APPENDIX A. THERAPY DESCRIPTIONS AND REFERENCES

Collagen

The term collagen is applied to a species of chemically distinct macromolecular proteins. The variety of collagen structures is one reason for their diverse roles in ulcer healing. The roles of collagen wound products in ulcer healing may be 1) to act as a substrate for hemostasis, 2) chemotaxis to cellular elements of healing such as granulocytes, macrophages, and fibroblasts, 3) to provide a scaffold for more rapid transition to mature collagen production and alignment, or 4) to provide a template for cellular attachment, migration, and proliferation (Purna 2000). FIBRACOL Collagen-Alginate wound dressing (Johnson and Johnson, New Brunswick, NJ) is an advanced wound care device composed of collagen and calcium alginate fibers. It received FDA approval in August of 1998 for topical use for burns and pressure, venous, and diabetic ulcers. Promogran (Johnson and Johnson) consists of 55% collagen and 45% oxidized generated cellulose. It was approved by the FDA in February of 2002. Promogran is an absorbent open-pored, sterile, freeze-dried matrix used as a topical treatment for chronic ulcers including diabetic and venous ulcers. Promogran is composed of natural materials which physically bind to and inactivate damaging proteases while binding and protecting growth factors. (Cullen 2002).

Biological Dressings

This category of wound healing therapies consists of biomaterials made from various components of the extracellular matrix (ECM). These acellular matrices are usually derived from animal or cadaver sources and have undergone processing to remove and retain specific elements of the tissue. A commonly used biologically active dressing, the OASIS Wound Matrix (Cook Biotech, West Lafayette, IN), is an ECM product derived from the small intestinal submucosa of pigs. It received FDA 510(k) approval in 2000 and is indicated for the treatment of diabetic ulcers, venous ulcers, and chronic vascular ulcers, in addition to several other dermatologic conditions. This product retains additional active components found within the ECM, including many growth factors (Hodde 2001; Hodde, 2005; McDevitt, 2003) and several elements of ground substance (Hodde, 1996; McPherson, 1998). OASIS becomes incorporated into the ulcer base and is thought to stimulate ulcer healing by providing a structural scaffold and the growth signals important to complex cellular interactions within ulcers, both of which are dysfunctional and contribute to the persistence of chronic ulcers (Hodde, 2007). Lacking a cellular component, these products have the benefit of a long shelf life and are relatively uncomplicated to administer.

Biological Skin Equivalents (BSE)

These wound-healing therapies are laboratory-derived tissue constructs, designed to resemble various layers of real human skin. They consist of cultured, metabolically active skin cells grown over a scaffold or mesh framework. Two commercially available skin equivalents with FDA approval for treating chronic leg ulcers are Dermagraft and Apligraf. Dermagraft (Advanced BioHealing, Inc., La Jolla, CA) is a dermal tissue substitute that received FDA approval in 2001 for treating diabetic foot ulcers lasting more than 6 weeks. It is formed by culturing human fibroblasts from neonatal foreskin and then growing these fibroblasts over a bioabsorbable polyglactin scaffold. As the cells proliferate *in vitro*, they secrete important components of the extracellular matrix and a large variety of local growth factors (Naughton, 1997). The product

is cryopreserved for storage and delivery, but metabolic activity is regained upon thawing and application to the wound bed (Mansbridge, 1998). Apligraf (Organogenesis, Inc., Canton, MA) is a similar skin substitute made from cultured skin cells but is a bilayer construct that contains both dermal and epidermal components. Apligraf (formerly known as Graftskin, Human Skin Equivalent, and Living Skin Equivalent) received FDA approval in 1998 for chronic venous ulcers and in 2000 was granted further approval for use in diabetic foot ulcers. The human cells in both layers, fibroblasts in the dermis and keratinocytes in the epidermis, are derived from purified cultures of neonatal foreskin. The final metabolically active product has a limited shelf life since it is not cryopreserved but delivered "fresh" to sites for clinical use. Both Apligraf and Dermagraft are metabolically active products thought to increase healing by stimulating fibrovascular ingrowth and epithelialization of host tissues (Ehrenreich, 2006; Límová, 2010). They do not "take" like traditional skin grafts that are meant to replace lost tissue with fully functioning skin, but instead become incorporated into the wound bed and stimulate regrowth of the host's own skin tissue (Ehrenreich, 2006; Límová, 2010; Mansbridge, 1999; Phillips, 2002).

Keratinocytes

Keratinocyte-based therapies for wound healing exist in a variety of forms. Use of cultured epidermal keratinocytes to treat chronic leg ulcers was first attempted with autologous (Hefton, 1986; Leigh, 1986) and allogeneic (Leigh, 1987) cells in 1986 and 1987, respectively. Since then, different keratinocyte sources have been utilized; the patient's own skin cells, donor cells from cadavers or patients undergoing cosmetic procedures, and bioengineered "immortalized" keratinocytes have all been used. In addition to using different cellular sources, therapies may vary in their use of fresh, cryopreserved, or lyophilized keratinocytes. These products differ in level of metabolic activity and ease of storage and transportation. Furthermore, various application strategies have been attempted for delivering keratinocytes onto wounds, including various suspension mediums (e.g., fibrin sealant), aerosolized sprays, cellular microcarriers, and gels. These products do not act as grafts or serve as permanent skin replacements, as they are rapidly replaced by the host's own keratinocytes (Kaawach, 1991; Burt, 1989; Auböck, 1988). They are thought to work by stimulating proliferation and migration of host epithelium from wound edges through the production of growth factors and other cytokines (DeLuca, 1992; Duinslaeger, 1994; McKay, 1991). Although there have been multiple studies focusing on keratinocyte use in chronic ulcers, currently the only commercially available products in the U.S. are not indicated for use in leg ulcers. However, there are various products on the market, and with ongoing efforts to expand indications and the continuing research focus in this area, an understanding of the current literature on the topic is important in recognizing the limitations and future expectations of keratinocyte-based wound healing

Platelet-derived Wound Healing - Platelet-derived Growth Factors (PDGF)

Human platelet-derived growth factor is a substance naturally produced by the body to help in wound healing. It works by helping to repair and replace dead skin and other tissues, attracting cells that repair wounds, and helping to close and heal the ulcers. (Pierce 1991). Regranex Gel (becaplermin 0.01%, Johnson & Johnson, New Brunswick, NJ) was approved by the FDA in 1997 for the treatment of diabetic foot ulcers. Regranex is a genetically engineered product that mimics PDGF in the body. It is indicated for treating lower-extremity neuropathic ulcers

that extend into the subcutaneous tissue or beyond, but which have an adequate blood supply. It is intended for use as an adjunct to traditional ulcer care strategies, such as initial sharp debridement, daily dressing changes, pressure relief and treatment of infection if present (Label indication 1997).

Platelet Rich Plasma

Platelet-rich plasma (PRP) is derived from newly drawn whole blood prepared by specialized centrifugation to create plasma having a platelet concentration above baseline. PRPs themselves are have been used in wound healing since 1985 and do not require FDA approval, but centrifuges used to spin whole blood for the creation of PRP do require approval. PRP contains a high level of platelets and a full complement of clotting and growth factors which aid in healing by attracting undifferentiated cells and activating cell division (Lacci 2010). Autologel System (Cytomedix Inc) received FDA approval in September of 2007 and consists of a table top centrifuge (AutoloGel II Centrifuge) and blood access and processing devices.

Silver

The therapeutic potential of silver has long been recognized, and reports of its use in chronic ulcers have been documented in surgical textbooks as early as 1617 (Klasen, 2000). Due to the broad bactericidal action of silver (Ip, 2006) and the understanding that wound healing is impaired when bacterial levels surpass a particular threshold (Bowler, 2001), multiple silver-based products have been developed to aid in wound healing. These products incorporate silver into topical creams (silver sulfadiazine or Silvadene; King Pharmaceuticals, Bristol, TN) or within various types of dressings, including foams (Contreet Ag; Coloplast, Marietta, GA), hydrocolloids (Contreet H; Coloplast, Marietta, GA), hydrofibers (Aquacel-Ag; Covatec, Skillman, NJ), alginates (Silvercel; Systagenix, Quincy, MA), film polymers (Arglaes; Medline, Mundelein, IL), and a polyethylene mesh with nanocrystalline silver (Acticoat-7; Smith and Nephew, Hull, UK). These products work through the release of reactive silver cations, [Ag^{+}], which may disrupt components of the bacterial cell wall, inhibit microbial respiratory enzymes and elements of the electron transport chain, and impair the synthesis and function of DNA and RNA (Atiyeh, 2007). Although these effects are desirable when directed against bacterial and fungal organisms, it is important to recognize the indiscriminant action of silver. Cytotoxicity of various host cells, including keratinocytes and fibroblasts, has been shown to occur from silver, and a delicate balance exists between the beneficial decrease in bacterial burden and the deleterious effects on host cells that can also delay wound closure (Atiyeh, 2007; Poon, 2004; Hollinger, 1996)

Intermittent Pneumatic Compression Therapy

Intermittent pneumatic compression (IPC) therapy is delivered through inflatable, single-patient-use, garments containing one or more air chambers. Garments are applied to the foot, calf, or calf and thigh and intermittently inflated and deflated with air by means of a powered pneumatic pump to simulate the normal ambulatory calf and foot pump. This action propels the blood of the deep veins towards the heart and benefits the non-ambulatory patient by increasing blood flow velocity in the deep veins and reducing stasis, decreasing venous hypertension, flushing valve pockets, and decreasing interstitial edema (Comerota 2011). Pneumatic compression devices

are cleared for marketing under the FDA 510(k) process as Class II devices intended for use in prevention of blood pooling in a limb by periodically inflating a sleeve around the limb. No clinical data was needed for FDA approval since they existed prior to the passage of the Medical Device Amendments of 1976.

Negative Pressure Wound Therapy (NPWT)

NPWT, also referred to as "vacuum assisted wound closure," is the process of creating a tightly sealed dressing around a wound and using a suction pump to apply a sub-atmospheric (or "negative") pressure evenly across the surface in a continuous or intermittent manner (Venturi, 2005). A drainage canister is attached to store fluid collected from wound suction. The first FDA approved, commercially available NPWT product was the Vacuum Assisted Closure™ device (Kinetic Concepts, Inc., San Antonio, TX), introduced to the market in 1995. Since then, the approved indications for its use have continually expanded and currently include diabetic foot ulcers, venous leg ulcers, and pressure ulcers, as well as several non-ulcerative conditions. Other NPWT devices include the Versatile 1™ (BlueSky Medical, Carlsbad, CA), which received FDA approval in 2004, and the Renasys™EZ and Renasys™Go (Smith and Nephew Inc., Largo, FL), approved in 2008 and 2009, respectively. These devices are proposed to enhance wound healing by increasing granulation tissue and local perfusion (Morykwas, 1997), reducing tissue edema, decreasing bacterial load (Morykwas, 1997), and stimulating cellular proliferation via induction of mechanical stress (Olenius, 1993; Saxena, 2004). NPWT may be used as either a primary treatment to achieve complete wound healing, or as a temporary therapy to prepare a wound so that another treatment can be attempted to achieve complete wound closure.

Electromagnetic Therapy (EMT)

EMT utilizes the electrical field created between large, oppositely charged capacitors or, more commonly, the electrical field that develops from exposure to an oscillating magnetic field (Lee, 1993). There are various potential mechanisms by which EMT may enhance wound healing. Normal human skin has been found to produce a steady state transcutaneous electrical potential (Foulds, 1983) that, upon epithelial disruption, short-circuits to produce an endogenous electrical current (Burr, 1940; Illingworth, 1980; Nuccitelli, 2003; Zhao, 2006) and a resultant electrical field (Nuccitelli, 2003; Zhao, 2006). This wound-induced electrical field has been shown to regulate cell division in wound healing (Song, 2002) and to guide the cellular migration through specific signaling pathways (Zhao, 2006; Fang, 1999). EMT is thought to work by mimicking or enhancing these natural wound-induced electrical fields. No EMT devices have received FDA approval for use in chronic wounds; however, these products have received approval for other indications and are commercially available. Despite the lack of FDA approval, the Centers for Medicare and Medicaid Services (CMS) has deemed EMT to be a reasonable adjuvant treatment for chronic ulcers of diabetic, venous, and arterial etiologies. Because of this, CMS covers the use of EMT for chronic ulcers not responding to standard care.

Hyperbaric Oxygen Therapy (HBOT)

HBOT involves the use of specialized compression chambers capable of delivering increased concentrations of oxygen (usually 100% O_2) under elevated atmospheric pressures (usually 1.5-3.0 ATA). This greatly increases systemic levels of oxygen (Sheffield, 1985), achieving arterial

oxygen tensions upwards of 2000 mmHg (normally 100 mmHg) and tissue oxygen tensions up to 500 mmHg (normally 55 mmHg) (Gill, 2004). Individual treatment sessions usually last between 45 and 120 minutes and may be done once or twice a day for a total of 10-30 sessions. HBOT is FDA approved for a dynamic list of indications, including wound healing, as deemed appropriate by the Undersea and Hyperbaric Medical Society. Examples of devices include the OxyHeal 1000 Monoplace Hyperbaric Chamber (OxyHeal Health Group, LaJolla, CA) and the Multiplace Hyperbaric Chambers (Makai Marine Industries, Inc., Boca Raton, FL), which received FDA approval in 2005 and 2004 respectively. The role oxygen plays in the process of normal wound healing is complex. Although hypoxia stimulates certain steps in wound healing (Knighton, 1983; Jensen, 1986), and the low oxygen levels in the center of a wound are important in initiating repair (Thackham, 2008), many key aspects of wound healing are oxygen dependent (Gordillo, 2003). These include collagen deposition (Jonsson, 1991), angiogenesis (Hopf, 2005), fibroblast and endothelial cell proliferation (Tompach, 1997), and bacterial clearance (Knighton, 1986; Allen, 1997; Hopf, 1997; Greif, 2000). By raising arterial oxygen tension and the blood-oxygen level delivered to a chronic wound (Rollins, 2006), HBOT is thought not only to supply a missing nutrient but also to promote the oxygen dependent steps in wound healing, to up regulate local growth factors (Thom, 2009), and to down regulate inhibitory cytokines (Thom, 2009). Although thought to be a relatively safe treatment, this delivery of concentrated oxygen in a compression chamber can be complicated by the increased pressure (e.g. ear and sinus barotrauma) or oxygen toxicity (e.g. acute cerebral toxicity and chronic pulmonary toxicity) (Plafki 2000; Sheffield, 2003).

Topical Oxygen Therapy (TOT)

Similar to HBOT, this category of products aims to promote ulcer healing by correcting the low oxygen levels found within chronic wounds. TOT was developed in an effort to overcome drawbacks inherent with HBOT and works to promote wound oxygenation through a physiological distinct mechanism. While HBOT uses a compression chamber to systemically deliver high O_2 levels under an elevated atmospheric pressure, TOT works by covering a wound with an airtight bag or chamber and using a portable device to fill the container with concentrated oxygen. Although this results in very slight elevations in local pressure (usually 1.004 - 1.013 ATA), this is far less than the levels reached in HBOT (up to 2.5 - 3.0 ATA) and is not considered truly “hyperbaric” (Feldmeier, 2005). TOT is thought to increase local oxygen levels by simple diffusion of the externally applied gas into superficial wound tissues (Fries, 2005). This method of wound oxygenation may induce angiogenesis through upregulation of specific growth factors (Gordillo, 2008; Scott, 2005) and has been postulated to promote cell motility, extracellular matrix formation, and angiogenesis by correcting hypoxia at the wound center (Gordillo, 2003). Examples of these products include the Hyper-Box Topical Wound Oxygen System (Qualtech House, Gateway, Ireland) that received FDA approval in 2008 and EpiFlo (Ogenix, Corp., Beachwood, OH), most recently approved in 2012 for chronic skin ulcerations due to diabetes and venous stasis. Although CMS covers use of HBOT in some chronic wounds, it does not reimburse for TOT.

Ozone Oxygen Therapy

Ozone is an oxidizing agent. When ozone molecules are administered via gas or liquid, the ozone is theorized to promote tissue healing. Healthy cells are reported to survive and multiply while defective cells, bacteria, and viruses are destroyed. Ozone has been used to treat medical conditions since the late 19th century, however, there is little known about its safety and efficacy. Ozone can be administered to chronic wounds using a technique known as ozone bagging, a technique in which the effected limb is sealed for up to two hours in a bag containing ozone. Alternatively, ozone-enriched water or vegetable oil may be applied to the skin. Opinions are mixed about the safety of ozone therapy. While some advocates suggest that there is a very low risk of side effects the fact that it is a toxic gas has caused others to question the safety. (Intelihealth, Natural Standard)

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APPENDIX B. SEARCH STRATEGY

Search Strategy:

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1 exp Skin Ulcer/ (31597)
2 exp Foot Ulcer/ (5874)
3 exp Leg Ulcer/ (15666)
4 exp Varicose Ulcer/ (3490)
5 exp Diabetic Foot/ (4864)
6 exp Wound Healing/ (83186)
7 exp Venous Insufficiency/ (5352)
8 or/1-7 (114315)

9 limit 8 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial) (6955)

10 randomized controlled trial.pt. (321315)
11 controlled clinical trial.pt. (83663)
12 random*.ti,ab. (545362)
13 placebo.ti,ab. (132724)
14 or/10-13 (736326)
15 (animals not (humans and animals)).sh. (3590935)
16 14 not 15 (659693)
17 8 and 16 (5990)

18 9 or 17 (8200)

19 limit 18 to (english language and humans and yr="1995 -Current") (5646) [a few more important limits]

20 artificial skin.mp. or exp Skin, Artificial/ (1844)
21 19 and 20 (65)
22 biological dressings.mp. or exp Biological Dressings/ (1128)
23 19 and 22 (38)
24 exp Negative-Pressure Wound Therapy/ or exp Lower Body Negative Pressure/ or negative pressure.mp. (5422)
25 19 and 24 (84)
26 exp Collagen/ or collagen.mp. (145508)
27 19 and 26 (287)
28 exp Silver/ or exp Silver Proteins/ or silver.mp. (37481)
29 19 and 28 (105)
30 exp Oxygen/ or topical oxygen.mp. (134274)
31 19 and 30 (51)
32 exp Hyperbaric Oxygenation/ or hyperbaric oxygen*.mp. (10425)
33 19 and 32 (62)
34 electromagnet*.mp. or exp Electromagnetic Phenomena/ (311999)

35 19 and 34 (55)
36 exp Platelet-Derived Growth Factor/ or platelet-derived.mp. or exp Growth Substances/ (570646)
37 19 and 36 (179)
38 exp Platelet-Rich Plasma/ or platelet-rich.mp. (5704)
39 19 and 38 (66)
40 exp Intermittent Pneumatic Compression Devices/ or pneumatic compress*.mp. or compress* therapy.mp. or compress* pump.mp. (1625)
41 19 and 40 (130)
42 21 or 23 or 25 or 27 or 29 or 31 or 33 or 35 or 37 or 39 or 41 (1014)

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes	
Yes	
Yes	
Yes	
Yes	
Yes. This report represents a monumental work effort. It is, in my judgment, the most comprehensive and objective review I have seen to date. The persons who prepared this report are to be commended for their efforts.	Thank you.
2. Is there any indication of bias in our synthesis of the evidence?	
Not sure that like was compared to like. I would worry about your RCT grading system if RCTs used for FDA approval (PDGF and synthetic skin) are graded lower than a NPWT study that was not really blinded. I also worry at all of your studies did not treat similar groups of individuals. For example, the HBO RCTs were very inconsistent with respect to the Wagner grade.	We assigned grades based on established criteria for evaluating risk of bias in RCTs. These criteria may be different than criteria for FDA approval. We agree that the populations varied from study to study and attempted to clarify that in the description of the studies.
No	
No	
No (reviewer provided citation for Lancet article [2012] on spray-applied cell therapy)	Thank you. We reviewed this citation. The treatment is not FDA approved (this was a phase 2 trial) and therefore is not eligible for inclusion in our review.
No	
No	
3. Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	
Yes – total contact cast literature	We did not consider total contact casting to be an “advanced wound care product.” Although it may be an important therapeutic option, it was not recommended by our topic stakeholders and is outside the scope of our review.
No	
No	

REVIEWER COMMENT	RESPONSE
Yes Considering collagen dressings as a stand-alone category presents challenges as they are frequently used as deliver vehicles for silver, growth factors, protease inhibitors, etc. This should be acknowledged as a limitation. As such there may be other studies to be considered for inclusion under collagen [1-5]; apligraf [6]; and silver.[2] 1. Blume, P., et al., Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. Wound Repair & Regeneration, 2011. 19(3): p. 302-8. 2. Gottrup, F., et al., Collagen/ORC/silver treatment of diabetic foot ulcers; A randomised controlled trial. Wound Repair and Regeneration, 2011. 19(2): p. A24. 3. Letendre, S., et al., Pilot trial of biovance collagen-based wound covering for diabetic ulcers. Advances in Skin & Wound Care, 2009. 22(4): p. 161-6. 4. Motzkau, M., et al., Expression of matrix-metalloproteases in the fluid of chronic diabetic foot wounds treated with a protease absorbent dressing. Experimental & Clinical Endocrinology & Diabetes, 2011. 119(5): p. 286-90. 5. Mulder, G., et al., Treatment of nonhealing diabetic foot ulcers with a platelet-derived growth factor gene-activated matrix (GAM501): results of a phase 1/2 trial. Wound Repair & Regeneration, 2009. 17(6): p. 772-9. 6. Sams, H.H., J. Chen, and L.E. King, Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery, 2002. 28(8): p. 698-703	We have clarified that the studies included in the collagen section are studies of an inert collagen matrix product. We have reviewed the suggested references: 1. This trial has been added. 2. An abstract – not eligible for inclusion (we were unable to find the data in a peer-reviewed publication) 3. A case series – not eligible for inclusion 4. This study has been mentioned in the collagen section but due to a difference in the goal of the study and incomplete reporting is not given as much attention as other trials 5. A "cohort" study – not eligible for inclusion 6. This report presents data from one site of a multisite trial that is included in the report (Veves 2001)
No. To the best of my knowledge, this report appears to have reviewed all of the pertinent information relevant to the topics studied.	Thank you
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
I am concerned that the device assessments were not as rigorous as the FDA approved products. Care needs to be made in recommendations. Also you did assess that HBO was inferior to shockwave and therapy that was later shown in the US to not be superior to standard off-loading of diabetic feet.	We identified and discussed one HBO trial conducted in Taiwan that directly compared HBO to shockwave therapy. We did not identify any trials meeting our inclusion criteria that directly compared shockwave therapy to standard off-loading of diabetic feet. We have added a paragraph with results from strictly controlled off-loading studies for comparison purposes.
Please see my comments within the body of the paper. *(Investigator NOTE: comments from body of paper have been added to list below)* The first 18 pages of the document need major revisions. After page 18, the material is written in more scientific manner which it appears more accurate than what is presented on the first initial pages. a. Page 1 Please define what you mean by diabetic ulcers. Arterial and venous ulcers can also happen in diabetic patients. How about neuropathic ulcers? Were they studied or reported in this paper? b. Page 1 Is your paper focused only on foot ulcers? Most venous ulcers occur in the legs. When studying the effectiveness of a device, please be more specific on location of the ulcers where the product was used.	The first 18 pages of the document are the executive summary and we attempted to condense a great deal of information into a more readable format. As the reviewer has noted, there are many important details about the studies and we have attempted to include the essential elements in the executive summary without simply repeating the full text of the report. a. The studies included in the section on diabetic ulcers are studies of populations described by the study authors as having diabetic ulcers. Diabetic ulcers are caused by peripheral neuropathy and/or peripheral vascular disease. The most common cause of neuropathic ulcers is diabetes and many of these studies included only patients with neuropathic ulcers. Most studies excluded patients with inadequate circulation. We have added that information to the report when it was provided by the study authors. b. The paper is not focused on foot ulcers. We have added the location of the ulcers (an overview in the executive summary and more information in the body of the report).

REVIEWER COMMENT	RESPONSE
c. Page 1 How about the impact of PVD and plantar pressures? I can heal a wound that is neuropathic or has infection as long as there is blood flow to the tissue!!!! d. Page 1 I am not sure the statement "venous disease accounts for the majority of chronic ulcers" is correct. Venous ulcers is seen mostly on non-American populations, but current research shows occurrence of PAD related ulcers in US population e. Page 1 Please define what you mean by diabetic ulcers? Are these patients who are diabetic with normal arterial, venous and nerve supplies? How are these patient populations different than those who have "arterial" ulcers or "venous ulcers? f. Page 3. Is this study shared with Dr. Robbins, our VA Central Office Chief of Podiatry? He needs to be informed on this study as this study can impact the podiatry field at the VA tremendously. His input on who should review this paper is important. g. Page 3 – overview of sizes of ulcers – Where are these ulcers? On the leg/shin area? Dorsal foot? Plantar foot? Each location will respond differently to different wound care product) h. Page 3 – KQ1 (diabetic ulcers) – Did all the subject studied for this question have normal blood flow and sensate feet? i. Page 4 – Collagen – Were there any beneficial effect in using collagen? Are you then telling the reader that using collagen on wounds is a waste of money? Is there any wound type that collagen can be helpful, i.e., draining wound? As a reader, I get the conclusion that I will be wasting my money and time if I used collagen. Is that what you want your readers to get out of this paragraph? j. Page 4 – Biological Dressings – Did all the subjects have normal blood flow? Please define what you mean by biological dressing. Are these different than biological skin equivalents? k. Page 4 – Biological Skin Equivalents – a) I am not sure what you mean metabolically active dermagraft. As a practitioner who uses dermagraft, I have never heard of this terminology. b) It is helpful to include how many (in average) dermagraft or apligraf application took in order to heal the wounds, as there is always the cost of care than can also impact treatment regimen used. Also in the past we were told that one application of apligraf was enough to get the wound to heal but now they are recommending weekly applications. The same goes for dermagraft. When dermagraft first hit the market, we could only use it up to 3 applications and now it is up to 7 applications. It is important to include how many graft applications these studies used in order to get the reported results. l. Page 5 – Platelet-rich Plasma – Please add how many applications of PRP it took to get the wound to heal? Was it daily, weekly, monthly application? m. Page 5 – Silver Products – Please be more specific as to exact type of silver products used. The silver ointment used for many years is silvadene cream which is cheaper than most other wound products. Now we have so many silver dressings with nano and micro size silver in it and each product is different based on its technology! So not all silver products are the same. The paragraph above can be very misleading, does not have any scientific value to it as it does not specify which specific silver technology you are referring to.	c. As noted in the overview of studies for KQ1, only one trial enrolled patients with strictly ischemic diabetic ulcers; in 27 of 35 trials, the ulcers were either neuropathic or patients with vascular disease were excluded. d. This statement is correct. In the US, venous disease is responsible for 72% of leg ulcers, mixed venous and arterial disease for 22%, and pure arterial disease for about 6%.References have been added. e. As noted in item "a" above, we categorized studies based on the study authors' descriptions of their included populations. We have added an overview of the studies which shows that, in most cases, studies of patients with diabetic ulcers excluded patients with inadequate blood flow. We recognize that patients with diabetes who are judged to have "adequate circulation" via clinical examination including pulses and blood pressure assessment may have microvascular arterial insufficiency. Nonetheless, we have categorized patients according to authors' definitions and included descriptions of the individual studies. f. Dr. Robbins was a member of the Technical Expert Panel for the report, provided input on the key questions, scope of review, study inclusion criteria and outcomes of interest (including categorization of populations and interventions) and has reviewed the report. g. We have added location to the overview of the studies. We also added this information to the results section in the full report and in the executive summary if there appeared to be differences in outcomes based on ulcer location. h. We have added this information to the overview of the studies. i. One study of collagen as a matrix material found a benefit for ulcer healing. We have clarified that other treatments may use collagen as a vehicle for delivery of the active substance (e.g., silver). j. One study excluded patients with severe arterial disease and the other included only patients with adequate circulation. We have defined biological dressings as acellular matrices with a biologically active component. We have defined biological skin equivalents as tissue constructs designed to resemble layers of human skin. k. The finding about metabolically active dermagraft was from an early trial (Naughton 1997). They found that some samples had lower metabolic activity (non-therapeutic range) and suggest that, as a result, the manufacturing process was modified to ensure that all samples have an appropriate therapeutic level. We have clarified this. We have also added information about the number of applications to the full report l. We have added this information to the executive summary and the report. m. This information was in the main report and has now been clarified in the executive summary.

REVIEWER COMMENT	RESPONSE
n. Page 5 – NPWT – Please be more specific. How much better improvement? 50%?, 60%, 70% better? Was it significantly or marginally better? How about time to gain complete healing? Or was this study based on wound reduction size only. Page 6-7 – KQ1 summary a) under Secondary Outcomes – were these ulcers "diabetic ulcers" or "arterial" ulcers? b) The above summary does not cover the answer to all of the questions specifically "Is efficacy dependent on ancillary therapies?" – not clearly covered for each individual treatment regimen and "Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?" – not clearly covered for each individual treatment regimen o. Page 7 - Biological Skin Equivalents – The comments above contradict the FDA reported studies. Apligraf was initially approved by the FDA in 1998 for use in venous ulcers. Later, its indication expended to include arterial/diabetic ulcers in 2000. So is FDA wrong? p. Page 8 – Silver Products – please be specific on type of silver dressing used q. Page 8 – Intermittent Pneumatic Compression Therapy – How about time to healing? Did the IPC reduce the time to healing? How about ulcer recurrence rate? r. Page 10 – KQ3 – How come this is different than the answers to other questions above? Are not there device/product-specific studies for arterial ulcers? How about use of collagen? skin substitutes i.e., apligraf? How about HBO therapy? PRP? This section is too brief and does not do the justice to treatment of Arterial ulcers which are the most common ulcers seen in our practices. s. Page 10 Discussion – In your discussion, please focus on positive findings. The studies may be of poor or moderate quality as such studies are often difficult to do. Please remember (and emphasize in your paper) that there are many reasons and factors affecting the occurrence of a wound, the needed treatment and the effectiveness of therapy. Each wound is different as it is the patient who owns the wound! That is not what was concluded previously in the previous pages!! t. Page 10 – "No treatment produced greater healing when compared to another advanced therapy." This statement is inaccurate! I do not believe that many of the studies (except a handful) compared one advanced therapy against another! u. Page 11 Paragraph beginning with "The findings for venous ulcers .. silver products (that is not what was concluded previously in the previous pages!!), electromagnetic therapy (this contradicts what was concluded previously in the previous pages!!), significantly better healing (really? How come this was not noted in the sections above?) v. Page 11 Paragraph beginning with "We identified only one study of … " Were these ulcers revascularized before use of apligraf or were they all ischemic wounds??? w. Main Report – Venous Leg Ulcer Description (70-90% of leg ulcers) – NOT foot ulcers! Location makes a huge difference on the etiology of the ulcer! x. Main Report – Arterial Leg Ulcer Description (6-10% of lower extremity ulcers) - Do these include ulcers in the foot? Or is it all in the leg. Please note, there is an anatomical difference when you talk about lower extremity, leg, or foot. Having said that you cannot combine the wound healing rate and success (or failure of) for all of these regions as each region heals differently? y. Main Report – Topical Oxygen Therapy Description – Is this even discussed in the above reported studies?	n. We have added the absolute risk difference for NPWT and the other treatments. o. We found significant improvement in percentage of ulcers healed with Apligraf for both diabetic and venous ulcers. We did not review FDA reasoning behind their approval process (which may have included studies and data not available or eligible for this report) and make no statement regarding their approval. p. We have added this information. q. The IPC trial did not report time to healing or ulcer recurrence. r. We agree that arterial ulcers and treatment for these are important. However, we identified only one trial specifically focused on arterial ulcers. We noted in the text that some of the patients in the diabetic ulcer studies may have had microvascular disease despite the fact that most studies excluded patients with macrovascular disease. Similarly, patients may have had mixed venous and arterial disease. This is an important area requiring future research. s. We have reported the findings from our review of RCTs. We highlight findings (both positive and negative) where data support strong evidence to affect practice and policy. We agree that it is important to highlight positive findings if there is at least moderate certainty of benefit. However, it is also important to note areas where treatments are not effective or there is insufficient evidence, so that clinicians and patients can avoid use of treatments of low value/low effectiveness. We recognize that all patients have unique clinical circumstances-this is not unique to patients with chronic wound care needs. As with any condition, intervention, and outcome we summarize the findings from the available evidence, rate the quality of individual studies, determine strength of evidence, and make comments about the broader applicability to patients typically seen. Based on this evidence clinicians can make judgments regarding extrapolation to individual patients though we suggest that our findings can serve as the foundation for implementation. t. We have clarified that far fewer of the studies eligible for our review included an advanced therapy comparator. u. We have clarified this section. Overall the findings were mixed for each product group but there were some individual trials with positive results. v. We have clarified that the patients had undergone revascularization. w. We have clarified ulcer location for studies cited throughout the report. x. The literature typically refers to arterial ulcers as a group in the lower extremity. It does not tease out foot vs. leg. We agree that there are different factors involved in healing of the foot vs. the leg. We have clarified ulcer location for studies cited throughout the report. y. The topic nominators requested that we include topical oxygen but no studies met our inclusion criteria. We have noted that in the report.

REVIEWER COMMENT	RESPONSE
The report and tables are comprehensive but limitations to the methodology are not highlighted in test. For example, recurrence of ulceration (or amputation) are usually lacking. Additionally, whether or not compliance with standard wound healing practices,(debridement, off-loading) is equally allocated between treatment and control groups is not highlighted.	We reported recurrence and amputation if reported by the study authors. We have added comments about compliance. Most studies indicated that off loading etc. was part of the treatment protocol but few reported compliance measures (for treatment or control groups).
1. As expected the results of the synthesis confirms the paucity of high level evidence to support the products used every day. The recommendations for criteria for future research are appreciated and will require that publications from this review be developed to get that word out. 2. Although the draft does speak somewhat to the limitations of the study I would recommend that it be highlighted and more specific to include important outcomes such as quality of life, recurrence, and prevention of amputations.	1. Thank you 2. We have added more specific information to the limitations and future research sections.
1. None of the citations described on page 77 have accompanying references. 2. In paragraph 3 of the discussion on page 77, greater emphasis should be placed the importance of offloading and adherence for DFU healing. The largest effect sizes for DFU healing in the literature are in offloading [1-3] causing leaders to suggest changes to the methodology for DFU trials.[4] This limitation should also be described on page 26 in the quality assessment section. Greater emphasis should also be placed on the importance of compression with VLU trials.[5] 3. The limitations and recommendations section do not adequately convey the magnitude of the problem associated with current industry sponsored trials' DFU inclusion/exclusion criteria. For example, ischemia and infection are either excluded or causes for censoring in DFU trials despite being highly prevalent conditions in clinical practice. For example, large cohort studies suggested a prevalence of clinically infected DFU's in 58-61% of patients [6, 7]; with up to 49% having peripheral arterial disease.[7] Fife also reports other populations that are excluded, including diabetes and significant comorbidities such as renal failure, ischemia, sickle cell, tobacco abuse, and steroid dependency [8] that are frequently encountered in practice. 4. In the executive summary, please provide point estimates for effect sizes in the silver, NPWT, and HBOT paragraphs on page 5.	1. The reference list is now complete. 2. We have added information about off-loading for DFU healing and compression for VLU (including the suggested references). Thank you for the reference suggestions. 3. We have added to these sections. Thank you for the reference suggestions. 4. We have added absolute risk reduction data to the executive summary.

REVIEWER COMMENT	RESPONSE
1. Armstrong, D.G., et al., Evaluation of Removable and Irremovable Cast Walkers in the Healing of Diabetic Foot Wounds: a Randomized Controlled Trial. Diabetes Care, 2005. 28(3): p. 551-4. 2. Armstrong, D.G., et al., Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care, 2001. 24(6): p. 1019-22. 3. Katz, I.A., et al., A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care, 2005. 28(3): p. 555-9. 4. Boulton, A.J. and D.G. Armstrong, Trials in neuropathic diabetic foot ulceration: time for a paradigm shift? Diabetes Care, 2003. 26(9): p. 2689-90. 5. Mustoe, T.A., K. O'Shaughnessy, and O. Kloeters, Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. Plast Reconstr Surg, 2006. 117(7 Suppl): p. 35S-41S. 6. Lavery, L.A., et al., Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis, 2007. 44(4): p. 562-5. 7. Prompers, L., et al., High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia, 2007. 50(1): p. 18-25. 8. Fife, C., Wound Care in the 21st Century. US Surgery, 2007: p. 63-64.	
I personally found the information related to biological skin equivalents to be most interesting. These treatment adjuncts are VERY expensive and it would appear from the report that they offer only modest benefit in wound healing compared to standard therapy and no significant improvement in shortening the time for ulcer healing. My "take home" message here was that these products should be used very judiciously, if at all.	Thank you.
5. Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.	Thank you – we will share these suggestions with the people responsible for dissemination of the report.
Yes. The wound clinics, podiatry sections, and possibly plastic surgery and general surgery sections if they deal with lower extremity wound care.	
Will likely impact criteria for use	
Yes, as stated above this synthesis will help us develop a guideline for the appropriate use of these expensive products using a combination of common sense and the evidence found in this study. We will have to resist the temptation to ban the use of products altogether but rather to place limits on how and where they are used. We must preserve the clinician's right to practice the art of medicine while recognizing we cannot continue to waste dollars on therapies that do not work. One telling point was that despite healing a wound faster or more completely there was no difference in all-cause mortality. This speaks to the need to develop algorithms that are interdisciplinary and address the systemic diseases as well as the wound.	

REVIEWER COMMENT	RESPONSE
This report has implications for National VA programs such as PACT and NSQIP. Results should be disseminated and presented at the VA's Annual Desert Foot Conference and HSR&D meeting. National presentations should also be considered at ADA and SAWC. The National PACT program may choose to study current use of advanced modality care in each strata using wound healing cameras to measure wound healing rates and appropriate use criteria and their effect on patient outcome in a pre & post-design.	
I would hope that the use of collagen products, biological dressings and platelet rich plasma would, for the most part, cease in most clinics treating the wounds described in the studies. On the other hand, the values of negative pressure wound therapy and hyperbaric oxygen in helping with wound healing in selected cases supports my own clinical experience in this area.	
6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
I worry that efficacy assessments do not always translate to general care of the VA	We appreciate this concern and have added the following statement to the discussion: "Our review assessed results from randomized controlled trials in selected populations and controlled settings. It is not well known how outcomes reported in these studies will translate to findings in daily practice settings including in Veterans Health Administration facilities. Patients were likely more compliant than typical patients and received very close monitoring. Therefore, results from these may overestimate benefits and underestimate harms in nonstudy populations."
You need to notify Dr. Jeff Robbins, the Chief of Podiatry at the VA central office about this report. He has a list of whom are most expert in the field within the VA. As there is a number of factors in treating wounds, the paper must emphasize the difficulty in performing studies and coming up with a conclusion on what is best for healing chronic wounds. The factors affecting doing a solid, strong study include but not limited to: the type of the wound, the host barriers, the host's associated comorbidities, the host's associated level of nutritional status, compliance with treatment, location of the ulcers (plantar vs. dorsal), degree of blood flow (not all small vessel disease act the same!), the host's medications, …	We thank the reviewer for these comments. Dr. Robbins is involved with this project.
1) This is a long report and while the tables and appendices are important they should probably come at the end and be referenced in the body of the document. 2) We could release the executive summary widely and reference the full document. I am concerned that the field clinicians will not read a 178 page document. 3) In addition I am interested in helping in the production of some publications based on these findings to share with the scientific community.	1 and 2) We recognize the length of the report. We believe the information included is needed to provide the "interested reader" the full body of evidence we considered. We agree clinicians and policy makers are unlikely to read the whole document. We have tried to highlight the main findings in the executive summary and are willing to conduct other dissemination activities including Cyberseminars, Management Briefs etc. to further convey the main messages to a wide audience. 3) We are considering derivative manuscripts from this report.
There is a growing chasm between operations and research. Those who conduct systematic reviews or meta-analyses frequently are not PI's conducting the studies or actively engaged in patient care.[1] A careful compilation of improvement opportunities for study designs should be created for both funding agencies (including industry) and PI's. These should also be disseminated to NIH and VA program officers. 1. Gottrup, F., Controversies in performing a randomized control trial and a systemic review. Wound Repair Regen, 2012. 20(4): p. 447-8.	We have cited several documents detailing recommendations for future research.
The report is extremely well done and readable as it stands. I have no recommendations for improvement.	Thank you.

APPENDIX D. EVIDENCE TABLES

Table 1. Study Characteristics Table

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Abidia 2003[49] United Kingdom Funding Source: NR Therapy Type: Hyperbaric oxygen (HBOT)	Inclusion: diabetes; ischemic lower extremity ulcers (>1 cm and <10 cm in maximum diameter); no signs of healing for >6 weeks despite optimum medical management; occlusive arterial disease confirmed by ankle-brachial pressure index <0.8 (or great toe <0.7 if calf vessels incompressible) Exclusion: planned vascular surgery, angioplasty, or thrombolysis	N=16 (of 18 randomized) Age (years): 71 Gender (% male): 50 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 19% # Work days missed: NR ABI: <0.8 for inclusion Wound location: foot Wound type: ischemic diabetic Wound size, mm^2 (median): HBOT 106; control 78 Wound grade (Wagner*, %): Grade I 6; II 94 Wound duration, months: HBOT 6; control 9 Comorbid conditions (%): History of CAD/CVD: (previous bypass 31, angioplasty 6) History of DM: 100 History of amputation: minor 19	Intervention (n=9): HBOT; 2.4 ATA for 90 minutes on 30 occasions over 6 weeks; multi-place chamber Control (n=9): sham (hyperbaric air) ALL: specialized multidisciplinary wound management program (off-loading, debridement, moist dressing) *Antibiotic Use:* As needed *Treatment Duration*: 6 weeks *Follow-up Duration*: 1 year *Study Withdrawal (%)*: 20 (n=2) *Treatment Compliance*: "The protocol was strictly followed throughout the study"	Allocation concealment: Adequate Blinding: Patients, investigators, outcome assessors Intention to treat analysis (ITT): No, two withdrawals not included in analysis Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Agrawal 2009[28] India Funding Source: NR Therapy Type: Platelet-derived Growth Factor	Inclusion: ≥30 years of age; Wagner stage I, II, III, or IV ulcers; foot ulcer duration >3 months; free of infection; adequate lower-limb blood supply (transcutaneous oxygen tension ≥30 mmHg), no or moderate peripheral vascular disease Exclusion: active neoplastic disease; diagnosis of active infection characterized by warmth, erythema, lymphangitis, lymphadenopathy, oedema, or pain; received immunosuppressive therapy during the preceding three months; liver disease, pulmonary tuberculosis, thyroid disorder uremia, alcoholism or renal insufficiency; undergoing vascular reconstruction or receiving steroid or anticoagulant therapy	N=28 Age (years): 55 Gender (% male): 68 Race/ethnicity: NR BMI: 25.7 Pre-albumin: NR HbA_1c (%): 8.8 Smoking: NR # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic Wound size: 41.5 cm^2 (ulcer size significantly larger in study group p=0.003) Wound grade: NR Wound duration: NR Infection: excluded Comorbid conditions (%): Diabetes: 100	Intervention (n=14): rhPDGF 0.01% gel at 2.2ug/cm^2/day Comparator (n=14): placebo gel at 2.2ug/cm^2/day ALL: standard regimen of high-quality care (included glycemic control, debridement, dressings, pressure relief) *Antibiotic Use*: as needed *Treatment Duration*: 12 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 18 (all from control group at week 12) *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Partial – 5 withdrawals from the control group with no reason for withdrawal
Aminian 2000[27] Iran Funding Source: Government Therapy Type: Platelet-Derived Growth Factor	Inclusion: chronic non-healing diabetic ulcers of at least eight weeks duration; controlled blood sugar; normal peripheral blood platelet count (>150,000/cu mm); negative history of malignancy Exclusion: determined to have non-diabetic ulcers	N=12 ulcers (7 patients) of 14 ulcers (9 patients) randomized Age (years): 60 Gender (% male): 100 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic ulcer Wound size: 5.9 cm^2 Wound grade: NR Wound duration: 12.9 wks Infection: NR Comorbid conditions (%): Diabetes: 100	Intervention (n=7 ulcers): autologous platelet extract (APE) + silver sulfadiazine dressing 12 hours on and 12 hours off Comparator (n=5 ulcers): saline solution and silver sulfadiazine 12 hours on and 12 hours off ALL: supportive, conventional care (debridement, blood sugar checked weekly, off-loading) *Antibiotic Use*: oral, if needed *Treatment Duration*: 8 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 22% *Treatment Compliance*: 1/9 pts withdrawn for non-compliance	Allocation concealment: Inadequate Blinding: Unclear Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes – 2 patients with 2 ulcers excluded after entering study (non-compliance, non-diabetic ulcer)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Armstrong 2005[81] Apelqvist 2008[82] United States (18 sites) Funding Source: Industry (not involved in analysis or write-up of manuscript; did not maintain veto power over final article) Therapy Type: Negative Pressure Wound Therapy	Inclusion: age ≥18; wound from diabetic foot amputation to transmetatarsal level of foot; evidence of adequate perfusion (transcutaneous O2 on dorsum of foot ≥30 mmHg or ABI ≥0.7 and ≤1.2, and toe pressure ≥30 mmHg); University of Texas grade 2 or 3 in depth Exclusion: active Charcot arthropathy of foot; wound from burn, venous insufficiency, untreated cellulitis or osteomyelitis, collagen vascular disease, malignant disease, or uncontrolled hyperglycemia (HbA_1c >12%); treated with corticosteroids, immunosuppressive drugs, or chemotherapy; VAC therapy in past 30 days, present or previous (past 30 days) treatment with growth factors; normothermic therapy, hyperbaric medicine, or bioengineered tissue	N=162 Age (years): 59 Gender (% male): 81 Race/ethnicity (%): Non-Hispanic white: 48; African-American: 17; Mexican-American: 32; Native American: 3 BMI: 31 Pre-albumin (g/L): 0.19 HbA_1c (%): 8.2 Smoking: 9% # Work days missed: NR ABI: 1.1 Wound location: foot Wound type: amputation Wound size: 20.7 cm^2 Wound grade: U of Texas 2/3 Wound duration: 1.5 months Comorbid conditions (%): History of DM: 100 (90% T2)	Intervention (n=77): VAC system; dressing changes every 48 hrs Comparator (n=85): standard care (moist wound therapy with alginates, hydrocolloids, foams, or hydrogels; dressing changes every day unless otherwise advised ALL: off-loading therapy as indicated; sharp debridement at randomization and as needed *Antibiotic Use*: NR *Treatment Duration*: wound closure or 112 days *Follow-up Duration*: none *Study Withdrawal (%):* 0 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Partial (independently assessed and confirmed closure with digital planimetry) Intention to treat analysis (ITT): Yes – no withdrawals Withdrawals/dropouts adequately described: Yes – no withdrawals
Belcaro 2010[38] Italy Funding Source: NR Therapy Type: Silver Oxide Ointment	Inclusion: *Venous Ulcer (VU) Patients:* chronic venous ulcers, venous microangiopathy, and peri-malleaolar ulcerations *Diabetic Ulcer (DU) Patients:* diabetic microangiopathy and plantar ulcers due to reduced arterial pressure, diabetic microangiopahty and neuropathy, and localized infection Exclusion: *Venous Ulcer Patients:* venous thrombosis or arterial problems in past year; severe ischemia and necrosis (based on Doppler detected tibial pulse) *Diabetic Ulcer Patients:* none reported	*Venous Ulcer Patients:* N=82 Age (years): 47 Gender (% male): 46 *Diabetic Ulcer Patients:* N=66 Age (years): 55.9 Gender (% male): 44 *Both Groups:* Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: plantar (DU) Wound type: venous, diabetic Wound size: VU 3.2 cm^2, DU 2.2 cm^2 Wound grade: NR Wound duration: NR Comorbid conditions (%): NR	Intervention (n=44 VU, n=34 DU): silver ointment around and at edges of ulcerated area twice daily after noninvasive washing; bandage and elastic stocking Comparator (n=38 VU, n=32 DU): cleansing & wound care; compression (mild for DU) *Antibiotic Use*: NR *Treatment Duration*: 4 weeks *Follow-up Duration*: No follow-up post tx *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): Yes (no withdrawals) Withdrawals/dropouts adequately described: Yes (none)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Bhansali 2009[30] India Funding Source: Industry (provided gel) Therapy Type: Platelet-derived Growth Factor	Inclusion: >20 years old with type 1 or 2 diabetes; at least one neuropathic plantar ulcer of Wagner grade ≥ 2 without X-ray evidence of osteomyelitis; ABI>0.9; controlled infection after run-in Exclusion: none reported	N=20 (24 ulcers) Age (years): 51 Gender (% male): 60 Race/ethnicity: NR BMI: 24 Pre-albumin: NR HbA_1c (%): 8.1 Smoking: NR # Work days missed: NR ABI: 1.05 Wound location: forefoot: 75%; mid: 20%; hind: 5% Wound type: diabetic Wound size: 14.6 cm^2 Wound grade: Wagner ≥ 2 Wound duration: <4 weeks=20%; >4 weeks=80% Infection: 45% Comorbid conditions (%): History of DM: 100% History of amputation: 35%	Intervention (n=13): 0.01% rh-PDGF-BB gel Comparator (n=11): standard wound care (saline soaked dressing) ALL: daily dressing changes; off-loading (85% total contact cast, 10% bedridden, 5% special shoe) *Antibiotic Use*: As needed *Treatment Duration*: 20 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No (open label) Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes (none)
Bishop 1992[63] United States (2 sites) Funding Source: Industry Therapy Type: Silver Products	Inclusion: age 21 to 90 years; venous stasis ulcers of at least 3 months duration; surface area 3 cm^2 to 50 cm^2; negative pregnancy test and using adequate contraceptive (women of childbearing age) Exclusion: hypersensitivity to any components of test medication; >10^5 bacteria/gram of tissue in the ulcer; systemic sepsis or presence of bone infection; ABI<0.5; hypercupremia (Wilson's disease); systemic immunosuppressive or cytotoxic therapy; insulin-dependent diabetes mellitus	N=86 (of 93 randomized) Age (years): 56 Gender (% male): 50 Race/ethnicity: white: 62; black: 33; other: 6 BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 33.7% currently # Work days missed: NR ABI: NR Wound location: "lower extremity" Wound type: venous stasis Wound size: 10.5 cm^2 Wound grade: NR Wound duration: 46.4 months Comorbid conditions (%): History of DM: 9%	Intervention (n=29): 0.4% tripeptide copper complex cream Comparator (n=28): 1% silver sulphadiazine cream Placebo (n=29): tripeptide vehicle ALL: applied daily following saline rinse; non-adherent dressing and elastic wrap; limb elevated when sitting; no standing >2 hrs *Antibiotic Use*: NR *Treatment Duration*: 4 weeks *Follow-up Duration*: 1 year *Study Withdrawal (%)*: 7.5 *Treatment Compliance*: patient diary and medication weighed at end of study; results NR	Allocation concealment: Unclear Blinding: Yes (evaluator) Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Partial (3 were immediate dropouts; 4 additional patients did not complete the trial; reasons not provided)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Blair 1988[64] United Kingdom Funding Source: NR Therapy Type: Silver Products	Inclusion: ulcers up to 10 cm^2 Exclusion: ABI<0.8	N=60 Age (years): 69 Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: NR Wound type: venous Wound size: 3.4 cm^2 Wound grade: NR Wound duration: 26.2 months since ulcer was last healed Comorbid conditions (%): NR	Intervention (n=30): silver sulphadiazine dressing (Flamazine) Comparator (n=30): non-adherent and non-occlusive dressing ALL: out-patient treatment; dressings changed weekly in venous ulcer clinic; standard high pressure graduated compression bandage over the dressing *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 7% *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Blume 2008[42] United States and Canada (29 sites) Funding Source: Industry Therapy Type: Negative Pressure Wound Therapy	Inclusion: diabetic adults (18+); stage 2 or 3 (Wagner's) calcaneal, dorsal, or plantar foot ulcer; ≥2 cm^2 after debridement; adequate blood circulation (dorsum transcutaneous O_2 test ≥30 mmHg); ABI 0.7-1.2 with toe pressure ≥30 mmHg or triphasic or biphasic Doppler waveforms at ankle Exclusion: active Charcot disease; electrical, chemical, or radiation burns; collagen vascular disease; ulcer malignancy; untreated osteomyelitis; cellulitis; uncontrolled hyperglycemia; inadequate lower extremity perfusion; normothermic or hyperbaric oxygen therapy; use of corticosteroids, immunosupressants, or chemotherapy; growth factor products; skin or dermal substitutes within 30 days; enzymatic debridement; pregnant or nursing	N=335 (of 341 randomized) Age (years): 59 Gender (% male): 78 Race/ethnicity (%): African-American: 15; Caucasian: 58; Hispanic: 24; Native American: 2; other: 1 BMI: NR Pre-albumin: 20.5 HbA_1c (%): 8.2 Smoking: 19% # Work days missed: NR ABI: 1.0 Wound location: calcaneal, dorsal, or plantar Wound type: diabetic ulcer Wound size: 12.3 cm^2 Wound grade: 2 or 3 Wound duration: 202 days Comorbid conditions (%): History of DM: 100	Intervention (n=172): NPWT - vacuum-assisted closure therapy; dressing changes every 48-72 hrs Comparator (n=169): advanced moist wound therapy (AMWT) Off-load: NPWT 97%; AMWT 98% *Antibiotic Use*: NR (28% treated for infection before randomization) *Treatment Duration*: 112 days *Follow-up Duration*: 3 and 9 months after closure *Study Withdrawal (%)*: NPWT: 32%; AMWT: 25% *Treatment Compliance*: 6/169 (4%) in NPWT group were non-compliant vs. 0% in AMWT group (not defined)	Allocation concealment: Adequate Blinding: Patients and physicians not blinded; unclear if outcome assessment was blinded Intention to treat analysis (ITT): Modified (received at least one post-baseline treatment) Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Blume 2011[15] United States (22 sites) Funding Source: Industry Therapy Type: Collagen	Inclusion: type 1 or 2 diabetes; over age 18 yrs; Wagner Grade 1 cutaneous lower extremity ulcer; 1.5-10.0 cm^2; present ≥6 wks; peripheral neuropathy; adequate blood flow ($TcpO_2$ >40mmHg or toe pressure ≥40mmHg) Exclusion: HbA_1c >12%; ulcer on heel; cellulitis; biopsy positive for beta hemolytic streptococci or total bacterial load >$1X10^6$ CFU/g; decrease in ulcer size >30% from screening to Tx day 1	N=52 Age (years): 56 Gender (% male): 77 Race/ethnicity (%): white 64, black 12, Hispanic 23, other 2 BMI: 34 Pre-albumin: NR HbA_1c (%): 8.0 Smoking: NR # Work days missed: NR ABI: NR Wound location: 89% plantar Wound type: diabetic Wound size: 2.9 cm^2 Wound duration: 15.1 months Comorbid conditions (%): History of DM: 100	Intervention (n=33): formulated collagen gel (FCG) (combined 1 dose and 2 dose groups) (NOTE: included 2nd intervention arm with non-FDA product) Comparator (n=19): standard care (debride, moist dressing) ALL: debridement; 2 wk standard care run-in; off-loading shoe *Antibiotic Use:* NR *Treatment Duration*: 12 weeks *Follow-up Duration*: None *Study Withdrawal (%)*: 6/5 (8/124) *Treatment Compliance*: see WD	Allocation concealment: Unclear Blinding: Investigators were blinded; other study personnel were not Intention to treat analysis (ITT): Yes for safety analysis; per-protocol for other outcomes Withdrawals/dropouts adequately described: Yes (including 2 in FCG group for non-compliance)
Brigido 2006[74] United States Funding Source: NR Therapy Type: Collagen	Inclusion: full thickness (Wagner grade II) chronic wound ≥6 weeks without epidermal coverage; non-infected; palpable/ audible pulse to the lower extremity Exclusion: none reported	N=28 Age (years): 64 Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): 8.0 Smoking: NR # Work days missed: NR ABI: NR Wound location: leg/foot Wound type: mixed Wound size: NR Wound grade: Wagner grade II Wound duration: NR Infection: excluded if infected Comorbid conditions (%): NR	Intervention (n=14): Graftjacket (single application); mineral oil soaked fluff compression dressing changed on days 5, 10, and 15 then weekly assessment Comparator (n=14): Curasol wound gel; gauze dressing; weekly debridement ALL: initial sharp debridement; off-loading with walking boot *Antibiotic Use:* NR *Treatment Duration*: 16 weeks *Follow-up Duration*: None *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes – all patients completed study

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Chang 2000[73] United States Funding Source: NR Therapy Type: Biological Skin Equivalent	Inclusion: non-healing foot ulcer or required partial open foot amputation; ABI <0.5 prior to revascularization surgery; underwent bypass or angioplasty within 60 days of inclusion Exclusion: ABI <0.7 after revascularization surgery; recent steroid use; chemotherapy; previous radiation; wound <2.0 cm^2; infected wound, necrotic tissue, exposed bone, or exposed tendons	N=31 Age (years): 70 Gender (% male): 77 Race/ethnicity (%): NR BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR (see inclusion criteria) Wound type: previously ischemic wounds s/p revascularization surgery Wound size: 4.8 cm^2 Wound duration: NR Infection: excluded Comorbid conditions (%): History of DM: 58% History of amputation: 45% History of PVD: 100% History of renal failure: 39%	Intervention (n=21): meshed (N=10) or unmeshed (N=11) tissue graft (Apligraf); non-adherent dressing, Unna boot & ace wrap; followed every 5-7 days (or more) for 1st month; Unna boot dressing changes each visit until graft maturation Comparator (n=10): moist saline gauze sponges with dry cotton gauze wrapping; changed 2x/day *Antibiotic Use:* NR *Treatment Duration*: wound closure or ≥ 6 months after randomization *Follow-up Duration*: same *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: Unclear if any dropouts
d'Hemecourt 1998[35] United States (10 sites) Funding Source: Industry Therapy Type: Platelet-derived Growth Factors	Inclusion: ≥19 years old; type 1 or 2 diabetes; at least one full thickness (Stage 3 or 4) diabetic ulcer of >8 weeks duration; wound size 1.0-10.0 cm^2; adequate arterial circulation Exclusion: osteomyelitis affecting target ulcer area; >3 chronic ulcers present at baseline; non-diabetic wounds; cancer at time of enrollment; use of concomitant medications (corticosteroids, chemotherapy, immunosuppressive agents); pregnant or nursing	N=172 Age (years): 58 Gender (% male): 74 Race/ethnicity (%): white: 85; black: 10; other: 5 BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: right leg: 3%; left leg: 4%; right foot: 47%; left foot: 47% Wound type: diabetic ulcer Wound size: 3.2 cm^2 Wound grade: 97% Stage III Wound duration: 42.3 weeks Infection: NR Comorbid conditions (%): Diabetes: 100	Intervention (n=30): becaplermin gel 100ug/g and standard care Comparator A (n=70): sodium carboxymethylcellulose Gel (NaCMC) and standard care Comparator B (n=68): standard care – sharp debridement, saline gauze dressing changes every 12 hours, off-loading *Antibiotic Use*: systemic control of infection if present *Treatment Duration*: 20 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 24 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Yes – patients, evaluators Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
DiDomenico 2011[26] United States Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: type 1 or 2 diabetes; Wagner grade 1 or University of Texas 1a ulcer; wound duration >4 weeks; area 0.5-4 cm^2; HbA_1c <12; ABI >0.75; palpable pulses on the study foot; able to comply with off-loading Exclusion: infection or gangrenous tissue or abscesses; exposed bone, tendon, or joint capsule; non-diabetic etiology; use of topical medications that may affect graft material; adjuvant therapy such as hyperbaric oxygen; wound depth <9 mm	N=28 patients (29 wounds) Age (years): NR Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: NR Wound type: diabetic ulcer Wound size: 1.9 cm^2 Wound grade: see inclusion Wound duration: see inclusion Comorbid conditions (%): NR	Intervention (n=17 wounds): Apligraf; up to 5 applications Comparator (n=12 wounds): Theraskin; up to 5 applications ALL: debridement, off-loading; dressing changes every other day or daily, as needed *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: to 20 weeks *Study Withdrawal (%):* NR *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: Yes
Dimakakos 2009[65] Greece Funding Source: NR Therapy Type: Silver Dressing	Inclusion: leg ulcer classified as exclusively infected and venous in origin Exclusion: pregnancy; psychiatric disorders; diabetes; collagen disease; steroid use; history of allergies; ABPI<1	N=42 Age (years): 60 Gender (% male): 38 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: leg Wound type: venous Wound size: NR Wound grade: NR Wound duration: 62% >1 mo Infection: excluded Comorbid conditions: 0% DM	Intervention (n=21): non-adhesive silver-releasing foam Comparator (n=21): non-adhesive foam ALL: cleansing with sterile water and 10% povidone iodine solution; compression bandage *Antibiotic Use*: as needed *Treatment Duration*: 9 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): No withdrawals/ dropouts reported Withdrawals/dropouts adequately described: None reported

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Donaghue 1998[17] United States Funding Source: Industry Therapy Type: Collagen	Inclusion: >21 years of age; serum albumin >2.5 grams/dl; adequate blood flow to lower extremity (palpable pulses); foot ulceration of at least 1 cm^2 Exclusion: severe renal or liver impairment (liver or creatinine tests 2 or more times higher than normal); presence of any disorder that may interfere with wound healing; evidence of osteomyelitis; clinical signs of infection; history of drug or alcohol abuse	N=75 Age (years): 59 Gender (% male): 72 Race/ethnicity: NR BMI: NR Pre-albumin: 3.7 HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic ulcer Wound size: 2.7 cm^2 Wound grade: Wagner I: 12%; II: 75%; III: 13% Wound duration: 172 days Infection: excluded Comorbid conditions (%): Diabetes: 100	Intervention (n=50): collagen-alginate Comparator (n=25): conventional treatment with saline-moistened gauze ALL: felted foam dressing with window at site of ulcer; use of healing sandals; patient self dressing change as required *Antibiotic Use*: NR *Treatment Duration*: 8 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 19 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Driver 2006[37] United States (14 sites including VA wound care clinics) Funding Source: Industry Therapy Type: Platelet Rich Plasma	Inclusion: type 1 or 2 diabetes; age 18-95; ulcer >4 weeks; HbA_1c <12%; index ulcer on plantar, medial, or lateral foot; area 0.5-20 cm^2; Charcot deformity free of acute changes & undergone structural consolidation; ulcer free of infection; no bone, muscle, ligament, or tendon exposure; ≥4 cm from any other wound; adequate perfusion Exclusion: investigational drug or device trial (30 days); ulcer size decrease ≥50% in 7 day run-in; non-diabetic ulcers; serum albumin <2.5 g/dL; hemoglobin <10.5 mg/dL; radiation or chemotherapy; renal dialysis; immune deficiency; known abnormal platelet activation disorder; peripheral vascular repair in past 30 days; known or suspected osteomyelitis; surgery required for healing; exposed tendon, ligaments, muscle, or bone; disorder that may affect compliance; alcohol or drug abuse (past year)	N=40 (of 72 randomized) Age (years): 57 Gender (% male): 80 Race/ethnicity: Caucasian: 60; Hispanic: 30; black: 7.5; other: 2.5 BMI: NR Pre-albumin: NR HbA_1c (%): 7.9 Smoking: NR # Work days missed: NR ABI: NR Wound location (%): right foot: 60; left foot: 40; toe: 38; heel: 40 (NR for 9 patients) Wound type: diabetic ulcer Wound size: 3.5 cm^2 Wound grade: NR Wound duration: NR Infection: excluded Comorbid conditions (%): Diabetes: 100	Intervention (n=40): platelet rich plasma (AutoloGel); applied twice weekly Comparator (n=32): saline gel (Normlgel); applied twice weekly *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: 3 months *Study Withdrawal (%):* 44 *Treatment Compliance:* NR	Allocation concealment: Adequate Blinding: Yes (patients, investigators, outcome assessors) Intention to treat analysis (ITT): Yes but focused on per protocol analysis due to protocol violations (n=24) and failure to complete treatment (n=8) Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Duzgun 2008[47] Turkey Funding Source: NR Therapy Type: Hyperbaric Oxygen (HBOT)	Inclusion: diabetic; ≥18 years; foot wound present for ≥4 weeks despite appropriate local and systemic wound care; wounds were categorized according to a modification of the Wagner classification; contraindication to hyperbaric oxygen therapy (untreated pneumothorax, COPD, history of otic surgery, upper respiratory tract infection, febrile state, history of idiopathic convulsion, hypoglycemia, current corticosteroid, amphetamine, catecholamine, or thyroid hormone use) Exclusion: none reported	N=100 Age (years): 61 Gender (% male): HBOT 74%; Std Care 54%; p<0.05 Race/ethnicity: NR BMI (>30, %): 63 (HBOT 80% Std Care 46%; p<0.05) Pre-albumin: NR HbA_1c (%): 8.4 Smoking: 56% # Work days missed: NR ABI: NR Wound location (%): foot Wound type: diabetic Wound size, cm^2: NR Wound grade (Wagner) (%): Grade II 18%; III 37%; IV 45% Wound duration, months: NR Comorbid conditions (%): History of DM: 100% History of HTN: 60% History of hyperlipidemia: 58%	Intervention (n=50): HBOT administered at maximum working pressure of 20 ATA; unichamber pressure room; volume of $10m^3$ at 2 to 3 ATA for 90 minutes + standard therapy; treatment was 2 sessions/day, then 1 session on the following day Comparator (n=50): standard therapy ALL: daily wound care (dressing changes, debridement); amputation when indicated *Antibiotic Use*: as needed *Treatment Duration*: 20 to 30 days *Follow-up Duration*: 92 weeks *Study Withdrawal (%)*: None reported *Treatment Compliance*: NR	Allocation concealment: Inadequate "according to a predetermined sequence wherein consecutively enrolled patients corresponding to an even random number received ST, and those corresponding to an odd random number received ST+HBOT" Blinding: None reported Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: None reported
Edmonds 2009[25] Europe, Australia (multi-site) Funding Source: NR Therapy Type: Biological Skin Equivalent	Inclusion: diabetes type 1 or 2; 18-80 years old; primarily neuropathic origin, not infected; present at least 2 weeks; surface area 1-16 cm^2; adequate vascular supply; able to follow treatment protocol (incl. off-loading) Exclusion: active Charcot foot; non-neuropathic origin; target ulcer with evidence of skin cancer; osteomyelitis at any location requiring treatment; infected target ulcer; medical condition which could impair healing; pregnant; corticosteroid use (current or prior); use of immunosuppressive agents; radiation therapy or chemotherapy; prior treatment of study wound; history of drug or alcohol abuse (in past year)	N=72 (of 82 randomized) Age (years): 59 Gender (% male): 86 Race/ethnicity (%): NR BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: plantar, forefoot Wound type: diabetic ulcer Wound size: 3.0 cm^2 Wound grade: NR Wound duration: 1.8 years Comorbid Conditions (%): Diabetes: 100	Intervention (n=33): Apligraf (at week 0 and weeks 4 and 8, if needed) + Mepitel contact layer dressing Comparator (n=39): Mepitel ALL: weekly debridement if needed; saline-moist dressing; off-loading *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: 24 weeks post-treatment *Study Withdrawal (%)*: 12 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Falanga 1998[54] United States (15 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion:18-85 years of age; ulcer due to venous insufficiency (clinical signs/symptoms); no significant arterial insufficiency (ABI>0.65); evidence of venous insufficiency (air plethysmography or photo-plethysmography (refilling time <20 seconds) Exclusion: clinical signs of cellulitis, vasculitis, or collagen vascular disease; pregnancy or lactation; uncontrolled diabetes; other impaired wound healing (renal, hepatic, hematologic, neurologic, or immunological disease); received corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy in past month	N=275 (of 309 randomized) Age (years): 60 Gender (% male): 52 Race/ethnicity(%): white 76; black 18; Asian 1; Hispanic 4 BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: >0.65 per inclusion Wound location: NR Wound type: venous Wound size: 1.2 cm^2 Wound duration: <6 months: 31%; 6-12 months: 21%; 1-2 years: 14%; >2 years: 35% Comorbid conditions (%): NR	Intervention (n=146): human skin equivalent (Apligraf) + elastic wrap; applied up to 5 times in first 3 wks (days 0, 3-5, 7, 14, and/or 21) until estimated area of graft "take" >50%; compression alone continued for total of 8 wks Comparator (n=129): compression therapy reapplied weekly for 8 wks *Antibiotic Use*: NR *Treatment Duration*: 8 weeks *Follow-up Duration*: 6 months *Study Withdrawal (%)*: unclear; analysis of 275/309 (89%) *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Partial – number of dropouts (n=72) is different than number not included in data analysis (n=34)
Falanga 1999[55] See Falanga1998[54] United States (15 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: same as above with ulcer duration of >1 year Exclusion: same as above	N=120 for efficacy analysis (demographics from n=122; 2 extra in treatment group by "double randomization") Age (years): 58 Gender (% male): 61 Race/ethnicity (%): white 71; black 22; Asian 0; Hispanic 6 Wound size: 1.74 cm^2 Wound duration >1 year: 100% Comorbid conditions (%): NR	Intervention (n=74): same as above Comparator (n=48): same as above *Antibiotic Use*: NR *Treatment Duration*: 8 weeks *Follow-up Duration*: 6 months *Study Withdrawal (%)*: NR for subset of patients *Treatment Compliance*: NR	Allocation concealment: Not applicable to subset Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: No – number of dropouts in subset not reported
Fumal 2002[79] Belgium Funding Source: NR Therapy Type: Silver Products	Inclusion: at least 2 similar looking chronic leg ulcers; minimal size 16 cm^2; no evidence for clinical infection Exclusion: neurological disorders; arterial occlusion; hypertension; diabetes; intake of antibiotics or any other drug acting on microcirculation or blood coagulation	N=17 patients (34 ulcers) Age (years): 55 NOTE: no other patient characteristics reported	Intervention (n=17 ulcers): 1% silver sulfadiazine cream applied 3x/week Comparator (n=17 ulcers): standard care ALL: saline rinse, hydrocolloid dressing, compression bandage *Antibiotic Use*: NR *Treatment Duration:* 6 weeks *Follow-up Duration:* none *Study Withdrawal (%):* NR *Treatment Compliance:* NR	Allocation concealment: NR Blinding: No Intention to treat analysis (ITT): Yes (no withdrawals reported) Withdrawals/dropouts adequately described: None reported

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Gentzkow 1996[21] Pilot study for Naughton United States (5 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: type 1 or 2 diabetes under reasonable control; ulcers on plantar surface or heel; full-thickness defect >1 cm^2; wound bed free of necrotic debris/infection and suitable for skin graft (no exposed tendon, bone, or joint; no tunnels or sinus tracts that could not be debrided); adequate circulation (clinical signs and ankle-arm index (AAI) >0.75); ability to complete 12-week trial Exclusion: >1 hospitalization during previous 6 months due to hypoglycemia, hyperglycemia or ketoacidosis; ulcers of nondiabetic origin; use of medications known to interfere with healing (e.g., corticosteroids, immunosuppressives, or cytotoxic agents); pregnancy	N=50 Age (years): 61 Gender (% male): 70 Race/ethnicity (%): NR BMI: NR HbA_1c (%): 8.4 Smoking: NR # Work days missed: NR ABI: ankle-arm index 1.0 Wound location: plantar surface or heel Wound type: diabetic ulcer Wound size: 2.4 cm^2 Wound grade: NR Wound duration: 55.6 weeks Comorbid conditions (%): NR	Intervention: Dermagraft *Group A* (n=12): weekly (8 pieces & 8 applications) *Group B* (n=14): every 2 wks (8 eight pieces & 4 applications) *Group C* (n=11): every 2 wks (4 pieces & 4 applications) Control *Group D* (n=13): standard wound therapy ALL: sharp debridement; saline-moist gauze; off-loading *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: mean 14 mos *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No
Hammarlund 1994[72] Sweden Funding Source: NR Therapy Type: Hyperbaric Oxygen (HBOT)	Inclusion: non-diabetic chronic (> 1 year duration) leg ulcers; distal blood pressure at ankle and first digit within normal range (≥100% and ≥70%, respectively, of upper arm blood pressure in mmHg) Exclusion: smoking; concomitant chronic conditions (e.g., diabetes, collagen disease); large vessel disease; ulcers showing tendency to heal (by visual inspection) during 2 months prior to study	N=16 Age (years, median): HBOT 71; control 63 Gender (% male): 50 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 0% (excluded) # Work days missed: NR ABI: NR Wound location: leg Wound type: venous Wound size: 992 mm^2 Wound grade: NR Wound duration: NR but >1 yr Comorbid conditions (%): History of DM: 0%	Intervention (n=8): HBOT at 2.5 ATA for 90 minutes 5 days/week; multi-place hyperbaric chamber; pressurized for total of 30 sessions over 6 weeks Comparator (n=8): placebo (hyperbaric air) ALL: continued pre-study treatment *Antibiotic Use*: NR *Treatment Duration*: 6 weeks *Follow-up Duration*: 18 weeks (12 from week 6) *Study Withdrawal*: 0 *Treatment Compliance*: 100%	Allocation concealment: Adequate Blinding: Patients, investigators Intention to treat analysis (ITT): Yes (none) Withdrawals/dropouts adequately described: Yes (none)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Hardikar 2005[29] India (8 sites) Funding Source: NR Therapy Type: Platelet-derived Growth Factor	Inclusion: type 1 or 2 diabetes; 18-80 years old; ≥1 full thickness chronic neuropathic ulcer of ≥4 weeks duration; stage 3 or 4 (Wound, Ostomy and Continence Nurses); infection controlled; area 1-40 cm^2; adequate perfusion of foot (by ultrasonography, pulse, ABI, ankle or toe pressure) Exclusion: arterial venous ulcers; osteomyelitis or burn ulcers; poor nutritional status (total proteins <6.5 g/dL); uncontrolled hyperglycemia (HbA_1c>12%), persistent infection; life threatening concomitant diseases; foot deformities; chronic renal insufficiency (sCr>3mg/dL); corticosteroid or immunosuppressant use; hypersensitivity to gel components; childbearing age, pregnant or nursing without contraceptive use	N=113 Age (years): 55 Gender (% male): 70 Race/ethnicity (%): native of India: 100 BMI: NR Pre-albumin: NR HbA_1c (%): 7.5 Smoking: NR # Work days missed: NR ABI: 1.06 Wound location: foot Wound type: diabetic Wound size: 12.8 cm^2 Wound grade: NR Wound duration: 22.6 weeks Comorbid conditions (%): History of DM: 100	Intervention (n=55): 100ug rh-PDGF (0.01%) gel applied daily with volume calculated based on ulcer size Comparator (n=58): placebo gel applied daily ALL: debridement, daily ulcer cleaning and dressing, off-loading *Antibiotic Use*: appropriate use of systemic antibiotics advised *Treatment Duration*: 20 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 18.6 *Treatment Compliance:* 97.3% (for gel application, dressing changes, and off-loading)	Allocation concealment: Unclear Blinding: Unclear (reported to be double-blind but not specified) Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Harding 2005[60] Multinational – Belgium, United Kingdom, Germany, and Poland (21 sites) Funding Source: Industry Therapy Type: Keratinocytes (LyphoDerm; freeze-dried lysate from cultured allogeneic epidermal keratinocytes)	Inclusion: age 30–85; clinical and documented (refilling time <20 sec or duplex ultrasound in past 12 months) venous insufficiency; no evidence of significant arterial insufficiency (ABI>0.8); ulcer duration >6 wks not healed with std care; size: 1-20 cm^2 Exclusion: arterial, decubitus, or diabetic ulcer; cellulitis or vasculitis; condition that impairs healing; systemic corticosteroids, immunosuppressive agents, radiation therapy, chemotherapy or surgical treatment/sclero-therapy (past 3 months or planned); bed/wheelchair-bound; clinically significant infected ulcer; consistently bleeding or excessively exudating wound; exposed bone/tendon/fascia; treatment with cell- or growth factor-derived therapies (past month or planned); DVT; other clinical study (past month); allergic to study materials; alcohol or drug abuse (past 5 years); ulcer margin change >3 mm during 4 wk run-in	N=194 (of 200 randomized) Age (years): 67.5 (median) Gender (% male): 39 Race/ethnicity (%): white: 100 BMI: 28.9 (median) Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI:1.1 (median) Wound location: leg (61% on medial side) Wound type: venous leg ulcers Wound size: 5.2 cm^2 (median) Wound grade: NR Wound duration: 43 weeks (median) Comorbid conditions (%): History of DM: 6 (12/194)	Intervention (n=95): LyphoDerm 0.9%; 8 applications (wks 0, 1, 2, 3, 4, 6, 8, 10) + standard care (dressing with hydrocolloid and compression therapy) Comparator (n=53): vehicle only + standard care Comparator (n=46): standard care ALL: 4 week run-in period with alginate, hydrocolloid, foam, hydrogel dressings, or petrolatum gauze and compression therapy *Antibiotic Use*: NR *Study Duration*: 28 wks (4 wk run in, 10 wk tx, 14 wk follow up) *Study Withdrawal (%)*: 8.2 (16/194) *Treatment Compliance*: 86.6% had no protocol deviation	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No (excluded 6 patients who weren't treated then one patient from std care group with no baseline data); due to protocol violations, created an "as treated" ITT group (n=193) and a PP group (n=167) Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Harding 2011[66] Europe (43 sites) Funding Source: Industry (reported that sponsor designed study and approved final article; authors had full control over contents of article) Therapy Type: Silver Products	Inclusion: ≥18 years; male or female; ABI ≥0.8; venous leg ulcer (CEAP classification C6); duration <24 months; size 5-40 cm^2; ≥3 of the following: pain between dressing changes, perilesional skin erythema, edema, foul odor, or high levels of exudate Exclusion: current antibiotics (week before inclusion); ulcers clinically infected or erysipelas; malignant; recent DVT or venous surgery (past 3 months); progressive neoplastic lesion treated by radiotherapy or chemotherapy; receiving immunosuppressive agents or high dose corticosteroids	N=281 Age (years): 70 Gender (% male): 35 Race/ethnicity: NR BMI: 30 Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: 1.04 Wound location: 2% foot, 47% ankle, 33% calf, 18% gaiter Wound type: venous Wound size: NR Wound grade: CEAP C6 Wound duration: 0.76 yr Comorbid conditions (%): NR	Intervention (n=145): AQUACEL Ag (4 wks); AQUACEL (4 wks) Comparator (n=136): Urgotul Silver (4 wks); Urgotul (4 wks) ALL: compression; dressing changes per clinical condition & exudate; cleansing; mechanical debridement if needed *Antibiotic Use*: NR *Treatment Duration*: 8 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 8% AQUACEL; 12% Urgotul *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): Modified (had at least one exposure to treatment) Withdrawals/dropouts adequately described: Yes
Ieran 1990[70] Italy Funding Source: NR Therapy Type: Electromagnetic (EMT)	Inclusion: skin lesions (ulcers due to idiopathic chronic venous insufficiency or post-phlebitic venous insufficiency) present at least for 3 months Exclusion: patients treated with steroids or affected by systemic diseases; concomitant arterial occlusive disease	N=37 (of 44 randomized) Age (years): 66 Gender (% male): 38 Race/ethnicity: NR BMI: NR, Obese 51% Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: leg Wound type: venous Wound size: <15 cm^2 - EMT 54% (mean 4.8), control 46% (5.0); >15 cm^2 - EMT 36% (mean 34.2), control 64% (39.9) Wound duration: 26 months Comorbid conditions (%): History of DM: 19	Intervention (n=22): EMT stimulator (single pulse of electrical current generating a magnetic field of 2.8 mT at a frequency of 75 Hz, with an impulse width of 1.3 ms for 3-4 hours daily) Comparator (n=22): sham EMT ALL: no elastic compression *Antibiotic Use:* as needed *Treatment Duration*: 90 days or until wound healed *Follow-up Duration*: at least one yr *Study Withdrawal (%)*: 16% (n=7) *Treatment Compliance*: Average stimulator use per day (hours) – intervention 3.8, control 3.7	Allocation concealment: Adequate Blinding: Patients, investigators Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Jacobs 2008[39] United States Funding Source: NR Therapy Type: Silver Sulfadiazine Cream (SSC)	Inclusion: Wagner grade 1 or 2 ulcerations of the foot; ulcer size 3 cm diameter or less; located on plantar aspect of foot; under care for diabetes mellitus; demonstration of biphasic or triphasic arterial sounds on arterial Doppler; ABI of ≥0.75 Exclusion: HbA_1c greater than 10%; non-palpable pulses or history of claudication or rest pain; clinical evidence of local sepsis (absence of malodor, exudates, or erythema extending >1 cm from the ulceration)	N=40 Age (years): NR Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): ≤10% for inclusion Smoking: NR # Work days missed: NR ABI: ≥0.75 for inclusion Wound location: plantar Wound type: diabetic ulcer Wound size: 3 cm diameter or less for inclusion Wound grade: Wagner 1 or 2 Wound duration: NR Comorbid conditions (%): History of DM: 100	Intervention (n=20): Bensal HP applied daily Comparator (n=20): SSC applied every 12 hours ALL: debride; off-loading of weight bearing and shoe pressure *Antibiotic Use*: NR *Treatment Duration*: 6 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes (none)
Jaiswal 2010[32] India Funding Source: NR Therapy Type: Platelet-derived Growth Factors	Inclusion: type I or type II diabetes and chronic ulcers of at least 4 weeks duration; IAET stage III and IV Exclusion: ankle brachial pressure index (ABI) <0.9	N=50 Age (years): 53 Gender (% male): 84 Race/ethnicity: NR BMI: 22.4 Pre-albumin: NR HbA_1c (%): NR Smoking (%): 18 # Work days missed: NR ABI: NR Wound location: lower limb Wound type: diabetic Wound size: 28.2 cm^2 Wound grade: IAET class III – 62%; class IV – 38% Wound duration (median wks): Intervention 5; Control 6 Infection: NR Comorbid conditions (%): History of DM: 100 History of amputation or previous ulcer: 4% History of PVD: 0%	Intervention (n=25): topical rhPDGF gel (PLERMIN) applied once daily Comparator (n=25): topical KY Jelly applied once daily ALL: off-loading in patients with plantar ulcers *Antibiotic Use*: NR *Treatment Duration*: 10 weeks *Follow-up Duration*: NR *Study Withdrawal (%):* NR *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Jørgensen 2005[77] Europe and North America (7 countries, 15 sites) Funding Source: Industry Therapy Type: Silver Products	Inclusion: chronic venous or mixed venous/ arterial leg ulcer with delayed healing process (area reduction of ≤0.5 cm in past 4 wks); ABI ≥0.65; compression therapy for 4 wks prior to inclusion; ulcer size ≥2 cm^2; max of 1.5 cm from edge of 10X10 cm dressing; at least 1 of a) increased exudate (past 4 wks), b) increased ulcer area pain (past 4 wks, per patient), c) discoloration of granulation tissue, d) foul odor (per study personnel) Exclusion: clinical infection; current use of antiseptics/antibiotics (1 wk prior to inclusion & through study); HbA_1c >10%, current systemic corticosteroids >10mg/d or other immunosuppressants from 4 wks prior to inclusion; disease that may interfere with healing	N=129 Age (years): 74 (median) Gender (% male): 36 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: 1.0 Wound location: "leg" Wound type: venous or mixed venous/ arterial Wound size: 6.4 cm^2 (median) Wound grade: NR Wound duration: 1.05 years (median) Comorbid conditions (%): NR	Intervention (n=65): sustained release silver foam dressing (Contreet Foam) Comparator (n=64): foam dressing without added silver (Allevyn Hydrocellular) ALL: compression therapy; dressing in place as long as clinically possible (max=7 days) *Antibiotic Use*: Excluded *Treatment Duration*: 4 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 15.5% *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No (open study) Intention to treat analysis (ITT): For safety outcomes; per-protocol analysis for performance outcomes Withdrawals/dropouts adequately described: Yes
Jude 2007[40] United Kingdom, France, Germany, Sweden (18 sites) Funding Source: Industry Therapy Type: Silver Products (dressing)	Inclusion: type 1 or 2 diabetes with HbA_1c ≤12%; serum creatinine ≤200 µmol/l; Grade 1 or 2 (Wagner) diabetic foot ulcer of non-ischemic etiology Exclusion: allergic to dressing components; known or suspected malignancy local to the study ulcer; taking systemic antibiotics >7 days prior to enrollment; inadequate arterial perfusion (ABI<0.8, great toe SBP<40 mmHg, or forefoot $TcPO_2$ <30 mmHg (supine) or <40 mmHg (sitting))	N=134 Age (years): 60 Gender (% male): 74 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): 8.0 Smoking: NR # Work days missed: NR ABI: 1.8 Wound location: 68% plantar; 32% non-plantar Wound type: 75.5% neuropathic, 24.5% neuroischemic Wound size: 3.7 cm^2 Wound grade (%): Wagner I 75.5; Wagner II 24.5 Wound duration: 1.3 yrs Comorbid conditions (%): History of DM: 100%	Intervention (n=67): sterile, non-woven sodium carboxymethyl-cellulose primary ionic silver (AQAg, 1.2%) dressing; in place up to 7 days or as indicated Comparator (n=67): sterile, non-woven calcium alginate (CA) dressing (moistened for use on dry wounds, changed daily on infected wounds) ALL: off-load of plantar ulcers *Antibiotic Use*: at clinician's discretion (15.5% at enrollment) *Treatment Duration*: 8 weeks or to healing *Follow-up Duration*: none *Study Withdrawal (%)*: 16 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): No (final wound evaluation for 65 of 67 in each group) Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Karatepe 2011[43] Turkey Funding Source: NR Therapy Type: Negative Pressure Wound Therapy	Inclusion: diabetic foot ulcer Exclusion: none reported	N=67 Age (years): 67.3 Gender (% male): 28 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): 85% poor control Smoking: NR # Work days missed: NR ABI: 93% > 0.7 Wound location: foot Wound type: diabetic ulcer Wound size: 32.4 cm^2 Wound grade: NR Wound duration: 9.9 weeks Comorbid conditions (%): History of DM: 100	Intervention (n=30): Negative Pressure Wound Therapy (no details provided) Comparator (n=37): Standard wound care (no details provided) *Antibiotic Use*: NR *Treatment Duration*: NR *Follow-up Duration*: 1 month after healing (mean of 4 months) *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes – no withdrawals Withdrawals/dropouts adequately described: Yes – no withdrawals
Kenkre 1996[71] United Kingdom Funding Source: Industry Therapy Type: Electromagnetic (EMT)	Inclusion: venous ulcer with unsatisfactory healing for at least the previous 4 weeks Exclusion: none reported	N=19 Age (years): 71 (Group 1 (59) significantly younger than Group 2 (78) & Comp. (73)) Gender (% male): 26 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: leg Wound type: venous Wound size: EMT 600 Hz: 63 mg (6 to 269) EMT 800 Hz: 81 mg (46 to 197) Control: 119 mg (35 to 526) Wound duration: 626 weeks Comorbid conditions (%): NR	Intervention 1 (n=5): EMT (Elmedistraal) - 600 Hz electric field and 25 mT magnetic field Intervention 2 (n=5): EMT (Elmedistraal) - 600 Hz electric field days 1-5 and 800 Hz days 6-30, and 25 mT magnetic field Comparator (n=9): sham (placebo) *Antibiotic Use: NR* *Treatment Duration*: 30 min week days for a total of 30 days *Follow-up Duration*: 4-week observation period (dressing changes only); final assessment on day 50 *Study Withdrawal (%)*: 0	Allocation concealment: Unclear Blinding: Patients, investigators (reported as double-blind) Intention to treat analysis (ITT): Yes (no dropouts) Withdrawals/dropouts adequately described: Yes (no dropouts)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Kessler 2003[48] France Funding Source: Foundation Therapy Type: Hyperbaric Oxygen (HBOT)	Inclusion: type 1 and type 2 diabetes; chronic foot ulcers (Wagner grades I, II, and III) Exclusion: gangrenous ulcers, severe arteriopathy (TcPo2<30 mmHg), emphysema, proliferating retinopathy, claustrophobia	N=27 (of 28 randomized) Age (years): 64 Gender (% male): 70 Race/ethnicity: NR BMI: 29.5 Pre-albumin: NR HbA_1c (%): 8.8 Smoking: NR # Work days missed: NR ABI: NR Wound location: heel/sole 61%, toe 39% Wound type: diabetic Wound size: 2.6 cm^2 Wound grade: Wagner I–III Wound duration: ≥3 months Comorbid conditions (%): History of CAD/CVD: 22 History of DM: 100	Intervention (n=15): HBOT; 2.5 ATA for two 90-min daily sessions of 100% O_2 breathing; multi-place hyperbaric chamber pressurized; 5 days/wk for 2 consecutive wks Comparator (n=13): Wound mgmt ALL: multi-disciplinary wound management program (off-loading, metabolic control, antibiotics) *Antibiotic Use: 63%* *Treatment Duration*: 2 weeks *Follow-up Duration*: 4 weeks *Study Withdrawal (%)*: 4% (n=1) *Treatment Compliance*: NR; hospitalized for first 2 weeks	Allocation concealment: Unclear Blinding: Outcome assessors (surface area of the ulcer) Intention to treat analysis (ITT): No, one withdrawal not included in analysis Withdrawals/dropouts adequately described: Yes
Krishnamoorthy 2003[56] Multinational (6 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: full thickness venous leg ulcer without exposure of muscle, tendon or bone; venous reflux in veins of superficial or deep systems; ulcer duration ≥2 months but ≤ 60 months; size of 3-25 cm^3; ABPI ≥ 0.7; < 50% healing from screening visit to day of first intervention (with use of multi-layer compression bandage during 14 day screening period) Exclusion: other causes of ulceration (rheumatoid vasculitis, diabetic foot ulcer); severe leg edema (could not be controlled with compression bandages); soft-tissue infections that would interfere with wound healing; impaired mobility; any underlying medical condition (e.g., PVD, renal disease)	N=53 Age (years): 69 Gender (% male): 42 Race/ethnicity (%): Caucasian: 94; black: 4; Asian: 2 BMI: 30.4 HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: 1.1 Wound location: leg Wound type: venous Wound size (median): 7.0 cm^2 Wound grade: NR Wound duration (median): 47.7 days Infection: NR Comorbid conditions (%): NR	Intervention: compression and Group 1 (n=13): 1 piece of Dermagraft applied weekly during the first 11 weeks (12 applications) Group 2 (n=13): 1 piece of Dermagraft applied at day 0, weeks 1, 4 and 8 (4 applications) Group 3 (n=14): 1 piece of Dermagraft applied at day 0 Comparator (n=13): compression therapy alone (Profore) *Antibiotic Use*: as needed *Treatment Duration*: 11 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 11.3 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Landsman 2008[20] United States (4 sites) Funding Source: NR Therapy Type: Collagen Compared with Biological Skin Equivalent	Inclusion: ≥18 years, insulin or non-insulin dependent diabetes; HbA_1c 5.5-12%; diabetic ulcer; epidermal ulcers without exposed bone or tendon; viable wound bed with granulated tissue (bleeding following debridement), ulcer size 1-16 cm^2; present ≥4 weeks Exclusion: malnourished; allergic to porcine products; hypersensitivity to Dermagraft; severe arterial disease (ABI <0.9); radiation at ulcer site; corticosteroids or immune suppressant use; immunocompromised; non-diabetic ulcer; vasculitis; severe rheumatoid arthritis; severe infection at wound site; osteomyelitis, necrosis, or avascular ulcer bed; hemodialysis; uncontrolled diabetes; active Charcot's neuroarthropathy	N=26 Age (years): 63 Gender (% male): 69 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: NR Wound type: diabetic ulcer Wound size: 1.9 cm^2 Wound grade: NR Wound duration: NR Comorbid conditions (%):NR	Intervention (n=13): extracellular matrix (OASIS); max of 8 applications Comparator (n=13): living skin equivalent (Dermagraft); max of 3 applications with reapplication at 2 and 4 wks if wound closure not achieved ALL: debrided and cleansed; saline moistened gauze left in place for 1 wk; off-loading (boot) *Treatment Duration*: 12 weeks *Follow-up Duration*: 8 weeks *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No
Lindgren 1998[58] Sweden Funding Source: Industry Therapy Type: Biological Skin Equivalent, Cryopreserved	Inclusion: out-patients; venous ulcers over medial part of the distal third of the legs as determined by clinical impression and ABI (cutoff not given) Exclusion: none reported	N=27 Age (years): 76 (median) Gender (% male): 33.3 Race/ethnicity: NR BMI: NR HbA1c (%): NR Smoking: NR # Work days missed: NR ABI: 1.0 Wound type: venous Wound size: 6.3 cm^2 Wound duration: <2 years: 44.4% >2 years: 55.6% Comorbid conditions (%): NR	Intervention (n=15): keratinocyte allograft + dressing (Mepitel) Comparator (n=12): dressing only ALL: CO2 laser debridement; if infection-free ≥1 wk then pneumatic compression, treatment & elastic compression; inspected on day 3; tx weekly; in bed for 24 hrs; feet elevated when sitting *Antibiotic Use*: as needed *Treatment Duration*: 8 weeks *Follow-up Duration*: 8 weeks *Study Withdrawal (%)*: 0% *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: No

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Londahl 2010[46] Sweden Funding Source: Foundation Therapy Type: Hyperbaric Oxygen (HBOT)	Inclusion: diabetes; ≥1 full-thickness wound; below ankle; >3 months; previously treated at diabetes foot clinic for at least 2 months; adequate distal perfusion or nonreconstructable peripheral vascular disease Exclusion: contraindications for hyperbaric treatment (severe obstructive pulmonary disease, malignancy, and untreated thyrotoxicosis); current drug or alcohol misuse; vascular surgery in the lower limbs within the last two months; participation in another study; suspected poor compliance	N=94 Age (years): 69 Gender (% male): 81 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c(%): 7.9 Smoking: 25% current # Work days missed: NR ABI: NR Wound location (%): toe 40; plantar forefoot 26; middle 14; malleoli 6; heel 12; dorsal 1 Wound type: diabetic Wound size: 3.0 cm^2 Wound grade (Wagner) (%): Grade II 26; III 56; IV 18 Wound duration, months: 9.5 Comorbid conditions (%): History of CAD/CVD: MI 29%; stroke 16% History of DM: 100% History of amputation: 11% major; 39% minor History of HTN: 75% History of hyperlipidemia: 88%	Intervention (n=49): HBOT; ATA of 2.5; multi-place hyperbaric chamber; compression of air for 5 minutes followed by 85-min daily (session duration 95 min); 5 days/wk; 8 weeks (40 treatment sessions) Comparator (n=45): placebo (hyperbaric air); same schedule ALL: standard treatment at multi-disciplinary diabetes foot clinic (debride, off-load, treatment of infection, revascularization, metabolic control) *Antibiotic Use*: Allowed *Treatment Duration*: 8 weeks *Follow-up Duration*: 1 year *Study Withdrawal (%)*: 20 (n=19) *Treatment Compliance*: 57% attended 40 sessions; 80% attended >35 sessions; compliance with standard tx NR	Allocation concealment: Unclear (“sealed envelopes”) Blinding: Patients, investigators, outcome assessments_ Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Marston 2003[23] United States (35 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: ≥18 years; type 1 or 2 diabetes; plantar forefoot or heel ulcer present ≥2 weeks; 1.0-20 cm^2; full thickness but no exposed muscle, tendon, bone, or joint capsule; no necrotic debris; healthy vascularized tissue present; ABI >0.7; adequate circulation to the foot (palpable pulse) Exclusion: gangrene on affected foot; underlying Charcot deformity; ulcer size changed (+ or -) by >50% during 2 wk screening; severe malnutrition (albumin <2.0); random blood sugar >450 mg/dl; urine ketones present; nearby non-study ulcer; on systemic corticosteroids, immunosuppressive/cytotoxic agents; AIDS or HIV-positive; at-risk for bleeding; cellulitis, osteomyelitis, or other infection	N=245 (ulcer duration >6wks) Age (years): 56 Gender (% male): 74 Race/ethnicity (%): Caucasian 72; Non-Caucasian 28 BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR (>0.7 for inclusion) Wound location: plantar forefoot (87%) or heel (13%) Wound type: diabetic ulcers Wound size: 2.4 cm^2 Wound duration: 53 wks (41 wks vs. 67 wks, p=NR) Comorbid conditions (%): History of DM 100	Intervention (n=130): Dermagraft; applied weekly up to 8 times over 12 week study Comparator (n=115): standard wound care ALL: sharp debridement + saline-moistened gauze dressings; ambulatory with diabetic footwear *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: 1 week follow-up to confirm closure *Study Withdrawal (%)*: 19 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No
McCallon 2000[44] United States Funding Source: NR Therapy Type: Negative Pressure Wound Therapy	Inclusion: diabetes; age 18-75 years; non-healing foot ulceration present >1 month Exclusion: venous disease; active infection not resolved by initial debridement; coagulopathy	N=10 (pilot study) Age (years): 52.8 Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: 9 forefoot, 1 midfoot Wound type: diabetic ulcer Wound size: NR Wound grade: NR Wound duration: NR Comorbid conditions (%): History of DM: 100	Intervention (n=5): continuous pressure (125 mmHg) for 48 hrs; dressing change then intermittent pressure (125 mmHg); dressing change/assessment every 48 hrs Comparator (n=5): saline moistened gauze; changed every 12 hrs; assessed 3 times/wk ALL: initial surgical debridement; bed rest or strict non-wt bearing *Antibiotic Use*: NR *Treatment Duration*: NR *Follow-up Duration*: Followed until delayed primary closure or wound healed by secondary intention *Study Withdrawal (%)*: 0 *Treatment Compliance*: NR	Allocation concealment: Inadequate Blinding: No Intention to treat analysis (ITT): Yes – no withdrawals Withdrawals/dropouts adequately described: Yes – no withdrawals

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Michaels 2009 a,b[67,68] England (2 locations) Funding Source: Government Therapy Type: Silver Products	Inclusion: active ulceration of lower leg, present for more than 6 weeks Exclusion: insulin-controlled diabetes mellitus; pregnancy; sensitivity or specific contraindications to the use of silver; ABI <0.8 in affected leg; maximum ulcer diameter <1 cm; atypical ulcers (e.g., suspicion of malignancy); coexisting skin conditions or vasculitis; receiving oral or parenteral antibiotic treatment	N=213 Age (years): 71 Gender (% male): 46 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 18.3% # Work days missed: NR ABI: NR Wound location: leg Wound type: venous Wound size: 72% <3 cm diam Wound grade: NR Wound duration: 38.5% present for >12 weeks Comorbid conditions (%): History of CAD/CVD: 14% history of MI or cardiac failure, 8% history of stroke or TIA	Intervention (n=107): silver-donating dressings (list of 6 approved for study) Comparator (n=106): non-silver dressings (any non-antimicrobial low-adherence dressing) ALL: multilayer compression bandage (per local practice); dressings changed weekly unless needed; other interventions used if clinically appropriate *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: to 1 year after entry *Study Withdrawal (%)*: 2.3% *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Miller 2010[78] Australia (2 sites) Funding Source Foundation, Government Therapy Type: Silver Products	Inclusion: lower leg ulcer; ABI ≥0.6; diameter ≤15 cm; ≥18 years; no topical antiseptic treatment in week before and no antibiotics 48 hrs before recruitment; no systemic steroids; no diagnosis of diabetes or malignancy related to ulcer; not receiving palliative care; no known contraindications to treatment products; ≥ 1 sign of infection or critical colonization (cellulitis, suppuration, lymphangitis, sepsis, bacteremia, changes in granulation tissue, increased or malodorous exudate, new areas of slough or wound breakdown, impaired or delayed wound healing, increased or new pain) Exclusion: none reported	N=266 (of 281 randomized) Age (years): 80 Gender (% male): 41 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: lower leg 97% Wound type: venous (74%), mixed (26.3%) Wound size: 705 mm^2 Wound grade: NR Wound duration: 54 weeks Comorbid conditions (%): History of DM: 0	Intervention (n=140): Acticoat (silver); clinician chose dressing Comparator (n=141): Iodosorb (iodine); clinician chose dressing ALL: treated until signs of critical colonization and infection absent 1 wk; non-antimicrobial dressing if no signs; required adherence to compression bandaging *Antibiotic Use*: 21% (55/266) *Treatment Duration*: 12 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 5 *Treatment Compliance*: Monitored compression bandage adherence	Allocation concealment: Adequate Blinding: No – open label Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Mostow 2005[53] United States, United Kingdom, Canada (12 Sites) Funding Source: Industry Therapy Type: Biological Dressings	Inclusion: chronic venous insufficiency (clinical presentation, history) and/or positive venous reflux; ≥18 years; ulcer >30 days; 1-49 cm^2; between knee and ankle; full thickness and non-healing; visible wound bed with granulation tissue Exclusion: infected, necrotic, or avascular ulcer bed; cellulitis, osteomyelitis, or exposed bone/ tendon/fascia; severe RA; uncontrolled CHF or diabetes (HbA_1c >12%); ABI <0.8; history of local radiation; corticosteroids or immune suppressives; known allergy or hypersensitivity to products; sickle cell disease; hemodialysis; malnutrition (albumin <2.5 g/dL); investigational drug or device treatment in last 30 days	N=120 Age (years): 64 Gender (% male): 42 Race/ethnicity (%): white 81; black 16; Asian 1; other 3 BMI: 31.9 HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR, all >0.8 by exclusion Wound type: venous Wound size: 11.1 cm^2 Wound duration: 1-3 months: 34.2%; 4-6 months: 15.8%; 7-12 months: 10.0%; >12 months: 36.7%; not specified: 3.3% Comorbid conditions (%): NR	Intervention (n=62): OASIS; each week to non-epithelialized portion Comparator (n=58): standard wound care ALL: weekly debride, dressing changes; non-adherent dressing + 4 layer compression bandaging *Antibiotic Use:* NR *Treatment Duration*: 12 weeks; control group offered cross-over to OASIS if not healed; treated for 4 weeks; continued for total of 12 weeks if initial improvement seen *Follow-up Duration*: 6 months; (retained 45% of ITT population) *Study Withdrawal (%)*: 20 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Naughton 1997[22] United States (20 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent – Dermagraft	Inclusion: diabetes; neuropathic full-thickness plantar surface foot ulcers of the forefoot or heel; ulcer size >1.0 cm^2 Exclusion: initial rapid healing in response to standard care during a screening period	N=235 (of 281 randomized) Age (years): NR Gender (% male): NR Race/ethnicity (%): NR BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: plantar forefoot or heel Wound type: Diabetic ulcer Wound size: NR Wound duration: NR Comorbid conditions (%): History of DM: 100	Intervention (n=109): Dermagraft; day 0 and weeks 1-7 (8 total) Comparator (n=126): standard wound care ALL: debridement, infection control, saline-moistened gauze dressings, and off-weighting *Antibiotic Use*: NR *Treatment Duration*: 12 weeks (8 week intervention) *Follow-up Duration*: to 32 weeks *Study Withdrawal (%)*: 16.4 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: “Single-blinded” Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: No

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Navratilova 2004[59] Czech Republic Funding Source: Government Therapy Type: Biological Skin Equivalent, cryopreserved versus lyophilized allografts	Inclusion: venous ulcer diagnosed by history, physical examination, and Doppler ultrasonography Exclusion: arterial ulcer; ulcer size <2 cm^2; duration <3months; uncompensated diabetes mellitus; pronounced anemia (hg <10.0g/dL); uncompensated heart insufficiency; pronounced hypoproteinemia (albumin <3.5g/dL); ABI <0.8; metastatic malignant tumor; systemic immunosuppressive therapy	N=50 Age (years): 63 Gender (% male): 36 Race/ethnicity: NR BMI: 30.1 HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR, >0.8 per exclusion Wound location: leg Wound type: venous ulcer Wound size: 10.7 cm^2 (cryopreserved 12.4 cm^2, lyophilized 9.0 cm^2) Wound duration: 23.7 months (cryopreserved 21 months, lyophilized 17 months) Comorbid conditions (%): NR	Intervention (n=25): single application of cryopreserved cultured epidermal keratinocytes; nonadherent silicone dressing and gauze bandages; dressings removed after 5 days then changed every 3 days Comparator (n=25): same except allografts of lyophilized cultured epidermal keratinocytes ALL: debride and dressings until clean & granulating wound base achieved; wet saline dressings 1-3 days before graft; hospitalized for graft; bed rest and limb elevation for 48 h after grafting *Antibiotic Use*: systemic; 1 day before allografts if infection *Treatment Duration:* single application *Follow-up Duration*: 3 months *Study Withdrawal (%)*: 0% *Treatment Compliance*: NR	Allocation concealment: No Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: None reported

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Niezgoda 2005[19] United States and Canada (9 Sites) Funding Source: Industry (provided study supplies) Therapy Type: Biological Dressings Compared to Platelet-derived Growth Factors	Inclusion: ≥18 years; type 1 or 2 diabetes; non-healing diabetic ulcer of >30 days; ulcer full thickness with size of 1-49 cm^2; visible wound bed with granulation tissue; Grade I, Stage A (UT classification) Exclusion: ulcer of non-diabetic etiology; uncontrolled diabetes (A1C >12%); documented severe arterial disease or low blood supply (TcPO2 <30 mmHg or toe-brachial index <0.70); on corticosteroids or immune suppressives; infected, necrotic, or avascular ulcer bed; cellulitis, osteomyelitis, or exposed bone/tendon/fascia; active Charcot or sickle cell disease; hemodialysis, malnutrition (albumin <2.5 g/dL); known allergy/hypersensitivity to products; treatment with any other investigational drug or device (past 30 days)	N=73 (of 98 randomized) Age (years): 58 Gender (% male): 60 Race/ethnicity %: NR BMI: 32.5 Pre-albumin: NR HbA_1c (%): 8.3 Smoking: NR # Work days missed: NR ABI: NR Wound location: 65% plantar Wound type: diabetic ulcer Wound size: 4.1 cm^2 Wound duration (%): 1-3 months: 49; 4-6 months: 16; 7-12 months: 15 >12 months: 19 Comorbid conditions (%): History of DM: 100% Type 1 - 49% OASIS, 22% PDGF Type 2 - 51% OASIS, 78% PDGF History of PVD: 0% severe	Intervention (n=37): OASIS; saline and secondary dressing; re-applied weekly as needed Comparator (n=36): PDGF (becaplermin/Regranex); patients applied daily; saline-moistened gauze dressing for 12 hrs then rinsed and covered ALL: off-loading; clean and debride weekly *Antibiotic Use*: NR *Treatment Duration*: 12 weeks; if not healed, crossover tx offered; treated for 4 weeks; continued for total of 12 weeks if initial improvement seen *Follow-up Duration*: 6 months (only 50% of per protocol sample) *Study Withdrawal (%)*: 26 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Omar 2004[57] United Kingdom Funding Source: Unclear (“statistical advice and guidance” from industry) Therapy Type: Biological Skin Equivalent, Dermagraft	Inclusion: chronic venous leg ulcers (based on clinical examination, duplex finding of venous dysfunction [all had evidence of superficial reflux, but no deep venous reflux or DVT]; and exclusion of other causes [especially arterial insufficiency, ABPI >0.9]); duration >12 wks; ulcer area 3–25 cm^2, clean ulcer bed with healthy granulation tissue Exclusion: none reported	N=18 Age (years): 60 Gender (% male): 61 Race/ethnicity: NR BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: 1.06 Wound type: venous leg ulcer Wound size: 10.7 cm^2 Wound duration: 119.3 weeks Comorbid conditions (%): NR	Intervention (n=10): Dermagraft at weeks 0, 1, 4 & 8 Comparator (n=8): non-adherent dressing ALL: cleaning, debridement, four-layer compression bandaging *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Unclear (“computer-generated code based on the order of admittance to the study”) Blinding: Yes (ulcer measurement) Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: None reported

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Reyzelman 2009[18] United States (11 sites) Funding Source: Industry (compensation to study personnel and consultants involved in data interpretation and writing; therapy provided at no charge) Therapy Type: Collagen	Inclusion: ≥18 years; type 1 or 2 diabetes; diabetic foot ulcer; 1-25 cm^2; absence of infection; adequate circulation to affected extremity (TcPO2 >30 mmHg, ABI 0.70–1.2, or biphasic Doppler waveforms in arteries of lower extremity) Exclusion: poor glycemic control (HbA_1c >12%); serum Cr >3.0 mg/dl; sensitivity to antibiotics used in preparation of cellular matrix; non revascularable surgical sites; ulcers probing to bone; wound recently treated with biomedical or topical growth factors	N=85 (of 86 randomized) Age (years): 57 Gender (% male): NR Race/ethnicity (%): NR BMI: 33.8 (based on n=83) HbA_1c (%): 7.9 Smoking: NR # Work days missed: NR ABI: NR Wound location (%): toe 28; foot 44; heel 17; other 11 Wound type: diabetic ulcer Wound size: 4.3 cm^2 Wound duration: 23.1 weeks (Note: range=0-139 weeks) Comorbid conditions (%): History of DM: 100; Type 1 – 8.2; Type 2 – 91.8	Intervention (n=47): single application - 4x4 cm human acellular dermal regenerative tissue matrix graft (GRAFTJACKET); sutured or stapled in place; silver-based non-adherent dressing (Silverlon) applied; secondary dressings as determined by investigator Comparator (n=39): standard care (moist-wound therapy with alginates, foams, hydrocolloids or hydrogels at discretion of physician); dressing changes daily or per treating physician ALL: surgical site prep. before tx; off-load (removable cast walker) *Antibiotic Use*: if infection present *Treatment Duration*: 12 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 8% *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes (included all but one intervention group patient who was removed from participation due to non-compliance) Withdrawals/dropouts adequately described: Yes
Romanelli 2007[75] Italy Funding Source: Industry Therapy Type: Biological Dressing	Inclusion: >18 years; mixed A/V leg ulcer by clinical and instrumental assessment; venous reflux by Doppler flow studies; ABPI >0.6 and <0.8; ulcer duration >6 weeks; 2.5-10 cm^2; >50% granulation tissue on wound bed Exclusion: diabetes; current smoker; ABPI <0.6; clinical signs of wound infection; necrotic tissue on wound bed; known allergy to treatment products; unable to follow protocol	N=54 Age (years): 63 Gender (% male): 48 Race/ethnicity (%): NR BMI: NR HbA_1c (%): NR (DM excluded) Smoking: 0 (excluded) # Work days missed: NR ABI: 0.6 to 0.8 Wound type: mixed A/V ulcers Wound size: 6 cm^2 Wound duration: 7.8 weeks Comorbid conditions (%): History of DM: 0 History of PVD: 100	Intervention (n=27): OASIS Comparator (n=27): Hyaloskin ALL: saline + secondary dressing; no compression; observed 2x/wk; dressing change as needed (approx. 1x/wk); all dressings applied in clinic *Antibiotic Use:* NR *Treatment Duration*: 16 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 7.4 (4/54) *Treatment Compliance*: NR	Allocation concealment: Inadequate (every other patient that was selected by clinician for study) Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Romanelli 2010[76] Italy Funding Source: Industry Therapy Type: Biological dressing	Inclusion: venous or mixed A/V leg ulcer; ABI 0.6-0.8; duration >6 months; size >2.5 cm^2; 50% granulation tissue on wound bed Exclusion: clinical signs of infection; ABI <0.6; necrotic tissue on wound bed; known allergy to treatment products; unable to follow protocol	N=50 Age (years): NR Gender (% male): 48 Race/ethnicity (%): NR BMI: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR but for inclusion 0.6-0.8 Wound location: leg Wound type: venous or mixed A/V ulcer Wound size: 24.4 cm^2 Wound duration: 7.1 weeks Comorbid conditions (%): NR	Intervention (n=25): OASIS Comparator (n=25): petroleum-impregnated gauze ALL: moistened with saline + secondary nonadherent dressing; assessed weekly for up to 8 wks; patients changed secondary dressing at home *Antibiotic Use:* NR *Treatment Duration*: 8 weeks *Follow-up Duration*: stated monthly follow-up for 6 months (results not reported) *Study Withdrawal (%)*: 4% (2/50) *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Saad Setta 2011[36] Egypt Funding Sources: NR Therapy Type: Platelet Rich Plasma	Inclusion: age 40-60 yrs; type 1 or 2 diabetes; normal peripheral platelet count (>150,000 mm^3) Exclusion: receiving or had received chemo or radiation therapy in past 3 months; screening serum albumin <2.5 ml/dl or hemoglobin <10.5 mg/dl or platelet count <100x10^9/l; peripheral vascular disease; bacteria count (study ulcer) >10^5 organisms/gram tissue;, exposed tendons, ligaments or bone	N=24 Age (years): NR Gender (% male): NR Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 33.3% # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic Wound size: 9.4 cm^2 Wound grade: NR Wound duration: ≥12 weeks Infection: NR Comorbid conditions (%): History of HTN: 70	Intervention (n=12): platelet rich plasma applied twice weekly (intervals of 3-4 days) Comparator (n=12): platelet poor plasma (same schedule) ALL: off-loading of ulcer area *Antibiotic Use*: NR *Treatment Duration*: 20 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: No (not reported)

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Schuler 1996[69] United States Funding Source: Industry Therapy Type: Intermittent Pneumatic Compression	Inclusion: age >18 years old; ulcers <50 cm^2; ulcers <2 years old Exclusion: ABI <0.9; cancer; massive leg edema due to congestive heart failure; cellulitis; osteomyelitis; sickle cell disease; use of steroids or vasoconstrictive medications; DVT or pulmonary embolism in previous 6 months; vein ligation or injection sclerotherapy in previous year	N=54 Age (years): 57 Gender (% male): 46 Race/ethnicity: NR BMI: 33 Pre-albumin: NR HbA_1c (%): NR Smoking (%): 31 # Work days missed: NR ABI: 1.1 Wound location: NR Wound type: venous ulcer Wound size: 9.9 cm^2 Wound grade: NR Wound duration: 306 days Comorbid conditions (%): NR	Intervention (n=28): below-knee gradient compression elastic stocking + external pneumatic compression; applied daily (1 hour in morning + 2 hours in evening) Comparator (n=26): Unna's boot ALL: leg elevation 2X/day *Antibiotic Use:* NR *Treatment Duration*: 6 months *Follow-up Duration*: NR *Study Withdrawal (%):* 13 *Treatment Compliance*: 93% (4 total dropped for non-compliance)	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Stacey 2000[62] Australia Funding Source: Government, Industry Therapy Type: Platelet Rich Plasma	Inclusion: venous ulceration based on ABI >0.9, venous refilling time < 25 seconds, blood tests negative for other causes of ulceration Exclusion: none reported	N=86 Age (years): 71 Gender (% male): 42 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: leg Wound type: venous ulcer Wound size: 4.9 cm^2 Wound grade: NR Wound duration: 12 weeks Comorbid conditions (%): NR	Intervention (n=42): bandage soaked in platelet lysate in phosphate buffered saline (PBS) Comparator (n=44): placebo (PBS) soaked bandage ALL: compression bandaging; dressings/bandages applied twice weekly *Antibiotic Use:* NR *Treatment Duration*: 9 months *Follow-up Duration*: NR *Study Withdrawal (%)*: 9 *Treatment Compliance*: NR	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Steed 1995, 2006[33,34] United States Funding Source: Industry (responsible for conduct of trial and all analyses) Therapy Type: Platelet-derived Growth Factors	Inclusion: ≥19 years; ulcer area 1-100 cm^2; chronic (≥8 weeks duration) non-healing; full-thickness; lower extremity ulcer resulting from diabetes; free of infection; adequate arterial blood supply Exclusion: nursing, pregnant, or of childbearing potential; hypersensitivity to study gel; >3 ulcers; ulcers from large-vessel arterial ischemia, venous insufficiency, pressure, or necrobiosis lipoidica diabeticorum; osteomyelitis; malignant or terminal disease; alcohol or substance abuse; thermal, electrical, or radiation burn wounds at site of target ulcer; receiving corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy	N=118 Age (years): 61 Gender (% male): 75 Race/ethnicity (%): white: 86; other: 14 BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic ulcer Wound size: 7.2 cm^2 Wound grade: NR Wound duration: 78 weeks Infection: NR Infection: Excluded Comorbid conditions (%): NR	Intervention (n=61): platelet-derived growth factor (PDGF-BB 100ug/g gel) applied once/day by patient or patient caregiver Comparator (n=57): placebo gel applied as above ALL: debridement as needed; instructed on off-loading *Antibiotic Use*: NR *Treatment Duration*: 20 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 27 *Treatment Compliance*: 98% (weight of gel tube, diary of dressing changes)	Allocation concealment: Adequate Blinding: Unclear Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Vanscheidt 2007[61] Europe (Hungary, Czech Republic, Germany) Funding Source: NR Therapy Type: Keratinocytes (autologous keratinocytes combined with fibrin sealant: BioSeed-S)	Inclusion: age 18-90; chronic venous leg ulcers (>3-month duration); area 2-50 cm^2 after sharp debridement (±5%); venous insufficiency (by Doppler sonography with reflux in superficial and/or deep veins, venous refilling time <20 seconds, duplex sonography, or phlebography); ulcer located below knee joint excluding ulcers of distal metatarsal area Exclusion: not able to get/apply compression therapy; ABI <0.8; vasculitis, severe rheumatoid arthritis, or other connective tissue diseases; previous surgery on venous system or sclerotherapy, phlebitis, or DVT in past 3 months; significant medical conditions that impair wound healing (e.g., renal and hepatic insufficiency or uncontrolled diabetes); known hypersensitivity to bovine proteins or other constituents of BioSeed-S (if randomized to that group); pregnant or breast-feeding women, or of childbearing age not using contraception during treatment phase	N=225 Age (years): 67 Gender (% male): 37 Race/ethnicity: NR BMI: 28.6 Pre-albumin: NR HbA_1c (%): NR Smoking: 19.1% # Work days missed: NR ABI: NR, but all >0.8 by criteria Wound location: below knee Wound type: venous leg Wound size: 2-10 cm^2: 60.4% (136/225) >10 cm^2: 38.7% (87/225) Wound grade: NR Wound duration: 3-12 months: 59.1%(133/225) >12 months: 40.9% (92/225) Comorbid conditions (%): NR	Intervention (n=116): *2 wks before Day 0* – skin biopsy to collect and cultivate autologous keratinocytes *Day 0* – debride, disinfect & rinse; applied autologous keratinocytes within fibrin sealant; pressure dressing; compression therapy; repeated up to 3X in first 3 mos; further applications allowed if >2 wks apart; compression therapy maintained throughout 6 months Comparator (n=109): *Day 0* – Same except non-adherent gauze; continuous compression therapy; sharp debridement and paraffin gauze as needed ALL: debrided, routine dressings and compression for 4 weeks prior to Day 0 (not randomized if responsive to std care after 2 wks) *Antibiotic Use:* NR *Treatment Duration*: up to 3 mos *Follow-up Duration*: 6 mos *Study Withdrawal (%)*: NR *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Veves 2001[24] United States (24 sites) Funding Source: Industry Therapy Type: Biological Skin Equivalent	Inclusion: type 1 or 2 diabetes; age 18-80 years; HbA_1c 6-12%; full thickness neuropathic ulcers ≥2 weeks in duration (excluded dorsum of foot and calcaneous); ulcer size 1-16 cm^2; dorsalis pedis and posterior tibial pulses audible by Doppler Exclusion: clinical infection at ulcer site; significant lower extremity ischemia; active Charcot's disease; ulcer of non-diabetic pathophysiology; significant medical conditions that would impair healing	N=208 (of 277 randomized) Age (years): 57 Gender (% male): 78 Race/ethnicity: white: 69; African American: 16; Hispanic: 13 BMI: 32 HbA_1c (%): 8.6 Smoking: NR Alcohol: NR # Work days missed: NR ABI: >1.0 54%; <0.8 10% Wound Type: neuropathic diabetic foot ulcer Wound size: 2.9 cm^2 Wound Duration: 11.3 months Comorbid Conditions (%): NR	Intervention (n=112): Graftskin (Apligraft); at baseline then weekly, if needed, for maximum of 4 weeks (max of 5 application) Comparator (n=96): saline moistened gauze ALL: scheduled dressing changes; off-loading *Antibiotic Use*: NR *Treatment Duration*: maximum of 4 weeks *Follow-up Duration*: 12 weeks with safety evaluation to 3 months *Study Withdrawal (%)*: 21 *Treatment Compliance*: 98%	Allocation concealment: Adequate- Blinding: No Intention to treat analysis (ITT): Modified (excluded 69 patients during 1 week run-in) Withdrawals/dropouts adequately described: Yes
Veves 2002[16] United States (11 sites) Funding Source: Industry Therapy Type: Collagen	Inclusion: ≥18 years of age; diabetic foot ulcer; ≥30 days duration; Wagner grade 1 or 2; area ≥1 cm^3; adequate circulation Exclusion: clinical signs of infection; exposed bone; concurrent condition that may interfere with healing; known alcohol or drug abuse; dialysis; corticosteroids; immunosuppressive agents; radiation or chemotherapy; hypersensitivity to dressing components; inability to be fitted with off-loading device; multiple ulcers on same foot	N=276 Age (years): 58.5 Gender (% male): 74 Race/ethnicity (%): white 63, African American 10; Hispanic 16; Native American 12 BMI: NR Pre-albumin: NR HbA_1c (%): 8.6 Smoking: NR # Work days missed: NR ABI: NR Wound location: foot Wound type: diabetic ulcer Wound size: 2.8 cm^2 Wound grade: NR Wound duration: 3 months (median) Infection: NR Comorbid conditions (%): NR	Intervention (n=138): collagen & oxidized regenerated cellulose dressing (Promogran); application frequency at clinicians' discretion Comparator (n=138): isotonic sodium chloride solution-moistened gauze ALL: surgical debridement at all study visits; dressing changes according to good clinical practice; off-loading *Antibiotic Use*: NR *Treatment Duration*: 12 weeks *Follow-up Duration*: NR *Study Withdrawal (%)*: 32 *Treatment Compliance*: >90% (both groups; tx, dressing change)	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Vin 2002[52] France (14 sites) Funding Source: Industry Therapy Type: Collagen	Inclusion: venous leg ulcers; free of infection; ≥30 days duration; ABPI ≥0.8; 2 cm-10 cm in any one dimension(if multiple ulcers largest was selected if ≥3 cm away from any other ulcer) Exclusion: unwilling to wear compression bandage continuously; immobile and unable to care for themselves; medical condition that may interfere with healing including carcinoma, vasculitis, connective tissue disease, and immune system disorders; received topical corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy in 30 days before study entry	N=73 Age (years): 73 Gender (% male): 35 Race/ethnicity: NR BMI: 28 Pre-albumin: NR HbA_1c (%): NR Smoking (%): 8 # Work days missed: NR ABI: 1.1 Wound location: leg Wound type: venous ulcer Wound size: 8.2 cm^2 Wound grade: NR Wound duration: 9.2 months Comorbid conditions (%): History of CAD: 11; History of DM: 14; History of HTN: 49	Intervention (n=37): Promogran dressing + Adaptec (petrolatum-impregnated dressing) Comparator (n=36): Adaptec only ALL: compression bandages; dressing changes 2x/wk or more *Antibiotic Use:* NR *Treatment Duration*: to 12 weeks *Follow-up Duration (mean)*: Promogran=65.9 days Adaptec=63.8 days *Study Withdrawal (%)*: 26 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Partial (investigator assessment validated by 2 clinicians) Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Viswanathan 2011[41] India Funding Source: Industry Therapy Type: Silver Products	Inclusion: type 2 diabetes; Wagner Grade I, II, or III ulcer Exclusion: clinical signs of severe infection; exposed bone; unwilling to participate in study	N=38 (of 40 randomized) Age (years): 59 Gender (% male): NR Race/ethnicity: NR Pre-albumin: NR HbA_1c (%): 10.7 Smoking: NR # Work days missed: NR ABI: NR Wound location: plantar (66% fore, 24% mid, 11% hind) Wound type: diabetic ulcer Wound size: 4.6 X 3.3 cm Wound grade: 29.0% I, 31.6% II, 39.5% III Wound duration: 14.5 days Comorbid conditions (%): History of DM: 100 History of PAD: 23.7	Intervention (n=20): diabetic wound cream (polyherbal formulation) Comparator (n=20): silver sulphadiazine cream ALL: daily dressing changes (saline wash, cream applied) *Antibiotic Use*: If ulcers showed clinical signs of infection *Treatment Duration*: unclear *Follow-up Duration*: 5 months *Study Withdrawal (%)*: 5 *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis: No Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Vuerstack 2006[80] Netherlands (2 sites) Funding Source: Industry (no influence on data analysis, data interpretation, writing of report, or manuscript submission) Therapy Type: Negative Pressure Wound Therapy	Inclusion: hospitalized with chronic venous, combined venous and arterial, or microangiopathic leg ulcers (>6 months duration); ambulatory; failed conservative local treatment for ≥6 months Exclusion: age >85 years; use of immune suppression; allergy to wound therapies; malignant or vasculitis origin; ABI <0.6	N=60 Age (years): 72 (median) Gender (% male): 23 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: 26% # Work days missed: NR ABI: 100 (median) Wound location: leg Wound type: venous (43%), combined arterial/venous (13%), arteriolosclerotic (46%) Wound size: 38 cm^2 Wound grade: NR Wound duration: 7.5 months Comorbid conditions (%): History of DM: 17% (type 2) History of HTN: 43% Immobility: 42%	Intervention (n=30; 28 received tx): vacuum-assisted; permanent negative pressure (125 mmHg) until skin graft + 4 days after graft Comparator (n=30; 26 received tx): daily local wound care and compression therapy until skin graft; standard care after graft ALL: initial necrosectomy; full-thickness punch skin graft when 100% granulation tissue on surface and wound secretion minimal; only toilet and basic hygiene mobility during treatment *Antibiotic Use*: 3.5% at baseline *Treatment Duration*: to closure *Follow-up Duration*: 12 months *Study Withdrawal (%)*: 10 *Treatment Compliance*: Inpatients	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Unclear (ITT for adverse events but unclear for other outcomes) Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Wainstein 2011[50] Israel Funding Source: NR, device supplied by manufacturer Therapy Type: Ozone-oxygen Therapy	Inclusion: adult (age ≥18 years); type 2 or type 1 diabetes; Wagner classification stage 2 or 3 or post-debridement stage 4 foot ulcer Exclusion: gangrenous foot ulcer; active osteomyelitis; history of collagen diseases; hyperthyroidism; pregnancy or nursing; HbA_1c >10.5%; ABI <0.65; hemoglobin <8 g/dL; liver function tests (alanine transaminase, aspartate transaminase, or c-glutamyl transpeptidase) elevated to more than three times the upper normal limit; serum creatinine >2.5 mg/dL or dialysis; known allergy to ozone	N=61 Age (years): 63 Gender (% male): 62 Race/ethnicity: NR BMI: NR Pre-albumin: NR HbA_1c (%): 8.6 Smoking: 8% current # Work days missed: NR ABI: 26% 0.65-0.8; 23% 0.8-1.0; 46% >1.0 Wound location: foot Wound type: diabetic Wound size (cm^2): ozone 4.9, sham 3.5 Wound grade: Wagner 2-4 Wound duration: 15.8 years Comorbid conditions (%): History of DM: 100%	Intervention (n=31): ozone-oxygen; *Phase I* – tx sessions 4x/wk for 4 wks or granulation in 50% of wound area; max of 1 day between txs (5 day week); gas concentration: 96% oxygen & 4% (80 lg/ mL) ozone; *Phase II* – tx sessions 2x/wk to complete 12 wk tx; gas concentration: 98% oxygen & 2% (40 lg/mL) ozone Comparator (n=30); sham tx; device circulated room air only ALL: debridement; daily wound dressings as needed; tx sessions=26 min *Antibiotic Use*: as needed *Treatment Duration*: 12 weeks *Follow-up Duration*: none *Study Withdrawal (%)*: 44 (27/61) *Treatment Compliance*: NR	Allocation concealment: Unclear Blinding: Double (patient and investigator) Intention to treat analysis (ITT): Yes, all randomized included Withdrawals/dropouts adequately described: Yes

Study, Year Country Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics Ulcer Type	Intervention Comparator Length of Follow-up	Study Quality
Wang 2011[45] Taiwan Funding Source: Research Fund through a University Therapy Type: Hyperbaric Oxygen (HBOT)	Inclusion: chronic non-healing foot ulcers of more than 3 months duration Exclusion: cardiac arrhythmia or pacemaker; pregnancy; skeletal immaturity; malignancy	N=77 (of 86 randomized) Age (years): 62 Gender (% male): NR Race/ethnicity: Asian BMI: NR Pre-albumin: NR HbA_1c(%): 8.4 Smoking: NR # Work days missed: NR ABI: 0.99 (HBOT 0.91, control 1.07; p=0.06 between groups) Wound location (%): plantar foot 71; dorsal foot 29 Wound type: diabetic Wound size, cm^2 (median): HBOT 7; control 4 (p=0.06) Wound grade (Wagner) (%): NR Wound duration, months (median): HBOT 6; control 6 Comorbid conditions (%): History of DM: 100%	Intervention: HBOT (n=45, 2 with bilateral ulcers); ATA of 2.5; 90 min 5 days/wk for 4 wks (20 sessions); multi-place hyperbaric chamber + standard treatment Comparator: extracorporeal shockwave therapy (dermaPACE device) (n=41, 5 with bilateral ulcers); dosage dependent on ulcer size – min of 500 impulses at E2 (0.23mJ/ mm^2 energy flux density) at 4 shocks/sec; 2 times/ wk for 3 wks (6 sessions) *Antibiotic Use*: per physician *Treatment Duration*: 3-4 weeks depending on therapy; some subjects received 2nd course *Follow-up Duration*: none *Study Withdrawal (%)*: 10 (n=9) *Treatment Compliance*: NR	Allocation concealment: Inadequate (odd-even) Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Wieman 1998[31] United States (23 sites) Funding Source: Industry Therapy Type: Platelet-derived Growth Factors	Inclusion: type I or II diabetes; ≥1 full thickness (IAET stage III or IV) wound of lower extremity present for ≥8 weeks; transcutaneous oxygen tension ($TcPo_2$) ≥30 mmHg Exclusion: osteomyelitis affecting target ulcer; post-debridement ulcer size exceeding 100 cm^2; non-diabetic ulcers; cancer; other concomitant diseases; receiving treatment or medication (radiation therapy, corticosteroids, chemotherapy, or immunosuppressive agents); nursing, pregnant, or of childbearing potential not using contraception	N=382 Age (years): 58 Gender (% male): 67 Race/ethnicity: white: 81; black: 12; Asian: 0.3; Hispanic: 6.3; other: 0.3 BMI: NR Pre-albumin: NR HbA_1c (%): NR Smoking: NR # Work days missed: NR ABI: NR Wound location: 55% foot dorsum Wound type: diabetic Wound size: 2.7 cm^2 Wound grade: IAET stage III/IV Wound duration: 49 weeks Infection: NR Comorbid conditions (%): NR	Intervention: becaplermin gel# A) 30ug/g (n=132): amount determined weekly at study visits B) 100ug/g (n=123): amount determined weekly at study visits Comparator (n=127): placebo ALL: daily treatment with gel, sharp debridement; moist saline dressings (2x/day), off-loading *Antibiotic Use*: as needed *Treatment Duration*: 20 weeks *Follow-up Duration*: 3 months *Study Withdrawal (%)*: 19 *Treatment Compliance*: 97.4% (no details provided) #Regranex 0.01%	Allocation concealment: Unclear Blinding: Unclear (reported to be double-blind but not specified) Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

NR=Not Reported; HbA_1c=Hemoglobin A_1c; DM=Diabetes Mellitus; HTN=Hypertension; CAD/CVD=Coronary Artery Disease/Cardiovascular Disease; PVD=Peripheral Vascular Disease; ITT=Intention to Treat Analysis; BMI=Body Mass Index; PRP=Platelet Rich Plasma; rhPDGF=recombinant human Platelet-derived Growth Factor; IAET=International Association of Enterostomal Therapy; IPC=Intermittent Pneumatic Compression; ABI=Ankle Brachial Index; NPWT=Negative Pressure Wound Therapy; HBOT=Hyperbaric Oxygen Therapy

*The Wagner grade system is a classification based on 6 wound grades (scored 0 to 5) to assess ulcer depth

Table 2. Primary Outcomes

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
DIABETIC ULCERS									
Collagen									
Blume 2011[15] (Formulated Collagen Gel)	12	45 (14/31) (p=ns)	31 (5/16)						
Reyzelman 2009[18] (Graftskin)	12	69.6 (32/46) (p=0.03)	46.2 (18/39)	5.7 ± 3.5 weeks (n=32) (p=ns)	6.8 ± 3.3 weeks (n=18)				
Veves 2002[16] (Promogran)	12	37 (51/138) (p=ns) Wound duration <6 months: 45 (43/95); (p=0.056) duration >6 months: 19 (8/43) (p=0.83) Wagner grade 1 or grade 2 – no difference Ulcer size <10 cm^2 or ≥10 cm^2 – no difference	28 (39/138) Wound duration <6 months: 33 (29/89) duration >6 months: 20 (10/49)	7.0 ± 0.4 weeks (p<0.0001)	5.8 ± 0.4 weeks				
Donaghue 1998[17] (Fibracol)	8	48 (24/50) (p=ns)	36 (9/25)	6.2 weeks (p=ns)	5.8 weeks				
Biological Dressings									
Niezgoda 2005[19] (OASIS vs PDGF)	12	49 (18/37) (p=0.06)	28 (10/36)	67 days p=0.25	73 days				
Landsman 2008[20] (OASIS vs. BSE [Dermagraft])	12	76.9 (10/13) (p=ns)	84.6 (11/13)	35.7 ± 41.5 days (p=0.73)	40.9 ± 32.3 days				
Biological Skin Equivalents									
Gentzkow 1996[21] (Dermagraft)	12	Group A: 50.0 (6/12) (p=0.03; A versus D) Group B: 21.4 (3/14) Group C: 18.2 (2/11)	Group D: 7.7 (1/13)	Group A: 12 weeks Group B: >12 weeks Group C: >12 weeks (medians)	Group D: >12 weeks p=0.056 when comparing groups A and D (medians)				

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Naughton 1997[22] (Dermagraft)	12 (then followed to 32 weeks)	38.5 (42/109) (p=0.14) Received Metabolically active Dermagraft: 48.7 (37/76) (p=0.008)	31.7 (40/126)	13 weeks (median)	28 weeks (median)				
Marston 2003[23] (Dermagraft)	12	30 (39/130) (p=0.049)	18 (21/115)	Reported that treatment group healed faster (p=0.04)					
Veves 2001[24] (Apligraf)	12	56 (63/112) (p=0.004)	38 (36/96)	65 days (median) p=0.003	90 days (median)				
Edmonds 2009[25] (Apligraf)	12	51.5 (17/33) (p=0.049)	26.3 (10/38)	84 days (median)	Not estimated since <50% had full closure				
DiDomenico 2011[26] (Apligraf vs. Theraskin)	12 20	41.3 (7/17) (p=ns) 47.1 (8/17) (p=ns)	66.7 (8/12) 66.7 (8/12)	6.9 ± 4.1 weeks (n=8) (p=ns)	5.0 ± 3.4 weeks (n=8)				
Platelet-derived Growth Factor									
Aminian 2000[27] (rhPDGF)	8	57 (4/7) Ulcers (p=0.08)	0 (0/5) Ulcers	6.5 +/- 3.7 weeks	No complete healing				
Agrawal 2009[28] (PDGF)	12	64 (9/14) (p<0.001)	21 (3/14)	NR	NR				
Hardikar 2005[29] (rhPDGF)	10 20	71(39/55) (p<0.001) 85 (47/55) (p<0.05[β])	31 (18/58) 53 (31/58)	46 days (p<0.001) 57 days (p<0.01)	61 days 96 days				
Bhansali 2009[30] (rhPDGF)	20	100 (13/13) (p=ns)	100 (11/11)	50.1 +/- 23.4 days (p=0.02)	86.1 +/- 30.7 days				
Wieman 1998[31] (rhPDGF – Bercaplermin gel)	20	100µg/g: 50 (61/123) (p=0.007) 30µg/g: 36 (48/132) (p=ns vs. placebo gel)	35 (44/127)	100µg/g: 86 days (p=0.01) 30µg/g: NR	127 days				

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Jaiswal 2010[32] (rhPDGF)	10	60 (15/25) (p=ns)	72 (18/25)						
Steed1995 2006[33,34] (rhPDGF)	20	48 (29/61) (p=0.01)	25 (14/57)	30 to 40 days shorter than control group (p=0.01)					
d'Hemecourt 1998[35] (PDGF [Bercaplermin gel) vs. NaCMC or Std care)	20	Gel: 44 (15/34) (p=0.04 vs. std care, p=ns vs. NaCMC)	NaCMC 36 (25/70) Std care: 22 (15/68)	Gel 85 days (p=ns vs. NaCMC or std care)	NaCMC: 98 days Std care: 141 days				
Platelet Rich Plasma									
Saad Setta 2011[36]	20	100 (12/12) (p=ns)	75 (9/12)	11.5 weeks (p<0.005)	17.0 weeks				
Driver 2006[37]	12	ITT: 33 (13/40) (p=ns) PP: 68 (13/19) (p=ns)	ITT: 28 (9/32) PP: 43 (9/21)	PP: 43 days (mean); 45 days (median) (p=ns)	PP: 47 days (mean); 85 days (median)				
Silver Products									
Belcaro 2010[38] (Silver Ointment)	4	39 (13/34) (p<0.05)	16 (5/32)						
Jacobs 2010[39] (Silver Cream (control tx))	6	40 (8/20) (p=ns)	30 (6/20) (Silver)						
Jude 2008[40] (Silver Dressing)	8 or healing	31 (21/67) (p=ns)	22 (15/67)	53 ± 1.8 days (p=ns)	58 ± 1.7 days	(all p=ns except as noted) Healed or Improved: 87.7% Plantar: 81.4% Non-plantar: 100% Baseline antibiotics: 91.7% (p=0.02) None: 86.8% Neuro: 91.2% Neuro-ischemic: 77.0%	70.8% Plantar: 69.6% Non-plantar: 73.7% Baseline antibiotics: 50.0% None: 73.8% Neuro: 71.7% Neuro-ischemic: 68.4%		
Viswanathan 2011[41] (Silver Cream (control tx))	20 (5 months)			43 ± 26.8 days (p=ns)	44 ± 30.7 days (Silver)				

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Negative Pressure Wound Therapy									
Blume 2008[42]	Ulcer closure or 112 days	43 (73/169) (p=0.007)	29 (48/166)	96 days (median)	Could not be estimated				
Karatepe 2011[43]	Re-epithel-ization			4 (1.9) weeks (p<0.05)	5 (1.4) weeks				
McCallon 2000[44]	Satis-factory healing	Patients remained in study until satisfactory healing		23 ± 17.4 days (n=5) (p=ns)	43 ± 32.5 days (n=5)				
Hyperbaric Oxygen Therapy									
Wang 2011[45] (vs. extracorporeal shock wave therapy)	4	First course of treatment 25 (10/40) (p=0.008) Second course 6 (1/17) (p=0.01)	First course of treatment 55 (24/44) Second course 50 (7/14)						
Löndahl 2010[46] (vs. sham)	52	52 (25/48) (p=0.03)	29 (12/42)						
Duzgun 2008[47] (vs. standard/ multi-disciplinary wound therapy)	92	66 (33/50) (p<0.001)	0/50						
		Wagner 2 100 (6/6) (p<0.001)	Wagner 2 0/12						
		Wagner 3 68 (13/19) (p<0.001)	Wagner 3 0/18						
		Wagner 4 56 (14/25) (p<0.001)	Wagner 4 0/20						
Kessler 2003[48] (vs. standard/ multi-disciplinary wound therapy)	4	14 (2/14) (p=ns)	0/13						

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Abidia 2003[49] (vs. sham)	6	62.5 (5/8) (p=0.12)	12.5 (1/8)						
	26	62.5 (5/8) (p=0.31)	25 (2/8)						
	52	62.5 (5/8) (p=0.03)	0 (0/8)						
Ozone-Oxygen Therapy									
Wainstein 2011[50]	24	40.6 (13/32)	reported as 33% n unclear						
VENOUS ULCERS									
Collagen									
Vin 2002[52] (Promogran)	12	ITT: 49 (18/37) (p=ns) PP: 41% (p=ns)	ITT: 33 (12/36) PP: 31%						
Biological Dressings (BD)									
Mostow 2005[53] (OASIS)	12 weeks 6 months	55 (34/62) (p=0.02) 6 months 67 (20/30) (p=ns)	34 (20/58) 6 months 46 (11/24)						
Biological Skin Equivalents									
Falanga 1998[54] Falanga 1999[55] (Apligraf)	6 months	63 (92/146) (p=0.02) Wound duration >1 yr 47 (34/72) (p<0.005)	49 (63/129) 19 (9/48)	61 days (median) (p=0.003) Duration >1 yr 181 days p < 0.005	181 days (median) Could not be determined				
Krishnamoorthy 2003[56] (Dermagraft)	12	Group 1: 38 (5/13) (p=ns) Group 2: 38 (5/13) (p=ns) Group 3: 7 (1/14) (p=ns)	Group 4: 15 (2/13)						

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Omar 2004[57] (Dermagraft)	12	50 (5/10) (p=0.15)	12 (1/8)						
Keratinocytes									
Lindgren 1998[58] (Cryopreserved, allogeneic cells)	8	13 (2/15) (p=ns)	17 (2/12)						
Navratilova 2004[59] (Cryopreserved vs. lyophilized)	12	Cryo-preserved 84 (21/25) (p=ns)	Lyophilized 80 (20/25)	Cryo-preserved 32 days (p=ns)	Lyophilized 27 days				
Harding 2005[60] (Lyophilized, allogeneic) NOTE: Control group is combined standard care and standard care + vehicle groups	24	"As treated ITT cohort" 38 (36/95) (p=0.11) "As randomized ITT cohort" 37 (36/98) (p=0.14)	"As treated ITT cohort" 27 (26/98) "As randomized ITT cohort" 27 (26/95)	139.7 ± 5.6 days (p=0.20)	148.5 ± 5.6 days				
Vanscheidt 2007[61] (Autologous, in fibrin sealant)	6 months	38 (44/116) (p=0.01)	22 (24/109)	176 days (median) (p<0.0001)	Median not reached (>201 days)				
Platelet Rich Plasma									
Stacey 2000[62] (PRP)	39	79 (33/42) (p=ns)	77 (34/44)						
Silver									
Belcaro 2010[38] (Silver Ointment)	4	42 (19/44) (p<0.05)	22 (8/38)						
Bishop 1992[63] (Silver Cream (control tx))	4	0/29 Tripeptide (p=0.01 vs. Silver; p=ns vs. placebo)	21 (6/28) (Silver) 3 (1/29) Tripeptide placebo			5.0‡ (Tripeptide) (p<0.0001 vs. other txs)	3.7 (Silver) 5.0 Tripeptide placebo		
Blair 1988[64] (Silver Dressing)	12	63 (19/30) (p=ns)	80 (24/30)						
Dimakakos 2008[65] (Silver Dressing)	9	81 (17/21) (p=0.02)	48 (10/21)	6.1 weeks (p=NR)	6.4 weeks				

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Harding 2011[66] (2 Silver Dressings)	8 (4 with silver, 4 without)	17 (24/145) AQUACEL (p=0.09)	15 (21/136) Urgotul			67 (97/145)† AQUACEL (p=0.01)	52 (69/136) Urgotul		
Michaels 2009 a,b[67,68] (Silver Dressing)	12 weeks and 1 year	12 weeks 60 (62/104) 1 year 96 (95/99) (both p=ns)	57 (59/104) 96 (90/94)	67 days (median) (p=ns)	58 days (median)				
Intermittent Pneumatic Compression									
Schuler 1996[69]	26	71 (20/28) (p=ns)	60 (15/25)						
Electromagnetic Therapy									
Ieran 1990[70]	12.9 (day 90)	67 (12/18) (p=0.05)	32 (6/19)	71 days	76 days	Excellent# 28 (5/18) Excellent and good# 83 (15/18) (both p=ns)	Excellent# 11 (2/19) Excellent and good# 53 (10/19)	Patient not restricted in activity 44 (8/18) Activity lasted <6 h 39 (7/18) (both p=ns)	Patient not restricted in activity 58 (11/19) Activity lasted <6 h 11 (2/19)
	52	89 (16/18) (p=0.005)	42 (8/19)						
	1 year follow-up from healing	67 (12/18) (p=0.008)	21 (4/19)						
Kenkre 1996[71]	Day 30	0/10 (p=ns)	11 (1/9)					-Groups A and B2 improved ability to walk up flight of stairs following tx -All groups improved in walking a distance of a block of houses -Baseline: "went out for entertainment less often" 58% (11/19); "less sociable to friends and neighbors" 37% (7/19); "went out visiting less frequently" 63% (12/19) -Day 30: 42% (8/19), 16% (3/19), and 37% (7/19), respectively	
	Day 50	All EMT 20 (2/10) EMT Group 1 20 (1/5) EMT Group 2 20 (1/5) (all p=ns)	22 (2/9)						
Hyperbaric Oxygen Therapy									
Hammarlund 1994[72]	18	25 (2/8) (p=ns)	0/8						

Study, year	Time of assess-ment (weeks)	Healed ulcers* % (n/N)		Mean time (± SD or SE)** to ulcer healing		Global assessment		Return to daily activities % (n/N)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
ARTERIAL ULCERS									
Chang 2000[73] (Biologic Skin Equivalent – Apligraf)	24	4 weeks 32 (7/21) 8 weeks 62 (13/21) 12 weeks 86 (18/21) 24 weeks 100 (21/21) (p<0.01 at all time points)	4 weeks 0/10 8 weeks 0/10 12 weeks 40 (4/10) 24 weeks Reported to be 75% (of 10 patients)	7 weeks (median) (p=0.002)	15 weeks (median)				
MIXED LOWER EXTREMITY ULCERS									
Brigido 2006[74] (Collagen)	16	86 (12/14) (p=0.01)	29 (4/14)	11.9 weeks	13.5 weeks				
Romanelli 2007[75] (Biological Dressing - OASIS)	16	81 (21/26) (p<0.001)	46 (11/24)						
Romanelli 2010[76] (Biological Dressing)	8	80 (20/25) (p<0.05)	65 (15/23)	5.4 weeks (p=0.02)	8.3 weeks				
Jørgensen 2005[77] (Silver-releasing Dressing)	4	10 (5/52) (p=ns)	9 (5/57)						
Miller 2010[78] (Silver Dressing)	12	64 (85/133) (p=ns)	63 (84/133)	Reported no significant difference in days to heal					
Fumal 2002[79] (Silver Cream)	NR			15 weeks (p=ns)	16 weeks				
Vuerstaek 2006[80] (NPWT)	At discharge (complete healing)	96 (27/28) (p=ns)	96 (25/26)	29 days (median) (p=0.0001)	45 days (median)				
AMPUTATION ULCERS									
Armstrong 2005[81] (NPWT)	Wound closure or 112 days	56 (43/77) (p=0.04)	39 (33/85)	56 days (median) (p=0.005)	77 days (median)				

SD=Standard deviation; SE=Standard error; tx=Treatment; Neuro=Neuropathic; ITT=Intention to treat population; PP=Per protocol population; NaCMC=sodium carboxymethylcellulose; PDGF=Platelet-derived growth factors; PRP=Platelet rich plasma; BSE=Biological skin equivalent; NPWT=Negative pressure wound therapy

*Complete healing was defined as follows:
Aminian 2000: 100% epithelialization
Brigido 2006: Complete epithelialization without drainage
Landsman 2008: Full epithelialization without drainage or bleeding
Hardikar 2005: Wound closure with full epithelization and no drainage or scab
Schuler 1996: Complete re-epithelialization of the entire wound bed
Vin 2002: 100% reduction in surface area, confirmed by planimetry and the investigator
Blume 2008: Skin closure (100% re-epithelization) without drainage or dressing requirements
Armstrong 2005: 100% re-epithelialization without drainage
Vuerstaek 2006: 2 stage procedure – preparation of wound for skin grafts (granulation tissue covered 100% of surface and secretion minimal) then transplantation of skin grafts with goal of complete healing; data are provided for complete healing
Wang 2011: Not reported
Löndahl 2010: Completely covered by epithelial regeneration and remained so until the next visit in the study. Wagner grade 4 ulcers were considered healed when the gangrene had separated and the ulcer below was completely covered by epithelial regeneration
Duzgun 2008: Total closure of the wound without the need for surgical intervention in the operating room (complete cure with bedside debridement)
Abidia 2003: Complete epithelialization
Kessler 2003: Not reported
Hammarlund 1994: Not reported
Ieran 1990: Completed epithelialization
Belcaro: Complete closure
Jacobs: Data are ulcers reported as “resolved” at end of 6 week study – primary outcome in study was wound size reduction so no definition of healed ulcers
Jude, Miller: 100% re-epithelialization
Viswanathan: Complete epithelialization either by secondary intention or by split skin graft
Bishop: “Total healing”
Blair: Not reported
Harding: “Healed”
Michaels: Complete epithelialization of the ulcer with no scab
Jørgensen: “Closed”

**Some studies reported median time (as noted)

[β]Several covariates were seen as important to the increased healing witnessed in the rhPDGF group: overall baseline ulcer size ($p<0.001$), use of antibiotics increased healing in the treatment group from 59% to 78% and placebo group from 22.7% to 36% leading to a significant relationship between antibiotic use and the efficacy of treatment drug ($p<0.05$)

[#]Rated by three different physicians unaware of the experimental condition

[‡]Composite score based on erythema, exudation, and granulation (0 to 9+ with lower scores indicating better physical state)

[†]Composite endpoint: wound volume reduction and final wound assessment of improvement

Table 3. Secondary Outcomes – Part A

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
DIABETIC ULCERS												
Collagen												
Reyzelman 2009[18] (Graftskin)	NR*	NR*	2 (1/46) (p=ns)	3 (1/39)	2 (1/46) (p=ns)	0/39						
Veves 2002[16] (Promogran)	12 (17/138) (p=ns)	19 (26/138)										
Donaghue 1998[17] (Fibracol)	Reported no difference in number of infections between groups											
Biological Dressings												
Niezgoda 2005[19] (OASIS vs. PDGF)	18 (9/50) (p=ns)	6 (3/48)					25% (2/8 at 6 months) (p=ns)	33% (2/6 at 6 months)			2 events (# pts not reported)	1 event
Biological Skin Equivalents												
Gentzkow 1996[21] (Dermagraft)	Group A: 17 (2/12) Group B: 29 (4/14) Group C: 27 (3/11) (all p=ns)	Group D: 23 (3/13)					Groups A, B, and C: 0 (of 11 healed) (p=ns)	Group D: 0 (of 1 healed)				
Naughton 1997[22] (Dermagraft)	Reported no difference between groups in occurrence of ulcer infections						Reported recurrence in a “comparable minority” in both groups		12 weeks	7 weeks		

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Marston 2003[23] (Dermagraft)	Infection 10.4 (17/163) (p=ns) Osteo-myelitis 8.6 (14/163) (p=ns) Cellulitis 7.4 (12/163) (p=ns) Overall 19.0 (31/163) (p=0.007)	Infection 17.9 (27/151) Osteo-myelitis 8.6 (13/151) Cellulitis 9.3 (14/151) Overall 32.5 (49/151)			8 (13/163) had surgical procedure (p=ns)	15 (22/ 151)						
Veves 2001[24] (Apligraf)	Infection 10.7 (12/112) (p=0.67) Osteo-myelitis 2.7 (3/112) (p=0.04) Cellulitis 8.9 (10/112) (p=ns)	Infection 13.5 (13/96) Osteo-myelitis 10.4 (10/96) Cellulitis 8.3 (8/96)	6.3 (7/112) (p=0.03)	15.6 (15/96)			5.9 (3/112) (p=0.42)	12.9 (4/96)				
Edmonds 2009[25] (Apligraf)	3 (1/33)[β] (p=ns)	0/39	0/33 (p=ns)	2.6 (1/39)			7 (1/15) (p=ns)	10 (1/10)				
Platelet-derived Growth Factor												
Wieman 1998[31] (rhPDGF)	100µg/g: 29 (36/123) (p=ns) 30µg/g: 23 (30/132) (p=ns)	31 (39/127)					NR Reported to be approximately 30% in all treatment groups at 3 month follow-up; number with follow-up data not reported				100µg/g: 6 (7/123) (p=ns) 30µg/g: 6 (8/132) (p=ns)	2 (2/127)
Steed 2006 1995[33,34] (rhPDGF)	Infection 11 (7/61) (p=ns) Cellulitis 5 (3/61) (p=ns) Overall 11.4% (p=ns)	Infection 16 (9/57) Cellulitis 12 (7/57) Overall 26.3%					26% (p=ns)	46%	8.6 weeks	8.5 weeks	7 (4/61) (p=ns)	11 (6/57)

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
d'Hemecourt 1998[35] (rhPDGF – Bercaplermin gel versis NaCMC gel or Std Care)	Gel Cellulitis: 3 (1/34) Osteo-myelitis: 9 (3/34) Infection: 21 (7/34) (all p=ns)	NaCMC Cellulitis: 10 (7/70) Osteo-myelitis: 10 (7/70) Infection: 30 (21/70) Std Cellulitis: 15 (10/68) Osteo-myelitis: 13 (9/68) Infection: 28(19/68)									Gel 6 (3/34) (all p=ns)	NaCMC15 (11/70) Std 15 (10/68)
Platelet Rich Plasma												
Driver 2006[37]							PP: 5 (1/13) (p=ns) at 12 weeks	PP: 0				
Silver Products												
Jude 2008[40] (Silver Ointment)	16 (11/67) (p=ns)	12 (8/67)										
Viswanathan 2011[41] Silver Cream (control tx)	5 (1/20) (p=ns)	0/20					47 (9/19) (p=ns)	42 (8/19)				
Negative Pressure Wound Therapy												
Blume 2008[42]	2.4 (4/169) (p=ns)	0.6 (1/166)	4.1 (7/169) (p=0.04)	10.2 (17/166)								
Hyperbaric Oxygen (HBOT)												
Löndahl 2010[46]			Major 6.1 (3/49) (p=ns)	Major 2.2 (1/45)	Open 0% PTA 12.2 (6/49) (p=ns)	Open 0% PTA 8.9 (4/45)						

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Duzgun 2008[47]			Minor-distal 8.0[b] (4/50) (p<0.01) Minor-proximal 0/50 (p<0.01)	Minor-distal 48.0[c] (24/50) Minor-proximal 34.0† (17/50)	Debride-ment† 0/50 (p=0.003)	Debride-ment† 18.0 (9/50) [Ulcer grade 2=8 Ulcer grade 3=1]						
Abidia 2003[49]	37.5 (3/8) (p=ns)	25 (2/8)	Major 12.5 (1/8) Minor 12.5 (1/8) (both p=ns)	Major 12.5 (1/8)	0/9 (p=ns)	11.1 (1/9) ††						
Ozone-Oxygen Therapy												
Wainstein 2011[50]	"wound infection" 3.1 (1/32)	"infection" 3.4 (1/29)	0/32	3.4 (1/29)								
VENOUS ULCERS												
Collagen												
Vin 2002[52] (Adaptec)	0 (0/37) (p=0.03)	14 (5/36)									19 (7/37) (p=ns)	11 (4/36)
Biological Dressings (BD)												
Mostow 2005[53] (OASIS)	1.6 (1/62) (p=0.11)	8.6 (5/58)					0 (0 of 19 healed ulcers at 6 months) (p=0.03)	30 (3 of 10 healed ulcers at 6 months)				

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Biological Skin Equivalents												
Falanga 1998[54] Falanga 1999[55] (Apligraf)	Cellulitis: 8 (12/146) (p=ns) Infection: Reported no difference between groups	Cellulitis: 8 (10/129)					12 (11/92)[a] (p=0.48) Wound duration >1 yr 18 (13/72) (p=ns)	16 (10/63)[a] 22 (12/54)			Reported no difference in pain between treatment groups	
Krishna-moorthy 2003[56] (Dermagraft)	Reported no differences in incidence of infection between groups											
Keratinocytes												
Navratilova 2004[59] (Cryo-preserved vs lyophilized allografts)											Reported pain significantly reduced (p<0.001) during 1st week after application in both groups	
Harding 2005[60] (Lyophilized, allogeneic) NOTE: Control group is combined standard care and standard care + vehicle group	14 (13/95) (p=ns)	11 (11/99)					22 (8/36) (p=0.78)	19 (5/26)			Tx Period: 4 (4/95) (p=ns) Follow-up Period: 2 (2/89) (p=ns)	2 (2/99) 0/91
Silver Products												
Bishop 1992[63] (Silver Cream (control tx)							No healed ulcers	At 1 yr 17 (1/6) (Silver) 0/1 (Tri-peptide placebo) (p=ns)				

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Dimakakos 2009[65] (Silver Dressing)											100% pain-free at 8 wks	62% pain-free at 9 wks
Harding 2011[66] (Silver Dressing)	11 (16/145)*** AQUACEL (p=ns)	9 (12/136) Urgotul										
Michaels 2009a,b[67,68] (Silver Dressing)							Of ulcers healed in 1st year 12 (11/95) (p=ns)	14 (13/90)				
Intermittent Pneumatic Compression												
Schuler 1996[69]											VAS score: 2.0 ± 1.4 (p=ns)	VAS score: 3.1 ± 2.3
Electromagnetic Therapy												
Ieran 1990[70]	Day 90 3 ulcers	11 ulcers					Among healed ≤90 days: 2 patients Among healed >90 days: 2 patients 25 (4 of 16 healed) (p=ns)	Among healed ≤90 days: 3 patients Among healed >90 days: 1 patient 50 (4 of 8 healed)			0.7 cm (from baseline 5.1 cm, based on 11 cm analog scale (p=ns)	1.4 cm (from baseline 5.3 cm, based on 11 cm analog scale

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Kenkre 1996[71]	Day 50 0/10 (p=ns)	Day 50 22.2 (2/9)									Pain in analog scale, mm (range) <u>Day1 600Hz</u> 60 (37-76) <u>Day 30</u> 17 (0-44), (p<0.05 from day 1) <u>Day1 800Hz</u> 62 (29-90) <u>Day 30</u> 36 (0-84), (p<0.05 from day 1)	Pain in analog scale, mm (range) <u>Day 1</u> 47 (0-68) <u>Day 30</u> 41 (0-88)
ARTERIAL ULCERS												
Chang 2000[73] (Apligraf)	14.3 (3/21) (p=ns)	0 (0/10)					4.8 (1/21) (p=ns)	0 (0/10)				
MIXED LOWER EXTREMITY ULCERS												
Brigido 2006[74] (Collagen))	21 (3/14) (p=ns)	36 (5/14)†										
Romanelli 2007[75] (Biological Dressing - OASIS)											3.7** (p<0.05)	6.2**
Romanelli 2010[76] (Biological Dressing - OASIS)	0/25 (p=ns)	0/25									0/25 (p=ns)	0/25

Study, year (Treatment)	Ulcers infected during treatment % (n/N)		Amputation % (n/N)		Revascularization/ surgery % (n/N)		Recurrence % (n/N)		Recurrence, mean or median time to (± SD or SE)		Pain/discomfort % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Jørgensen 2005[77] (Silver-releasing Dressing)											Both groups reported de-creased pain during treatment	
Vuerstack 2006[80] (NPWT)	0 (p=ns)	3 (1/30)					52 (12/23) (p=ns)	42 (10/24)	4th month (median) (p=ns)	2nd month (median)	Pain as AE: 10 (3/30) (p=ns) SF-MPQ[d] Baseline: 9 (4) 8 weeks: 1 (1) PPI[e] Baseline: 2.5 (1) 8 weeks: 0.2 (0.7) (both p<0.05)	3 (1/30) 10 (3) 1 (1) 3.1 (1) 0.4 (0.6)
AMPUTATION ULCERS												
Armstrong 2005[81] (NPWT)	17 (13/77) (p=0.04)	6 (5/85)	3 (2/77) (p=0.06)	11 (9/85)								

NR=Not Reported, NPWT=Negative Pressure Wound Therapy; PTA=Percutaneous Transluminal Angioplasty; VAS=Visual Analog Scale for pain (0-100 mm); NaCMC=sodium carboxymethylcellulose; PDGF=Platelet-derived growth factors; PRP=Platelet rich plasma; BSE=Biological skin equivalent; NPWT=Negative pressure wound therapy

[†]No patient required antibiotic treatment or hospital stay. Numbers include infection at the wound site such as periwound erythema or local cellulitis

*Any infections were treated and not otherwise reported unless leading to a further adverse event

**Pain at end of treatment (VAS with 0=none, 10=severe)

[β]One patient reported as having multiple infections (osteomyelitis during treatment, and cellulitis during follow-up)

†Debridement=operative surgical debridement of the wound was all that was required to achieve closure

††Required an "urgent vascular intervention"

***Infection and infestation

[a]Measured as recurrence at 12 months in those with complete wound closure at 6 months

[b]HBOT: distal wounds Wagner 3=1; Wagner 4=3

[c]Control: distal wounds Wagner 2=4; Wagner 3=17; Wagner 4=3. Proximal wounds Wagner 4=17

[d]Short Form-McGill Pain Questionnaire (SF-MPQ: 0-45, with 45 reflecting maximum sensory and affective score); mean (SD); significant decrease over time

[e]Present Pain Intensity (PPI: 1-5, mild to excruciating); mean (SD);significant decrease over time and significantly lower in VAC group at baseline and 8 weeks

Table 4. Secondary Outcomes – Part B

Study, year (Treatment)	Hospitalization % (n/N)		Required home care % (n/N)		Quality of life Mean/median (±SD/SE)		*Other (note)* % (n/N)		*Other (note)* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
DIABETIC ULCERS										
Biological Skin Equivalents										
Marston 2003[23] (Dermagraft)							Surgical procedure related to study ulcer: 8 (13/163) (p=0.07)	15 (22/151)		
Negative Pressure Wound Therapy										
Karatepe 2011[43]					Reported positive effect of NPWT on mental (p=0.03) & physical (p=0.004) health (SF=36) compared to standard treatment					
McCallon 2000[44]							Delayed primary closure 80 (4/5) (p=ns)	Delayed primary closure 40 (2/5)		
Hyperbaric Oxygen Therapy										
Löndahl 2010[46]	Leading to study withdrawal 6.1 (3/49) (p=ns)	4.4 (2/45)								
VENOUS ULCERS										
Biological Dressings										
Mostow 2005[53] (OASIS)	Hospitalization resulting in failing to complete study 3 (2/62) (p=ns)	0/58								

Study, year (Treatment)	Hospitalization % (n/N)		Required home care % (n/N)		Quality of life Mean/median (±SD/SE)		*Other (note)* % (n/N)		*Other (note)* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Keratinocytes										
Harding 2005[60] (Lyophilized, allogeneic) NOTE: Control group is combined standard care and standard care + vehicle group	2 (2/95) (p=ns)	1 (1/99)								
Platelet Rich Plasma (PRP)										
Stacey 2000[62]	Reported 2 hospitalizations leading to withdrawal but group not reported									
Silver Products										
Michaels 2009a,b[67,68] (Silver Dressing)					EQ-5D 12 weeks 0.73 (n=81) 1 year 0.75 (n=61) SF-6D 12 weeks 0.69 (n=73) 1 year 0.71 (n=55) (all p=ns)	 12 weeks 0.70 (n=76) 1 year 0.668 (n=58) 12 weeks 0.70 (n=68) 1 year 0.67 (n=53)				
MIXED LOWER EXTREMITY ULCERS										
Romanelli 2007[75] (OASIS)							Mean time to dressing change 6.4 ±1.4 days	2.4 ±1.6) (p<0.05)	Comfort w/ treatment 2.5 (p<0.01) (0=excellent, 10=critical)	6.7

Study, year (Treatment)	Hospitalization % (n/N)		Required home care % (n/N)		Quality of life Mean/median (±SD/SE)		*Other (note)* % (n/N)		*Other (note)* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Jørgensen, 2005[77] (Silver-releasing Dressing)					EQ-5D 0.79 (p=ns) (1=perfect health, 0=death)	0.79	Odor present 19 (10/52) of ulcers (p=0.03)	39 (22.57)	Dressing changes associated with leakage 19 (10/52) (p=0.002)	49 (28/57)
Vuerstack 2006[80] (NPWT)					EQ-DSI[a] Baseline 40 (13) 8 weeks 76 (17)	Baseline 45 (19) 8 weeks 77 (14)	Wound bed prep time (median): 7 days (p=0.005)	17 days	Skin graft survival: 83% (p=0.01)	70%
AMPUTATION ULCERS										
Armstrong 2005[81] Apelqvist 2008[82] NPWT	Inpatient stay, mean days: 10.6 (p=ns)	9.9					Overall procedures, mean #: 43 (p<0.001)	120	Clinic visits, mean #: 4 (p<0.05)	11

NPWT=Negative pressure wound therapy; EQ-5D=EuroQol 5D; SF-6D=Single index measure generated from SF-36 data; SF-36=Short-Form 36
[a]EuroQol Derived Single Index (EQ-DSI) with higher score reflecting better health status; significant increase over time (both groups)

Table 5. Secondary Outcomes – Part C

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
DIABETIC ULCERS												
Collagen												
Blume 2011[15] (Formulated Collagen Gel)	6 (2/33) (p=ns)	0										
Reyzelman 2009[18] (Graftskin)	6 (3/47) (p=ns)	5 (2/39)	Same as WD due to AE	Same as WD due to AE	0/47 (p=ns)	0/39						
Veves 2002[16] (Promogran)			Non-serious AE: 27 (37/138) Serious AE: 18 (25/138) (both p=ns)	Non-serious AE: 25 (34/138) Serious AE: 25 (35/138)	1.4 (2/138) (p=ns)	4.3 (6/138)						
Donaghue 1998[17] (Fibracol)	Reported that overall 7% (5/75) patients withdrew due to AE; no difference between groups											
Biological Dressings												
Niezgoda 2005[19] (OASIS vs. PDGF)			Reported no difference in proportion of patients with complications or AEs		2 (1/50) (p=ns)	0/48						
Biological Skin Equivalents (BSE)												
Gentzkow 1996[21] (Dermagraft)							Reported no adverse device effects					
Naughton 1997[22] (Dermagraft)			Reported no difference between groups in occurrence of intercurrent events									
Marston 2003[23] (Dermagraft)			67 (87/130) (p=ns)	73 (84/115)								

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Veves 2001[24] (Apligraf)	5.4 (6/112) (p=ns)	9.4 (9/96)			1/208; treatment group not specified							
Edmonds 2009[25] (Apligraf)	3 (1/33) (p=ns)	10 (4/39)	Serious AE (Tx phase) 12 (4/33) (p=ns)	13 (5/39)	3 (1/33) (p=ns)	0 (0/39)	0 (0/33) (p=ns)	0 (0/39)				
DiDomenico 2011[26] (Apligraf vs. Theraskin)			29 (5/17) (p=ns)	25 (3/12)								
Platelet-derived Growth Factor												
Agrawal 2009[28] (PDGF)							7 (1/14) (p=ns)	0 (0/14)				
Hardikar 2005[29] (rhPDGF)	4 (2/55) (p=ns)	5 (3/58)			0/55 (p=ns)	0/58						
Bhansali 2009[30] (rhPDGF)			Reported no adverse events in either group									
Wieman 1998[31] (rhPDGF – Bercaplermin gel)	100µg/g: 11 (13/123) 30µg/g: 13 (17/132) (both p=ns)	10 (13/127)			100µg/g: 1 (1/123) 30µg/g: 2 (3/132) (both p=ns)	2 (3/127)						
Jaiswal 2010[32] (rhPDGF)			Reported no local or systemic side-effects in either group									
Steed 2006 1995[33,34] (rhPDGF)			Overall 51 (31/61) (p=ns) Tx Related 16 (10/61) (p=ns)	Overall 60 (34/57) Tx Related 18 (10/57)	0 (p=ns)	4 (2/57)						

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**
d'Hemecourt 1998[35] (PDGF [Bercaplermin gel] versus NaCMC or Std Care)	Gel 15 (5/34) (p=ns vs. both controls)	NaCMC 11 (8/70) Std 24 (16/68)	Gel 65 (22/34) (p=ns vs. both controls)	NaCMC 81 (57/70) Std 71 (48/68)	Gel 3 (1/34) (p=ns vs. both controls)	NaCMC 1 (1/70) Std 3 (2/68)			Wound-related events: Gel 21 (7/34) (p=ns vs. both controls)	NaCMC 27 (19/70) Std 37 (25/68)		
Platelet Rich Plasma												
Driver 2006[37]			Total of 122 events, 60 (49%) in PRP group, 62 (51%) in control group (p=ns)		3 (1/40) (p=ns)	3 (1/32)						
Silver Products												
Belcaro 2010[38] (Silver Ointment)	0/34 (p=ns)	0/32	0/34 (p=ns)	0/32			0/34 (p=ns)	0/32				
Jacobs 2010[39] (Silver Cream (control tx))	0/20 (p=ns)	0/20	0/20 (p=ns)	0/20			0/20 (p=ns)	0/20				
Jude 2007[40] (Silver Dressing)	12 (8/67) (p=ns)	19 (13/67)	37 (25/67) (p=ns)	39 (26/67)	1.5 (1/67) (p=ns)	1.5 (1/67)			Study-related events 16 (11/67) (p=ns)	13 (9/67)		
Viswanathan 2011[41] (Silver Cream (control tx))	5 (1/20) (p=ns)	0/20	0/19 (Per-protocol)	0/19	0/20 (p=ns)	5 (1/20)						
Negative Pressure Wound Therapy												
Blume 2008[42]	11.2 (19/169) (p=ns)	9.0 (15/166)			1.8 (3/169) (p=ns)	1.8 (3/166)						
McCallon 2000[44]	0/5 (p=ns)	0/5			0/5 (p=ns)	0/5						

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Hyperbaric Oxygen Therapy												
Löndahl 2010[46]	2.0 (1/49) (p=ns)	6.7 (3/45)			2.0 (1/49) (p=ns)	6.7 (3/45)	Oxygen toxicity 0/49 (p=ns)	0/45	Baro-traumatic otitis 2.0 (1/49)‡ (p=ns)	0/45‡*	Dizziness 2.0 (1/49) Worsen cataract 2.0 (1/49)	Minor head injury 2.2 (1/45)
Duzgun 2008[47]	0/50 (p=ns)	0/50										
Kessler 2003[48]	6.7 (1/15) (p=ns)	0/13	6.7 (1/15) (p=ns)	0/13	0/15 (p=ns)	0/13			Baro-traumatic otitis 6.7 (1/15) (p=ns)	0/13		
Abidia 2003[49]	0/9 (p=ns)	11.1 (1/9)*	0/9 (p=ns)	11.1 (1/9)*	0/9 (p=ns)	0/9						
VENOUS ULCERS												
Collagen (COL)												
Vin 2002[52] (Promogran)	14 (5/37) (p=ns)	14 (5/36)					14 (5/37) (p=ns)	14 (5/36)				
Biological Dressings (BD)												
Mostow 2005[53] (OASIS)	9.6 (6/62) (p=ns)	10.3 (6/58)	Reported no difference in proportions of patients with AEs between groups (8 events in OASIS group, 15 in control)		1.6 (1/62) (p=ns)	0/58	3 events in 62 patients	3 events in 58 patients				
Biological Skin Equivalents												
Falanga 1998[54] Falanga 1999[55] (Apligraf)	2.1 (3/146) (p=ns)	5.4 (7/129)			3.4 (5/146) (p=ns)	3.1 (4/129)						

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Krishnamoorthy 2003[56] (Dermagraft)	Group 1: 0/13 Group 2: 1/13 Group 3: Unclear† (all p=ns)	Group 4: 0/13	Group 1: 18 AE's, 1 serious Group 2: 15 AE's, 1 serious Group 3: 15 AE's, 4 serious	Group 4: 17 AE's, 0 serious	No deaths							
Keratinocytes												
Harding 2005[60] (Lyophilized, allogeneic) NOTE: Control group is combined standard care and standard care + vehicle group			Local AE: Tx phase 22 (21/95) Follow-up 8 (7/89) General AE: Tx phase 25 (24/95) Follow-up 16 (14/89) (all p=ns)	23 (23/99) 5.5 (5/91) 23 (23/99) 14 (13/91)	1 (1/95) (p=ns)	0/99	Reported no differences between treatment groups in "sensations such as burning, stinging, pain, or itching"					
Vanscheidt 2007[61] (Autologous, in fibrin sealant)			33 (38/116) (63 events) (p=ns for patients) Serious AEs: 10 (12/116) (12 events)	25 (27/109) (51 events) 10 (11/109) (14 events)	0.9 (1/116) (p=ns)^	0.9 (1/109)						
Platelet Rich Plasma												
Stacey 2000[62]	5 patients withdrew from study w/ allergy to paste bandage and 1 w/ trauma on leg from bandages; not detailed by group											

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Silver Products												
Belcaro 2010[38] (Silver Ointment)	0/44 (p=ns)	0/38	0/44	0/38 (p=ns)			0/44 (p=ns)	0/38				
Bishop 1992[63] (Silver Cream - control tx)							Reported no statistical differences among treatment groups					
Blair 1988[64] (Silver Dressing)							13 (4/30) (p=ns)	0/30	Deterio-ration due to cellulitis 7 (2/30) (p=ns)	3 (1/30)		
Dimakakos 2009[65] (Silver Dressing)									0 (0/21) due to tx	0 (0/21) due to tx		
Harding 2011[66] (Silver Dressing)	6 (9/145) AQUACEL (p=ns)	9 (12/136) Urgotul	Any AE 50 (72/145) Related AE 23 (33/145) (both p=ns)	42 (57/126) 18 (24/136)	0/145 (p=ns)	1.4 (2/136)						
Michaels 2009ab[67,68] (Silver Dressing)	1 (1/107) (p=ns)	0/106			12 week tx 0/107 (p=ns) 1st year 4 (4/107) (p=ns)	0/106 4 (4/106)						
Intermittent Pneumatic Compression												
Schuler 1996[69]	4 (1/28) (p=ns)	7.7 (2/26)					0 (0/28) (p=ns)	3.8 (1/26)				
Electromagnetic Therapy												
Ieran 1990[70]	9.1 (2/22)# (p=ns)	0/22			0/22 (p=ns)	0/22						

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Kenkre 1996[71]	0/10 (p=ns)	0/9	68 (13/19) Results not reported by treatment arm		0	NR	Moderate/ severe headache 20 (2/10) Sense of heat, tingling, and "needles and pins" in limbs 30 (3/10)	0/9 33 (3/9)				
ARTERIAL ULCERS												
Chang 2000[73] (Biologic Skin Equivalent - Apligraf)	0/21 (p=ns)	0/10	14.3 (3/21) (p=ns)	0/10	4.8 (1/21) (p=ns) (after ulcer had healed)	0/10						
MIXED LOWER EXTREMITY ULCERS												
Brigido 2006[74] (Collagen)			AEs were comparable between treatment arms									
Romanelli 2007[75] (Biological Dressing – OASIS)	0/27 (p=ns)	0/27	0/27 (p=ns)	0/27	0/27 (p=ns)	0/27						
Romanelli 2010[76] (Biological Dressing – OASIS)	0/25 (p=ns)	0/25	0/25 (p=ns)	0/25	0/25 (p=ns)	0/25						
Jørgensen 2005[77] (Silver-releasing Dressing)			Device-related AEs 6 (4/65) (p=ns)	5 (3/64)					↑ ulcer size 14 (9/65) (p=ns)	25 (16/64)		
Miller 2010[78] (Silver Dressing)			8 (13/140) (p=ns)									
Vuerstack 2006[80] (NPWT)			40% (p=ns)	23%	13 (4/30) (p=ns)	7 (2/30)						

Study, year (Treatment)	Withdrawals due to adverse events % (n/N)		Patients with ≥1 adverse event (%) n/N		All-cause mortality % (n/N)		Allergic reactions to treatment % (n/N)		*Treatment specific adverse events* % (n/N)		*Treatment specific adverse events* % (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
AMPUTATION ULCERS												
Armstrong 2005[81] (NPWT)			52 (40/77) (p=ns)	54 (46/85)								

AE=Adverse event; PP=Per protocol population; NaCMC=sodium carboxymethylcellulose; PDGF=Platelet-derived growth factors; PRP=Platelet rich plasma; BSE=Biological skin equivalent; NPWT=Negative pressure wound therapy

‡2 patients in each group required myringotomy with tube placement due to pain caused by the inability to equilibrate air pressure through the eustachion tube

#allergic reaction to drugs, diagnosed as having rheumatoid arthritis

†3 withdrawals reported in text; 2 withdrawals reported in Figure 1 in article; Table 1 in article includes >1 serious adverse event only in Group 3

^1 additional death in screening phase; treatment group not reported

APPENDIX E. COMMON METHODOLOGICAL ERRORS AND RECOMMENDATIONS FOR FUTURE CLINICAL TRIALS OF WOUND HEALING

1. Common Methodological Errors in Studies of Wound Care

Source:

European Wound Management Association

Gottrup F, Apelqvist J, Price P. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. *J Wound Care.* 2010;19:239-68.

- Lack of validation of subjective assessments
- Lack of description of objective or subjective measures
- Lack of comparable baselines for patient groups
- Lack of blinding for the evaluation of primary outcomes
- Incorrect randomization methods
- Poor definition of primary and secondary objectives
- Number of patients not based on *a priori* sample size calculation
- Randomization method poorly/not described
- Time to wound healing not a primary objective
- Intention-to-treat analysis not used
- Heterogeneous study population
- Number of and reason for dropouts not stated
- No specification of adjuvant treatments
- Small sample size combined with multiple outcome measures
- Reporting of multiple outcomes over multiple time points (increased chance of type 1 error)
- Poor overall study reporting

2. Recommendations for Clinical Trials of Wound Healing

Sources:

Center for Medical Technology Policy

Center for Medical Technology Policy. Effectiveness Guidance Document: Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds. Version 2.0, October 1, 2012. Available at: http://www.cmtpnet.org/effectiveness-guidance-documents/negative-pressure-wound-therapy-egd/. Accessed October 2012.

European Wound Management Association

Gottrup F, Apelqvist J, Price P. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. J Wound Care. 2010;19:239-68.

Panel on Wound Care Evidence-Based Research

Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research obtained using a Delphi process. Wound Repair Regen. 2012;20:284-93.

US Food and Drug Administration

FDA. Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment. 2006. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071324.pdf. Accessed September 2012.

1. "Chronic" needs to be defined or replaced with "non-healing."
2. Studies should be multi-center to include a range of settings.
3. Studies should focus on one wound type with stratification by risk factors for not healing.
4. Exclusion criteria should be minimal to increase generalizability; rationale for inclusion and exclusion criteria should match the goals of the study.
5. Randomization is critical; baseline wound characteristics have a major effect on outcomes. Non-randomized trials should be considered only when there are barriers to conducting randomized trials that can be identified and explained.
6. Interventions should be clearly described and consistent across all patients.
7. Simultaneous and/or sequential interventions should be evaluated when appropriate.
8. Standard care should be clearly defined and consistent across study sites or balanced using stratification of study sites for multi-site studies; large cohort studies with each wound type should establish outcomes achieved with standard care.
9. Protocols for pain management and treatment of comorbid conditions should be standardized in all study arms.
10. Comparator arms in studies of dressings, medications, etc. should be a "vehicle control arm" with the same components except for the active agent; if the effect of the "vehicle" is not known, there should also be a standard care group only.
11. Blinding of subjects and investigators should be employed if feasible; blinded assessment by a third-party evaluator should be considered if blinding of investigators and patients isn't possible.
12. Outcome assessment tools should be pre-specified and protocols standardized across patients and across study sites for multi-site studies.
13. The patient population should be appropriate for the treatment and type of wound to be studied.
14. A substantial proportion of patients should be drawn from clinical settings where wound care is delivered.
15. Chronic ulcers might heal because patients become more compliant with standard therapy when enrolled in a trial; studies should include a run-in period of standard care (1-2 weeks) with entry criterion based on change in ulcer size during the run-in phase to exclude those healing because of compliance.
16. Endpoints should be chosen based on the purpose of the intervention; important outcomes include:
    a. incidence of complete closure (defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart); closure should be confirmed by an independent source; trial should include at least

3 months follow-up following closure to distinguish actual healing from transient wound coverage; partial healing should not be a primary endpoint except partial healing to facilitate surgical wound closure; if purpose of intervention is something other than healing, endpoints should be pre-defined and validated scoring systems used,

b. accelerated wound closure (decreased time to healing); monitoring intervals should be sufficiently short to detect meaningful difference in time to closure between treatment groups; ideally all patients would be followed until healing is achieved,
c. quality of healing (e.g., scarring, contour and feel of healed skin, normalization of skin markings or pigmentation),
d. quality of wound care (e.g., prevention or cure of infection, reduced pain and/or decreased blood loss with debridement, pain), and
e. activities of daily living, quality of life, limb salvage, dressing performance.

17. Potential sources of bias include:
    a. selection bias – allocation concealment is important,
    b. performance bias – clearly define standard care; blind outcome assessment; include independent assessment of outcomes,
    c. attrition bias – document reasons for drop-out; plan for drop-outs, including withdrawals due to wound deterioration,
    d. detection bias – define outcomes; follow-up to detect recurrence, and
    e. publication bias – trials may not be published or available in indexed journals.
18. National or formal wound registries should be developed.