Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure With Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers

A multicenter randomized controlled trial

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OBJECTIVE — The purpose of this study was to evaluate safety and clinical efficacy of negative pressure wound therapy (NPWT) compared with advanced moist wound therapy (AMWT) to treat foot ulcers in diabetic patients.

RESEARCH DESIGN AND METHODS — This multicenter randomized controlled trial enrolled 342 patients with a mean age of 58 years; 79% were male. Complete ulcer closure was defined as skin closure (100% reepithelization) without drainage or dressing requirements. Patients were randomly assigned to either NPWT (vacuum-assisted closure) or AMWT (predominately hydrogels and alginates) and received standard off-loading therapy as needed. The trial evaluated treatment until day 112 or ulcer closure by any means. Patients whose wounds achieved ulcer closure were followed at 3 and 9 months. Each study visit included closure assessment by wound examination and tracings.

RESULTS — A greater proportion of foot ulcers achieved complete ulcer closure with NPWT (73 of 169, 43.2%) than with AMWT (48 of 166, 28.9%) within the 112-day active treatment phase ($P = 0.007$). The Kaplan-Meier median estimate for 100% ulcer closure was 96 days (95% CI 75.0–114.0) for NPWT and not determinable for AMWT ($P = 0.001$). NPWT patients experienced significantly ($P = 0.035$) fewer secondary amputations. The proportion of home care therapy days to total therapy days for NPWT was 9,471 of 10,579 (89.5%) and 12,210 of 12,810 (95.3%) for AMWT. In assessing safety, no significant difference between the groups was observed in treatment-related complications such as infection, cellulitis, and osteomyelitis at 6 months.

CONCLUSIONS — NPWT appears to be as safe as and more efficacious than AMWT for the treatment of diabetic foot ulcers.

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In 2005, the Centers for Disease Control and Prevention estimated the prevalence of diabetes in the U.S. to be 20.8 million people (1). A disabling complication with this disease is foot ulcer development (2,3), which leads to nonhealing chronic wounds that are difficult to treat. Moreover, diabetic foot ulcers (DFUs) are a significant risk factor for nontraumatic foot amputations in individuals with diabetes (4).

Various DFU treatments have been reported in the literature, including advanced moist wound therapy (AMWT) (5,6), bioengineered tissue or skin substitutes (7,8), growth factors (9,10), electric stimulation (11), and negative pressure wound therapy (NPWT) (12). Treatment success depends on ulcer chronicity, patient compliance, appropriate off-loading of the appendage, and the mechanisms of action of the therapy.

NPWT is a noninvasive system that creates a localized controlled subatmospheric (negative) pressure environment. In this study, NPWT was provided by the V.A.C. Therapy system (KCI USA, San Antonio, TX), which promotes wound healing by delayed primary or secondary intention through creating a moist wound environment, preparing the wound bed for closure, reducing edema, and promoting formation and perfusion of granulation tissue. Vacuum-assisted closure therapy is indicated for use in all care settings and for a variety of wound types including diabetic foot ulcers.

This multicenter randomized controlled trial (RCT) evaluated the safety and efficacy of NPWT compared with AMWT (predominately hydrogels and alginates) for the treatment of DFUs. The cost-benefit analysis will be reported in a future publication.

RESEARCH DESIGN AND METHODS

— The patient population consisted of diabetic adults ≥18 years with a stage 2 or 3 (as defined by Wagner's scale) calcaneal, dorsal, or plantar foot ulcer ≥2 cm^2 in area after debridement (13). Adequate blood circulation (perfusion) was assessed by a dorsum transcutaneous oxygen test ≥30 mmHg, ankle-brachial index values ≥0.7 and ≤1.2 with toe pressure ≥30 mmHg, or Dopp-

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J.C.L. has received honoraria as a speaker for KCI USA.

Abbreviations: AMWT, advanced moist wound therapy; ATP, active treatment phase; DFU, diabetic foot ulcer; ITT, intention-to-treat; NPWT, negative pressure wound therapy; RCT, randomized controlled trial.

ler arterial waveforms that were triphasic or biphasic at the ankle of the affected leg. Patients with recognized active Charcot disease or ulcers resulting from electrical, chemical, or radiation burns and those with collagen vascular disease, ulcer malignancy, untreated osteomyelitis, or cellulitis were excluded from the study. Patients with uncontrolled hyperglycemia (A1C >12%) or inadequate lower extremity perfusion were not enrolled. Exclusion criteria also included ulcer treatment with normothermic or hyperbaric oxygen therapy; concomitant medications such as corticosteroids, immunosuppressive medications, or chemotherapy; recombinant or autologous growth factor products; skin and dermal substitutes within 30 days of study start; or use of any enzymatic debridement treatments. Pregnant or nursing mothers were excluded from study participation.

The NPWT system used in this study was vacuum-assisted closure therapy. The system consists of three components: a negative pressure generating unit with a disposable canister, a pad with evacuation tube, and a reticulated, open cell sterile polyurethane or a dense open-pore polyvinyl alcohol foam dressing cut to fit the wound. The system unit is programmed to deliver controlled negative pressure ranging from 50 to 200 mmHg. NPWT was applied to the ulcer as specified by manufacturer's guidelines (14), and treatment was continued until ulcer closure, sufficient granulation tissue formation for healing by primary or secondary intention, by day 112.

AMWT dressings were used according to Wound, Ostomy and Continence Nurses Society guidelines (6) and institutional treatment protocols, consistent with standards of care for treating DFUs. Skin substitutes, cytokines, recombinant human platelet-derived growth factors, or similar therapies as outlined in the exclusion criteria were not used in either group during the active treatment phase (ATP).

The primary efficacy end point was incidence of complete ulcer closure. Secondary end points included a reduction in ulcer surface area over time, time to achieve ulcer closure by either surgery or secondary intention, and a reduction in complications, including secondary amputations. Complete ulcer closure was defined as skin closure (100% reepithelization) without drainage or dressing requirements.

The sample size was based on a type I error probability set at 0.05, with 80% power. Detection of a 20% difference between treatment groups required 206 evaluable patients with a treatment-to-study ratio of 1:1. Sample size was set at 338 to account for subject withdrawal or loss to follow-up.

Randomization was accomplished by generating blocks of numbers through http://www.randomizer.org. Numbers were assigned to a treatment group and sealed in opaque envelopes containing black paper labeled with treatment and patient ID. Envelopes were sequentially numbered before clinical trial site distribution. At patient randomization, treatment was assigned on the basis of the next sequentially labeled envelope.

U.S. Food and Drug Administration guidelines (15) state that in some devices, it is impractical or unethical to implement a control treatment that mimics the test product and allows masking. In this study, the physical differences between treatment regimens (e.g., hydrogels and NPWT) can be so distinctive that it is not possible to blind either the patient or physician to the treatment after random assignment.

This study was a prospective RCT initiated at 37 diabetic foot and wound clinics and hospitals. A total of 342 patients were enrolled at one Canadian and 28 U.S. sites. (A complete list of the participating centers and investigators can be found in the APPENDIX.) Before randomization, patients were screened for neuropathy, adequate perfusion, and glycemic control. All foot ulcers were assessed and debrided as needed within 2 days of randomization.

Patients were examined weekly for the first 4 weeks (day 28) then every other week until day 112 or ulcer closure by any means. At each study visit, ulcers were assessed for area via wound tracing, ulcer closure, and/or adequate granulation tissue formation. NPWT dressing changes were performed every 48–72 h, no less than three times per week. Patients randomly assigned to AMWT were treated on the basis of the manufacturer's guidelines. All patients received off-loading therapy as deemed necessary. Patients achieving ulcer closure were followed at 3 and 9 months.

Statistical analysis

The KCI Global Biometrics Group conducted the safety and effectiveness data analyses for this trial. Primary analysis was based on an intention-to-treat (ITT) dataset composed of all randomly assigned patients who gave informed consent and received at least one postbaseline treatment.

Continuous demographic variables (age, sex, and others) were summarized for the study population as descriptive statistics (number and mean ± SD), median, minimum, and maximum values, and 95% two-sided CIs and compared between groups with a two-sample *t* test or Wilcoxon rank-sum test.

An interim ITT analysis of the primary end point was performed at the enrollment of 275 patients to confirm the consistency of trial design assumptions with observed data. The Lan-DeMets group sequential boundaries (two-sided symmetric boundaries) were calculated using the O'Brien-Fleming α-spending function.

Data were analyzed on the basis of differences in incidence of closure between treatment groups and assessed with a test of proportions, using χ^2 or Fisher's exact test, as appropriate. Treatment differences in ulcer area (square centimeters) were calculated (ulcer area [square centimeters] = ulcer length [centimeters] × ulcer width [centimeters] × $\pi/4$) and analyzed using ANCOVA with baseline area used as a covariate. Median time to closure was based on number of days from baseline until closure via Kaplan-Meier survival analysis. Patients not achieving closure were censored using last date of observation.

RESULTS — Figure 1 describes patient flow through each stage of this RCT including discontinued patients. During the course of the study, 384 patients consented and were screened for inclusion from August 2002 through August 2005. Of these, 42 patients were excluded owing to inclusion/exclusion criteria, patient refusal to participate, or withdrawal of consent, and 342 were enrolled. Seven patients did not receive treatment, and 335 patients were analyzed. All patient data collected during the ATP were included in the ITT analyses.

The data suggest that no statistically significant demographic differences existed between treatment arms (Table 1). The mean patient population age was 58 years and the patients were predominantly male (78.5%). Percentages of patients treated for study ulcer infections at baseline were 29.6% (50 of 169) for NPWT and 27.1% (45 of 166) for AMWT. The randomization method resulted in an

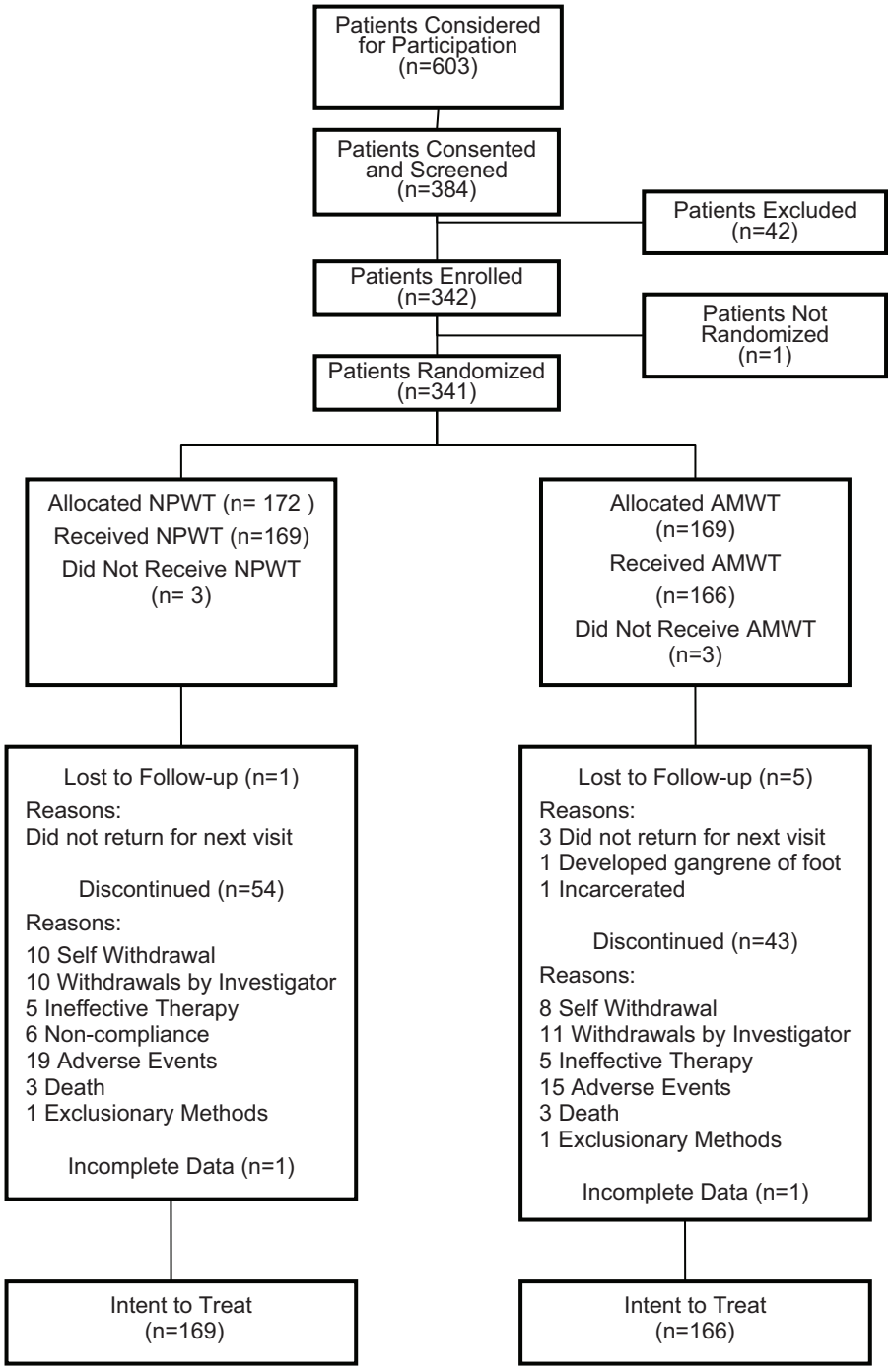

Figure 1—*Consort statement. The ITT group was defined per ICH-E9 guidelines, and no center affect was found.*

even distribution of characteristics between treatment groups.

Patients receiving off-loading were 164 of 169 (97.0%) for NPWT and 162 of 166 (97.6%) for AMWT. Patients were treated in both acute and home care settings. The proportion of home care therapy days to total therapy days was 9,471 of 10,579 (89.5%) for NPWT and 12,210 of 12,810 (95.3%) for AMWT.

Efficacy

Complete ulcer closure was defined as skin closure (100% reepithelization) without drainage or dressing requirements. Within the ATP, the NPWT group proportion was significantly ($P = 0.007$) greater for complete ulcer closure than that for the AMWT group (73 of 169 [43.2%] vs. 48 of 166 [28.9%]). For patients completing the ATP, analysis significantly ($P = 0.001$) confirmed that a greater percentage of NPWT-treated ulcers (60.8%, 73 of 120) achieved ulcer closure than AMWT-treated ulcers (40.0%, 48 of 120). After sufficient wound bed preparation, 9.5% (16 of 169) NPWT-treated ulcers and 8.4% (14 of 166) AMWT-treated ulcers were surgically closed by split thickness skin grafts, flaps, sutures, or amputations. Kaplan-Meier median time to complete ulcer closure was 96 days (95% CI 75.0–114.0) for NPWT ($P = 0.001$). AMWT median time to complete ulcer closure could not be estimated.(Fig. 2). The duration of therapy for NPWT was 63.6 ± 36.57 days (mean ± SD) versus 78.1 ± 39.29 days for AMWT.

To further evaluate effects of NPWT, 75% ulcer closure, degree of granulation tissue formation, and ulcer area reduction were assessed. Significantly more NPWT patients (105 of 169, 62.1%) achieved 75% ulcer closure than AMWT patients (85 of 166, 51.2%; $P = 0.044$). Kaplan-Meier median estimates for 75% ulcer closure were 58 days (95% CI 53.0–78.0) for NPWT and 84 days (95% CI 58.0–89.0) for AMWT ($P = 0.014$). In assessing ulcer area, a significant difference between NPWT (-4.32 cm^2) and AMWT (-2.53 cm^2) from baseline was achieved on day 28 ($P = 0.021$).

The clinical treatment effect on wound bed preparation was assessed in 46 patients (24 NPWT and 22 AMWT), who presented with 0–10% granulation at baseline and achieved 76–100% granulation. Of these, 17 of 24 (70.8%) NPWT and 8 of 22 (36.4%) AMWT patients achieved 76–100% granulation tissue formation ($P = 0.019$). Kaplan-Meier median estimates for 76–100% granulation tissue formation were 56 days (95% CI 42.0–84.0) for NPWT and 114 (95% CI 44.0–ND) for AMWT ($P = 0.022$).

Safety

Table 2 reports treatment-related rates for secondary amputations, edema, wound infection, cellulitis, osteomyelitis, staphylococcal infection, and infected skin ulcers at 6 months. Significantly ($P = 0.035$) fewer amputations were observed in NPWT patients (7 of 169, 4.1%) compared with AMWT patients (17 of 166, 10.2%). The majority of these amputations (2 and 13, respectively) were minor amputations. In all other categories, no significant differences were observed.

Table 1—*Patient demographics*

Characteristics	NPWT	AMWT
n	169	166
Age (years)	58 ± 12	59 ± 12
Sex (male/female)	141/28 (83/17)	122/44 (73/27)
Race		
African American	28 (16.6)	22 (13.3)
Caucasian	95 (56.2)	100 (60.2)
Hispanic	41 (24.3)	40 (24.1)
Native American	3 (1.8)	3 (1.8)
Other	2 (1.2)	1 (0.6)
Weight (kg)	99.2 ± 25.1	93.8 ± 25.6
Height (cm)	175.0 ± 9.6	175.0 ± 12.4
Current smoker	34 (20.1)	32 (19.4)
Currently use alcohol	37 (21.9)	45 (27.1)
Type of diabetes		
Type 1	15 (8.9)	14 (8.4)
Type 2	154 (91.1)	152 (91.6)
Prealbumin (g/l)	21.1 ± 7.6	19.9 ± 7.9
Albumin (g/l)	3.4 ± 0.6	3.4 ± 0.8
A1C	8.3 ± 2.0	8.1 ± 1.9
Ankle-brachial index (mmHg)	1.0 ± 0.2	1.0 ± 0.2
Transcutaneous oxygen tension (mmHg)	43.2 ± 10.4	43.3 ± 12.5
Loss of protective sensation*	150 (90.4)	143 (88.8)
Ulcer duration before treatment (days)	198.3 ± 323.5	206.0 ± 365.9
Baseline wound area (cm^2)	13.5 ± 18.2	11.0 ± 12.7
Received off-loading therapy	164 (97.0)	162 (97.6)
Treated for ulcer infection prior to randomization	50 (29.6)	45 (27.1)
Therapy received at treatment initiation		
NPWT	169 (100)	
Hydrogel		78 (47.0)
Alginate		31 (18.7)
Other		28 (16.9)
Saline		17 (10.2)
Collagen		11 (6.6)
Hydrocolloid		1 (0.6)

Data are means ± SD or *n* (%). *Percentage based on available data.

CONCLUSIONS — Results of the largest NPWT RCT to date demonstrate that NPWT is as safe as and more efficacious than AMWT in the treatment of DFUs. A significantly greater number of NPWT patients achieved complete ulcer closure and granulation tissue formation than AMWT patients. This result was supported by a significant reduction in median time needed to heal DFUs. For both treatments, ~90% of therapy days occurred in the home care setting.

No significant difference was observed in ulcer-related complications such as infection, cellulitis, and osteomyelitis. However, the study showed that AMWT patients had more than twice as many secondary amputations as those receiving NPWT.

Chronic DFUs present a significant challenge to treating physicians (16). Treatment involves multiple modalities including debridement, assessment, and treatment of infection, revascularization if indicated, and sufficient off-loading of the foot (17). A key component of the healing process is debridement because it enables removal of devitalized and necrotic tissue. Debridement is critically important to the initiation of healing. NPWT and other wound healing technologies work in conjunction with debridement as the foundation upon which the wound healing process can begin (18). As observed in this clinical trial, the use of NPWT in concurrence with debridement of the affected foot increases the number of DFUs healed and decreases the length of time required for ulcer healing compared with AMWT. In addition, the prescription of off-loading may have also contributed to positive results in both groups. Therefore, it appears that NPWT in addition to established standards of care enhances successful healing and closure of DFUs.

In this study, 14.3% more NPWT patients achieved complete ulcer closure in less median time to closure than AMWT patients. This result parallels the findings by Argenta and Morykwas in 1997 (12), who reported that the success of NPWT in chronic wounds is associated with removal of excess interstitial fluid, an increase in vascularity and associated decrease of bacterial colonization, and stimulation of granulation tissue formation through the response of wound tissue to the mechanical forces exerted by the application of negative pressure through the foam dressing. In separate studies, Saxena et al. (18) and Greene et al. (19) have further elucidated the role of open pore foam dressing in the creation of micromechanical deformations of the wound surface. These micromechanical deformations are caused when negative pressure draws tissue into the foam pores. This stretches cells and promotes cell division that stimulates granulation tissue formation (18).

Table 2—*Results of safety analysis*

MedDRA System Organ Class	NPWT	AMWT	*P* value*
n	169	166	
Secondary amputations	7 (4.1)	17 (10.2)	0.035
Edema	5 (3.0)	7 (4.2)	0.571
Wound infection	4 (2.4)†	1 (0.6)‡	0.371
Cellulitis	4 (2.4)	1 (0.6)	0.371
Osteomyelitis	1 (0.6)	0 (0.0)	—
Staphylococcus infection	1 (0.6)	0 (0.0)	—
Infected skin ulcer	1 (0.6)	2 (1.2)	0.620

Data are *n* (%). *Fisher's exact test. †1 moderate, 3 mild. ‡1 moderate. MedDRA, Medical Dictionary for Regulatory Activities.

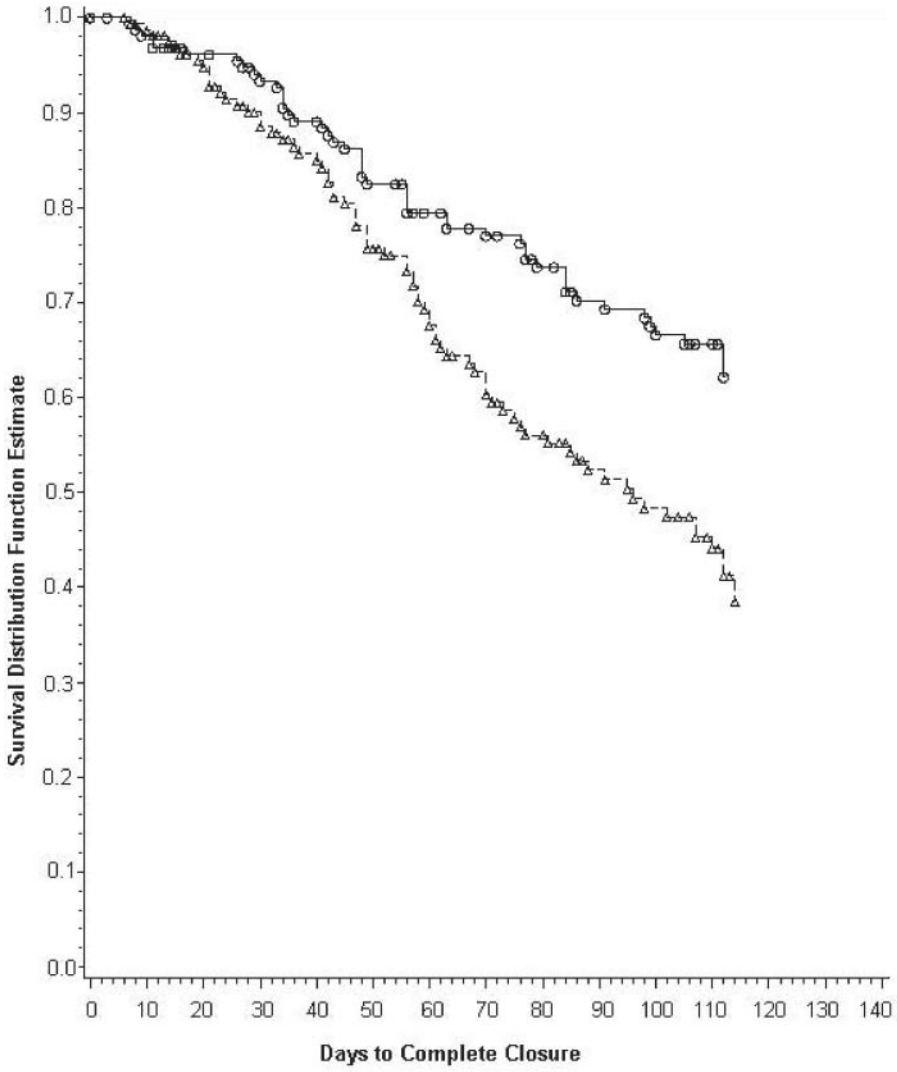

Figure 2—*Kaplan-Meier estimates for time to complete ulcer closure* ($P = 0.001$). △, NPWT; ○, AMWT.

As use of NPWT has increased, its use for wound bed preparation in conjunction with either delayed primary or secondary wound closure has also increased. In 2005, Armstrong and Lavery (20) reported that NPWT may be an alternative therapy to achieve an improved granulating wound bed in diabetic foot wounds to prepare the wound bed for other closure techniques. As shown by these data and in previous studies, NPWT promotes granulation tissue formation, thereby allowing the clinician to determine the course of closure.

DFUs are a significant risk for amputation (4). In this study, the incidence of secondary amputations was significantly less ($P = 0.035$) for NPWT (4.1%) than for AMWT (10.2%). This finding substantiates other reports, in which diabetic foot wounds treated with NPWT showed a trend toward fewer secondary amputations ($P = 0.060$) than those treated with AMWT (20). Although the exact mechanism of the decrease in secondary amputations remains unclear, treatment of DFUs with NPWT appears to promote significant healing.

In summary, this study of 342 patients with DFUs showed that NPWT is as safe as and more efficacious than AMWT for the treatment of diabetic foot ulcers.

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Conference abstracts reporting preliminary and interim study data were presented at the 2003 Symposium on Advanced Wound Care; 2nd World Union of Wound Healing Societies Meeting, Paris, France, 8–13 July 2004; 2007 Symposium on Advanced Wound Care, Tampa, Florida, 28 April–1 May, 2007; and the 2007 Annual Scientific Meeting of the American Podiatric Medicine, Philadelphia, Pennsylvania, 16–19 August, 2007.

APPENDIX

Investigators who enrolled patients for the V.A.C. Therapy Diabetic Foot Ulcer Study were as follows: Charles Anderson, MD, Madigan Army Medical Center, Tacoma, WA; David Armstrong, DPM, North Chicago VA Medical Center and Rosalind Franklin University, North Chicago, IL; Jose Ayala, DPM, Valley Baptist Hospital, Brownsville, TX; John Bennett, DPM, Des Moines University, Des Moines, IA; Scott Berman, MD, Tucson Vascular Surgery, Tucson, AZ; Peter Blume, DPM, North American Center for Limb Preservation, New Haven, CT; Milton Boden, MD, Aim Research, Atlanta, GA; William Bogey, MD, East Carolina University, Greenville, NC; Marc Dolce, DPM, Cleveland Foot and Ankle Clinic, Cleveland, OH; Kenneth Dolynchuk, MD, Saint Boniface General Hospital, MB, Winnipeg, Canada; Vickie R. Driver, DPM, Madigan Army Medical Center, Tacoma, WA; Tamara Fishman, DPM, Primary Foot Care Center, Incorporated, North Miami Beach, FL; Robert Frykberg, DPM, Carl T. Hayden VA Medical Center, Podiatry Section, Phoenix, AZ; Andrew Gentile, MD, Tucson Vascular Surgery, Tucson, AZ; Gabriel J. Halperin, DPM, Innovative Medical Technologies, Los Angeles, CA; Allen Holloway, MD, Maricopa Medical Center, Phoenix, AZ; John Lantis, MD, Saint Luke's Roosevelt, New York, NY; Brock Liden, DPM, Circleville Foot and Ankle, LLC, Circleville, OH; Jeffrey Page, DPM, Carl T. Hayden VA Medical Center, Podiatry Section, Phoenix, AZ; Marc Passman, MD, Vanderbilt University Clinical Trials Center, Nashville, TN; Wyatt Payne, MD, Bay Pines Veterans Affairs Medical Center, Bay Pines, FL; Alexander Reyzelman, DPM, Bay Area Foot Care, Castro Valley, CA; Bret Ribotsky, DPM, Podiatric Success, Inc., Boca Raton, FL; Bhavesh Shah, DPM, South Texas Foot Institute, Poth, TX; David Skrobot, DPM Genesis Health Care System, Zanesville, OH; Rodney Stuck, DPM, Hines Veterans Affairs Hospital, Hines, IL; Arthur Tallis, DPM, Hope Research Institute, Phoenix, AZ; Mike Vaardahl, DPM, Banner Health at North Colorado Medical Center, Greely, CO; Jodi Walters, DPM, Southern Arizona Veterans Affairs Medical Center, Department of Sur-

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