

## A Prospective Comparison of Diabetic Foot Ulcers Treated With Either a Cryopreserved Skin Allograft or a Bioengineered Skin Substitute

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**Abstract:** *Background.* It was hypothesized that the rate of wound closure and the number of grafts required will be the same when treating diabetic foot ulcers with TheraSkin®, a cryopreserved split-thickness skin allograft (SSA), as compared to Apligraf®, a bioengineered skin substitute (BSS). *Methods.* A prospective study using sequentially enrolled patients seen in a large podiatric practice encompassing multiple locations was conducted. Patients were sequentially enrolled and treated with either BSS or SSA. All other factors of treatment were standardized across the patient population. Data analysis included an analysis of co-factors in each group in order to determine if anything else may have influenced the outcomes. *Results.* Data from 17 wounds (16 patients) treated with BSS and 12 wounds treated with SSA were analyzed. The average wound sizes were comparable, as was the average number of applications utilized. These data revealed that 41.3% of the wounds treated with BSS closed within 12 weeks, as compared to 66.7% of the wounds treated with SSA. At 20 weeks, 47.1% of the wounds in the BSS group closed, while 66.7% of the SSA wounds closed. There were a comparable number of adverse events in each group, none of which were a direct result of the biologic material being used. *Conclusion.* SSA resulted in a higher percentage of wounds closing after 12 and 20 weeks, as compared to wounds treated with BSS. There were no adverse events noted that were directly related to either graft material.

**F**oot ulcers continue to be one of the most serious complications of diabetes. Although their etiology is multifactorial, the general approach to treatment will include relief from mechanical pressure, optimization of blood flow, reduction of bacteria load, and careful regulation of blood glucose. Regardless of the many factors that contribute to the development of foot ulcers, treatment has historically centered on the use of protective shoe gear and local wound care including debridement and application of specialized dressings.

Sheehan et al<sup>1</sup> reported that wounds that fail to progress during the first month of treatment rarely progress to full closure unless more aggres-

sive therapy is attempted. Partially in response to this, and other similar studies, many wound care specialists have turned to advanced biologics in their treatment regimen. Various types of decellularized collagen, recombinant growth factors, and biologic skin substitutes, such as Apligraf® (Organogenesis, Canton, MA) and DermaGraft® (Advanced Biohealing, Westport, CT), are commonly used early in the treatment process to stimulate the wound to achieve an aggressive response.

Although numerous studies have demonstrated the efficacy of each of these advanced biologics, the high cost associated with these treatments has forced the clinician to ask whether or not the sometimes modest gains in the closure rate and healing time are justified. Langer and Rogowski<sup>2</sup> pointed out that there might be a place for these treatments for a chronic wound that is otherwise unresponsive to conventional treatments. However, the trend has been to introduce advanced biologics more readily, and this may ultimately drive costs higher since the cost of the biologic is spread out over fewer visits, which increases the ratio of time to heal to treatment expenses. There have also been a variety of analyses that consider quality of life and the potential value of more rapid healing, as well as reduced infection risks. Ultimately, costs associated with the use of an advanced biologic must be weighed against the value of saving a leg, and most clinicians and patients agree that even small advantages are worthwhile.

Despite the widespread use of advanced biologics for the treatment of diabetic foot ulcers, data comparing one modality to another are scarce. Landsman et al<sup>3</sup> compared a biologic skin substitute to a decellularized collagen material and found no statistically significant difference in outcomes. The authors hypothesized that although the two biologics worked by different modes of action, the study indicated that there was no significant difference in outcomes.

The current investigation is a prospective, randomized study comparing a bioengineered skin substitute to a human skin allograft. Apligraf is a bioengineered skin substitute (BSS) that is composed of fibroblasts and keratinocytes grown on a bovine collagen substrate. The material is delivered to the clinician in a special container and contains living cells that can be applied directly to the wound. The second active biologic is TheraSkin® (Soluble Systems, Newport News, VA), a cryopreserved split-thickness human skin allograft (SSA). SSA is harvested in 24 hours or less (post-mortem) and is cryogenically processed to preserve the living cellular elements. Af-

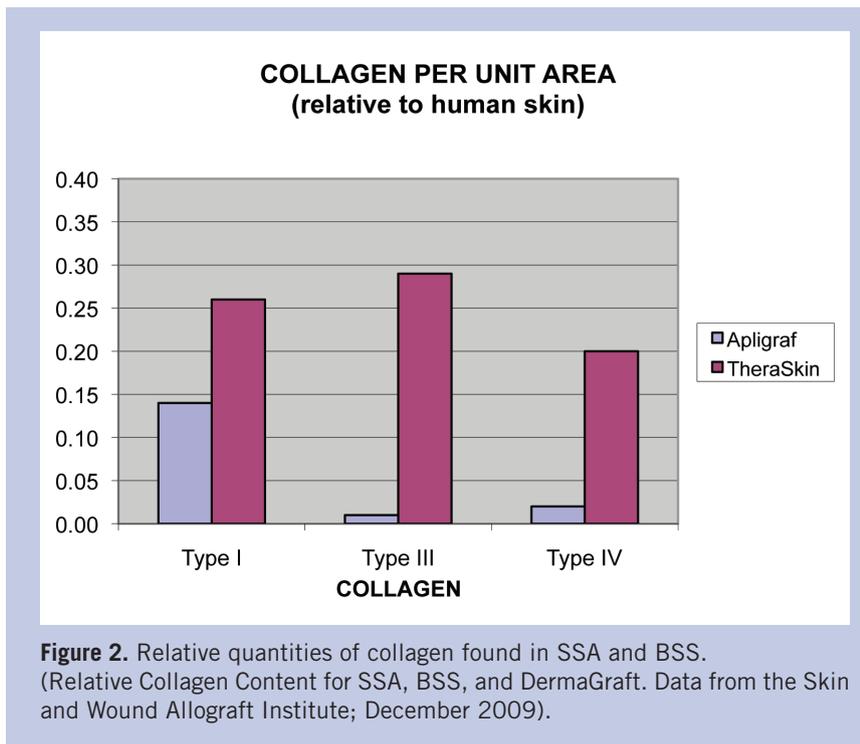
Growth Factors	Cytokines	Collagen
PDGFA	TNF	Type I
PDGFD	IL1a	Type III
VEGFA	IL1B	Type IV
VEGFD (FiGF)	IL2	Type V
EGF	IL3	Type VI
IGF	IL4	Type IX
TGFA	IL5	Type X
FGF2	IL6	Type XI
TGFB1	IL12	Type XII
TGFB3	IL13	Type XIV
HGF	IL16	Type XV
BMP7	IL17A	Type XVII
	IL18	Type XVIII
	IL25, 27, 32	Type XX

**Figure 1.** Growth factors, cytokines, and collagen present in SSA cryopreserved split-thickness skin allograft.

*Growth factors, cytokines, and collagen found in SSA as determined by independent laboratory testing (University of Albany, Protein Analysis Study, October 2009 and University of Maryland, Institute of Human Virology, Baltimore, MD, March 2010).*

ter confirming the safety of the material, this tissue graft is delivered to the clinician who goes through a simple rinsing process before applying it to the wound. Previous studies have demonstrated that SSA is both safe and effective.<sup>4</sup> SSA contains the full array of growth factors and cytokines normally found in human skin, because it is actual human skin (Figure 1).<sup>5</sup> When compared to BSS, SSA contains a larger amount of key collagens important to wound healing (Figure 2).<sup>5</sup>

The authors hypothesized that the rate of wound closure and the number of grafts required would be the same when treating diabetic foot ulcers with SSA, a cryopreserved split-thickness skin allograft, as compared to BSS, a bioengineered skin substitute. The authors' hope is that this study's outcomes will help clinicians make an informed decision about which advanced biologic will meet their needs when treating difficult diabetic foot ulcers.



#### KEYPOINTS

- Regardless of the many factors that contribute to the development of foot ulcers, treatment has historically centered on the use of protective shoe gear and local wound care, including debridement and application of specialized dressings.
- The authors hypothesized that the rate of wound closure and the number of grafts required would be the same when treating diabetic foot ulcers with SSA, a cryopreserved split-thickness skin allograft (TheraSkin), as compared to BSS, a bioengineered skin substitute (Apligraf).

#### Methods

This clinical trial was a randomized, prospective study. Subjects were sequentially enrolled over a 2-year period from 2008 through 2009. The two cohorts consisted of:

**Apligraf (BSS):** Treated with standard wound debridement as needed and off-loading with a fixed ankle walker. No dressing changes were performed during the first week to allow the graft material to become incorporated on the surface of the wound. Subsequently, dressing changes were performed every other day or on a daily basis, as needed, depending on the extent of wound exudates. The graft was covered with a porous, non-adherent dressing material prior to application of gauze dressing. Each patient could receive up to five BSS

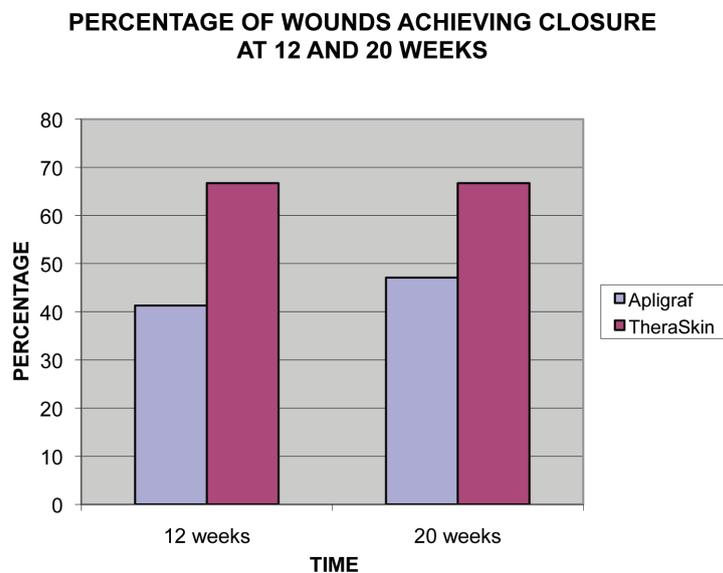
in accordance with the manufacturer's recommendations.

**TheraSkin (SSA):** Treated with standard wound debridement as needed and off-loading with a fixed ankle walker. No dressing changes were performed during the first week to allow the graft material to become incorporated on the surface of the wound. Subsequently, dressing changes were performed every other day or on a daily basis, as needed, depending on the extent of wound exudates. The graft was covered with a porous, non-adherent dressing material prior to application of gauze dressing. Each patient could receive up to five SSA, in accordance with the manufacturer's recommendations.

All patients were drawn from a large, multi-office podiatric practice with several clinicians. An independent institutional review board (IRB), prior to implementation, approved the protocol and informed consent. The study protocol and treatment regimen were reviewed at two clinical investigators' meetings to standardize all wound care.

In order to qualify for participation in this study, all participants had to sign an IRB-approved informed consent, and meet the inclusion/exclusion criteria (Table 1). Patients were followed and data were recorded on a weekly basis for the first 12 weeks, and then bi-weekly through the 20th week. After week 12, data were recorded on a monthly basis until wound closure. Patients were monitored for adverse events at every visit throughout the study. Adverse events were recorded and reported when observed.

Data collection included documentation of clinical appearance, wound measurements (cross-sectional area, depth, and wound stage), and adverse events such as infection or worsening of the wound. A multivariate analysis was used to determine if the two groups were comparable regarding wound characteristics, as well as basic demographics of each group (eg, age, sex). Endpoints were either total wound closure or wound evaluation during week 20. Wound progress was measured using 2 parameters: A) time to closure (ie, full epithelialization), and B) change in wound surface area. The number of grafts necessary to achieve closure was also recorded.



**Figure 3.** Percentage of wounds achieving closure after 12 and 20 weeks.

**Table 1.** Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>Type 1 or 2 diabetes with Wagner 1 or University of Texas 1a ulcer</li> </ul>	<ul style="list-style-type: none"> <li>No evidence of clinical infection</li> </ul>
<ul style="list-style-type: none"> <li>Wound present for at least 4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>No evidence of gangrenous tissue or abscesses</li> </ul>
<ul style="list-style-type: none"> <li>HgA1c &lt; 12</li> </ul>	<ul style="list-style-type: none"> <li>No exposed bone, tendon, or joint capsule</li> </ul>
<ul style="list-style-type: none"> <li>Patient able to comply with standardized off-loading regimen</li> </ul>	<ul style="list-style-type: none"> <li>No ulcers due to non diabetic etiology such as venous leg ulcers, or secondary to radiation or acute trauma</li> </ul>
<ul style="list-style-type: none"> <li>Ulcer between 0.5 cm<sup>2</sup> and 4 cm<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>No topical medications or dressing materials which could alter the graft material</li> </ul>
<ul style="list-style-type: none"> <li>ABI &gt; 0.75</li> </ul>	<ul style="list-style-type: none"> <li>No adjuvant therapy such as hyperbaric oxygen or topical formulations containing growth factors</li> </ul>
<ul style="list-style-type: none"> <li>Palpable pulses on study foot (at least dorsalis pedis or posterior tibial artery)</li> </ul>	<ul style="list-style-type: none"> <li>Wound depth &lt; 9 mm</li> </ul>

## Results

In this study, 29 wounds from 28 patients were assessed according to the study protocol with 17 wounds receiving BSS and 12 receiving SSA. It should be noted that a problem occurred with randomization, which resulted in uneven blocks of patients being enrolled in the two cohorts. Consequently, more subjects were treated with BSS than with SSA. There were no statistically significant differences in the study subject demographics regarding age, BMI, wound location, or sex. Average wound size was 1.89 cm<sup>2</sup> for BSS and 1.82 cm<sup>2</sup> for SSA ( $P = 0.89$ ).

The study evaluated the percentage of wounds that achieved complete closure and the rate of wound closure at each visit. The authors report that 41.3% of the wounds treated with BSS

and 66.7% of the wounds treated with SSA achieved closure at 12 weeks (Figure 3). At 20 weeks, this value increased to 47.1% for BSS and remained at 66.7% in the SSA group since no additional wounds closed between weeks 12 and 20 (Figure 3).

In both groups, most patients received only a single application of either BSS or SSA. The decision to reapply either graft was based on the clinician's assessment of wound progression, as well as the appearance of the previous graft on the wound bed. The average number of BSS applied was 1.53 (SD = 1.65) and the average number of SSA applied was 1.38 (SD = 0.29). Wounds were reassessed on a weekly basis for the first 12 weeks, and then monthly thereafter. The average time to closure in the BSS group was 6.86 weeks (SD = 4.12) and was 5.00 weeks (SD = 3.43) in the SSA group.

**Table 2.** Summary of study results.

Graft	n	% closed at 12 weeks	% closed at 20 weeks	Average no. of grafts (SD)	Time to closure (weeks [SD])
BSS	17	41.3%	47.1%	1.53 (1.65)	6.86 (4.12)
SSA	12	66.7%	66.7%	1.38 (0.29)	5.00 (3.43)

**KEYPOINTS**

- In both groups, most patients received only a single application of either BSS or SSA. The decision to reapply either graft was based on the clinician's assessment of wound progression, as well as the appearance of the previous graft on the wound bed.
- The average number of BSS applied was 1.53 (SD = 1.65) and the average number of SSA applied was 1.38 (SD = 0.29).

There were no unexpected adverse events in this study. The only complications noted were infection and increase in wound size noted in both groups—three patients in the SSA group and 5 patients in the BSS group. One infection in the SSA group required brief hospitalization for antibiotic therapy; the wound went on to heal uneventfully. A summary of data can be found in Table 2.

**Discussion**

In this study, the relative efficacy of SSA and BSS for the treatment of diabetic foot ulcers was examined in a prospective, randomized study using a single group of clinicians. Care was standardized in both groups, and the demographics of the study subjects were found to be comparable between cohorts. Due to an unintentional error in the randomization scheme, more patients were enrolled in the BSS group than in the SSA group. Since the average wound size and subject demographics appear to be statistically indistinguishable between the two cohorts, the investigators believe that this approach to enrollment did not adversely impact the outcomes.

Based on the data from this study, it appears that the use of SSA was more likely to result in wound closure during the first 12 weeks, as compared to comparable wounds treated with BSS. Additionally, wounds treated with SSA closed more quickly and required slightly fewer grafts than wounds treated with BSS.

Although the treatment protocol was otherwise completely uniform across both groups, the decision to reapply either graft was solely at the discretion of the clinician who was treating the wounds, which resulted in a less than average number of grafts necessary to achieve closure in both BSS and SSA cohorts. A review of the literature demonstrates that more than 1 graft is normally used with either product when treating diabetic foot ulcers. A previous study with SSA demonstrated that an average of 2.03 grafts (SD = 1.47) and 3.23 grafts (SD = 2.77) were needed for closure at 12 and 20 weeks, respectively, but wounds in the previous study included larger and deeper

wounds than those in the present study.<sup>4</sup> A previous study with BSS demonstrated that an average of 4 grafts was needed, but this study also used larger wounds than the present study.<sup>6</sup>

Although both products contributed to closure in a significant number of cases, the SSA closed a greater percentage of the wounds and closed them more rapidly than BSS. The authors believe that there are several factors that may account for this difference. The BSS contains adult bovine collagen, which is used as a substrate for supporting the cellular components. Conversely, SSA is produced from a human split-thickness skin graft, which contains the full variety of collagen materials normally found in human skin. Independent verification of this showed that the quantity and variety of collagen found in SSA is greater than that found in BSS (Figure 3).

SSA has a fully developed extracellular matrix that includes significant deposits of growth factors and cytokines. In comparison, the extracellular matrix of BSS is developed *in vitro*, and has an immature complement of growth factors and cytokines due to a lack of prolonged cellular deposition and the use of neonatal tissues.

BSS contains two lines of cells produced from neonatal foreskin. These keratinocytes and fibroblasts are deposited on the bovine substrate and are thought to proliferate in culture through to the time of implantation on the wound surface. SSA also contains living cells at the time of tissue harvest, which are cryopreserved prior to application of the graft to the wound bed. In both cases, it is important to recall that when these cells are applied to the wound they are always considered to be “non-self,” and will always trigger an immune response that leads to apoptosis and disassembly into component parts. It remains unknown what percentage of cells are still alive at the time of implantation with either material, or what the rate of cellular death is in the days following implantation.

Although this study was not designed to consider costs, there are several obvious differences in this respect. The cost of the SSA is around half the cost of BSS for a similar sized piece of material. The value of faster closure associated with SSA may also have benefits in terms of costs and quality of life.

**Conclusion**

In the current prospective study, SSA closed a greater percentage of wounds than BSS and did so at a faster rate. Head-to-head comparisons such as this are unusual. The current format facilitated a meaningful comparison based on the otherwise uniform nature of the treatments given,

**KEYPOINTS**

- Based on the data from this study, it appears that the use of SSA was more likely to result in wound closure during the first 12 weeks, as compared to comparable wounds treated with BSS.
- Wounds treated with SSA closed more quickly and required slightly fewer grafts than wounds treated with BSS.
- The present study supports the use of both graft materials, and suggests that there is a need for future experiments to determine the optimal number of grafts to be used, as well as refining the criteria for reapplication.

consistency in wound and patient characteristics in the two cohorts, and treatment by a single group of clinicians who followed a set treatment protocol.

Although the randomization scheme used in this study resulted in two cohorts of uneven sizes, it did not appear to be a factor in the outcomes since the characteristics of the two groups were otherwise indistinguishable.

One issue that came to light was the fewer number of grafts needed in order to achieve closure. It may be that more wounds would have closed in a shorter period of time if more grafts had been used. It is not possible to determine this from the present study. However, even if there was some slight underutilization, the wound closure rates were comparable to other previous studies. Future studies may focus on determining the optimal number of grafts required, as well as more objective criteria for when the grafts should be applied.

Nonetheless, even with these shortcomings, the data remain compelling. SSA closed 66.7% of the wounds with an average closure time of 5.00 weeks, which is consistent with a previous study that demonstrated a closure rate of 59.30% at 12 weeks and 70.59% at 20 weeks with wounds from the same size range (1.38 cm<sup>2</sup>–3.18 cm<sup>2</sup>, [2nd quartile]) with an average of two applications of SSA needed.<sup>4</sup> The closure rate of 41.3% at 12 weeks and 47.1% at 20 weeks with BSS is lower than the closure rate reported in previous studies,<sup>6,7</sup> but may be attributed to the use of fewer BSS or a variety of other differences in the current protocol, as compared to those prior studies.

The current study supports the use of both graft materials, and suggests that there is a need for future experiments to determine the optimal number of grafts to be used, as well as refining the criteria for reapplication.

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## COMMENTARY

## A Prospective Comparison of Diabetic Foot Ulcers Treated With Either Cryopreserved Skin Allograft or Bioengineered Skin Substitute

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Comparative research and product evaluation is a new endeavor, which should be applauded and supported. Dr. Didomenico and colleagues are to be commended for their attempts to meet that goal. Before any meaningful data is to result from comparative product evaluation, the use of the products must be maximized if the data is to be useful. Unfortunately, the data collected leaves much to be desired. As reported, the treatment of diabetic foot ulcers with Apligraf resulted in a 12-week healing rate of 41.3% and a 20-week healing rate of 47.1%. For the other product, TheraSkin, the healing rate at 12 weeks was 66.7% and at 20 weeks was 66.7%. These healing rates for TheraSkin are reasonable and comparable to a retrospective evaluation of its effect where a healing rate for diabetic foot ulcers was 60% at 12 weeks and 74% at 20 weeks.<sup>1</sup> In light of previously reported data, the healing rates with Apligraf in this comparative study are surprisingly low. In the original clinical trials, Veves et al<sup>2</sup> treated diabetic foot ulcers with Apligraf and achieved a 56% healing rate at 12 weeks. In a subsequent study, Steinberg et al<sup>3</sup> noted a 55% healing rate at 12 weeks, and Edmonds et al<sup>4</sup> reported a 51% healing rate at 12 weeks with ulcers averaging 2.5 cm<sup>2</sup> and receiving an average of 1.8 applications per patient. Other studies have shown even more impressive healing rates. In a Phase IV, randomized, diabetic foot ulcer trial by Sheehan et al,<sup>5</sup> the 12-week healing rate for diabetic foot ulcers was 70% utilizing 1.27 applications per patient. This compares favorably to the results of Treadwell et al<sup>6</sup> who reported 72% healing at 12 weeks with an average of 1.4 applications per patient with an even higher healing rate of 80% at 12 weeks with appropriate wound bed preparation.

What could make the difference in the previously reported and the currently observed healing rates? Many times an apparent failure of a product is not the failure of the product, but a failure to use the product appropriately. In the manuscript the authors describe that care of the wounds post application involved “no dressing changes being performed during the first week” and “subsequently, dressings changes were performed every other day, or on a daily basis, as needed.” This may be a potential source of the problem.

The Application Protocol for TheraSkin recommends that the original dressing be left in place for 5–7 days and then “re-dress [the] wound if necessary.”<sup>7</sup> It appears that daily or every other day dressing changes may not be indicated for TheraSkin. The Application and Aftercare instructions for

Apligraf plainly state that at the first dressing change should be 5 to 10 days after application; the primary, non-adherent dressing should be left undisturbed and the primary dressing should be only removed 14 to 21 days after application with care being taken “not to disturb or debride the wound bed.” Subsequent dressing changes are recommended only at weekly intervals.<sup>8</sup> These recommendations are made so that neither the tissue engineered skin nor the wound bed is disturbed while the living cells are interacting with the wound bed to produce a positive clinical outcome. If excessive drainage necessitates more frequent dressing changes, the bandage is only changed down to the non-adherent dressing, which is left undisturbed and only changed weekly. It is known that manipulating the wound bed or too frequent changes of the non-adherent dressing can lessen the effectiveness of the tissue engineered skin and damage the wound bed, resulting in prolongation of the inflammatory wound microenvironment and delaying healing. Is it possible that this recommendation of too frequent dressing changes led to reduced healing for patients treated with Apligraf? Is it possible that the outcomes using TheraSkin could have been even better with fewer dressing changes?

The manuscript states that each patient was seen on “a weekly basis for the first 12 weeks, and then bi-weekly through the 20th week.” This implies that the patient or family member may have been doing the daily or every other day dressing changes. It is our experience that patients are unable to change a dressing with the care and expertise required for the management of a wound treated with a skin graft, tissue engineered skin, or other advanced wound care product. If we, as clinicians, believe a wound is best treated with any advanced therapeutic product, it behooves us to invest the time and skill in managing the wound to ensure the best possible clinical outcome. There is considerable monetary investment in any of these products, and as such, we should strive to get the most from that investment; providing appropriate follow-up care is one way to assure that.

The authors are to be congratulated for completing this comparative effectiveness study. There is no doubt that TheraSkin is a good product for the treatment of diabetic foot ulcers with good outcomes being obtained. Unfortunately, this study does not appear to demonstrate a true superiority over the bi-layered tissue engineered skin substitute. We look forward to seeing more comparative effectiveness research, but we must strive to assure

that the effectiveness of each product is maximized so that a true comparison is possible.

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