is reflected by a reduced median preparation time of 58% during the first time period (Fig 2). The overall complete healing time was reduced by 35% (Fig 1). These data demonstrate that V.A.C. is an extremely valuable tool in wound bed preparation.

With this randomized clinical trial, we sought to assess the effect of V.A.C. therapy on wound healing in patients with recalcitrant CLU irrespective of underlying etiology. This approach may have increased the external validity of our findings, but it imposes some limitations on the interpretation of the results, especially since the number of patients is insufficient to perform subgroup analyses for each type of CLU individually. Nevertheless, keeping in mind this limitation, V.A.C. therapy resulted in a decreased wound preparation time and total wound healing time within each CLU group (ie, venous, arteriolosclerotic, or combined venous/arterial). For the venous and arteriolosclerotic ulcers, but not for the combined venous/arterial ulcers, this difference reached statistical significance (data not shown).

In the past, two main factors have been documented to exert an important influence on wound healing. First, it has been shown that chronic wound exudate may disturb normal wound healing because these fluids contain lower amounts of growth-promoting cytokines, persistent elevated inflammatory cytokines, and proteolytic enzymes.[3,14] Second, the considerable effects of mechanical forces on wound shape and tissue growth have been reported.[32] V.A.C. therapy has been repeatedly used successfully to positively influence both factors by removing excess interstitial fluid and transmitting mechanical forces to the surrounding tissue.[15,16,33]

In support of this notion, a recent report indicated that reduced levels of matrix metalloproteinases 1, 2, and 13 during V.A.C. presumably result in reduced collagen breakdown.[34] Further, active reduction of excessive wound fluid also results in decompression of small blood vessels, restores microcirculation, and increases oxygen and nutrient delivery to the wound. All these factors notably improve the rate of granulation tissue formation.[16,33] The positive influences of mechanical forces on the growth of tissues, especially in stimulating cell migration and mitosis during V.A.C., are also documented.[16,33,35] Further, an occlusive environment, as created by adhesive transparent dressings during V.A.C., markedly supports maintenance of a controlled, moist wound environment and reduces the chance of infection.[16,33,35] All of these factors have been shown to result in improved wound healing.

A critical aspect in the survival of a skin graft is an adequate contact with the granulated wound bed. With conventional treatment using compression bandages, the survival rates of skin grafts is usually much lower owing to excessively exudative wound bed surfaces and surfaces subjected to motion.[23] These difficulties can be overcome though by application of V.A.C., as demonstrated by Scherer et al[23] and confirmed in our study (Table III) by the higher percentage of adhered skin grafts (80% vs 70%, $P < .011$).

One of the major problems in leg ulcer treatment is the high frequency of relapses.[13] Interestingly, recurrence rates in CLUs after treatment with V.A.C. therapy compared with standard wound care modalities have not been reported to date, to the best of our knowledge.

Table IV. Mean (SD) quality-of-life scores in the V.A.C. vs control group

Week	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
EQ-5D									
V.A.C.	40 (13)	39 (16)*	47 (15)	62 (13)	70 (17)	74 (16)	73 (17)	76 (17)	77 (14)
Controls	45 (19)	49 (19)*	51 (18)	60 (16)	62 (18)	68 (17)	74 (15)	76 (12)	76 (17)
SF-MPQ									
V.A.C.	9 (4)	10 (5)	6 (3)	5 (3)	4 (2)	2 (2)	2 (2)	1 (1)	1 (1)
Controls	10 (3)	10 (4)	7 (4)	6 (3)	4 (2)	3 (2)	2 (2)	2 (2)	1 (1)
PPI									
V.A.C.	2.5 (1)*	3 (1)	1.9 (1)	1.4 (1)	1 (1)	0.5 (1)*	0.3 (0.5)*	0.2 (0.4)*	0.2 (0.7)*
Controls	3.1 (1)*	3.2 (1)	2.6 (1)	1.8 (1)	1.3 (1)	1.4 (1)*	1 (1)	0.5 (1)	0.4 (0.6)

V.A.C., Vacuum-assisted closure; *EQ-5D*, EuroQol = 5 Dimensions index; *SF-MPQ*, Short Form-McGill Pain Questionnaire; *PPI*, Present Pain Intensity.
*Mann Whitney *U* test, $P < .05$.

Table V. Average costs of treatment

	Conventional treatment (n = 30)	*V.A.C. (n = 30)*	P
V.A.C. related products ($)	0	847	
Bandages and dressings ($)	4770	2391	
Personnel costs ($)	508	583	
Nurse costs ($)	175	124	
Total ($)	5452	3881	.001*

*Mann-Whitney *U* test, $P < .05$.

Table VI. Adverse events

	Conventional treatment (n = 30)	*V.A.C. (n = 30)*
Erysipelas	0	1
Pain	1	3
Cutaneous damage secondary to therapy*	2	7
Wound infection	1	0
Postoperative bleeding at donor site	2	0
Nonhealing ulcer	1	1*

V.A.C., Vacuum-assisted closure.
*Mann Whitney *U* test, $P < .05$.

Without any doubt, it would be of great advantage in daily practice if V.A.C. revealed lower recurrence rates than standard wound care regimens. We observed 12 recurrences (52%) in the V.A.C. group and 10 relapses (42%) after standard wound care at the 12-month follow-up (Table III). Although this difference was not significant, larger study cohorts are certainly needed to determine a putative positive effect of V.A.C. with respect to ulcer recurrence rates.

Recently, socioeconomic and QOL studies in patients with CLUs revealed the broad impact of this long-neglected health care problem on everyday routine.[36] Persoon et al[36] convincingly demonstrated a strong correlation between the amount of time spent on ulcer care, feelings of anger, and the QOL of patients. In our study, the overall subjective QOL measured by the EQ-DSI and pain scores improved significantly in both groups within 8 weeks but did not differ significantly. Still, the improvement in QOL was achieved more rapidly in the V.A.C. group despite an initial decrease during the first week of treatment (Table IV). This may be explained by an accelerated wound preparation phase with V.A.C. A possible explanation for the initial decrease during V.A.C. treatment might be that patients experienced the necessity of strict bed rest as a factor negatively influencing QOL.

Wound care costs for the treatment of CLUs following standard protocols were significantly higher than those in the V.A.C. group. The biggest part of this cost difference was caused by higher personnel costs and longer hospitalization time due to slower wound healing in the control group. We are aware that this wound care time might not represent the real situation, because in daily practice, most patients with leg ulcers will be discharged once the ulcers are almost closed.

Several recently developed products have shown favorable results in the treatment of chronic (venous) leg ulcers compared with compression therapy, including bilayered bioengineered skin substitute,[37] cultured allogeneic human skin equivalent,[10] and porcine small intestine submucosa.[10] Because V.A.C. therapy has a strong beneficial effect on wound bed preparation, combination with one of these products, after a well granulating wound bed has been created with V.A.C. therapy, may improve treatment of recalcitrant CLU.

CONCLUSION

This prospective randomized controlled trial demonstrated that V.A.C. therapy leads to a significant improvement in wound management of recalcitrant CLUs. Therefore, V.A.C. therapy should be considered as the treatment of choice for CLUs. Future prospective studies with inclusion of more patients will be needed though to determine the effects of V.A.C. with respect to ulcer recurrence rates.[38]

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AUTHOR CONTRIBUTIONS

Conception and design: JDV, JW, MHAN
Analysis and interpretation: JDV, TV
Data collection: JDV
Writing the article: JDV, TV
Critical revision of the article: TV, JF, JCMV, MHAN
Final approval of the article: JDV, TV
Statistical analysis: PN
Overall responsibility: JDV

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