Matched-cohort study comparing bioactive human split-thickness skin allograft plus standard of care to standard of care alone in the treatment of diabetic ulcers: A retrospective analysis across 470 institutions

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ABSTRACT

This retrospective, matched-cohort study analyzed 1,556 patients with diabetic ulcers treated at 470 wound centers throughout the United States to determine the effectiveness of a cryopreserved bioactive split-thickness skin allograft plus standard of care when compared to standard of care alone. There were 778 patients treated with the graft in the treatment cohort, who were paired with 778 patients drawn from a pool of 126,864 candidates treated with standard of care alone (controls), by using propensity matching to create nearly identical cohorts. Both cohorts received standard wound care, including surgical debridement, moist wound care, and offloading. Logistic regression analysis of healing rates according to wound size, wound location, wound duration, volume reduction, exposed deep structures, and Wagner grade was performed. Amputation rates and recidivism at 3 months, 6 months, and 1 year after wound closure were analyzed. Diabetic ulcers were 59% more likely to close in the treatment cohort compared to the control cohort ($p = 0.0045$). The healing rate with the graft was better than standard of care across multiple subsets, but the most significant improvement was noted in the worst wounds that had a duration of 90-179 days prior to treatment ($p = 0.0073$), exposed deep structures ($p = 0.036$), and/or Wagner Grade 4 ulcers ($p = 0.04$). Furthermore, the decrease in recidivism was statistically significant at 3 months, 6 months, and 1 year, with and without initially exposed deep structures ($p < 0.05$). The amputation rate in the treatment cohort was 41.7% less than that of the control cohort at 20 weeks (0.9% vs. 1.5%, respectively). This study demonstrated that diabetic ulcers treated with a cryopreserved bioactive split-thickness skin allograft were more likely to heal and remain closed compared to ulcers treated with standard of care alone.

INTRODUCTION

Diabetic ulcers are among the most difficult types of wounds to treat, because the number and variety of comorbidities can be substantial, also making it difficult to conduct randomized, prospective studies that are reflective of treatment effects on patients in the real-world setting. For example, numerous studies will exclude excessively large wounds, wounds with exposed muscle and tendon, and wounds from patients who are morbidly obese, have markedly elevated HbA1C, or are smokers.[1–4] In the real world, however, most patients with diabetic ulcers have one or more of these issues present. In a review of randomized controlled trials (RCTs), as many as 50% of the patients with

AATB	American Association of Tissue Banks
AE	adverse event
BMI	Body Mass Index
BSA	bioactive split-thickness skin allograft
CTP	cellular and/or tissue-based products
DFU	diabetic foot ulcer
EMR	electronic medical record
FDA	United States Food and Drug Administration
ITT	intent-to-treat
PAR	percent area reduction
RCT	randomized controlled trial
SD	standard deviation

diabetic foot ulcers (DFUs) normally seen in a clinical setting would likely have been excluded from 15 out of 17 trials.[1] The exclusion of clinically relevant aspects related to the etiology of DFUs also results in unrealistically high healing rates.[2]

Well-conducted matched-cohort studies using real-world, registry data can provide critical insights that cannot be determined from an RCT.[3,5]By matching patient characteristics in the control and study cohorts, one can determine if a study treatment is potentially beneficial on patients in standard clinical practice. Analysis of big registry data extracted directly from electronic health records minimizes bias by ensuring accurate point-of-care data capture, while preventing post-hoc vetting of outcomes, resulting in more realistic wound outcomes and high quality and reliable data.

For over 100 years, human skin allografts have been used in wound healing and have been considered the standard of care.[6–8] Forty years ago, there was a boom in CTPs in wound care following concerns over limited availability of tissue, disease transmission, and unsophisticated processing techniques.[6] Thousands of human organ transplantations are now safely done each year because of the improved donor selection and procurement processes and advanced processing techniques.

Bioactive skin allograft (BSA) is a cryopreserved human split-thickness allograft that contains living cells, signaling molecules, and a native human, vascularizing extracellular matrix.[9,10] The tissue is procured from an organ donor within 24-hours postmortem in compliance with strict industry standards developed by the FDA and the American Association of Tissue Banks (AATB). The donor criteria for BSA surpass the FDA and AATB criteria, with BSA created from less than 2% of donated tissue. No disease transmission has been reported. After procurement, a series of antibiotics cleans the allograft, and proprietary processes are used to cryopreserve the final product. Both an autograft and a living human skin allograft will vascularize, but while the former takes permanently, the host removes the epidermal cells and antigenic components of the BSA 7-14 days post application, while retaining and incorporating the dermal scaffold and collagen matrix.[6] The dermal scaffold resolves tissue defects, and cellular and molecular activity further promotes wound healing.

Over the past decade, BSA has shown to be safe and effective on DFUs, venous leg ulcers, and wounds with exposed structures.[10–15] We report herein a very large, matched-cohort, multicenter study that determined the effectiveness of the BSA plus standard of care on diabetic ulcers when compared to standard of care alone.

MATERIALS AND METHODS

Study design and population

In this retrospective, matched-cohort study that compared the effectiveness of BSA (TheraSkin; SolSys Medical, Newport News, VA) on diabetic ulcers to standard of care alone, we analyzed data collected from electronic medical records (EMR) of patients visiting outpatient wound care centers managed by a large wound-management company (Healogics, Jacksonville, FL) between January 1, 2012 and October 25, 2018. Clinicians at these centers are trained in a standardized evidence-based approach to wounds that starts with a diagnostic work-up summarized in a 9-step algorithm; the company also provides clinical practice guidelines for clinicians to follow through the treatment course.

This study adhered to the 1975 Declaration of Helsinki. The Quorum Review IRB approved this study and determined that the retrospective analysis of HIPAA–deidentified data was exempt from patient consent requirements. Description of the study and its analysis followed the STROBE guidelines.

The patient data from all participating institutions were collected in the same company-proprietary EMR to ensure reporting consistency. Data were extracted from an initial pool of 650,309 diabetic ulcers treated at 470 wound care centers located within the United States. Analysis followed an agreed-upon statistical analysis plan (SAP). We selected ulcers that had been treated with either BSA (treatment cohort) or standard of care alone (control cohort). Table 1 provides the detailed inclusion and exclusion criteria. After excluding ineligible patients and those with significant missing data (i.e. wound characteristics) and/or lack of treatment documentation, we were left with data from 126,888 patients (126,864 patients treated with standard of care and 778 patients treated with BSA) (Figure 1).

We defined standard of care as local wound care consisting of debridement, offloading, and the application of any type of nonbiologic wound dressings, such as hydrogels, saline-moistened gauze, and antimicrobial dressings. Subjects receiving BSA may have used any or all of the same dressings. In addition, BSA was normally covered with a nonadherent dressing material to prevent it from being pulled off by overlying bandages. In the BSA cohort, subjects received the product at the physician's discretion, and application was performed in accordance with the manufacturer's recommendations for preparation.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults aged ≥18 years • Diabetic foot ulcer, Wagner grade 1-4 present for ≥30 days on patients diagnosed with Types 1 and 2 diabetes • Ulcer located on foot, leg, or toe • Wound area ≥ 1 cm^2 and ≤ 50 cm^2	• Ulcers treated at skilled nursing facilities • Ulcers treated with advanced biological products other than BSA • Patients in the control cohort who received any cellular and/or tissue-based products • Patients that demonstrated 50% or more closure of their wounds 4-weeks prior to the study treatment period

BSA = Bioactive split-thickness skin allograft.

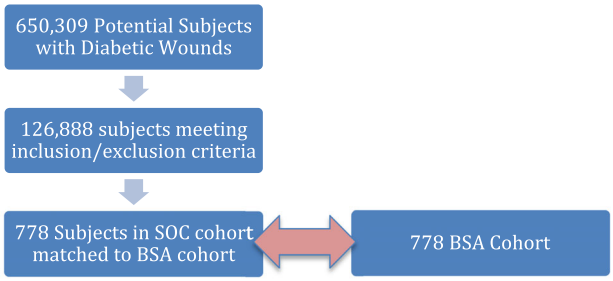

Figure 1. Strategy for initial patient selection. [Color figure can be viewed at wileyonlinelibrary.com]

PROPENSITY SCORE MATCHING TO GENERATE CONTROL COHORT

In order to determine if there were any benefits associated with the treatment of diabetic ulcers with BSA, we used propensity-matched cohorts to ensure that the treatment and control groups had similar characteristics. The 778 wounds treated with BSA were matched in pairs to 778 wounds from the sample of 126,864 diabetic ulcers treated with standard of care using propensity score matching for the following 8 variables (Tables 1 and 3).

- Wound area (cm^2)
- Wound depth (mm)
- Wound duration (the number of days that the wound was present prior to initiation of treatment in the study; for the BSA cohort, the time was measured up until initial treatment with BSA; in the control cohort, the time was measured up until initiation of standard of care at one of the study centers).
- Wound stage (using the Wagner classification; Table 2)[16]
- Wound location (limited to the toes, anywhere on the foot but not including the ankle, and/or lower leg)
- Whether the patient was palliative
- Number of complicating comorbidities
- BMI.

Complications and comorbidities included were Alzheimer's disease, coronary artery disease, cellulitis, chronic obstructive pulmonary disease, congestive heart failure, end stage renal disease, immunosuppressive conditions, morbid obesity, peripheral vascular disease (arterial and venous), smoking status, and venous insufficiency.

Propensity-matched cohorts were constructed using the Matchit package version 3.0.2 in R (R Foundation, 2018). The propensity is built on a logit-linked generalized linear model, and then matching is constructed using the nearest neighbor method. The overall mean distance reduction is measured to identify sufficient fit.

The nonmatched data had a mean difference in distance of 0.0019 across all eight variables, with a maximum empirical quantile function distance of 0.7124. In comparison, the matched pairs had a mean difference in distance of <0.0001 with a maximum empirical quantile function distance of 0.01, indicating the control cohort was generally well-matched to the characteristics of the BSA cohort vs. the nonmatched data. Table 3 compares the matched attributes

Table 2. Comparison of matched attributes among final diabetic ulcer cohorts

	After matching		
Variables of interest	Treatment $N = 778$	Control $N = 778$	Statistical significance
Gender			
Male	66.6%	64.3%	0.3430
Race			
White	67.10%	63.11%	0.0988
Black	12.98%	15.04%	0.2419
Other	19.92%	21.85%	0.3492
Mean age (years)	65.67	62.95	<0.0001
Wound area at first assessment (cm^2)	13.08	13.46	0.2987
Wound depth at first assessment (mm)	3.73	3.65	0.0661
Wound duration at first assessment (days)	124.84	124.85	0.0016
Stage			
Grade 1	31.23%	29.56%	0.4741
Grade 2	49.10%	51.16%	0.4166
Grade 3	15.81%	15.42%	0.8322
Grade 4	3.86%	3.90%	0.9674
Location			
Lower leg	21.21%	22.37%	0.5796
Foot	68.76%	68.12%	0.7860
Toe	10.03%	9.51%	0.6021
Palliative patient	2.40%	1.80%	0.8392
Number of complicating comorbidities	0.47	0.46	0.4798
Patient BMI	24.98	22.15	<0.0001

BSA = bioactive split-thickness skin allograft.

Table 3. Wagner classification of diabetic foot ulcerations[17]

Grade	Description
0	Intact skin
1	Superficial ulcer extending through skin or subcutaneous tissue
2	Ulcer that extends to deep fascia including tendon, bone, or joint capsule
3	Deep ulcer in the presence of an abscess or osteomyelitis
4	Gangrene is present in toes or forefoot
5	Gangrene is present in midfoot or hindfoot

across the 2 cohorts. The BSA cohort matching improved imbalances among the nonmatched vs. the matched pairs for all variables except for palliative patients, although the percent of palliative patients is not significantly different across the groups. While the disparity in BMI improved with propensity matching, a significant difference still remained between groups with those in the BSA cohort having a significantly higher mean BMI than those in the control cohort (p <0.002) (Table 3).

Patient enrollment starting points

Prior to their enrollment, all subjects included in this study were given a 4-week window of observation while receiving standard of care. Potential study subjects who were in active treatment or demonstrated 50% or more closure of their wounds within that initial time period were excluded from analysis. For the control cohort, time to closure was measured from the completion of the 4-week observation period. For the BSA cohort, time to closure began with the first date of BSA application. The modified intent-to-treat (MITT) population included all wounds in both cohorts that were enrolled in the study after the 4-week observation period. The completed treatment population included all wounds that completed the study.

Healing rates

Healing was defined as full epithelialization of the wounds with no open areas. Among the MITT population, we also analyzed the mean percent area reduction (PAR) of the wounds; mean PAR was based on an assessment of all wounds included in this study except those that grew to more than four times the original size over the course of treatment. Numerous healing factors were analyzed, including the percentage of total wound closure, wound duration prior to enrollment, and the initial Wagner grade. Wagner grades (1–4) were analyzed both collectively and individually among the cohorts. The closure rate was also examined based on wound location (toe, foot, or lower leg). Additionally, the disposition of the patients after 20 weeks of treatment (i.e., discharge outcomes), amputation rates (including all amputations from partial toe to below the knee) within the first 20 weeks after treatment initiation, and recidivism (recurrence) rates at 3 months, 6 months, and 1 year were examined in each cohort. Wounds that initially had exposed deep structures (i.e., muscle, tendon, and/or bone) were analyzed separately for recidivism, as these wounds are more difficult to achieve and maintain closure. For the BSA cohort only, the mean number of allografts required to achieve closure was also analyzed.

Additional statistical analysis

Descriptive statistics were used to test frequencies of patient, wound, and outcome measures. The mean and standard deviation (SD) were calculated for continuous measures. A comparative analysis was performed to determine the time to heal in both the MITT and completed treatment populations. For nonnormally distributed values, nonparametric analyses were performed, including χ^2 tests for proportions and Mann Whitney U tests for comparison of continuous variables. A logistic regression model was calculated to determine the overall odds of healing for ulcers in both cohorts; a Hosmer-Lemeshow test validated the model's fit.

Cox proportional hazard models were constructed to account for confounding factors when determining the effect of BSA on time to heal. These models were fit using the propensity-matched data sets using the survival package in R. Initial models were constructed with no covariates to generate Kaplan-Meier curves. Subsequent models were constructed with the following covariates and their 2-way interactions:

- Wound location
- Wound stage
- Wound volume at initial assessment (small: <5 cm^2, average: 5-40 cm^2, or larger: >40 cm^2)
- PAR at 4 weeks (significantly decreasing: >2.5% area reduction, stagnant: (±2.5% change in area from initial assessment), or significantly increasing (>2.5% increase in area)

Final models that retained only significant variables were constructed. The model's fit was measured using R^2 and model concordance between predicted and actual values. The likelihood ratio, Wald, and Score tests were used for each model's fit.

Model coefficients were analyzed. An analysis of variables that significantly affect the time to heal was done. Additionally, a data set consisting of predictions for each of the members of the Cartesian product of the regressors was created. From this data set, Kaplan-Meier curves for different scenarios were created and analyzed.

RESULTS

Overall healing rates

There were 778 subjects enrolled into each cohort. In the BSA cohort, 778 subjects comprised the MITT population and 459 subjects (59%) comprised the completed treatment population. In the control cohort, 778 subjects comprised the MITT population and 376 subjects (48.3%) comprised the completed treatment population. Figure 2 provides the reasons for why subjects did not complete the study. Based on the MITT population, there was a statistically significant difference in the overall healing rate between the control cohort and the BSA cohorts (55.9% vs. 66.8%, respectively, p = 0.0045). Table 4 provides more detailed breakdowns of wound closure rates.

Healing rates by Wagner grade

All analyzed wounds were classified as Wagner grades 1-4 (Table 3). Healing rates were significantly greater in the BSA cohort with grade 4 ulcers (Control: 40.0% vs. BSA: 66.7%, p = 0.04) (Table 4). The overall mean number of BSA allografts required to achieve closure in the BSA cohort was 2.9 applications (SD: 2.2). The mean number of allografts for Grade 1 ulcers was 2.7 (SD: 2.0), for Grade 2 ulcers was 3.1 (SD: 2.3), for Grade 3 ulcers was 2.9 (SD: 2.0), and for Grade 4 ulcers was 2.5 (SD: 1.9).

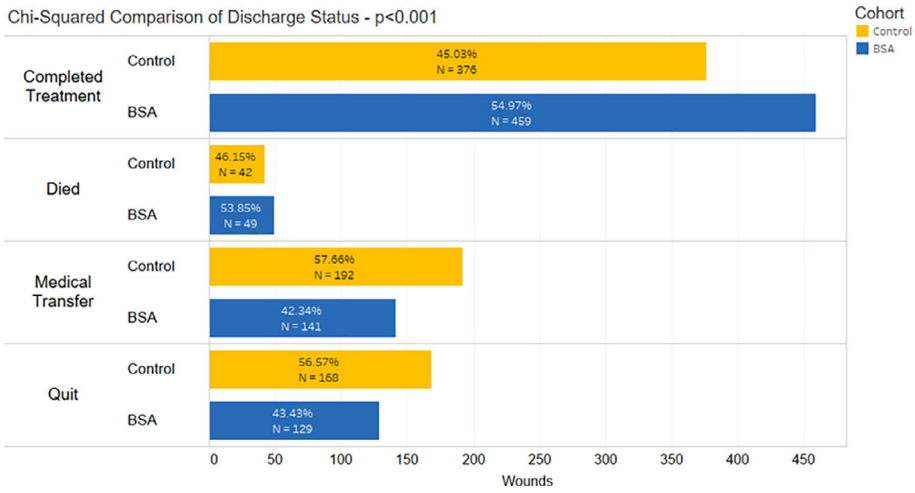

Figure 2. Treatment discharge outcomes-diabetic ulcers.

Healing rates by wound duration

The duration of wounds ranged from <90 days to over 2 years in both cohorts (Table 4). This difference in healing rates was statistically significant for ulcers that had a duration of 90-179 days (Control: 46% vs. BSA: 65.1%, $p = 0.0073$). For wounds between 90 and 179 days old, an average of 2.84 applications of BSA were used.

Healing rates by location

There was no difference in closure rate of wounds by location comparing the control vs. BSA cohort *Healing rates in wounds that had exposed muscle, tendon, and/or bone is exposed*

There were 548 ulcers in the control cohort and 535 ulcers in the BSA cohort that had exposed structures. Among these

Table 4. Detailed wound outcomes, by cohort

Parameter	Control, *n* (%)	BSA, *n* (%)	*p* value
Percent of healed wounds	59.9% (466/778)	66.8% (520/778)	0.0045
Percent of healed wounds, by Wagner Grade[a]			
Grade 1	66.1% (152/230)	74.1% (180/243)	0.058
Grade 2	60.6% (241/398)	64.7% (247/382)	0.024
Grade 3	50.8% (61/120)	59.4% (73/123)	0.18
Grade 4	40.0% (12/30)	66.7% (20/30)	0.04
Percent of healed wounds, by duration prior to study treatment			
<90 days	65.9% 391/593	69.7% (389/558)	0.17
90-179 days	46% (40/87)	65.1% (71/109)	0.0073
180 days – 1 year	38.9% (14/36)	57.1% (32/56)	0.089
1-2 years	40.0% (14/35)	59.3% (16/27)	0.14
>2 years	25.9% (7/27)	42.9% (12/28)	0.19
Percent of healed wounds, by location			
Foot	57.2% (303/530)	63% (337/535)	0.053
Lower leg	68.4% (119/174)	77.58% (128/165)	0.15
Toe	59.5% (44/74)	70.5% (55/78)	0.058
Percent of healed wounds that had exposed, deep structures	57% (312/548)	63.6% (340/535)	0.036
Mean percent area reduction (SD)	-68.8% (0.69)*	-76.8% (0.60)[†]	0.017

BSA = bioactive split-thickness skin allograft.
*Based on 742 ulcers.
[†]Based on 730 ulcers.

Table 5. Other outcomes, by cohort

Parameter	Control, % (*n*)	BSA, % (*n*)	*p* value
Amputation rate	1.5 (12/778)	0.9 (7/778)	0.25
Rate of patient death	5.4 (42/778)	6.3 (49/778)	0.45

ulcers, a statistically significant number of ulcers closed in the BSA cohort compared to the control cohort (63.6% vs. 57%, $p = 0.036$) (Table 4). Wounds with exposed muscle, tendon, or bone received an average of 2.98 applications of BSA.

Mean PAR

The mean reduction in PAR for wounds treated with BSA was 76.8% (SD: 0.69), which is significantly higher than the control cohort, which had a mean PAR of 68.9% (SD: 0.60) ($p = 0.005$) based on a Mann Whitney U Test (Table 4).

Amputation rates following treatment

The amputation rates were less than 2% in the first 20 weeks following initiation of treatment (Table 5). There was no statistically significant difference in amputation rate between the two groups.

Other outcomes

There was no statistically significant difference in the rate of subjects who died during the study between the groups (Control: 5.4% vs. BSA: 6.3%) (Figure 2; Table 5). Although there was a higher percentage of subjects who discontinued treatment prior to healing (21.6% vs. 16.5%) and a higher percentage of subjects requiring additional transfer for additional medical care in the control cohort (24.7% vs. 18.1%), these differences were not statistically significant. Subjects in the BSA cohort were also significantly more likely to be compliant with treatment from initiation through completion (59.0% vs. 48.3%, $p < 0.0001$), significantly less likely to have a worsening of their health that required a medical transfer (i.e., to a hospital or skilled nursing facility) (18.1% vs. 24.7%, $p = 0.012$), and significantly less likely to quit their treatment regimen (16.6% vs. 21.6%, $p = 0.0019$), when compared to subjects in the control cohort.

Recidivism

There were 651 ulcers with recidivism data available in the control cohort and 684 in the BSA cohort. For all time points for all wounds, there was a statistically significant reduction in recidivism rates when BSA was used vs. standard of care (Table 6). There were 450 ulcers that had exposed structures with recidivism data available in the control cohort and 451 in the BSA cohort. For all time points for wounds with exposed structures, the BSA cohort had a statistically significantly reduced recidivism rate compared to the control cohort ($p < 0.05$) (Table 6).

Table 6. Recidivism rates, by cohort

Time period posthealing	Control, *n* (%)	BSA, *n* (%)	*p* value
All healed diabetic ulcers			
3 months	27.8% (181/651)	23.1% (158/684)	0.049
6 months	33.0% (215/651)	25.9% (177/684)	0.0042
1 year	40.2% (261/651)	35% (239/684)	0.042
Healed diabetic ulcers that had exposed, deep structures			
3 months	26.7% (120/450)	19.7% (89/451)	0.014
6 months	32.2% (145/450)	22.4% (101/451)	0.0009
1 year	40.3% (181/450)	31.4% (141/451)	0.0053

BSA = Bioactive split-thickness skin allograft.

Overall odds of healing

A logistic regression model was calculated with a Hosmer-Lemeshow *p*-value of 0.45, indicating that the null hypothesis should not have been be rejected and the model was of a sufficient fit. The odds of ulcers in the BSA cohort achieving wound closure was 1.59 (CI of odds ratio (1.34,1.84)) compared to 1.00 in the control, with increasing log odds by 0.47 ($p = 0.0002$). This translates to a 59% increase in the odds of healing in the BSA cohort.

Time-to-heal

Figure 3 shows Kaplan-Meier time-to-heal curves for all diabetic ulcers and for diabetic ulcers of Wagner grade 4 located on the foot. Though the Cox proportional hazard models did identify variables significantly impacting the percent of wounds open at *n* weeks, the use of the BSA does not create a statistically significant difference in time-to-heal.

The full Cox proportional hazard model for diabetic ulcers had a concordance of 0.627 and an R^2 of 0.121. The Wald test, likelihood ratio test, and logrank test all had *p*-values of less than 0.0001 with 43 degrees of freedom.

DISCUSSION

In this study, 778 subjects treated with BSA were drawn from 470 wound centers and were precisely matched by multiple parameters (including wound size, location, Wagner grade, and duration prior to treatment, and general health parameters of the patients) to a cohort of 778 subjects treated with standard of care, drawn from a pool of 126,864 potential patients. In this way, the study presented here utilizes a large number of patients with ulcers whose primary difference in outcomes can be attributed to whether they were treated with BSA or standard of care. The matching was statistically verified (Table 3), and the very large sample size included is particularly useful for exploring larger, more severe wounds not normally included in smaller RCTs,[1–4] as well as allowing for analysis of various key outcomes in a variety of subsegments, including wound duration, location, grade, and ultimate outcomes. Furthermore, the strict inclusion and exclusion criteria employed in this study helped to reduce the potential influence of confounding variables. The

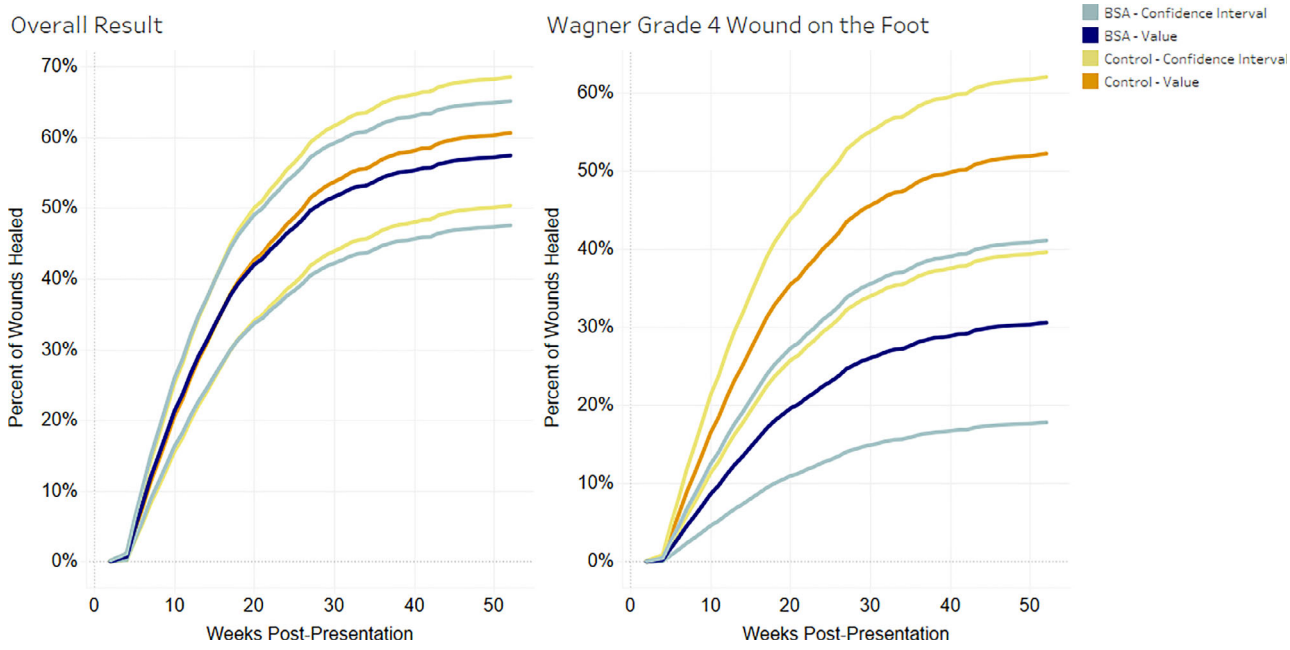

Figure 3. Percentage of diabetic wounds closed; (a) overall results; (b) results for Wagner grade 4 foot ulcers

results clearly demonstrate that there is a statistically significant advantage to treating diabetic ulcers with BSA in nearly every category and scenario when compared to standard of care. While other CTP therapies have been shown to be effective in the management of DFU, our study shows that BSA application is associated with improved clinical outcomes and lower recidivism in severe DFU with less than three applications.

The advantage of the EMR database utilized in this study is that data collection and reporting was consistent across all 470 institutions. More importantly, each company-managed center is trained in a standardized diagnostic and treatment pathway, which helps to decrease variations in care.

On average, patients treated with BSA required 2.9 grafts to achieve closure. In general, this was not a simple population to treat, with an average initial wound size of over 13 cm^2 and an average initial wound duration of approximately 4 months. Multiple regression analysis demonstrated that wounds treated with BSA were 59% more likely to heal than those treated with standard of care. Furthermore, most of the wounds in study had exposed muscle, tendon, and/or bone (control: 70.4%; BSA: 68.8%). This is particularly important because data show these wounds are associated with higher amputation rates.[16,18] Until now, few CTPs have been clinically proven to be effective in this more complex subset of diabetic ulcers.[21]

This study also showed a statistically significant improvement in recidivism rates after 3 months, 6 months, and 1 year among wounds treated with BSA compared to wounds treated with standard of care. In 2017, Armstrong et al. reported that nearly 40% of diabetic ulcers reoccurred within 1 year after healing,[19] which was very close to the 40.2% recidivism rate observed at 1 year in the control cohort (Table 5). Subjects treated with BSA demonstrated a 12% lower recidivism rate after 1 year. Based on this analysis, not only are wounds treated with BSA more likely to close, they are more likely to stay closed on a longer term basis. This was also true for wounds with exposed deep structures. One possible explanation for the reduced recidivism associated with BSA could be due to mechanism of action of BSA, which in addition to living cells and signaling molecules, also provides a native human extracellular matrix structural scaffold that becomes incorporated into the wound bed.[6]

The healing rate with BSA from this study is in line with rates reported in previous studies involving BSA. In a previous retrospective study of 54 Wagner 1 and 2 DFUs, the wounds in the 4th quartile (the largest fourth of the wounds tested) demonstrated closure rates of 44.4% after 12 weeks and 71.43% after 20 weeks.[10] This rate compares with the current study's closure rate of 66.8% after 20 weeks. However, the severity of the wounds in the current study was greater, with Wagner 3 and 4 ulcers included. Interestingly, the previous study with less severe wounds required 3.2 grafts for wound closure at 20 weeks compared to the 2.9 grafts required in the current study.

A prospective study analyzed the healing rate of large wounds (mean area was 16 cm^2) with exposed muscle, tendon, and/or bone that were treated with BSA.[11] A 93.3% closure rate after 20 weeks was reported, although 24% of the patients also had negative pressure wound therapy at the same time as BSA application.

A randomized prospective study in which BSA was compared to a laboratory-created substitute (Dermagraft) again demonstrated consistent closure rates for DFUs.[12] The mean wound area was 5.45 cm^2. The BSA closed 63.64% of the

wounds with an average closure time of 8.9 weeks, while Dermagraft only closed 33.3% of the wounds after 12 weeks.

One limitation of this study was that all data were extracted retrospectively from EMRs, which could lead to some potential inaccuracies if a provider did not document the condition and treatments of the wound properly. We have little direct insight to the level of compliance provided by study participants. Another study limitation was insufficient data were available in the EMRs to factor limb vascularity and HbA1c into the matching scheme. It is possible that these factors may have varied between the cohorts. Also, the tendency toward treating patients with BSA after failure with standard of care may also have diminished the quality of the subject match. Another consideration is the application regimen used by the clinicians treating with BSA. Although the average number of grafts used is very similar to prior studies, it is unclear if the frequency of application and the use of dressing materials and cleansing agents were uniform from site to site. Amputation rates among patients with DFUs is a reflection of the severity of the ulceration, speed of wound closure, vascular status, patient compliance, infection, and a host of other factors that play a role in wound healing.[16,18] Although rates can be measured comparatively using EMR data by creating treatment groups, absolute rates are far lower than those reported in prospective trials because it is hard to capture outcomes of patients transferred to other facilities in which procedures take place. Finally, while we did an exhaustive matching process to ensure the similarities between groups, all factors cannot be measured.

Another limitation is potentially the lack of direct comparison to other advanced treatment modalities for diabetic wounds. For new biological products, the FDA requires direct comparison to current SOC. From a payor perspective, such an analysis could prove helpful in determining reimbursement. However, the current data does not allow for such a direct comparison. Furthermore, other advanced therapies such as negative pressure wound therapy and hyperbaric oxygen therapy (HBOT) were used at the discretion of individual clinicians; their use did not statically alter the results of this study.

In conclusion, this large, matched-cohort study across 470 institutions demonstrates that there is a statistically significant advantage to treating diabetic ulcers with BSA over standard of care. The evidence presented here indicated that BSA is appropriate for wounds that are Wagner grade 1-4 and is efficacious in cases where there is exposed muscle, tendon, and bone. Furthermore, the study demonstrated that the recidivism rate is significantly reduced in wounds treated with BSA. The study outcomes are consistent with both prior retrospective studies and randomized prospective studies previously published and provide evidence of the clinical benefit of BSA in a complex patient population in a standardized clinical practice that cannot be captured by more strictly controlled trials.

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CONFLICTS OF INTEREST

Solsys Medical provided the funding to Healogics Research Services for the access to the iHeal EMR database and subsequent data analysis. Dr. Hanna Gordon and Katie Bakewell (NLP Logix) performed the statistical analysis as representatives of Healogics Research Services. Dr. Marissa Carter (Strategic Solutions) is a consultant to Solsys Medical. The other authors have no relevant conflict of interest to disclose.

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