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Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

Chronic ulcers (i.e., ulcers that are unresponsive to initial therapy or that persist despite appropriate care) are estimated to affect over 6 million people in the United States.[1] The incidence is expected to increase as the population ages and as the number of individuals with diabetes increases.[1] Chronic ulcers negatively affect the quality of life and productivity of the patient and represent a financial burden to the health care system.[1,2,3] Within the Veterans Health Administration, during fiscal year 2011, there were over 227,000 ulcer encounters (inpatient and outpatient) involving over 54,000 patients and nearly 77,000 new ulcers.(Source: PAVE ProClarity Cubes (Prevention of Amputations in Veterans Every ProClarity Cubes)).

We focus on chronic ulcers of the lower extremity, in particular, ulcers attributed to either diabetes, venous disease, or arterial disease. Because advanced wound care therapies are typically used for ulcer healing following amputation, we also included post-amputation wounds. Identifying the ulcer etiology is important because the correct diagnosis is one factor in determining appropriate wound care interventions.[4] Treatment modalities and wound care therapies are also selected based on patient factors, past treatment, and provider choice. A brief description of each ulcer type is provided below. We recognize that a non-healing ulcer is likely a result of multiple factors and comorbid conditions. We categorize included studies as diabetic, venous, or arterial according to the study author's description of the ulcer type.

ULCER TYPES

Diabetic Ulcers

Approximately 15% to 25% of individuals with diabetes develop a foot ulcer at some point in their lifetime and an estimated 12% of those patients require lower extremity amputation.[1] Diabetic foot ulcers account for nearly 2/3 of all nontraumatic amputations.[4] Ulcer healing is complicated by diabetic neuropathy, decreased cellular synthesis, and susceptability to infection.[5] Neuropathy can be categorized as sensory (loss of protective sensation), motor (the anatomic structure of foot is deformed creating areas where pressure from an ill-fitting shoe can create ulcers), or autonomic (resulting in denervation of sweat glands so the skin becomes dry and cracked predisposing the foot to infection, calluses etc.).[3,4] Diabetic ulcers are typically located on the plantar aspect of the foot, over the metatarsal heads, or under the heel.[6] The ulcers are characterized by even wound margins, a deep wound bed, cellulitis or underlying osteomyelitis, granular tissue (unless peripheral vascular disease is also present), and low to moderate drainage.[6] Patients should be assessed for adequacy of circulation (claudication or extremity pain at rest, diminished or absent pulses, cool temperature, pallor on elevation, ABI), although due to issues with non-compressible vessels, toe pressures, ultrasonography, or other noninvasive vascular studies may be needed.[7] Diabetic ulcers are typically graded using the Wagner[8] classification:

Grade 0 – no open lesions in a high-risk foot
Grade 1 – superficial ulcer involving full skin thickness but not underlying tissue

Grade 2 – deeper ulcer; penetrating to tendon, bone, or joint capsule
Grade 3 – deeper ulcer with cellulitis or abscess formation, often with osteomyelitis or tendinitis
Grade 4 – localized gangrene
Grade 5 – extensive gangrene involving the whole foot

The University of Texas Diabetic Wound Classification System is also used.[9] This system incorporates ischemia and infection in ulcer assessment. Standard treatment for Grade 1 and 2 diabetic ulcers includes debridement of necrotic tissue, infection control, local ulcer care (keeping the ulcer clean and moist but free of excess fluids), mechanical off-loading, management of blood glucose levels, and education on foot care.[4,7] Osteomyelitis is a serious complication and a delay in diagnosis is associated with significant morbidity (e.g., non-healing, ulcer sepsis, limb loss).[5]

Venous Leg Ulcers

The most common cause of lower extremity ulcers is venous insufficiency. This accounts for 70-90% of leg ulcers.[1,5] The ulcers develop within the setting of venous hypertension; elevated pressures are most commonly caused by valvular incompetence and result in an inefficient return of venous blood upon muscle contraction. Although a number of initiating factors may lead to the valvular incompetence of deep or perforating veins (e.g., deep vein thrombosis, phlebitis, trauma, surgery, or obesity), the resulting clinical picture of chronic venous insufficiency is the same. The congested vessels and pooling of blood result in increased vascular permeability. Water, proteins, and red blood cells leak out into the interstitial space, and pericapillary fibrin deposition occurs. This results in the symptoms of leg edema, hyperpigmentation (from extravasation of red blood cells and hemosiderin buildup), and lipodermosclerosis. Ulcers are thought to develop in this setting of venous stasis for a number of reasons: pericapillary fibrin deposits limit diffusion of oxygen and nutrients to skin tissue; leaked extravascular proteins may trap growth factors and matrix materials necessary for preventing and repairing the breakdown of tissue; and the accumulation or "trapping" of white blood cells may cause the release of proteolytic enzymes and inflammatory mediators.[10] Venous ulcers occur most commonly in the leg (compared with the foot predominance of arterial and diabetic ulcers) and are characteristically found over the medial malleolus. These ulcers are often shallow and can be very large relative to other types of ulcers.[11] Standard treatment is centered on the use of mechanical compression and limb elevation to reverse tissue edema and improve venous blood flow by increasing the hydrostatic pressure.[12]

Arterial Leg Ulcers

Ulcers associated with peripheral artery disease, also commonly known as ischemic ulcers, account for approximately 10% of lower extremity ulcers.[3] This ulcer type develops due to arterial occlusion, which limits the blood supply and results in ischemia and necrosis of tissue in the supplied area. This occlusion is most commonly from atherosclerotic disease, so major risk factors for ischemic ulcers are the same as those in peripheral arterial disease (PAD); cigarette smoking, diabetes, hyperlipidemia, and hypertension.[3] Similarly, patients with ischemic ulcers will complain of PAD-related symptoms such as intermittent claudication or pain that continues despite leg elevation. Other signs of decreased limb perfusion may also be present, such as a shiny, atrophic appearance of the skin, diminished leg hair, cold feet, and dystrophic nails.[4,6]

Evidence of diminished arterial blood flow may be established by finding diminished or absent pedal pulses or, most importantly, by measuring an ankle-brachial index (ABI).[4,5] Because ischemic ulcers are related to poor perfusion, they typically occur at the most distal sites (e.g., the tips of toes) or in areas of increased pressure (e.g., over bony prominences). These painful ulcers often present as well-demarcated, deep lesions, giving the lesions a classically described "punched-out" appearance.[5] Care for ischemic ulcers is centered on reestablishing blood flow and minimizing further losses of perfusion. With severe ischemia, the primary methods for achieving this are vascular surgery and lifestyle modifications. It is important to avoid treatment with mechanical compression if arterial occlusion is a contributing source for the development of an ulcer, as this leads to a worsening of tissue ischemia and necrosis.[4]

ADVANCED WOUND CARE THERAPIES

If ulcers do not adequately heal with standard treatment, additional modalities may be required. We define advanced wound care therapies as interventions used when standard wound care has failed. A large and growing array of advanced wound care therapies of different composition and indications have been developed though their efficacy, comparative effectiveness and harm is not well established. Therapies included in this review are: collagen products (COL), biological dressings (BD), biological skin equivalents (BSE), keratinocytes, platelet-derived growth factor (PDGF), platelet-rich plasma (PRP), silver products, intermittent pneumatic compression therapy (IPC), negative pressure wound therapy (NPWT), electromagnetic therapy (EMT), hyperbaric oxygen (HBOT), topical oxygen, and ozone oxygen. Because collagen may be a vehicle to deliver other bioactive ingredients, we have included in the collagen section only studies of collagen as a matrix material.

A complete description of these therapies, including reference citations, is presented in Appendix A; a brief description follows.

Collagen: Naturally occurring proteins known as collagens have diverse roles in ulcer healing including 1) acting as a substrate for hemostasis, 2) chemotactic properties that attract granulocytes, macrophages, and fibroblasts to aid healing, 3) providing a scaffold for more rapid transition to mature collagen production and alignment, or 4) providing a template for cellular attachment, migration, and proliferation.

Biological Dressings: These dressings consist of biomaterials made from various components of the extracellular matrix and are theorized 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.

Biological Skin Equivalents: These products are laboratory-derived tissue constructs, designed to resemble various layers of real human skin. They are thought to increase healing by stimulating fibrovascular ingrowth and epithelialization of host tissues.

Keratinocytes: Keratinocyte-based therapies for wound healing exist in a variety of forms and are proposed to work by stimulating proliferation and migration of host epithelium from wound edges through the production of growth factors and other cytokines.

Platelet-Derived Growth Factors: These products are designed to help repair and replace dead skin and other tissues by attracting cells that repair wounds and helping to close and heal the ulcers.

Platelet-Rich Plasma: Plasma with a high platelet concentration aids wound healing by attracting undifferentiated cells and activating cell division.

Silver Products: Multiple silver-based products have been developed to aid wound healing due to their broad bactericidal action. Cytotoxicity to host cells, including keratinocytes and fibroblasts, may delay wound closure.

Intermittent Pneumatic Compression: Delivered through inflatable garments containing one or more air chambers, compression propels deep venous blood towards the heart. This treatment 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.

Negative Pressure Wound Therapy: This therapy involves creating a tightly sealed dressing around a wound and using a suction pump to apply negative pressure evenly across the surface in a continuous or intermittent manner. This process is proposed to enhance wound healing by increasing granulation tissue and local perfusion, reducing tissue edema, decreasing bacterial load, and stimulating cellular proliferation via induction of mechanical stress.

Electromagnetic Therapy: This process uses the electrical field that develops from exposure to an oscillating magnetic field. The treatment is thought to work by mimicking or enhancing natural wound-induced electrical fields produced in normal human skin.

Hyperbaric Oxygen Therapy: This therapy requires specialized compression chambers capable of delivering increased concentrations of oxygen (usually 100% oxygen) under elevated atmospheric pressures. Many key aspects of ulcer healing are oxygen dependent and raising arterial oxygen tension and the blood-oxygen level delivered to a chronic ulcer is thought to supply a missing nutrient, promote the oxygen dependent steps in ulcer healing, up regulate local growth factors, and down regulate inhibitory cytokines.

Topical Oxygen Therapy: These products aim to promote ulcer healing by correcting the low oxygen levels found within chronic ulcer.

Ozone Oxygen Therapy: Ozone is an oxidizing agent theorized to promote tissue healing by assisting in the destruction of defective cells, bacteria, and viruses.

PURPOSE AND SCOPE OF REVIEW

A large and growing array of advanced wound care therapies of different composition and for different indications has been developed though the effectiveness, comparative effectiveness, and potential harm is not well established. The purpose of this review is to synthesize the evidence on advanced wound care therapies for treatment of non-healing diabetic, venous, and arterial lower extremity ulcers. We focus on FDA-approved therapies used in adult patients. Our outcomes of interest are complete healing and time to complete healing. Secondary outcomes and adverse events are also reported.

METHODS

TOPIC DEVELOPMENT

This project was nominated by Rajiv Jain, MD (Chief Consultant, Office of Patient Care Services) and Jeffrey Robbins, DPM (Director, Podiatry Service). Our key questions were developed with input from a technical expert panel. We also received guidance from Carolyn Robinson, NP, MSN, and Eric Affeldt, DPM, both from the Minneapolis VA Health Care System.

We address the following key questions:

1. What are the efficacy and harms of therapies for diabetic ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?
2. What are the efficacy and harms of therapies for venous ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?
3. What are the efficacy and harms of therapies for arterial ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

SEARCH STRATEGY

We searched MEDLINE (Ovid) for randomized controlled trials (RCTs) published from 1995 to August 2012 using standard search terms. We limited the search to articles with adults and published in the English language. Search terms included: skin ulcer, foot ulcer, leg ulcer, varicose ulcer, diabetic ulcer, diabetic foot, wound healing, venous insufficiency, artificial skin, biological dressings, negative-pressure wound therapy, collagen, silver, topical oxygen, hyperbaric oxygen, electromagnetic, platelet-derived growth factor, platelet-rich plasma, and intermittent pneumatic compression devices. The search strategy is presented in Appendix B.

We did a similar search of the Cochrane Library, and obtained additional articles by a hand-search of reference lists of pertinent studies and systematic reviews and suggestions from members of our technical expert panel.

STUDY SELECTION

Titles and abstracts were reviewed by researchers trained in the critical analysis of literature. Full text versions of potentially eligible articles were retrieved for review. Our inclusion criteria were as follows:

- Randomized controlled trials
- Studies reported in the English language
- Studies involving adults (18 years and older)

- Intervention must involve collagen-based products, biologic dressings, biologic skin equivalents, keratinocytes, platelet-derived growth factors, platelet-rich plasma, silver products, intermittent pneumatic compression therapy, negative pressure wound therapy, electromagnetic therapy, or hyperbaric or topical oxygen
- Study reports patient outcomes of interest (healed ulcers or time to healing)
- Study published in a peer-reviewed publication after 1995

DATA ABSTRACTION

We abstracted the following data for each included study: author, date of publication, country where study was conducted, funding source, Therapy type, sample characteristics (gender, age, race/ethnicity, body mass index [BMI], hemoglobin A_1c [HbA_1c], smoking status, work days missed, ankle-brachial index [ABI]), ulcer characteristics (type, size, location, grade, duration, infection status), comorbid conditions (hypertension, peripheral vascular disease [PVD], cardiovascular disease, diabetes, or amputation), study inclusion and exclusion criteria, treatment groups, intervention characteristics (product descriptions and application frequency/ duration), treatment duration, follow-up duration, study withdrawals, treatment compliance and study quality (allocation concealment, blinding, analysis approach, description of withdrawals). We abstracted primary outcomes (ulcers healed, time to complete ulcer closure, patient global assessment, and return to daily activities) and secondary outcomes (ulcer infection, amputation, revascularization surgery, ulcer recurrence, time to ulcer recurrence, pain or discomfort, hospitalizations, need for home care, quality of life, all-cause mortality, study withdrawals due to adverse events, and allergic reactions to treatment), by ulcer type, for each treatment. We assessed outcomes following treatment and at follow-up, or as reported. All abstraction was done by trained research personnel and verified by a second research associate under the supervision of a Principal Investigator.

QUALITY ASSESSMENT

We assessed the quality of studies pertaining to the key questions. Individual randomized studies were rated as good, fair, or poor quality based the following criteria: allocation concealment, blinding, analysis approach, and description of withdrawals – a modification of the Cochrane approach to determining risk of bias.[13] We assessed studies for applicability to U.S. Veterans.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by key question and intervention. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question or clinical topic, and drew conclusions based on qualitative synthesis of the findings. Where feasible, results were pooled.

RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence using the method reported by Owens et al.[14] The overall evidence was rated as: (1) high, meaning high confidence that the evidence reflects the true effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, meaning there is low confidence that the evidence reflects the true effect; or (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion.

PEER REVIEW

A draft version of this report was reviewed by clinical content experts as well as clinical leadership. Their comments and our responses are presented in Appendix C.

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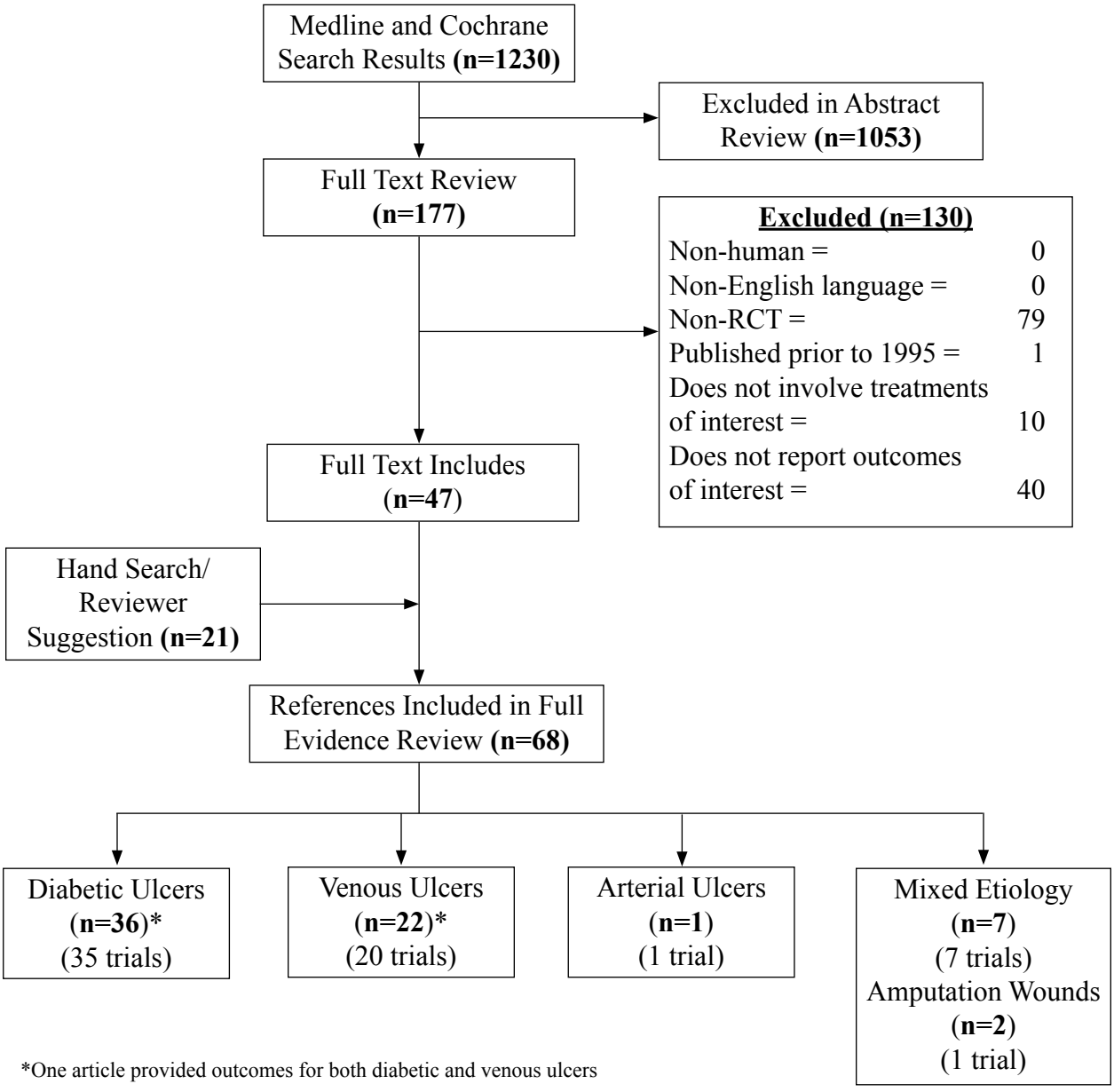
RESULTS

LITERATURE FLOW

We reviewed 1,230 titles and abstracts from the electronic searches. After applying inclusion/exclusion criteria at the abstract level 1,053 references were excluded. We retrieved 177 full-text articles for further review and another 130 references were excluded leaving 47 included references. We added 21 articles from reviewing reference lists of relevant articles and systematic reviews for a total of 68 articles on 64 trials. We grouped the studies by ulcer etiology to address our key questions (see Figure 1).

Figure 1. Literature Flow Diagram



*One article provided outcomes for both diabetic and venous ulcers

KEY QUESTION #1. What are the efficacy and harms of therapies for diabetic ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Overview of Studies

Table 1 contains an overview of studies of treatments for diabetic ulcers.[15-50] Thirty-six articles (35 trials) met eligibility criteria including 4 trials of collagen (n=489 randomized), 2 trials of biological dressings (n=124), 7 trials of biological skin equivalents (one trial included a biological dressing arm) (n=989), 9 trials (in 10 articles) of platelet-derived growth factors (one trial included a biological dressing arm) (n=990), 2 trials of platelet-rich plasma (n=96), 4 trials of silver products (n=280), 3 trials of negative pressure wound therapy (n=418), 5 trials of hyperbaric oxygen therapy (n=326), and 1 trial of ozone-oxygen therapy (n=61). Twenty-five trials compared an advanced wound care therapy to standard care or placebo. In nine trials, the comparator was a different advanced therapy. One trial included both comparators.

Overall, the mean age of study participants ranged from 51 to 71 years; in the majority of studies the mean age was between 55 and 65 years. Between 28% and 100% were male although in all but 3 studies, 60% or more were male. Few studies reported race. In those reporting, 58% to 86% were white, 8% to 16% were black, 6% to 30% were Hispanic, and 2% to 12% were Native American. Mean ulcer sizes ranged from 1.9 to 41.5 cm^2, however, the mean ulcer size was greater than 10 cm^2 in only 6 of 29 studies reporting. Mean ulcer durations ranged from 14.5 days to 21.6 months with durations of greater than 1 year in 6 of 21 studies reporting.

In 26 trials the ulcer was described as a "foot" ulcer, in 7 trials the ulcer was described as a "lower extremity" ulcer, and in 2 trials ulcer was described only as a "diabetic ulcer." Of the "foot" ulcer trials, 7 provided more detail. Three trials included only plantar ulcers and 1 included only calcaneal, dorsal, and plantar ulcers. In 1 trial, 38% of ulcers were located on the toes and 39% on the heel, in a second trial, 68% were plantar and 32% were non-plantar, and in third trial 61% were on the heel and sole and 39% were on the toes. The ulcer type was further described as neuropathic in 11 trials, ischemic in 1 trial, neuroischemic in 1 trial, and mixed in 3 trials. Of the remaining trials, 16 had inclusion criteria related to adequate circulation or exclusion criteria related to severe arterial disease and 3 did not specify criteria related to circulation.

Collagen

Four randomized controlled trials with a total enrollment of 489 patients compared the efficacy of collagen to standard care for the treatment of diabetic ulcers.[15-18] Three of the trials described the ulcers as "foot" ulcers; one included lower extremity and foot ulcers.[15] A fifth trial of 19 patients with type 2 diabetes and chronic diabetic foot lesions randomized participants to collagen or to standard care.[51] The focus of this trial was on changes to biomarkers over 5 days of treatment. The authors did report that, at a mean treatment duration of 26 days, 8 of 13 patients treated with collagen (62%) achieved wound closure. In the standard care group, no wound closure was observed and after a mean of 19 days, patients received a different treatment (not specified). Due to the incomplete reporting, we have not included this study in the summary of collagen trials (below).

The four included studies were conducted in the United States and industry funded. Study quality was rated fair for all trials. Participants had mean age of 57 years; 74 percent were male (Table 2). Collagen trial durations were eight[17] and twelve weeks.[15,16,18] The studies included non-healing diabetic ulcers of at least four weeks in duration. One study included a 2 week run-in with standard care (debridement, moist dressings, and off-loading) and excluded individuals with a greater than 30% decrease in ulcer size during the run-in period.[15] Inclusion criteria allowed for all ulcers greater than 1.0 cm^2, and the average enrolled ulcer size was 3.1 cm^2. None of the trials reported a difference between treatment arms in ulcer size or ulcer duration. Infected ulcers were excluded from all studies and use of antibiotics during the trial was not reported to be on an "as needed" basis in one trial. In all trials, adequate circulation was required for inclusion. Standard care included off-loading in all trials with one study reporting asking about compliance with off-loading at each visit. Compliance with therapy was reported to be greater than 90% in one study (patients kept a diary of dressing changes).[16] Two studies excluded patients for non-compliance but did not report how that was determined.[15,18] The fourth study did not report compliance.[17] One of the trials included a second intervention arm with a non-FDA approved product.[15] Results from that treatment arm are not reported. A complete summary of patient demographics and ulcer characteristics is presented in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

All studies reported the percentage of ulcers healed by study completion. One study (n=86) found collagen (Graftjacket) to significantly improve ulcer healing compared to standard care (70% versus 46%; ARD=23%, 95% CI 3% to 44%).[18] The difference was maintained after adjusting for baseline ulcer size. There was no significant difference in the percentage of healed ulcers with Promogran (37% versus 28%),[16] Fibracol (48% versus 36%),[17] or formulated collagen gel (45% versus 31%)[15] compared to standard care. One study reported a trend toward a higher percentages of ulcers healed in ulcers of less than 6 months duration (45% versus 33%, p=0.06); ulcer size (<10 cm^2 versus ≥10 cm^2) was not a factor.[16] Two studies found no difference between collagen and standard care in time to complete healing[17,18] while in a third study, time to healing was significantly shorter in patients receiving standard care (7.0 weeks versus 5.8 weeks, p<0.0001).[16]

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Table 1. Overview of Therapies for Diabetic Ulcers

Study, year	N Randomized	Treatment	Product	Comparator	Healed ulcers	Mean time to ulcer healing	Global assessment	Return to daily activities	Ulcers infected during treatment	Amputation	Revascularization/ surgery	Recurrence	Time to recurrence	Pain/discomfort	Hospitalization	Required home care	Quality of life	Withdrawals due to adverse events	Patients with ≥ 1 adverse event	All-cause mortality	Allergic reactions to treatment
Blume 2011[15]	52	Col	Formulated Collagen Gel	Standard	-													-			
Veves 2002[16]	276	Col	Promogran	Standard	-	↓			-										-	-	
Donaghue 1998[17]	75	Col	Fibracol	Standard	-	-			-									-			
Reyzelman 2009[18]	86	Col	Graftjacket	Standard	+	-				-	-							-	-	-	
Niezgoda 2005[19]	98	BD, PDGF	OASIS	PDGF (becaplermin)	-	-			-			-		±					-	-	
Landsman 2008[20]	26	BD, BSE	OASIS	Dermagraft	-	-															
Gentzkow 1996[21]	50	BSE	Dermagraft	Standard	+	-			-			-									-
Naughton 1997[22]	281	BSE	Dermagraft	Standard	-	±			-			-	±						-		
Marston 2003[23]	245	BSE	Dermagraft	Standard	+	+			-		-								-		
Veves 2001[24]	277	BSE	Apligraf (Graftskin)	Standard	+	+			-	+		-						-			
Edmonds 2009[25]	82	BSE	Apligraf	Standard	+	-			-	-		-						-	-	-	-
DiDomenico 2011[26]	28	BSE	Apligraf	Theraskin	-	-													-		
Aminian 2000[27]	9	PDGF	Autologous platelet extract	Silver sulfadiazine	-	±															
Agrawal 2009[28]	28	PDGF	rhPDGF	Placebo gel	+																-
Hardikar 2005[29]	113	PDGF	rhPDGF	Placebo gel	+	+												-		-	
Bhansali 2009[30]	20	PDGF	rhPDGF	Standard	-	+													-		
Wieman 1998[31]	382	PDGF	Regranex (2 doses)	Placebo gel	+	+			-			-		-				-		-	
Niezgoda 2005 See BD studies above[19]	98	PDGF	Becaplermin	Biologic dressing (OASIS)	-	-			-			-		±					-	-	
Jaiswal 2010[32]	50	PDGF	rhPDGF	Inactive gel	-														-		
Steed 1995, 2006[33,34]	118	PDGF	rhPDGF	Placebo gel	+	+			-			-	±	-					-	-	
d'Hemecourt 1998[35]	172	PDGF	Becaplermin gel	NaCMC gel or standard care	+ vs std*	-			-					-				-	-	-	

Study, year	N Randomized	Treatment	Product	Comparator	Healed ulcers	Mean time to ulcer healing	Global assessment	Return to daily activities	Ulcers infected during treatment	Amputation	Revascularization/ surgery	Recurrence	Time to recurrence	Pain/discomfort	Hospitalization	Required home care	Quality of life	Withdrawals due to adverse events	Patients with ≥ 1 adverse event	All-cause mortality	Allergic reactions to treatment
Saad Setta 2011[36]	24	PRP	PRP	Platelet poor plasma	-	+															
Driver 2006[37]	72	PRP	AutoloGel	Placebo gel	-	-						-							-	-	
Belcaro 2010[38]	66	Silver Ointment	Aidance	Standard	+													-	-		-
Jacobs 2008[39]	40	Oak Bark Extract	Bensal HP	Silver cream	-													-	-		-
Jude 2007[40]	134	Silver Dressing	AQUA-CEL	Calcium dressing	-	-	-		-									-	-	-	
Viswanathan 2011[41]	40	Poly-herbal Cream		Silver cream		-			-			-						-	-	-	
Blume 2008[42]	341	NPWT	V.A.C.	Advanced moist wound therapy	+	±			-	+								-		-	
Karatepe 2011[43]	67	NPWT	V.A.C.	Standard care		+											+				
McCallon 2000[44]	10	NPWT	V.A.C.	Saline gauze		-												-		-	
Wang 2011[45]	86	HBOT		EST	↓																
Löndahl 2010[46]	94	HBOT		Sham	+					-	-				-			-		-	-
Duzgun 2008[47]	100	HBOT		Standard	+					+	+							-			
Kessler 2003[48]	28	HBOT		Standard	-													-	-	-	
Abidia 2003[49]	18	HBOT		Sham	+				-	-	-							-	-	-	
Wainstein 2011[50]	61	Ozone-oxygen	Ozoter	Sham	-				-	-								-			

BD – Biological Dressing; BSE – Biological Skin Equivalent; Col – Collagen; EST – Extracorporeal Shock Wave Therapy; HBOT – Hyperbaric Oxygen Therapy; NaCMC - Sodium Carboxymethylcellulose; NPWT – Negative Pressure Wound Therapy; PDGF – Platelet-derived Growth Factor; PRP – Platelet Rich Plasma

+ Treatment group better than comparator ($p < 0.05$)

- Treatment group demonstrated no significant benefit

↓ Treatment group worse than comparator

± Significance could not be determined

* + versus std, - versus gel

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Table 2. Summary of Baseline Characteristics: Collagen

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	4	489 total	52 - 276
Age (years)	3	57	56 - 59
Gender (% male)	3	74	72 - 77
Race/Ethnicity (%)		-	-
White	2	63	63 - 64
Black	2	10	10 - 12
Other	2	27	25 - 28
Pre-Albumin	1	3.7	-
HbA_1C (%)	3	8.4	7.9 - 8.6
Ulcer Size (cm^2)	4	3.1	2.7 - 4.3
Ulcer Duration (months)	4	5.1	3 - 15.1
Infection (%)	4	0	-
Study Duration (weeks)	4	11.3	8 - 12

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

No difference between Graftjacket and standard care was reported for need for amputation or revascularization surgery.[18] In two studies reporting, there was no significant difference in ulcers infected during treatment between collagen ulcer treatment and standard care.[16,17] Only one study reported the percentage of patients experiencing infection – 12% in the intervention group, 19% in the standard care group.[16] No differences were observed between collagen and standard care in the incidence of adverse events (serious [18% versus 25%] or non-serious [27% versus 25%]),[16] adverse events resulting in study withdrawal (7% overall in one study, 6% versus 0% in a second study, and 6% versus 5% in a third study),[15,17,18] or all-cause mortality (0% in one study, 1.4% versus 4.3% in another study).[16,18]

Biological Dressings

Two studies enrolling 124 patients met eligibility criteria and reported on use of biological dressings in ulcers of diabetic etiology.[19,20] One study described the ulcers as "foot" ulcers; the second study did not provide any information on ulcer location. Both studies were multisite RCTs that took place in the United States; one study also had sites in Canada.[19] One of the trials was of fair quality, industry sponsored, with average ulcer area of 4.1 cm^2 at baseline.[19] The other study was of poor quality, did not include financial disclosures, and had a smaller average baseline ulcer size of 1.9 cm^2.[20] Mean age in the two studies was 59 years and 62% of the enrolled patients were male. Both studies excluded patients with infected ulcers and severe arterial insufficiency. One study reported baseline differences in the distribution of type 1 and type 2 diabetes and the proportion of plantar surface ulcers.[19] One trial included a 1 week run-in period with standard care but did not report if patients were excluded following the run-in period. Compliance with off-loading was monitored in one study.[20] Additional details of the studies are provided in Table 3 and Appendix D, Table 1.

Table 3. Summary of Baseline Characteristics: Biological Dressings

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	2	124 total	26 - 98
Age	2	59	58 - 63
Gender (% male)	2	62	60 - 69
Race/Ethnicity	NR	-	-
BMI	1	33	-
HbA_1c (%)	1	8.3	-
ABI	2[a,b]	-	-
Ulcer Size (cm^2)	2	3.5	1.9 - 4.1
Ulcer Duration	2[c]		
Study Duration (weeks)	2	12	12

[a]Niezgoda, 2005[19] reported a mean Toe-Brachial-Index (TBI) of 1.00
[b]Mean ABI for Landsman, 2008[20] was not reported, but all participants were >0.65 by exclusion criteria
[c]Landsman 2008:[20] No mean, but >5 weeks duration before treatment per inclusion; Niezgoda 2005:[19] 1-3 months: 49.3%, 4-6 months: 16.4%, 7-12 months: 15.1%, >12 months: 19.2%

Primary Outcomes (Appendix D, Table 2)

Biological dressings were tested against other advanced ulcer care therapies in both studies. One study, a non-inferiority study compared OASIS Wound Matrix biological dressing to rhPDGF [Regranex].[19] For the 73 patients completing the trial, OASIS was no different than rhPDGF for ulcer healing (49% of the OASIS arm and 28% of the Regranex arm had complete ulcer healing at 12 weeks) or time to healing (67 days for OASIS, 73 days for Regranex). The second study compared OASIS to the biological skin equivalent Dermagraft in 26 patients over 12 weeks.[20] No significant difference was noted in complete ulcer healing (77% in OASIS, 85% in Dermagraft) or average time to healing (36 days with OASIS; 41 days with Dermagraft). No comparisons could be made within or between studies regarding the use of ancillary therapies or their effect on healing outcomes.

One study reported on the possible effect of baseline patient characteristics on efficacy, finding in an *a priori* subgroup analysis that the biological dressing did not improve healing of ulcers on the plantar surface compared to rhPDGF. The biological dressing significantly healed more ulcers in patients with type 2 diabetes ($p=0.03$) but not type 1 diabetes. It is important to note that these subgroup analyses were based on very small sample sizes and only the comparison involving plantar surface ulcers was pre-specified.[19]

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Only one study reported any of our secondary outcomes of interest. There were no differences between treatment groups for ulcers infected, ulcer recurrence, pain, proportion of patients experiencing an adverse event, or all-cause mortality.[19]

Biological Skin Equivalents

We identified a total of seven studies that evaluated use of biological skin equivalents in diabetic ulcers; four discussed the use of Dermagraft and three discussed the use of Apligraf. All described the ulcers as "foot" ulcers with no further details on ulcer location. Three fair quality trials with sample sizes of 245,[23] 281,[22] and 50[21] compared Dermagraft (up to 8 grafts) to standard care. A small study (n=26) of poor quality compared Dermagraft (up to 3 grafts) to a biological dressing.[20] All four Dermagraft studies were multisite RCTs that took place in the United States, and all included only ulcers greater than 1.0 cm^2 at baseline (average ulcer size ranged from 1.86 cm^2 to 2.4 cm^2). One study did not report study sponsorship;[20] the others were all industry sponsored. Of the three studies of Apligraf, one was a small trial of poor quality enrolling patients from a single podiatric practice (n=29).[26] Apligraf (up to 5 treatments) was compared to cryopreserved split-thickness skin allograft. This study included ulcers 0.5 to 4.0 cm^2 in size (mean of 1.86 cm^2) and followed patients for 20 weeks. The two other Apligraf trials compared Apligraf to standard care. One enrolled 82 patients in the European Union and Australia[25] and the other enrolled 277 patients in the United States.[24] The trial in Europe and Australia allowed up to 3 treatments over 8 weeks. The trial in the United States allowed up to 5 treatments over 5 weeks. Both were multicenter studies of good quality that included ulcers between 1 and 16 cm^2 in size (average area was approximately 3.0 cm^2) with 12 weeks as the primary endpoint. Overall, 6 of the 7 trials excluded patients with infection and required adequate circulation. The remaining trial did not report on these factors. None of the trials reported on antibiotic use. A run-in period with standard care was included in 4 trials[20,22,24,25] with 2 trials excluding patients whose ulcers decreased in size during the run-in period.[24,25] Five trials reported no differences between treatment groups at baseline; one reported lower age in the control group[21] and one did not report on the groups at baseline.[22] Four of the studies monitored compliance with off-loading either checking the condition of a shoe liner,[20] having patients keep a diary of ambulation,[23] or asking patients about off-loading.[24,25] Additional information is provided in Appendix D, Table 1 and Table 4, below.

Table 4. Summary of Baseline Characteristics: Biological Skin Equivalents

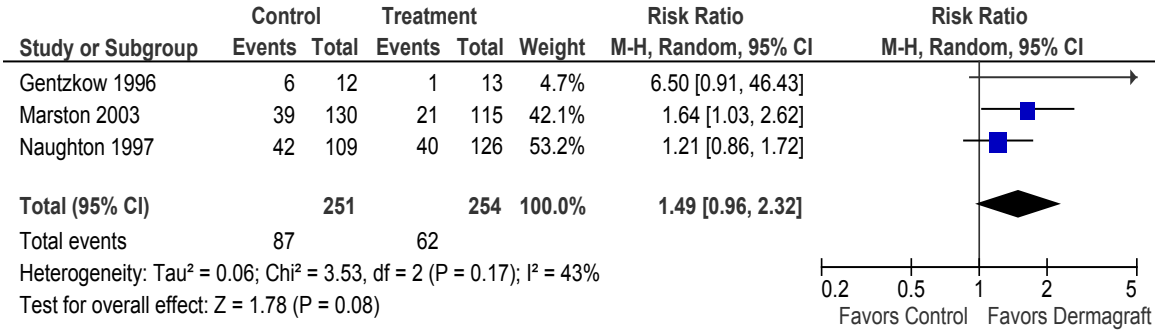
Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	7	989 total	26 - 281
Age	5	57	56 - 63
Gender (% male)	5	77	69 - 86
Race/Ethnicity	2[a]		
White	2	71	69 - 72
Other	2	28	28 - 29
BMI	2	32	31 - 32
HbA_1c (%)	2	8.6	8.4 - 8.6
ABI	3[b,c]	1	1
Ulcer Size (cm^2)	6	2.6	1.9 - 3.0
Ulcer Duration (weeks)	4	57.1	49.0 - 95.7
Study Duration (weeks)	7	11	8 - 12

[a]Marston, 2003: Caucasian (72%), Non-Caucasian (28%)
Veves, 2001 White (69.5%), African-American (16.6%), Hispanic (13.5%)
[b]Marston, 2003: all participates were >0.7 by exclusion criteria
[c]Veves, 2001: 0.65-0.80: 9.6%, 0.80-1.00: 33.2%, >1.0: 54.4%

Primary Outcomes (Appendix D, Table 2)

Three studies compared Dermagraft to standard care. Two of these showed statistically significant improvements in ulcer healing. One reported that Dermagraft resulted in an increased incidence of complete ulcer healing (30.0% versus 18.3%, p=0.049) and resulted in a faster time to closure (p=0.04).[23] The second study also found a benefit in the proportion of completely healed ulcers with weekly Dermagraft administration (50% versus 8%, Fisher's exact test p=0.03). A statistical benefit in time to closure was not reached (p=0.056) due to small group sizes.[21] The third trial comparing Dermagraft to standard care did not show a benefit for the treatment group when taken as a whole.[22] However, among patients who received a metabolically active Dermagraft at least for the first implant, the percentage of ulcers healed was significantly higher than those who received standard care (49% versus 32%, p<0.01).[22] In this older trial, some of the Dermagraft samples were found to have a level of metabolic activity outside of the therapeutic range. We pooled the findings from the three studies of Dermagraft versus standard care (Figure 2). The overall risk ratio was 1.49 (95% CI 0.96 to 2.32) indicating a non-significant benefit of Dermagraft over standard care in ulcer healing. The fourth study compared Dermagraft (up to 3 applications) to the biological dressing OASIS in 26 patients and, as noted above, found both produced similar improvements for incidence and time to complete ulcer healing.[20]

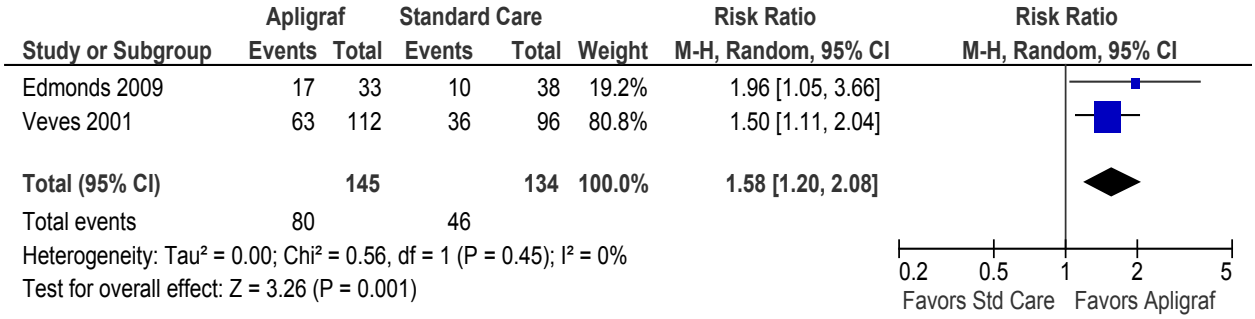
Figure 2. Proportion of Diabetic Ulcers Healed - Biological Skin Equivalent (Dermagraft) versus Standard Care



*Gentzkow 1996 – Analysis is for Group A (one piece of Dermagraft applied weekly) versus Control

The two largest studies of Apligraf used standard care (sharp debridement, moist dressings, and off-loading) as the comparator. The largest study[24] showed significant benefit for Apligraf in complete ulcer healing at 12 weeks (56% versus 38%, p=0.004) and for median time to closure (65 versus 90 days for control, p=0.003). The second trial[25] also showed a significant benefit for Apligraf for incidence of complete ulcer healing (52% versus 26%, p=0.049), but the benefit of more rapid healing did not reach statistical significance (p=0.059) before trial enrollment was prematurely terminated due to registration difficulties. Pooled analysis of these trials (Figure 3) shows a significant overall benefit of Apligraf over standard care (ARD=21%, 95% CI 9% to 32%; RR=1.58, 95% CI 1.20 to 2.08, I^2=0%). The third study compared Apligraf to cryopreserved split-thickness skin allografts. This small (n=29 ulcers), poor-quality study did not report statistically significant differences between treatments for the incidence of complete ulcer healing or time to complete healing.[26]

Figure 3. Proportion of Diabetic Ulcers Healed - Biological Skin Equivalent (Apligraf) versus Standard Care



No comparisons could be made within or between studies regarding the use of ancillary therapies. However, in one study, were allowed to be ambulatory, using extra-depth custom inserts or healing sandals.[23] Patients recorded being on their feet an average of 8 hours a day. Most other studies limited patients to use of a wheelchair or crutches for large portions of the study or asked patients to limit ambulation to a minimal level. While no controlled comparisons can be made, it is important to note that use of Dermagraft in this trial still produced a beneficial effect. This suggests the benefits of this biological skin equivalent may be maintained when applied to clinic patients not willing or able to limit ambulation for several months during the period of treatment.

Two of the Dermagraft studies reported on factors associated with ulcer healing. In one study, neither patient age, gender, ulcer size or duration, diabetes type, ankle-arm index, nor HbA_1c were significantly associated with time to closure.[21] Another study reported outcomes based on ulcer location.[23] There was a trend for more forefoot/toe ulcers (n=214) to heal with Dermagraft (29.5% versus 19.6%, p=0.065). For heel ulcers (n=31), 33% of those treated with Dermagraft achieved closure compared to 8% in the control group (p=0.01). This trial was originally intended to include ulcers of any duration. At interim analysis, the benefits of Dermagraft on ulcer healing were not statistically significant when considering all patients, but a statistically significant benefit was evident for the treatment of ulcers present for more than 6 weeks prior to entering the 2 week screening. This resulted in a trial amendment to change the desired study population and further enroll only chronic ulcers of more than 6 weeks.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Rate of recurrence was reported for two of the Dermagraft studies with no difference between the Dermagraft and standard care groups.[21,22] Similarly, two studies reported no significant difference in rate of recurrence between Apligraf and standard care.[24,25] Three Dermagraft studies[22-23] and one Apligraf study[25] reported no differences between a biological skin equivalent and standard care in incidence of ulcers infected during treatment. One Dermagraft study found a significantly lower incidence of infection, osteomyelitis, and cellulitus (combined) in the Dermagraft group than in the standard care group (19% versus 33%, p=0.007).[23] One Apligraf study found a significantly lower incidence of osteomyelitis (but not infection or cellulitis) in the advanced therapy group compared to standard care (2.7% versus 10.4%, p=0.04).[24] One study reported fewer amputations among patients treated with Apligraf than standard care (6% versus 16%,

p=0.03)[24] although a second study found no significant difference.[25] No studies reported pain or discomfort. Six studies reported a low number of patients experiencing adverse events, adverse events leading to study withdrawal, or all-cause mortality with no differences between the biological skin equivalent and either standard care[21-25] or allograft.[26]

Platelet-Derived Wound Healing (Platelet-Derived Growth Factors, PDGF)

Nine randomized controlled trials enrolling a total of 990 patients evaluated the efficacy of platelet-derived growth factors (PDGFs) used in the treatment of diabetic ulcers. Comparator treatments included standard care or placebo,[28-34] biological dressing,[19] silver sulfadiazine,[27] and either standard care or sodium carboxymethylcellulose (NaCMC) gel.[35] Ulcer locations were described as lower limb or lower extremity in 5 studies,[29,31-35] foot in 2 studies,[28,30] with one specifying plantar surface,[30] and not defined in 2 studies.[19,27] Four studies were conducted in India,[28-30,32] three in the United States,[31,33-35] one in the United States and Canada,[19] and one in Iran.[27] Five of nine studies reported a funding source; four received industry funding[19,31,33-35] and one reported government support.[27] The mean age of the participants was 58 years; 69 percent were males (Table 5). PDGF trials ranged in duration from eight to twenty weeks and all included chronic, non-healing, diabetic ulcers of at least four weeks in duration. Three studies excluded patients with infection and the remaining studies required infection to be controlled before starting the study therapy. Six trials allowed antibiotics during the study on an as needed basis. Eight studies reported only including patients with adequate blood flow; one provided no information on blood supply. Three studies reported monitoring compliance with care. One tracked dressing changes and off-loading,[29] one provided a diary to record dressing changes,[33,34] and the third reported compliance but did not specify what was monitored.[31] Two studies included a run-in period.[27,29] Inclusion criteria across studies allowed for ulcer sizes ranging from 1 cm^2 to 100 cm^2; average ulcer size was 7.3 cm^2. One study reported a significant difference in ulcer area at baseline with larger ulcers found in the PDGF arm (54.3 cm^2 versus 28.7 cm^2 in the control arm, p=0.003).[28] As noted in the section on biological dressings (above) one trial reported baseline differences in ulcer location (plantar vs. non-plantar) and distribution of type 1 and type 2 diabetes between groups.[19] No trials reported a difference between treatments in ulcer duration or use of ancillary therapies. Two studies were good quality,[32-34] 5 were fair quality,[19,28,30,31,35] and 2 were poor quality.[27,29] A complete summary of study characteristics is presented in Appendix D, Table 1.

Table 5. Summary of Baseline Characteristics: Platelet-Derived Growth Factor

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	9	990 total	9 - 382
Age (years)	9	58	51 - 61
Gender (% male)	8	69	60 - 100
Race/Ethnicity (%)			
White	3	83	81 - 86
Black	2	11	9.9 - 12
Hispanic	1	6	-
Asian	1	<1	-
Indian	1	100	-
Other	3	4	0.3 - 14
BMI	4	27.4	22.4 - 32.5

HbA_1c (%)	3	8.0	7.5 - 8.8
ABI	2	1.1	1.1
Ulcer Size (cm^2)	9	7.3	2.7 - 41.5
Ulcer Duration (weeks)	5[a]	48	13 - 78
Infection	4	0	-
Study Duration (weeks)	9	16	8 - 20
History of Amputation	2[b]	35	-
History of PVD	1	0	-

[a]Jaiswal 2010[32] reported a median of 5 weeks
[b]Jaiswal 2010[32] reported amputation or previous ulcer (2%) and was not included in the calculation

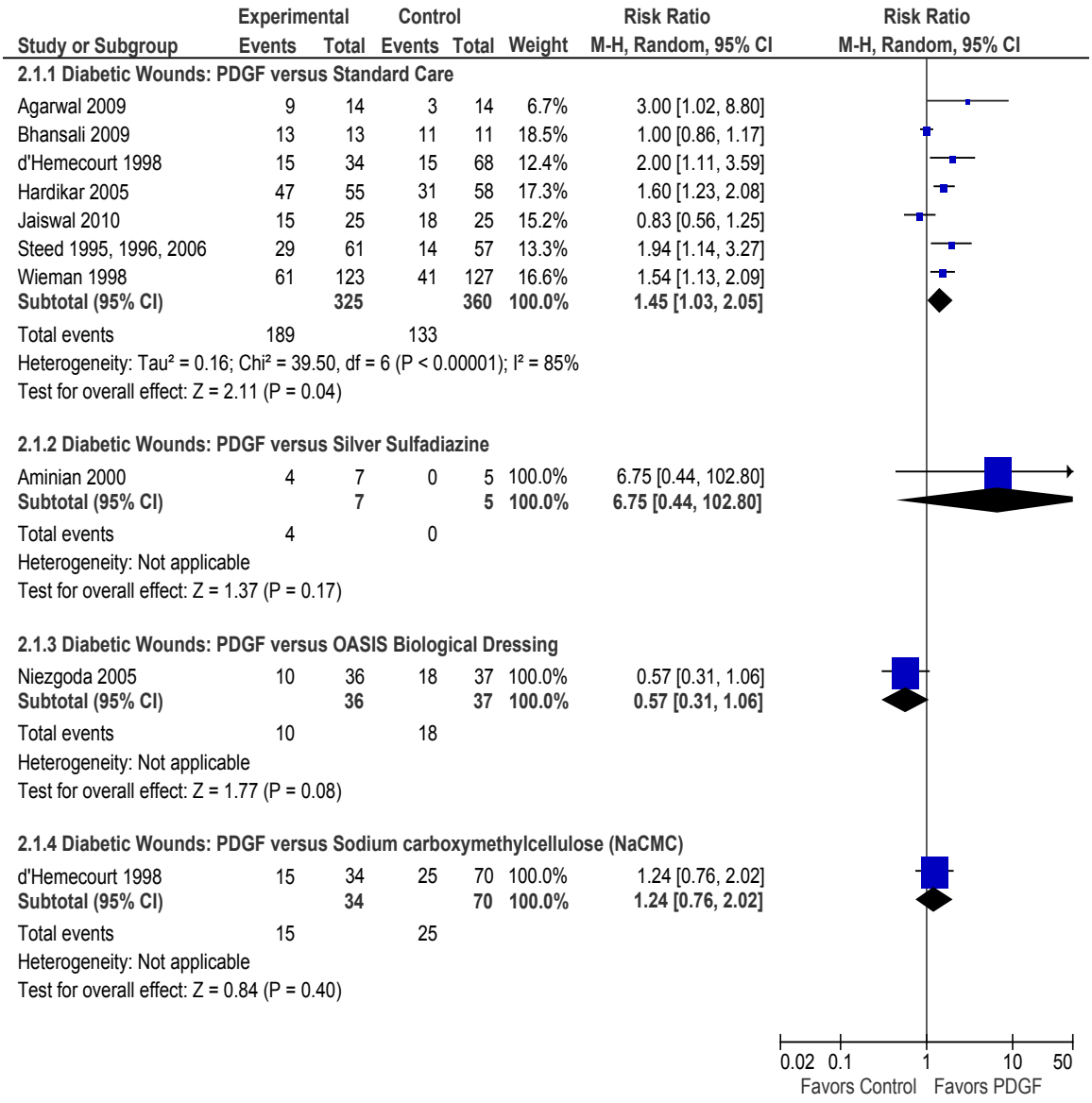
Primary Outcomes (Appendix D, Table 2)

All nine trials reported the percentage of ulcers healed by study completion for PDGF and comparator. Seven of nine compared PDGF to placebo or inactive gel[28,29,31-34] or to standard ulcer care[30,35] and three of nine compared PDGF to another advanced wound therapy.[19,27,35] A pooled analysis of the studies comparing PDGF to placebo gel or standard ulcer care (Figure 4) found significantly greater healing with PDGF (ARD=21%, 95% CI 14% to 29%; RR=1.45, 95% CI 1.03 to 2.05) but there was substantial heterogeneity (I^2=85%). Five of the seven individual trials also showed significantly greater healing with PDGF with individual risk ratios ranging from 1.60 to 3.00.

Separate analyses of studies with placebo gel and standard care as comparators revealed a significant finding for the 5 placebo gel studies (RR=1.45, 95% CI 1.07 to 1.97, I^2=63%) and a non-significant finding for the 2 standard care studies (RR=1.40, 95% CI 0.33 to 5.95, I^2=96%). Pooling only studies rated as good or fair quality showed no benefit of PDGF compared to placebo gel or standard care (RR=1.45, 95% CI 0.94 to 2.23) with substantial heterogeneity (I^2=80%). An analysis based on the country in which the study was conducted found a significant benefit of PDGF over placebo gel in 2 studies done in the United States (RR=1.54, 95% CI 1.19 to 2.00, I^2=0%) but not in 3 studies done in India (RR=1.39, 95% CI 0.77 to 2.51, I^2=79%). Significant results favoring PDGF were also found for studies with more than 100 patients (k=3), but not studies with less than 100 (k=2) and studies with treatment lasting 20 weeks (k=3) but not studies less than 20 weeks (k=3 due to multiple reporting times in one trial). Ulcer size did not appear to be a factor with non-significant findings when pooling the 2 studies with the largest ulcer sizes (greater than 25 cm^2) or the 3 studies with ulcer size less than 25 cm^2.

Three of nine studies reported the percentage of ulcers healed by study completion for PDGF compared to another advanced wound therapy. The percentage of ulcers healed did not differ significantly for PDGF compared to biological dressings (OASIS),[19] silver sulfadiazine,[27] or NaCMC gel[35] (Figure 4).

Figure 4. Proportion of Diabetic Ulcers Healed – Platelet-Derived Growth Factor versus Comparator



Five studies reported time to complete ulcer closure for PDGF compared to placebo gel or standard care.[29-31,33-35] Four of the five studies reported significantly shorter time to ulcer healing in PDGF compared to placebo gel or standard care (differences of 30 to 40 days);[29-31,33,34] one study found no significant difference.[35] In studies comparing PDGF to another advanced therapy, time to complete ulcer closure did not differ significantly for PDGF compared to biological dressings (OASIS),[19] silver sulfadiazine,[27] or NaCMC gel.[35]

Several individual studies looked at factors associated with ulcer healing. In one study, ulcers less than 9 cm^2, ulcers located on non-weight-bearing surfaces, and the use of antibiotics significantly improved healing.[29] Another study reported that healing did not vary by age and baseline HbA_1c but that compliance with off-loading was positively associated with healing (p not reported).[31] As noted above, healing of plantar surface ulcers was comparable for patients treated with either a biological dressing or rhPDGF.[19]

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Four studies reported the percentage of ulcers infected during treatment with no significant differences between PDGF and placebo or standard care,[31,33-35] a biological dressing,[19] or NaCMC gel.[35] Three studies reported ulcer recurrence with no significant differences between PDGF and placebo or standard care[31,33,34] or a biological dressing.[19] Time to recurrence was similar between PDGF and placebo in the one study reporting that outcome.[33,34] Pain or discomfort was reported in four studies with no significant differences between PDGF and placebo or standard care,[31,33-35] a biological dressing,[19] or NaCMC gel.[35] Three studies found no significant difference between PDGF and placebo gel or standard care[29,31,35] or between PDGF and NaCMC gel[35] for patient withdrawals attributed to adverse events. Two studies reported no adverse events during the study period[30,32] and three studies found no significant difference in the occurrence of adverse events between treatment groups (PDGF versus placebo gel,[33,34] standard care,[35] biological dressing,[19] or NaCMC.[35] All-cause mortality was reported in five studies with no significant difference between PDGF and standard care, placebo, or other advanced treatments.[19,29,31,33-35] Only one study reported allergic reaction to the treatment with no difference between PDGF and placebo gel.[28]

Platelet Rich Plasma (PRP)

Two randomized controlled trials met eligibility criteria and compared the efficacy of PRP to placebo gel[37] or platelet poor plasma (PPP).[36] One study was conducted in the United States and reported government funding[37] and one was done in Egypt with no funding source reported.[36] Study quality was rated as poor for one trial[36] and fair for the second.[37] Ulcer location was described only as "foot" for one study;[36] the other study included plantar, medial, and lateral ulcers (including 38% on the toes and 29% on the heel).[37] One study reported patient age (57 years) and gender (80% male).[37] The trial durations were twelve[37] or twenty weeks,[36] and included chronic, non-healing ulcers greater than four[37] or twelve[36] weeks in duration. Treatments were applied two times a week with 3 to 4 day intervals between dressing changes until the respective study duration was complete or healing had occurred. Both studies excluded patients with infection and inadequate blood flow. Antibiotic use was not reported nor was compliance with treatment. One study reported no baseline differences between groups;[36] the second reported differences in race in the per protocol analysis sample.[37] One study included a 1-week run-in period and excluded patients if ulcer area decreased by more than 50%.[37] Inclusion criteria allowed for all ulcers greater than 0.5 cm^2; the average enrolled ulcer size was 5.6 cm^2. Neither trial reported a difference between treatment arms in ulcer size, ulcer duration, or ancillary therapies. Additional baseline characteristics are presented in Table 6. A complete summary of study characteristics is presented in Appendix D, Table 1.

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Table 6. Summary of Baseline Characteristics: Platelet Rich Plasma

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	2	96 total	24 - 72
Age (years)	1	57	-
Gender (% male)	1	80	-
Race/Ethnicity (%)			
White	1	60	-
Black	1	7.5	-
Hispanic	1	30	-
Other	1	2.5	-
HbA_1c (%)	1	7.9	-
Smoking	1	33.3	-
Ulcer Size (cm^2)	2	5.6	3.5 - 9.4
Infection	1	0	-
Study Duration (weeks)	2	11	12 - 20
History of HTN (%)	1	70	-

Primary Outcomes (Appendix D, Table 2)

Both trials reported the percentage of ulcers healed by study completion for PRP compared to PPP (100% versus 75%)[36] or placebo gel (33% versus 28%).[37] Neither difference was significant. One study[36] reported a significantly shorter time to healed ulcers for PRP compared to PPP (11.5 versus 17 weeks, $p<0.005$); the other study found no significant difference between treatment groups.[37]

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

One study reported no difference in ulcer recurrence at 12 weeks between PRP and placebo gel.[37] This trial also reported no significant differences in adverse events or all-cause mortality.[37] The second study did not report any secondary outcomes.

Silver Products

Four trials enrolling a total of 280 patients met eligibility criteria.[38-41] One study compared silver ointment to standard care[38] and one compared a silver dressing to a calcium-based dressing.[40] In two trials, silver cream was the control group; the interventions were oak bark extract[39] and a polyherbal treatment.[41] The studies were done in the United States,[39] Europe,[40] Italy,[38] and India.[41] Two reported industry support[40,41] and two did not report a funding source. Enrollments ranged from 40[39,41] to 134.[40] Ulcer locations were described as "foot" for two studies[38,40] with one specifying that 68% were plantar and 32% were non-plantar.[40] The other two studies included only plantar surface ulcers.[39,41] One study excluded patients with infection (with antibiotic use during the trial not reported),[39] one study excluded patients with "severe" infection and allowed antibiotic use during the trial,[41] one study stratified patients based on antibiotic use,[40] and one noted that infection was the cause of some of the included ulcers (antibiotic use not reported).[38] Three studied required adequate blood supply;[38-40] the fourth allowed patients with peripheral arterial disease.[41] None of the studies included a run-in period with standard care, none reported monitoring compliance with therapy, two specified off-loading as part of standard care, and none reported baseline differences between treatment groups. All studies were of fair quality. Study characteristics are summarized in Table 7; more detail is provided in Appendix D, Table 1.

Table 7. Summary of Baseline Characteristics: Silver Products

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	4	280 total	40 - 134
Age (years)	3	58.7	55.9 - 60.0
Gender (% male)	2	58.6	44 - 74
Race/Ethnicity (%)	NR		
HbA_1c (%)	2	8.6	8.0 - 10.7
ABI	1	1.8	-
Ulcer Size (cm^2)	2[a]	3.2	2.2 - 3.7
Ulcer Duration (months)	2	12.3	0.48 - 15.6
Infection (%)	1[b]	100	-
Study Duration (weeks)	3	6.6	4 - 8
History of PVD	1	23.7%	-

[a]One study included only ulcers ≤3 cm in diameter; one study reported mean length of 4.6 cm and mean width of 3.3 cm
[b]Three studies excluded patients with clinical signs of infection or taking antibiotics at screening

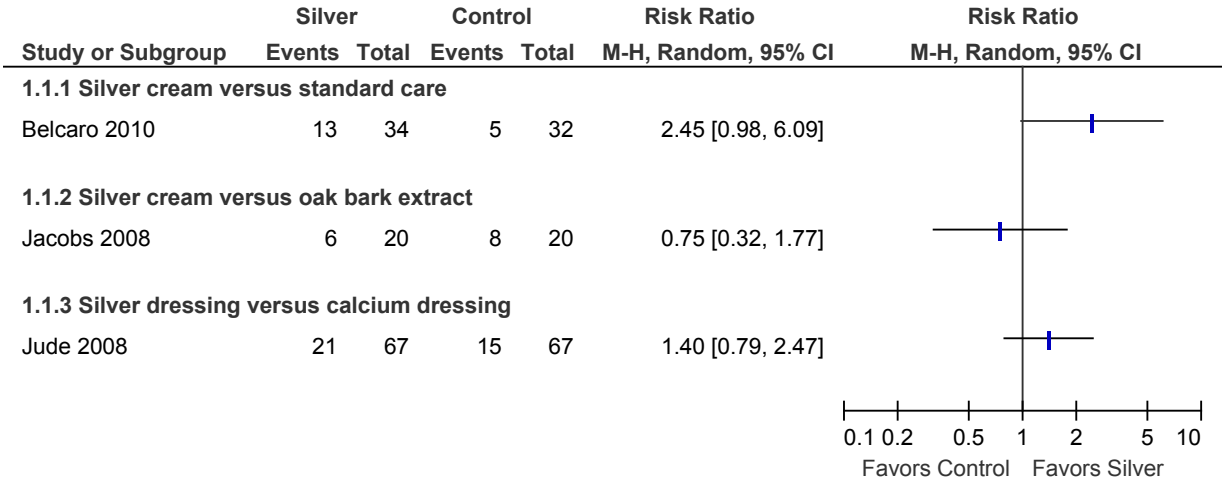
One study included only ulcers with a diameter of 3 cm or less.[39] In the other studies, the mean ulcer size was 2.2 cm^2,[38] 3.7 cm^2,[40] or 4.6 cm (length) and 3.3 cm (width).[41] Mean ulcer duration was 14.5 days in one study[41] and 1.3 years in another.[40] Two studies did not report duration. Two studies included only Wagner Grade 1 or 2 ulcers[39,40] while a third included Grade 1, 2, or 3 ulcers.[41]

Three studies were done to assess the efficacy and safety of the intervention for ulcer healing.[38,40,41] The fourth study was focused on reduction in size of the ulcer.[39]

Primary Outcomes (Appendix D, Table 2)

Three of the four studies reported percentage of ulcers healed. In one study, the percentage of ulcers healed at 4 weeks was significantly higher in the group treated with silver ointment than the group receiving standard care (39% versus 16%, ARD=23%, 95% CI 2% to 43%, $p<0.05$). Mean size of the ulcers included in the study was 2.2 cm^2.[38] Mean time to healing was not reported. In two other studies that reported healing, one found no difference in healed ulcers after 6 weeks of treatment, between an oak bark extract and a silver cream (40% versus 30%, respectively).[39] The second study found no difference in healed ulcers (31% versus 22%) or time to healing (53 days versus 58 days) for a silver dressing compared to a calcium dressing.[40] The findings for proportion of ulcers healed are presented in Figure 5. The study comparing silver and calcium dressings also reported a global assessment of healing with 88% of ulcers healed or improved in the silver dressing group compared to 71% in the calcium dressing group (a non-significant difference).[40] Subgroup analyses based on location (plantar, non-plantar) and type of ulcer (neuropathic, neuroischemic) also were non-significant. The only significant finding was a greater percentage of ulcers healed or improved (92% versus 50%) in the silver dressing group among patients taking systemic antibiotics at baseline.[40] The third study reported only time to healing with no difference between a polyherbal extract and a silver cream (43 days versus 44 days).[41]

Figure 5. Proportion of Diabetic Ulcers Healed – Silver Products



Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Few secondary outcomes were reported. Two studies found no difference in ulcers infected during treatment when a silver dressing was compared to a calcium dressing[40] or a silver cream was compared to a polyherbal cream.[41] There was also no difference in ulcer recurrence between a silver cream and a polyherbal cream (42% versus 47%, respectively).[41] Adverse events and withdrawals from the study due to adverse events were comparable for the two treatment groups within each of the four studies. In three studies, no patients experienced adverse events.[38,39,41] In the fourth study, 37% of patients in the silver dressing group experienced an adverse event compared to 39% of those in the calcium dressing group.[40] Serious adverse events were reported in 12% and 16% of participants, respectively, with study-related adverse events in 16% and 13%, respectively.[40] All-cause mortality was reported in two studies. Overall values were low (maximum of 1 patient per group) with no differences between a silver dressing and a calcium dressing[40] or a silver cream and a polyherbal cream.[41] Two studies assessed allergic reactions to treatments but reported no events.[38,39]

Negative Pressure Wound Therapy

Three trials of NPWT met inclusion criteria. In one study, a small pilot study with 10 patients, the goal of NPWT was to prepare the ulcer for final closure.[44] In the other two studies, with enrollments of 341[42] and 67[43] the goal was ulcer healing. All three studies compared NPWT to standard care. Ulcer location was described as "foot" for two studies[43,44] and calcaneal, dorsal, or plantar for the third study.[42] Two studies were done in the United States[42,44] and one in Turkey.[43] One study received industry support[42] while no source of funding was reported for the other two studies.[43,44] One study was of good quality.[42] Quality of the other two studies could not accurately be assessed due to either incomplete reporting[43] or the fact that the study was a small pilot study.[44] Study characteristics are presented in Table 8 and Appendix D, Table 1.

Table 8. Summary of Baseline Characteristics: Negative Pressure Wound Therapy

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	3	418 total	10 - 341
Age (years)	3	60	53 - 67
Gender (% male)	2	70	28 - 78
Race/Ethnicity (%)			
White	1	58	-
Black	1	15	-
Hispanic	1	24	-
Native American	1	2	-
Other	1	1	-
Pre-Albumin	1	20.5	-
HbA_1c (%)	1	8.2	-
Smoking	1	19	-
ABI	1	1.0	-
Ulcer Size (cm^2)	2	15.7	12.3 - 32.4
Ulcer Duration (weeks)	2	26	10 - 29
Study Duration (weeks)	2 [a]	10	8 - 12

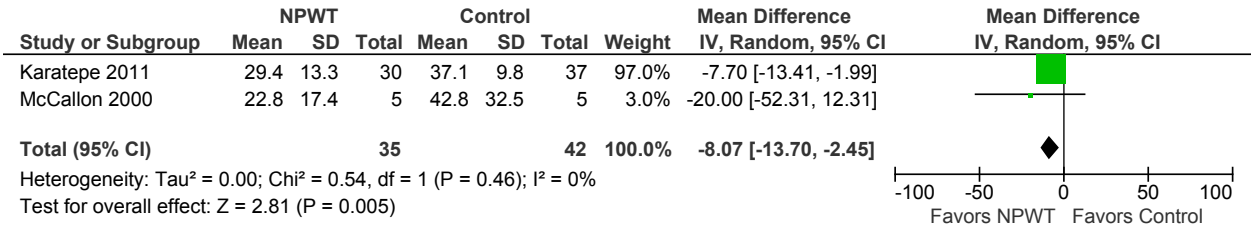
[a]One study followed participants to healing (mean of 4 months)

The mean age of study participants was 60 years. Two studies reported gender with 78%[42] and 28%[43] male. Only one study reported race with 58% Caucasian, 24% Hispanic, and 15% African-American.[42] Initial ulcer sizes and ulcer durations were reported in the two studies with complete healing as the goal. Mean size (duration) was 12.3 cm^2 (29 weeks) in one study[42] and 32.4 cm^2 (10 weeks) in the other.[43] No study reported on comorbid conditions other than diabetes. Two studies reported excluding patients with either venous disease[44] or inadequate lower extremity perfusion.[42] These studies also excluded patients with active or uncontrolled infection. Antibiotic use during the trial was not reported but both reported that off-loading was a component of care for all[44] or 97.5%[42] of patients. One study reported excluding patients for non-compliance but did not specify how that was determined.[42] None of the trials required a run-in period with standard care and two reported no baseline differences between groups.[42,43]

Primary Outcomes (Appendix D, Table 2)

Percentage of ulcers healed was reported in only one of the trials.[42] In that trial, 43% of the patients treated with NPWT experienced ulcer healing compared to 29% of those treated with standard care (ARD=14%, 95% CI 4% to 24%, $p<0.05$). Median time to ulcer healing was 96 days (13.7 weeks) in the NPWT group but could not be estimated in the standard care group. In the second trial with complete healing as the goal, mean time to healing was reported to be significantly shorter (4.2 versus 5.3 weeks, $p<0.05$) among patients receiving NPWT compared to those receiving standard care.[43] The third trial reported satisfactory healing (definitive closure of the ulcer) at a mean of 3.3 weeks in the NPWT group and at a mean of 6.1 weeks in the standard care group; the difference was not significant.[44] In the NPWT group, 80% (4 of 5) ulcers achieved complete closure by delayed primary intention (skin graft, myocutaneous flap, or suture closure by surgeon) compared to 40% (2 of 5) in the standard care group. We pooled time to complete healing data from these two studies (Figure 6) and found a significant benefit for patients treated with NPWT (mean difference=-8.07, 95% CI -13.70 to -2.45, $p=0.005$).

Figure 6. Time to Complete Healing, Diabetic Ulcers – Negative Pressure Wound Therapy



Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

In one study, although more ulcers became infected during NPWT (2.4% versus 0.6% in the standard care group, p=ns), significantly fewer patients in the NPWT group required a secondary amputation (4.1% versus 10.2%, p<0.05).[42] One study reported a positive effect of NPTW on the mental (p=0.03) and physical (p=0.004) health components of the SF-36 compared to conventional treatment.[43] Two studies reported no significant differences in withdrawals due to adverse events or all-cause mortality.[42,44]

Hyperbaric Oxygen Therapy (HBOT)

HBOT versus Standard Care With or Without Sham

Four RCTs evaluating adjunctive hyperbaric oxygen therapy (HBOT) for the treatment of chronic diabetic ulcers met inclusion criteria (Table 9).[46-49] One of the trials enrolled patients with ischemic diabetic ulcers.[49] Ulcers were described as located on the lower extremity,[49] below the ankle,[46] and "foot".[47] One study reported that 61% of the ulcers were on the heel or sole and 39% were on the toe.[48] A total of 240 patients, 123 receiving HBOT and 117 receiving control, with a mean age of 65 were enrolled. Most patients were male (57%). Comorbidities were not uniformly reported but some of the trials reported histories of coronary or cardiovascular disease, hypertension, or hyperlipidemia (see Appendix D, Table 1). The trials were conducted in Europe[46,48,49] or Turkey.[47]

Table 9. Summary of Baseline Characteristic: Hyperbaric Oxygen Therapy versus Standard Care/Sham

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	4	244 total	18 - 100
Age (years)	4	65	61 - 71
Gender (% male)	4	57	32 - 81
Race/Ethnicity (%)	NR		
HbA_1c (%)	3	8.2	7.9 - 8.8
Smoking	3	39	19 - 56
History of CAD/CVD (%)	2	27	22 - 29
History of Amputation (%)	3	36	11 - 39
History of HTN (%)	2	67	60 - 75
Wagner Wound Grade I (%)	1*	6	-
Wagner Wound Grade II (%)	3*	28	18 - 94
Wagner Wound Grade III (%)	3*	42	0 - 56
Wagner Wound Grade IV (%)	3*	29	0 - 45
Treatment Duration (weeks)	4	2 - 8	
Follow-up Duration (weeks)	4	2 - 92	

*One trial reported I through III with no further detail

Inclusion varied by ulcer grade, size, and duration (Table 10). Based on Wagner classification, 28% were wound grade 2 (range 18 to 94), 42% wound grade 3 (range 0 to 56), and 29% ulcer grade 4 (range 0 to 45).[46,47,49] One trial reported Wagner grades 1-3 with no further details.[48] Mean ulcer sizes at baseline were 2.6 $cm^{2(48)}$ and 3.0 cm^2.[46] One trial specified ulcer size between >1 cm between <10 cm.[49] Duration of ulcers required for inclusion ranged from at least 4 weeks to at least 3 months. Two studies allowed patients with infected ulcers to enroll,[47,49] one study enrolled patients when the infection was controlled,[46] and the third excluded patients with severe sepsis.[48] All trials allowed antibiotics, as needed. One study enrolled patients with ischemic ulcers,[49] two studies excluded patients with ischemia,[46,48] and one did not report exclusion criteria related to ischemia.[47] In three of the studies, the patients had to have completed at least 6 weeks of standard care.[46,48,49] These trials also specified off-loading as part of standard care. One study excluded patients for suspected poor compliance,[46] one noted that the protocol was followed,[49] one hospitalized patients for 2 weeks,[48] and one did not report on compliance.[47] There were variations between trials on the applications of HBOT. Treatment pressure (atmospheres absolute) ranged from 2 to 3 ATA, typically around 2.5 ATA. Treatment periods ranged from 2 weeks[48] to 8 weeks[46] with the number of sessions ranging from 20 to approximately 40. One session was 90 minutes. The control arms utilized standard multi-disciplinary ulcer care but two of the trials also used an adjunct blinded sham procedure.[46,49] Mean follow-up times ranged from 2 weeks[48] to 92 weeks.[47]

The aggregate study quality of the included trials was fair. Only one study satisfactorily met the four study quality domains.[49] In one study, there were statistically significant differences at baseline in the percentage of males, current smokers, obese patients, all more prevalent in the HBOT arm.[47]

Table 10. Ulcer Size, Ulcer Duration, and Definitions of Closure: Hyperbaric Oxygen Therapy versus Standard Care/Sham

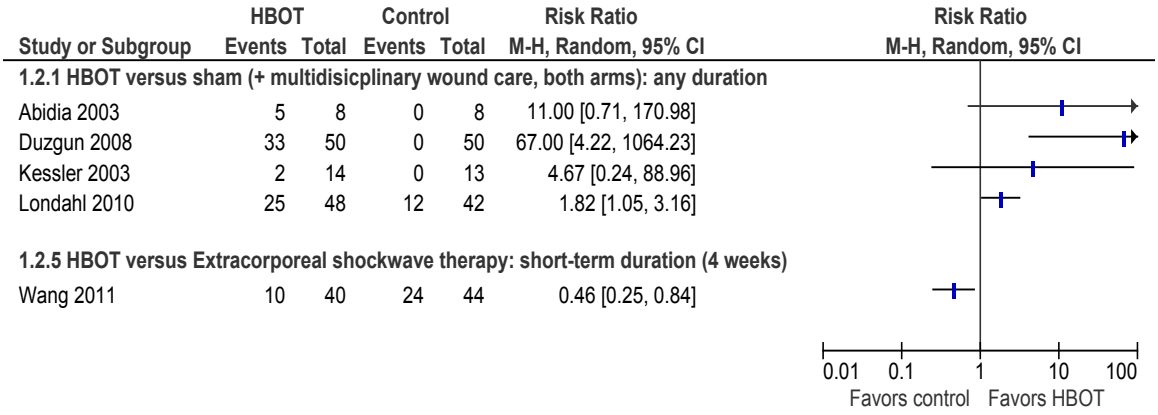
Study / Location	Mean ulcer size, cm^2 (range or SD)	Duration of ulcer, months (range)	Definition of ulcer closure
Löndahl 2010 / Sweden[46]	HBOT: 3.1 (0.6 to 55) Control: 2.8 (0.6 to 55)	HBOT: 9 (3 to 44) Control: 10 (3 to 39)	Complete epithelial regeneration and remaining so until the next visit in the study
Duzgun 2008 / Turkey[47]	HBOT: NR Control: NR	HBOT: NR Control: NR	Total closure of the ulcer without the need for surgical intervention in the operating room
Abidia 2003 / UK[49]	HBOT: 10.6 (1.2 to 82.3) Control: 7.8 (1.8 to 86.6)	HBOT: 6 (2 to 18) Control: 9 (3 to 60)	Complete epithelialization
Kessler 2003 / France[48]	HBOT: 2.31 (2.18) Control: 2.82 (2.43)	HBOT: NR, ≥3 mos Control: NR, ≥3 mos	Not reported

Primary Outcomes (Appendix D, Table 2)

Due to variations in follow-up durations all of the trials could not be statistically pooled (Figure 7). Three of the trials had a follow-up duration of at least one year[46,47,49] and one trial evaluated ulcer healing within 2 weeks of therapy.[48] One long-term, placebo-controlled trial (1-year of follow-up) reported that 52% of patients allocated to adjunctive HBOT had completely healed ulcers compared to 29% of patients in the control arm (RR=1.85, 95% CI 1.05 to 3.16).[46] Another smaller sham-controlled trial (n=18) found a higher proportion of patients[49] with healed ischemic diabetic ulcers with adjunct HBOT compared to control at one year, 63% versus 0% (p=0.026, Fisher's exact test), respectively. Another long-term study (n=100) with a mean follow-up

duration of 92 weeks reported that 66% of patients receiving adjunct HBOT had completely healed ulcers without requiring surgery versus 0% of the patients in the standard therapy arm ($p<0.001$).[47] In the short-term trial by Kessler, within 2 weeks of therapy 2 of 14 patients had complete healing versus none of the 13 patients in the control group.[48] None of the studies reported mean time to healing.

Figure 7. Proportion of Diabetic Ulcers Healed – Hyperbaric Oxygen Therapy



Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

In one study, four major amputations and eight minor amputations were performed within the first year but differences between the HBOT and sham treatment groups were not significant.[46] A second study also reported no differences between HBOT and sham treatment in major or minor amputations.[49] One study, however, did report fewer distal and proximal amputations and fewer debridement procedures in the HBOT group than in the standard therapy group.[47] All of the standard therapy patients required some form of surgical management (i.e. debridement, graft or flap, or distal amputation) to achieve ulcer closure compared to 8 (16%) patients in the HBOT group.[47]

Other reported secondary outcomes included no difference between HBOT and sham treatment in the number of percutaneous transluminal angioplasty procedures done[46] and no difference between HBOT and sham treatment in ulcers infected during treatment.[49]

Adverse events, reported in 2 studies,[48,49] and withdrawals due to adverse events, reported in all 4 studies.[46-49] did not differ between HBOT and sham treatment or standard care. Three trials reported all-cause mortality with no deaths in 2 studies[48,49] and a non-significant difference between HBOT and sham treatment in the third.[46] Two studies observed barometric otitis in one patient in the HBOT group and no patients in the sham treatment or standard care groups.[46,48] No incidences of oxygen toxicity were reported.

HBOT versus Extracorporeal Shockwave Therapy

One comparative effectiveness study conducted in Taiwan compared HBOT (38 patients/40 feet) to extracorporeal shockwave therapy (EST, 39 patients/44 feet).[45] Mean age of the patients was 62 years; gender was not reported. Median size of the ulcers was 7 cm^2 (range 2 to 12) in the HBOT group and 4 cm^2 (range 1.5 to 9) in the EST group, a nearly statistically significant

difference (p=0.059). Median duration of the ulcers was 6 months. Patients with active infection were excluded but could be enrolled when no sepsis or necrosis. Antibiotics were used as needed during the trial. There were no inclusion or exclusion criteria related to blood supply and no run-in with standard care. HBOT was performed in a sealed multi-place chamber at a pressure of 2.5 ATA five times per week for a total of 20 treatments over four weeks duration. EST was performed with a dermaPACE device (Sanuwave, Alpharetta, GA). Treatment dosage was dependent on ulcer size with a minimum of 500 impulses at energy setting E2 (equivalent to 0.23 mJ/mm^2 energy flux density) at a rate of 4 shocks per second. Treatments were conducted two times per week totaling 6 treatments over 3 weeks duration. Study quality was rated as poor due to an inadequate method of allocation concealment and lack of blinding (patients and healthcare providers). Nine patients were excluded from the final analyses, two in the EST group due to poor compliance (not defined) and seven in the HBOT group due to incomplete follow-up data. The definition of a completely healed ulcer was not reported.

Completely healed ulcers were reported in 25% in the HBOT group versus 55% in the EST group (RR=0.46, 95% CI 0.25 to 0.84) after one course of therapy, four weeks for HBOT and three weeks for EST. No ulcers worsened in either group but there were significantly more unchanged ulcers in the HBOT group compared to the EST group, 60% versus 11%, respectively. Twenty-seven patients (EST 12 patients/14 feet and HBOT 15/17 feet) with improved but incomplete healing received a second course of treatment four-to-six weeks from the first treatment. Only one ulcer of 17 (6%) completely healed in the HBOT group compared to seven of 14 (50%) ulcers in the EST group (p=0.005). Four patients receiving HBOT developed middle ear barotraumas and sinus pain. No adverse events were reported in the EST group.

Ozone-Oxygen Therapy

One fair quality, double-blinded trial compared ozone-oxygen therapy to sham (placebo) for diabetic foot ulcers of at least 8 weeks in duration at study initiation.[50] A total of 61 patients, 32 in the ozone group and 29 in the sham group, were randomized. Mean age was 63 years and the proportion of men was 62%. Patients with infected ulcers (but no gangrene or active osteomyelitis) were included with antibiotic treatment as needed. Those with an ABI less than 0.65 were excluded. Most patients had diabetes type 2 (97%) and the baseline ulcer size was slightly larger in the ozone group (4.9 cm^2) compared to the sham group (3.5 cm^2). The ulcers were Wagner classification stage 2/3 or stage 4 following debridement. Study duration was 24 weeks. Patients received treatment or sham for 12 weeks followed by another 12 weeks until wound assessment. In the ozone group, therapy was divided into two phases. The patients initially received treatment sessions with the Ozoter device (OZ Recovery Tecnologies, Ramat Gan, Israel) four times weekly up to 4 weeks, or until granulation appeared in 50% of the wound area. Gas concentrations were 96% oxygen and 4% ozone with intervals between treatments not to exceed 1 day in 5 days a week. In the second phase, the sessions were reduced to two times weekly to complete the 12 weeks of treatment, and gas concentration was altered to 98% oxygen and 2% ozone. The control group received sham treatments with the ozone device circulating air only. Each treatment session lasted 26 minutes. The method of allocation concealment was unclear. Patients and investigators were blinded to mode of therapy. The intention-to-treat analyses included all enrolled patients and study withdrawals were adequately described. A per-protocol analysis, including only "completers," was also conducted.

After 24 weeks there was no statistically significant difference in the proportion of patients with completely healed wounds between the ozone group and sham group. In the ozone group, 41% of the patients had full wound closure versus 33% in the sham group (p=0.34). A large percentage of the study population discontinued prematurely, 16 (50%) in the ozone group and 11 (38%) in the sham group (p=0.44). When the analysis was limited to completers (n=34, 56% of the patients), complete wound closure was reported in 81% of the ozone group compared to 44% of the sham group (p=0.03). Post-hoc subgroup findings in patients with ulcers of 5 cm^2 or less found that active treatment resulted in 100% closure compared to 50% in the sham treatment group (p=0.006).

No differences were reported between active and sham therapy for ulcers infected during treatment, amputation, or withdrawals due to adverse events. Seven patients withdrew from the trial due to adverse events or complications, five in the ozone group and two in the sham group. Adverse events or complications in the ozone group included osteomyelitis, fever, wound infection, and pulmonary congestion. Events in the sham group included amputation and infection.

Summary of Key Question 1

Nine different advanced wound care therapies used for treatment of diabetic ulcers provided information on our primary and secondary outcomes. Most compared outcomes to standard care, placebo or sham treatments with few reporting comparative effectiveness findings versus other advanced wound care therapies. Advanced wound care therapies included collagen, biological dressings, biological skin equivalents, platelet-derived growth factors, platelet-rich plasma, silver products, negative pressure wound therapy, hyperbaric oxygen therapy, and ozone-oxygen therapy. We summarize our primary and secondary outcome findings below. We found insufficient evidence to address the question whether efficacy and comparative effectiveness differed according to patient demographics, comorbid conditions, treatment compliance, or activity level.

Primary Outcomes

Advanced wound care therapies using platelet-rich plasma or ozone oxygen therapy did not improve diabetic ulcer healing compared to standard care (2 studies) or another advanced care therapy (1 study). Other therapies provided mixed results. Four studies compared collagen products to standard care with only one study reporting significantly better healing in the collagen group (70% versus 46%, p=0.03). Pooled results from three studies indicate that the biological skin equivalent Dermagraft compared to standard care results in a non-significant improvement in ulcer healing favoring Dermagraft (35% versus 24%, low strength of evidence, see Executive Summary Table 1). We found moderate strength of evidence that the biological skin equivalent, bi-layer Apligraf, improved healing compared to standard care (55% versus 34%; p=0.001; 2 studies). While pooled results from studies of platelet-derived growth factor showed improvement in the percentage of ulcers healed compared to placebo or standard care (58% versus 37%; p=0.04; 7 studies) the strength of evidence was low due to high heterogeneity of results between studies. One good quality study provided moderate strength evidence that negative pressure wound therapy improved healing more than standard care (43% versus 29%,

p<0.05). Three long-term, fair quality studies of HBOT reported significantly better healing with HBOT (52% to 66%) than sham therapy or standard care (0% to 29%).

Few studies reported time to ulcer healing and other primary outcomes. We found no benefit in time to ulcer healing for collagen, biological dressings, or silver products. We found mixed but generally negative results for biological skin equivalents (1 of 4 Dermagraft and 1 of 3 Apligraf studies showing benefit compared to standard care), platelet-derived growth factors (4 of 8 studies reporting showing benefit compared to placebo or standard care), platelet-rich plasma (1 of 2 studies showing benefit compared to another advanced therapy), and negative pressure wound therapy (1 of 3 studies showing benefit compared to standard care). Strength of evidence was low or insufficient for all findings related to time to ulcer healing. One study of a silver dressing versus a calcium dressing reported a global outcome of healed or improved ulcers with no difference between groups. No studies reported on return to daily activities.

Secondary Outcomes

The most commonly reported secondary outcomes were ulcers infected during treatment and ulcer recurrence. No study reported a benefit for these outcomes for any of the advanced therapies reviewed. Fewer amputations were reported in three studies (one each of a biological skin equivalent, negative pressure wound therapy, and hyperbaric oxygen therapy all compared to standard care) while five studies reported no difference. Few studies reported other secondary outcomes of interest including revascularization or surgery, pain or discomfort, hospitalization, need for home care, or quality of life. No significant differences between treatment groups (including 12 studies comparing an advanced therapy to standard care, 3 studies comparing one advanced therapy to another advanced therapy, and 1 study with both standard therapy and advanced therapy comparison arms) were seen in all-cause mortality though studies were not designed to assess this outcome. We found no significant differences in study withdrawals due to adverse events or allergic reactions to treatment.

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Table 11. Strength of Evidence - Advanced Wound Care Therapies for Diabetic Ulcers

Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Collagen	Standard care	Percentage of ulcers healed	4 (483)	One study reported significant improvement compared to standard care. Three studies reported no significant difference between collagen and standard care. Trials were rated as fair quality.	Low
		Mean time to ulcer healing		One trial found a significant difference favoring standard care; two found no difference.	Low
Biological Dressings	Advanced therapy control (*PDGF, BSE)*	Percentage of ulcers healed	2 (99)	Two fair quality trials showed no difference compared to other advanced wound care therapies.	Low
		Mean time to ulcer healing		No trial was significantly different versus control.	Low
Biological Skin Equivalents [BSE] - *Dermagraft*	Standard care	Percentage of ulcers healed	3 (505)	A trend toward statistically significant improvement compared to standard care (RR=1.49, 95% CI 0.96 to 2.32, I^2=43%). Trials were rated as fair quality.	Low
		Mean time to ulcer healing		Inconsistent results, with one trial reporting a significant difference versus standard care. Trials were rated as fair quality.	Low
BSE -*Apligraf*	Standard care	Percentage of ulcers healed	2 (279)	Two trials of fair quality found statistically significant improvement versus standard care (RR=1.58, 95% CI 1.20 to 2.08, I^2=0%).	Moderate
		Mean time to ulcer healing		One trial reported a significant difference between *Apligraf* and standard care.	Low
BSE -*Apligraf*	Advanced therapy control (*Skin allografts -Theraskin)*	Percentage of ulcers healed	1 (29 ulcers)	One fair quality trial found no significant difference versus *Theraskin*.	Low
		Mean time to ulcer healing		No significant difference versus *Theraskin*.	Low
Platelet Derived Wound Healing [PDGF]	Placebo /standard care	Percentage of ulcers healed	7 (685)	Overall statistically significant improvement versus placebo (RR 1.45 [95% CI 1.03 to 2.05]) but results were inconsistent (I^2 85%). Overall study quality was rated as fair.	Low
		Mean time to ulcer healing	5 (731)	Overall, PDGF demonstrated shorter duration of time to ulcer healing versus placebo.	Low
PDGF	Advanced therapy control (*BSE, silver, sodium carboxy-methylcellulose)*	Percentage of ulcers healed	3 (189)	No significant differences compared to an advanced therapy comparator. Trials were rated as fair quality.	Low
		Mean time to ulcer healing		No significant differences compared to an advanced therapy comparator.	Low
Platelet-Rich Plasma [PRP]	Placebo gel, Platelet-Poor Plasma	Percentage of ulcers healed	2 (96)	Neither of the studies (fair to poor quality) demonstrated a significant difference between PRP and its respective control.	Low
		Mean time to ulcer healing		Significantly shorter healing time compared to platelet-poor plasma. No significant difference versus placebo gel.	Low

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Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Silver Products	Standard care or advanced therapy controls *(calcium-based dressing, oak bark extract, polyherbal cream*	Percentage of ulcers healed	4 (280)	One trial found silver ointment more effective than standard care. Two trials found no difference in healing between a silver cream or dressing and another advanced care product. Studies were of fair quality.	Low
		Mean time to ulcer healing	2 (174)	Two trials found no difference between silver and another advanced wound care product.	Low
Negative Pressure Wound Therapy [NPWT]	Standard care (*Advanced moist wound therapy, saline gauze*)	Percentage of ulcers healed	1 (335)	One trial of good quality found 43% in the NPWT group experienced ulcer healing compared to 29% treated with standard care (RR=1.49, 95% CI 1.11 to 2.01).	Moderate
		Mean time to ulcer healing	3 (432)	Results for time to healing were inconsistent based on 3 trials of mixed quality.	Low
Hyperbaric Oxygen Therapy (HBOT)	Sham or standard care	Percentage of ulcers healed	4 (233)	Three long-term studies of fair quality found significant improvement with adjunctive HBOT versus sham or standard care; one short-term study found no difference.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient
HBOT	Advanced therapy control (*Extracorporeal shockwave therapy*)	Percentage of ulcers healed	1 (84)	One trial of poor quality found adjunctive HBOT less effective than extracorporeal shockwave therapy.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient
Ozone-Oxygen Therapy	Sham	Percentage of ulcers healed	1 (61)	One trial of fair quality found no significant difference between ozone-oxygen and sham.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient

*Number of ulcers evaluated for the primary outcome

The evidence is rated using the following grades: (1) high strength indicates further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate strength denotes further research may change our confidence in the estimate of effect and may change the estimate; (3) low strength indicates further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence is unavailable or does not permit a conclusion.

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KEY QUESTION #2. What are the efficacy and harms of therapies for venous ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Overview of Studies

Table 12 contains an overview of studies of therapies for venous ulcers.[52-72] Twenty trials (in 22 articles) met eligibility criteria including 1 trial of collagen (n=73), 1 trial of biological dressings (n=120), 3 trials of biological skin equivalents (n=380), 4 trials of keratinocytes (n=502), 1 trial of platelet-rich plasma (n=86), 6 trials of silver products (n=771), 1 trial of intermittent pneumatic compression therapy (n=54), 2 trials of electromagnetic therapy (n=63), and 1 trial of hyperbaric oxygen therapy (n=16). Sixteen trials compared an advanced wound care therapy to standard care or placebo. In four trials, the comparator was a different advanced therapy.

Overall, the mean age of study participants ranged from 56 to 73 years and 26% to 61% were male. In 5 studies reporting race, 62% to 100% were white, 0% to 33% were black, 0% to 6% were Hispanic, and 0% to 2% were Asian. Mean ulcer sizes ranged from 1.2 to 11.1 cm^2 with ulcer durations of 7 to 626 weeks.

In 14 trials, the ulcer was described as a "leg" ulcer (with 1 trial specifying the location as medial distal one-third of the leg). In 2 trials, the ulcer was described as a "lower extremity" ulcer (with 1 trial specifying that 80% of the ulcers were on the angle or calf). Three trials did not report the ulcer location describing the ulcer only as a "venous ulcer." In 12 trials, the diagnosis of venous ulcer was based on clinical signs or symptoms of venous insufficiency. The remaining 8 trials required either patients to have adequate arterial circulation or specifically excluded patients with known arterial insufficiency.

Collagen

One fair quality RCT enrolled 73 patients with a venous leg ulcer and followed them over twelve weeks of treatment with Promogran or standard wound care.[52] Standard care included compression therapy. Participants in the study had an average age of 73 years; 35 percent were males. Patients with infected ulcers and ulcers linked to diabetes were excluded; an ABI of greater than 0.8 was required for inclusion. The trial did not include a run-in period with standard care and compliance with treatment was not reported. The mean ulcer size was 8.2 cm^2 and the mean ulcer duration was 9.2 months. The study reported no significant difference between treatment arms in ulcer size, ulcer duration, or ancillary therapies. Demographic and ulcer characteristics are reported in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

The percentage of venous ulcers healed by study completion did not differ significantly between the Promogran and standard wound care groups (49% versus 33%, p=0.18; ARD=16%, 95% CI -7% to 38%).[52] The effects of patient factors or ancillary therapies on outcomes were not reported.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Significantly fewer ulcers were infected during treatment with collagen compared to standard care (0% versus 14%, p=0.03). No significant differences between collagen and standard care were noted for the percentage of withdrawals due to adverse events or percentage of patients having an allergic reaction to treatment.[52]

Biological Dressings

One study, enrolling 120 patients,[53] compared OASIS Wound Matrix plus compression therapy to compression therapy alone (standard care) in treatment of chronic leg ulcers unresponsive to standard therapy. This industry-sponsored study was of fair quality and took place in multiple sites across the United States, United Kingdom, and Canada. Patients with infected ulcers, uncontrolled diabetes, or an ABI less than 0.8 were excluded. Compliance with treatment was not reported. The average ulcer size at baseline was 11.1 cm^2. The mean age of the patients was 64 years, 42% were male, and 81% were white. Thirty-four percent of ulcers were present for 1 to 3 months; 37% were present for more than 12 months. Additional study characteristics are presented in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

Treatment with OASIS resulted in a statistically significant improvement in incidence of ulcer healing, with 55% of treated patients achieving complete healing at 12 weeks, versus 34% in the standard care group (ARD=20%, 95% CI 3% to 38%; p=0.02) but not at 6 months (67% versus 46%, p=ns).[53]

Debridement was only performed if deemed clinically necessary. This allowed for covariate and subgroup analysis comparing those who received baseline debridement to those who did not. Covariate analysis showed that OASIS had a consistently higher rate of healing compared to standard care regardless of debridement status, but subgroup analysis found the difference between study groups was exaggerated in patients who received baseline debridement. Sixty-three percent of OASIS patients who underwent baseline debridement healed at 12 weeks, versus 30% of standard care patients who received initial debridement (p=0.02).[53] Covariate analysis also showed the higher incidence of healing with OASIS was consistently observed when accounting for the presence of vascular disease (p=0.03), type 2 diabetes (p=0.02), endocrine disease (p=0.03), and hypertension (p=0.02).

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

At 6 months follow-up, there was a significant difference in recurrence (0% of healed ulcers originally treated with OASIS versus 30% of healed ulcers in the standard care arm, p=0.03). There was no difference between groups in ulcers infected during treatment. Two patients in the OASIS group were hospitalized and unable to complete the study versus none in the standard care group (p=ns).[53] No statistically significant differences between treatment groups were reported for withdrawals due to adverse events, proportion of patients with adverse events, all-cause mortality, or allergic reaction to treatment.

Table 12. Overview of Therapies for Venous Ulcers

Study, year	N Randomized	Treatment	Product	Comparator	Healed ulcers	Mean time to ulcer healing	Global assessment	Return to daily activities	Ulcers infected during treatment	Amputation	Revascularization/ surgery	Recurrence	Time to recurrence	Pain/discomfort	Hospitalization	Required home care	Quality of life	Withdrawals due to adverse events	Patients with ≥ 1 adverse event	All-cause mortality	Allergic reactions to treatment
Vin 2002[52]	73	Col	Promogran	Non-adherent	-				+					-				-			-
Mostow 2005[53]	120	BD	OASIS	Compression bandage	+				-			+			-			-	-	-	±
Falanga 1998[54]	309	BSE	Apligraf	Compression bandage	+	+			-			-		-				-		-	
Falanga 1999[55] (subset of Falanga 1998; pts with ulcer duration > 1 yr)	120	BSE	Apligraf	Compression bandage	+	+						-									
Krishnamoorthy 2003[56]	53	BSE	Dermagraft	Compression bandage	-				-									-	±	-	
Omar 2004[57]	18	BSE	Dermagraft	Compression bandage	-																
Lindgren 1998[58]	27	Keratinocyte	Keratinocyte sheets + pneumatic compression therapy	Pneumatic compression therapy	-																
Navratilova 2004[59]	50	Keratinocyte	Cryopreserved keratinocytes	Lyophilized keratinocytes	-	-								-							
Harding 2005[60]	200	Keratinocyte	Keratinocytes	Vehicle + std care or std care only	-	-			-			-		-	-				-	-	-
Vanscheidt 2007[61]	225	Keratinocyte	Keratinocytes (autologous)	Compression bandage	+	+													-	-	
Stacey 2000[62]	86	PRP	Platelet lysate	Placebo	-																
Belcaro 2010[38]	82	Silver Ointment	Aidance	Standard	+													-	-		-
Bishop 1992[63]	93	Tri-peptide Copper Complex		Silver Cream (Silvadene) or Tri-peptide placebo	↓*		+					-		-							-

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Study, year	N Randomized	Treatment	Product	Comparator	Healed ulcers	Mean time to ulcer healing	Global assessment	Return to daily activities	Ulcers infected during treatment	Amputation	Revascularization/ surgery	Recurrence	Time to recurrence	Pain/discomfort	Hospitalization	Required home care	Quality of life	Withdrawals due to adverse events	Patients with ≥ 1 adverse event	All-cause mortality	Allergic reactions to treatment
Blair 1988[64]	60	Silver Cream	Flamazine	Non-adherent + Non-occlusive dressing	-																-
Dimakakos 2009[65]	42	Silver Dressing		Standard	+	±								±							
Harding 2011[66]	281	Ionic Silver Dressing	AQUA-CEL	Lipidocolloid silver	-		+		-					-				-	-	-	
Michaels 2009a, b[67,68]	213	Silver Dressing	6 options	Non-silver dressing	-	-						-					-	-		-	
Schuler 1996[69]	54	IPC		Unna's Boot (Compression)	-									-				-			-
Ieran 1990[70]	44	EMT	Dermagan	Sham	+	±	-	-	±			-		-				-		-	
Kenkre 1996[71]	19	EMT	Elmedistraal	Sham	-			±	-					+				-		-	-
Hammarlund 1994[72]	16	HBOT		Sham	-																

BD – Biological Dressing; BSE – Biological Skin Equivalent; Col – Collagen; EMT – Electromagnetic therapy; EST – Extracorporeal Shock Wave Therapy; HBOT – Hyperbaric Oxygen Therapy; IPC – Intermittent Pneumatic Compression Therapy; NaCMC - Sodium Carboxymethylcellulose; NPWT – Negative Pressure Wound Therapy; PDGF – Platelet-derived Growth Factor; PRP – Platelet Rich Plasma

+ Treatment group better than comparator ($p < 0.05$)
- Treatment group demonstrated no significant benefit
↓ Treatment group worse than comparator
± Significance could not be determined
* (+ for silver)

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Biological Skin Equivalents

We identified three RCTs related to the use of biological skin equivalents in ulcers of venous etiology. Two studies evaluated the use of Dermagraft for ulcers described only as "leg" ulcers. One study evaluated the use of Apligraf but did not describe the ulcer location. The comparator in all three studies was standard care including compression bandages. One Dermagraft study was a small (n=18), single center trial of fair quality that was done in the UK.[57] No study sponsor was reported. The other Dermagraft study was a small (n=53), industry sponsored trial of fair quality that took place in six centers across the UK and Canada.[56] Both studies allowed ulcers with an initial area of 3 to 25 cm^2 and took place over a period of 12 weeks. The Apligraf study was a large (n=309), industry-sponsored study of fair quality, which took place at 15 sites across the U.S.[54] The average ulcer size in this study was significantly smaller than the other studies, with a mean ulcer area of 1.2 cm^2 at baseline. This trial followed patients for 6 months. None of the studies reported compliance with standard care. None reported differences between study arms at baseline but one did not report a statistical analysis.[56] No study enrolled patients with infected ulcers; only one reported allowing antibiotics as needed.[56] All of the studies excluded patients with arterial insufficiency. One included a 14 day run-in period with compression.[56] Summary baseline data are presented in Table 13. Additional information about the studies is presented in Appendix D, Table 1.

Table 13. Baseline Study Characteristics: Biological Skin Equivalents

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	3	380 total	18 - 309
Age	3	62	60 - 69
Gender (% male)	3	51	42 - 61
Race/Ethnicity (%)			
White	2	79	76 - 94
Black	2	16	4 - 18
Other	2	5	2 - 5
BMI	1	30.4	30.4
ABI	2[a]	1.1	1.06 - 1.1
Ulcer Size (cm^2)	3	2.5	1.2 - 10.7
Ulcer Duration	3[b]		
Study Duration (weeks)	3	9	8 - 12

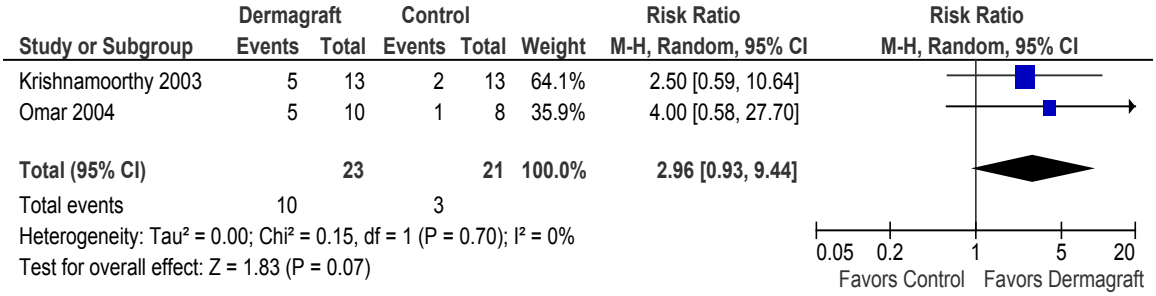
[a]Mean/median ABI not reported in one study, but all participants were >0.65 by exclusion criteria
[b]All 3 studies reported ulcer duration in a different format: Krishnamoorthy 2003:[56] *median* duration of 47.7 *days*; Omar, 2004:[57] *mean* duration of 119.3 *weeks*; Falanga, 1998:[54] <6 months: 30.6%, 6-12 months: 21.1%, 1-2 years: 13.8%, >2 years: 34.5%

Primary Outcomes (Appendix D, Table 2)

In two small studies of Dermagraft, there was no significant difference in healed ulcers compared to standard care.[56,57] Pooled results are presented in Figure 8. The overall risk ratio was 2.96 (95% CI 0.93 to 9.44, I^2=0%). The large trial using Apligraf did show a significant benefit compared to standard compression bandage therapy for incidence of complete ulcer healing at 6 months (63% versus 49%; ARD=14%, 95% CI 3% to 26%; p=0.02) and median time to closure (61 days versus 181 days, p=0.003).[54] A similar pattern was observed when only ulcers of greater than 1 year duration were considered.[55] Additional subgroup analyses from this trial found significant differences in treatment efficacy for certain patient subpopulations. In ulcers with

a duration less than 6 months at the beginning of the study time to ulcer healing did not differ significantly between biological skin equivalent and standard care. In ulcers present for over 6 months, significantly more rapid healing was observed in the biological skin equivalent group (median of 92 days versus 190 days for control, p=0.001). Similarly, a significant benefit in time to closure was seen for biological skin equivalent compared to standard compression bandage therapy in patients with deeper ulcers (83 days versus 183 days, p=0.003). Stratification by initial ulcer area found that Apligraf significantly improved ulcer healing ($p<0.05$) when used in both large (defined as greater than 1000 mm^2) and small ulcers.[54] The effect of ancillary therapies on treatment efficacy could not be assessed from any of the studies.

Figure 8. Proportion of Venous Ulcers Healed - Biological Skin Equivalent (Dermagraft) versus Compression Bandage



*Kishnamoorthy 2003 – Analysis is for Group 2 (4 pieces of Dermagraft applied on day 0, and weeks 1, 4, and 8) versus compression bandage

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Two studies, one of Dermagraft[56] and one of Apligraf[54] reported no difference between treatment with biological skin equivalent or standard compression bandage therapy in the incidence of infection. The Apligraf study also reported no difference in the incidence of cellulitis.[54] Rate of recurrence was reported in the Apligraf study. No significant difference was seen in the percentage of ulcers recurring within one year (12% versus 16% of control patients)[54] with similar findings for the subgroup with ulcers of greater than 1 year duration.[55] In the Apligraf study, there was also no difference in pain between treatment groups.[54] Of the two studies that reported adverse events, both reported no differences between biological skin equivalent and standard compression bandage therapy in withdrawals due to adverse events.[54,56] There was also no difference in all-cause mortality. One study reported no difference in the incidence of adverse events or serious adverse events.[56] No instances of immune intolerance or reactivity to grafts were reported.

Keratinocytes

Four RCTs met eligibility criteria and looked at the use of keratinocytes in venous ulcers. Three studies described the ulcers only as "leg" ulcers; one specified the location as medial distal one-third of the leg.[58] These trials had marked heterogeneity across several important parameters: keratinocyte source (autologous or allogeneic); cellular state of keratinocytes (fresh, frozen, or lysed); comparators (other keratinocyte product, standard of care); and study size, protocols, and quality. This variability hampered aggregation and the ability to generalize results. The four studies consisted of the following: a large, multinational study of fair quality that took place in Belgium, Germany, Poland, and the UK[60] (n=200); a large, multinational study of fair quality that took place in Hungary, Germany, and the Czech Republic[61] (n=225); a smaller study of poor quality that took place at a single site in the Czech Republic[59] (n=50); and a small study of fair quality that took place in Sweden[58] (n=27). Inclusion criteria for ulcer size varied. One study included ulcers between 1 and 20 cm^2; the median size was 5.2 cm^2.[60] Another study included ulcers of 2 to 50 cm^2 with 60% of the study ulcers between 2 and 10 cm^2 and 39% over 10 cm^2.[61] The third study included ulcers greater than 2 cm^2 and the mean ulcer size was 10.7 cm^2.[59] In the last study, all ulcers were greater than 2 cm^2 with a mean ulcer size of 8.4 cm^2.[58] One study reported having industry sponsorship;[60] the other studies did not include financial disclosures. One study reported study compliance and identified protocol violations in 5.3%.[60] Three of the studies either excluded patients with infection or required treatment before study entry; one did not report infection status.[61] Two studies reported antibiotic use during the study, either for cellulitis[58] or prior to graft placement, if infection was present.[59] All of the studies excluded patients with arterial insufficiency; one study excluded patients with diabetic ulcers.[60] None of the studies reported significant differences between study arms at baseline. Two of the studies included a run-in period with standard care, either 2 weeks[61] or 4 weeks.[60] Summary baseline characteristics are reported in Table 14. Additional study characteristics are presented in Appendix D, Table 1.

Table 14. Baseline Study Characteristics: Keratinocytes

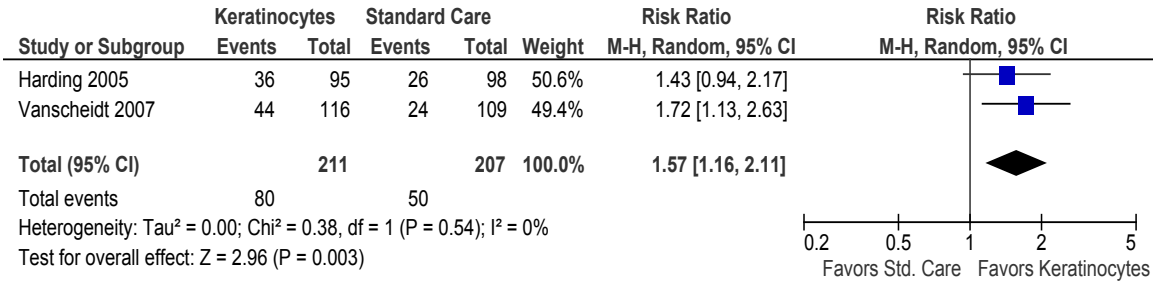
Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	4	502 total	27 - 225
Age	2[a]	66	63 - 67
Gender (% male)	4	38	33 - 39
Race/Ethnicity (%)	1		
White	1	100	-
BMI	2[b]	28.9	28.6 - 30.1
Smoking (%)	1	19.1	-
ABI	2[c]		
Ulcer Size (cm^2)	2[d]	9.2	6.3 - 10.7
Ulcer Duration (weeks)	1[e]	102.7	-
Study Duration (weeks)	4	23	8 - 26
History of DM	1	6%	-

[a]Two additional studies reported median ages of 76 years and 67.5 years
[b]One additional study reported median BMI of 28.9
[c]Two studies reported median ABI of 1.0 and 1.1; all patients in 2 other studies had ABI >0.8 per exclusion criteria
[d]Two other studies reported ulcer size using other formats: Harding, 2005:[60] median ulcer size=5.2 cm^2; Vanscheidt, 2007:[61] ulcer size 2-10 cm^2: 60.4%; ulcer size >10 cm^2: 38.7%
[e]3 additional studies reported ulcer duration in other formats: Harding, 2005:[60] *median* duration of 43 weeks; Lindgren, 1998:[58] <2 years: 44.4%, >2 years: 55.6%; Vanscheidt, 2007:[61] 3-12 months: 59.1%, >12 months: 40.9%

Primary Outcomes (Appendix D, Table 2)

One trial demonstrated significant improvements in both proportion of ulcers healed (38% versus 22%, p=0.01) and median time to complete healing (176 days versus more than 201 days, p<0.0001) when BioSeed-S (autologous keratinocytes in fibrin sealant) was compared to standard compression bandage therapy. In subgroups of patients with ulcers of 12 months or less, greater than 12 months, 2 to 10 cm^2, or greater than10 cm^2, the proportion of ulcers healed was significantly greater in the keratinocyte group only for patients with larger ulcers at baseline (greater than 10 cm^2). Time to ulcer healing was significantly higher for patients treated with keratinocytes in all of the subgroups.[61] In other studies, no statistical differences in ulcer healing were seen when cryopreserved, cultured epidermal allografts (CEA) were compared with pneumatic compression therapy,[58] when cryopreserved CEA were compared to lyophilized CEA,[59] and when lyophilized keratinocytes were compared to a combined control group of standard compression therapy and standard therapy plus keratinocyte vehicle.[60] Pooled ulcer healing results for the two studies comparing keratinocyte treatment to standard care (with compression therapy) are presented in Figure 9. The absolute risk difference was 14%, 95% CI 5% to 23%. The overall risk ratio was 1.57 (95% CI 1.16 to 2.11, I^2=0%) indicating a significant overall benefit of keratinocyte therapy compared to standard care. Two studies reported time to healing with no differences between treatment groups in either study, one a comparison of keratinocytes to standard care,[60] the other a comparison to another advanced therapy.[59] No comparisons could be made within or between studies regarding the effect of ancillary therapies on treatment efficacy.

Figure 9. Proportion of Venous Ulcers Healed - Keratinocytes versus Standard Care



*Harding 2005 – Analysis is for the "as treated" ITT cohort.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Few secondary outcomes were reported. In one study, the percentage of ulcers infected during treatment, ulcer recurrence, and pain during treatment or follow-up did not differ between keratinocyte therapy and a combined (standard care and vehicle) control group.[60] Another study reported that pain was significantly reduced during the first week after treatment application with no difference between the two keratinocyte products.[59] Only the two large studies reported adverse events.[60,61] One study reported 65 events in 38 patients in the keratinocyte group and 51 events in 27 patients in the compression therapy group. Of the 116 patients receiving keratinocyte therapy, 1 experienced a minor adverse event "certainly" related to the treatment, 2 were "probably" related, and 6 were "possibly" related.[61] The other study reported no difference between advanced treatment and a combined standard care and vehicle control group in "burning, stinging, pain, or itching" sensations.[60] There was no difference in all-cause mortality between treatment groups in either study.

Platelet Rich Plasma (PRP)

One RCT enrolling 86 patients with ulcers described only as "leg" ulcers, compared the efficacy of PRP to placebo over 39 weeks.[62] This fair quality trial was conducted in Australia and funded by a combination of industry and government sources. Both groups received standard compression therapy. The authors did not report inclusion or exclusion criteria related to infection, whether there was a run-in period with standard care, or whether compliance with treatment was monitored. Patients were required to have an ABI greater than 0.9 for inclusion. The mean age of participants was 71 years; 42 percent were male. Mean ulcer size was 4.9 cm^2 and the mean ulcer duration prior to enrollment was 3 months. The study reported no significant difference between treatment arms in ulcer size, ulcer duration, or ancillary therapies. Treatments were applied twice weekly until wound healing or up to the 9 month study duration. Demographic and ulcer characteristics are reported in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

There was no significant difference between PRP and placebo in the percentage of ulcers healed at study completion (79% versus 77%, p=ns).[62] Time to complete healing was not reported.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Two hospitalizations leading to study withdrawal were reported but the treatment group the patients were assigned to was not provided. There were 6 withdrawals from the study due to adverse events (5 with allergy to the paste bandage and 1 with leg trauma related to the bandages) but the treatment group was not reported.[62]

Silver Products

We identified six studies of silver products used to treat venous ulcers.[38,63-68] Two studies compared a silver dressing to a dressing without silver,[65,67,68] two compared silver ointment to standard care,[38,60] one compared silver cream to a tri-peptide copper cream or tri-peptide placebo (with silver as the control treatment),[63] and one compared an ionic silver dressing to a lipidocolloid silver dressing.[66] The studies were conducted in the United States,[63] the United Kingdom,[64,67,68] Greece,[65] Italy,[38] and Europe.[66] Enrollments ranged from 42 to 281 with a total enrollment of 771. Two studies were of good quality[64,66] and four were of fair quality. A summary of study characteristics is presented in Table 15 with additional information about the studies in Appendix D, Table 1.

Table 15. Summary of Baseline Characteristics: Silver Products

Characteristic	Number of Studies Reporting	Mean (unless noted)	Range
Number of Patients Randomized	6	771 total	42 - 281
Age (years)	6	65.6	47 - 71
Gender (% male)	5	41.6	35 - 50
Race/Ethnicity (%)			
White	1	62	-
Black	1	33	-
Other	1	5	-
BMI	1	30	-
Smoking, Current (%)	2	22.7	18.3 - 33.7
ABI	1	1.04	-
Ulcer Size (cm^2)	3[a]	6.0	3.2 - 10.5
Ulcer Duration (months)	3[b]	19.4	9.0 - 46.4
Infection (%)	4[c,d]	-	-
Study Duration (weeks)	6	8.6	4 - 12
History of Diabetes (%)	2[e]	9	-
History of MI or Cardiac Failure (%)	1	14	-
History of Stroke or TIA (%)	1	8	-

[a]One study reported that 72% were <3 cm diameter; another reported that 52% were <3 cm diameter
[b]One study reported that 38.5% were >12 weeks
[c]Three studies reported excluding 1) $>10^5$ bacteria/gram of tissue, systemic sepsis or bone infection; 2) clinically infected ulcers or receiving local or systemic antibiotics (included ulcers with at least 3 of the following: pain, perilesional skin erythema, edema, foul odor, or high levels of exudate); or 3) receiving oral or parenteral antibiotics
[d]One study included only patients with infected ulcers
[e]One study excluded patients with diabetes

Ulcers were described as "leg" ulcers in 3 studies[64,65,67,68] and lower extremity ulcers in 1 study.[63] One study did not specify ulcer location[38] and one reported that 47% were ankle, 33% calf, 18% gaiter, and 2% foot ulcers.[66] Three studies excluded patients with signs of infection or patients who were receiving antibiotics;[63,66-68] all patients had infected ulcers in two studies,[64,64] and one did not report infection status.[38] Only one reported use of antibiotics, as needed.[65] All trials excluded patients with arterial insufficiency. None of the trials included a run-in period with standard care. Compression bandaging was part of standard care in all of the trials; one trial reported monitoring compliance with treatment but did not provide results based on compliance.[63] Four studies reported no baseline differences between treatment groups while one noted gender distribution and height varied (not found to be related to outcomes),[63] and one found differences in BMI and ulcer location (right versus left leg).[67,68] Two studies reported mean ulcer sizes of 3.2 cm^2[2(38)]and 3.4 cm^2.[64] The latter study included only ulcers up to 10 cm^2. One study reported a mean ulcer size of 10.5 cm^2 with ulcers of 3 cm^2 to 50 cm^2 included in the trial.[63] Another study included ulcers between 5 cm^2 to 40 cm^2 but did not report a mean size.[60] One study reported that 72% of the study ulcers were less than 3 cm in diameter[67,68] and a second study reported that 52% were less than 3 cm in diameter.[65] Ulcer duration was reported in 4 studies. In three studies, the mean ulcer duration ranged from 9 months to 46.4 months.[64-66] In the fourth study, only ulcers of greater than 6 weeks were included; 38.5% were of greater than 12 weeks.[67,68] The studies were designed to address effectiveness and safety with one looking at non-inferiority of a new silver product.[66]

Primary Outcomes (Appendix D, Table 2)

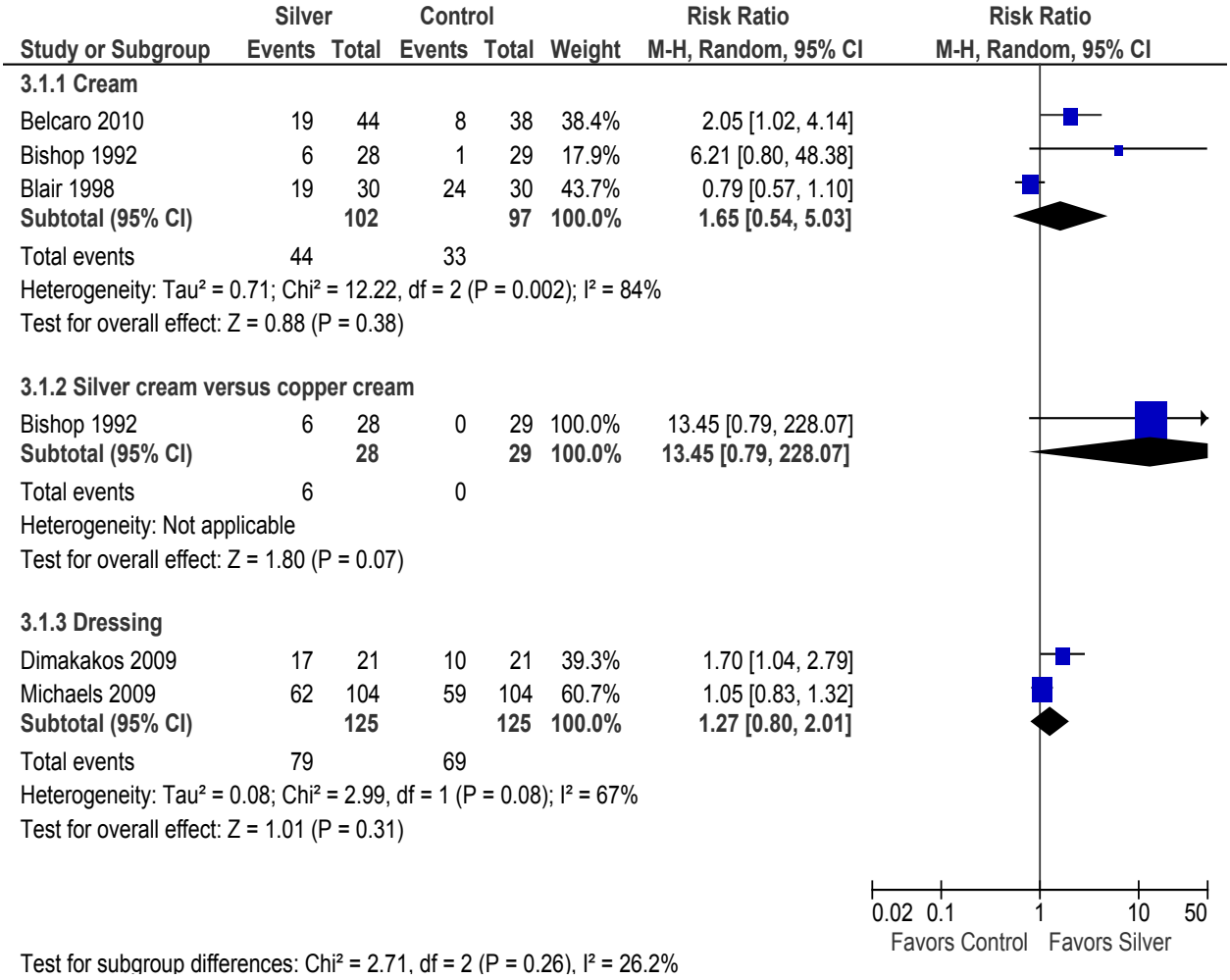
All six studies reported ulcer healing. Two studies found significantly greater rates of healing in the silver cream/ointment groups at 4 weeks when compared to standard care (42% versus 22%, $p<0.05$)[38] or to copper cream (21% versus 0%, p=0.01).[63] No difference was found between silver cream and the copper cream placebo (31% versus 3%, p=0.05).[63] One study comparing silver cream to a non-adherent and non-occlusive dressing found no benefit for the silver cream at 12 weeks (63% versus 80%).[64] Pooled results from three studies (Figure 10) showed no statistically significant difference in ulcer healing with silver cream (range 21% to 63%) versus standard care or placebo copper cream (range 3% to 80%) with evidence of large heterogeneity (RR=1.65, 95% CI 0.54 to 5.03, I^2=84%).

One study found a higher rate of ulcer healing in the silver dressing group compared to standard care (non-silver dressing) at 9 weeks (81% versus 48%, p=0.02).[65] The two remaining studies found no difference at 8 weeks between two silver-based dressings (17% versus 15%)[66] and no differences at 12 weeks (60% versus 57%) or 1 year (96% in both groups) between a silver and a non-silver dressing.[67,68] Pooled data from two studies of silver versus non-silver dressings (Figure 10) again show no statistically significant difference with evidence of heterogeneity (RR=1.27, 95% CI 0.80 to 2.01, I^2=67%).

Two studies presented data on factors related to healing. In one study comparing silver to non-silver dressings, female gender (p=0.01) and smaller ulcer size (up to 3 cm versus above 3 cm; p=0.008) were significant predictors of healing at 12 weeks.[67,68] In the other study, the significant overall benefit of the silver dressing compared to standard care was also observed among the 30 study ulcers of less than 0.5 cm depth with 93% healing in the silver group versus 56% in the non-silver group (p=0.04). For ulcers greater than 0.5 cm depth (12 of the 42 study ulcers) there was no benefit of the silver dressing (57% versus 20%).[65] In the silver dressing group, 100% (6/6) of ulcers with a high degree of exudation were healed following treatment; in the non-silver group, none of 8 ulcers with a high degree of exudation were healed.[65]

Two studies, both comparing silver dressings to non-silver dressings, reported time to healing. One study found no difference between groups (medians of 67 [silver] and 58 [non-silver] days),[67,68] the other study reported mean times to healing of 6.1 weeks (silver) and 6.4 weeks (non-silver) but whether the difference was significant was not reported.[65] Silver cream was superior to tri-peptide copper cream in a composite measure of the degree of erythemia, exudation, and granulation[63] and an ionic silver dressing was superior to a lipidocolloid silver dressing in a composite outcome of healed or markedly improved ulcers.[66]

Figure 10. Proportion of Venous Ulcers Healed – Silver Products



Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

One study reported on ulcers infected during treatment with no difference between an ionic silver dressing (11%) and a lipidocolloid silver dressing (9%).[66] Two studies reported on ulcer recurrence. In one study, no difference was observed in recurrence between ulcers treated with a silver dressing versus a non-silver dressing (12% versus 14%).[67,68] Another study reported that 17% of the ulcers treated with silver cream recurred. There were no healed ulcers in the tri-peptide copper cream group and the one healed ulcer in the tri-peptide placebo cream group did not recur.[63] Pain was assessed in three studies, one comparing silver cream to tri-peptide copper cream,[63] one comparing an ionic silver dressing to a lipidocolloid silver dressing,[66] and one comparing a silver dressing to a non-silver dressing.[65] No differences between treatment groups were observed in the two studies comparing advanced wound therapies.[63,66] In the third study, it was reported that 100% of patients in the silver dressing group were pain-free by the end of the eighth week of treatment; 62% of the standard care (non-silver dressing) patients were pain-free after 9 weeks of treatment.[65] Quality of life was reported in one study, a comparison of silver and non-silver dressings. No difference was found between groups at either 12 weeks (post-treatment) or 1 year.[67,68] Study withdrawals due to adverse events were documented in

three studies with no differences between silver cream and standard care,[38] two silver dressings,[66] or silver and non-silver dressings.[67,68] In one study, there were no withdrawals and no adverse events.[38] In the second study, the percentages of patients withdrawing were 6% (ionic silver dressing group) and 9% (lipidocolloid silver dressing group).[66] Overall adverse event rates were 50% and 42%, respectively; study-related adverse event rates were 23% and 18%. The third study reported one withdrawal in the silver dressing group.[67,68] No differences were observed between two silver dressings or a silver and a non-silver dressing in all-cause mortality with post-treatment (8 or 12 weeks) rates of 0% to 1.4%[66,67,68] and a 1 year follow-up rate of 4% (both treatment groups).[67,68] Allergic reactions to treatment were reported in 3 studies with no differences between silver cream and standard care,[38] silver cream and copper cream,[63] or silver cream and non-adherent dressing.[64] One study reported no treatment-related adverse events associated with a silver or non-silver foam dressing.[65]

Intermittent Pneumatic Compression Therapy

One fair quality RCT followed 54 patients over 26 weeks comparing intermittent pneumatic compression (IPC) therapy to compression bandaging (Unna's boot).[69] Ulcer location was not reported and the trial did not include a run-in period. The mean age of the participants was 57 years; 46% were male. Mean ulcer area was 9.9 cm^2 and mean ulcer duration was 44 weeks. Patients with an ABI of less than 0.9 were excluded; no information was provided about infection status or antibiotic use. The study reported no significant differences between treatment arms in ulcer size or ulcer duration but there were gender differences. In addition to IPC treatment (HRx, Kendall Healthcare Products Co., Mansfield MA) twice a day for 3 hours total, patients in the IPC group wore a HomeRx Therapeutic (Kendall) below-knee gradient compression elastic stocking. It was reported that 93% complied with therapy. Demographic and ulcer characteristics are reported in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

There was no significant difference between IPC therapy and Unna's boot in percentage of ulcers healed (71% versus 60%, p=ns).[69] It was noted that 100% of ulcers less than 3 cm^2 healed regardless of the treatment group.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Pain ratings on a visual analog scale (VAS) did not differ between intermittent pneumatic compression and compression bandaging.[69] There were no significant differences between treatment groups in the percentage of withdrawals due to adverse events or the percentage of patients having an allergic reaction to treatment.

Electromagnetic Therapy

Two RCTs evaluated electromagnetic therapy (EMT) compared to sham for the treatment of ulcers due to venous insufficiency.[70,71] Both studies included "leg" ulcers with no further detail on ulcer location. One study was conducted in the UK[71] and one in Italy.[70] Neither study included a run-in period with standard care. One study reported that patients with arterial occlusive disease were excluded. This study also prohibited standard compression therapy and monitored use of EMT by a clock built into the device.[70] Neither study reported inclusion or exclusion criteria for infection. A total of 63 patients, 32 receiving EMT and 31 receiving control were enrolled. The overall mean age in one study was 71 years with a significant difference ($p<0.05$) in age between groups (EMT 600 Hz mean age=59; EMT 600 Hz mean age=78; control mean age=71).[71] The mean age in the second study was 66 years and two-thirds of the patients were female.[70] Comorbidities were not uniformly reported (see Appendix D Table 1). Information about ulcer size and duration is presented in Table 16 (below). In one trial, mean ulcer duration was significantly longer in the placebo group than in the two active treatment groups.[71] Patients in both trials had to have had unsatisfactorily healing venous ulcers of at least 4 weeks duration. The aggregate study quality of the included trials was fair. Funding for one study was provided by industry;[71] the funding source for the second trial was not reported.[70]

EMT in one trial was applied with a single pulse of electrical current generating a magnetic field of 2.8 micro Teslas (mT) at a frequency of 75 Hz with an impulse width of 1.3 ms over 3 to 4 hours a day up to 90 days or until the ulcer healed.[70] No compression therapy was administered during the study. In the second trial, there were two treatment arms of EMT, 600 Hz and a magnetic field of 25 mT, and 800 Hz and a magnetic field of 25 mT.[71] Treatments were delivered 5 days a week for 30 days followed by a month of observation.

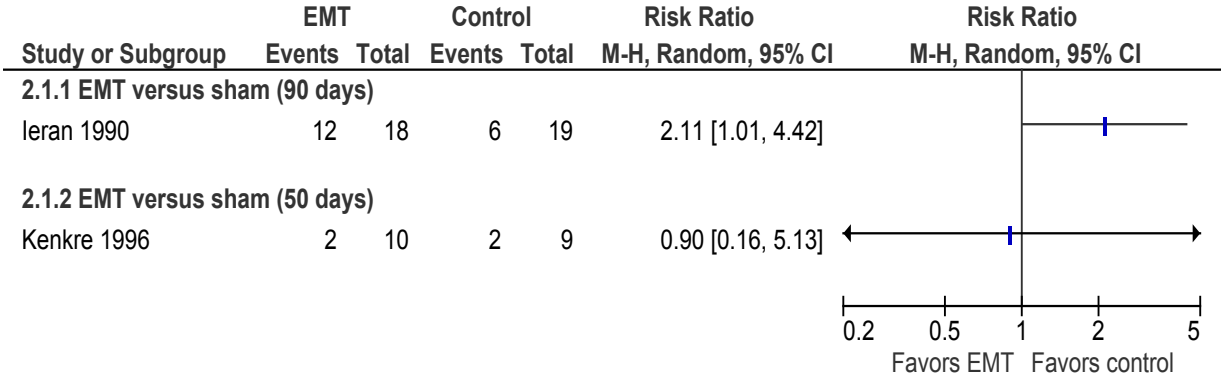
Table 16. Ulcer Size, Ulcer Duration, and Definitions of Closure: Electromagnetic Therapy

Study / Location	Mean ulcer size, (range or SD)	Duration of ulcer, (range)	Definition of ulcer closure
Kenkre 1996 / UK[71]	EMT 600 Hz: 63 mg (6 to 269) EMT 800 Hz: 81 mg (46 to 197) Control: 119 mg (35 to 526)	EMT 600 Hz: 230.4 weeks (36 to 728) EMT 800 Hz: 418 weeks (36 to 1368) Control: 962.6 weeks (160 to 2548)	NR
Ieran 1990 / Italy[70]	EMT: <15 cm^2 4.8, >15 cm^2 34.2 Control: <15 cm^2 5.0, >15 cm^2 39.9	EMT: 30 months (3 to 360) Control: 23 months (3 to 240)	Complete epithelialization

Primary Outcomes (Appendix D, Table 2)

Due to variations in follow-up durations the trials were not statistically pooled. Individual trial risk ratios are presented in Figure 11. The longer-term trial reported a statistically significant difference in healed ulcers in favor of EMT therapy.[70] At day 90, 67% of patients in the EMT group had healed venous ulcers versus 32% of patients in the sham control group arm (ARD=35%, 95% CI 5% to 65%; RR=2.11, 95% CI 1.01 to 4.42).[70] At one-year following the initiation of treatment, 16 patients (89%) in the EMT had healed ulcers compared to 8 patients (42%) in the sham control arm (RR=2.11, 95% CI 1.22 to 3.67). In the second trial, at 50 days from initiation of therapy, 20% of the patients in the combined EMT groups had healed venous ulcers compared to 22% of the patients in the sham control group (RR=0.90, 95% CI 0.16 to 5.13).[71]

Figure 11. Proportion of ulcers healed – Electromagnetic Therapy versus Sham



One trial reported average times to healing of 76 days in the EMT group and 71 days in the sham control group but the significance of this difference was not reported.[70] Effectiveness of treatment was also reported. Based on assessment by three physicians blinded to treatment, 15 patients in the EMT group were rated as "excellent" (n=5), or "good" (n=10) compared to 10 patients in the sham control group (2 and 8, respectively). Four patients in the control group and no EMT patients had ulcers rated as "bad" (worsening) (p=0.02). The percentage of patients considered "not restricted" in activity did not differ significantly between the EMT and sham groups.[70] The second trial also reported on activity level. Patients in the 800 Hz and sham control groups improved in their ability to walk up a flight of stairs following treatment.[71] All treatment arms improved in walking a distance consistent with a block of houses and frequency of participating in social activities.

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

One study reported ulcer recurrence.[70] At follow-up of one year or greater after healing, ulcers recurred in 4 EMT patients and 4 sham control patients. The proportion of healed ulcers after at least one year of follow-up from time of healing was 67% in the EMT group (12 patients) and 21% in the sham control group (4 patients) (RR=3.17, 95% CI 1.25 to 8.03). Both studies reported ulcers infected during treatment. In one study, at day 90, infected ulcers were reported in 3 EMT and 11 control patients.[70] In the other study, no EMT patients and 2 control group patients had infected ulcers.[71] Both studies also reported pain scores. In one study, there was no significant difference between the groups in the amount of pain reported at day 90.[70] In the other study, there were significant reductions ($p<0.05$) in pain scores from baseline to day 30 for both EMT groups with a non-significant reduction in the control group. The reductions in pain scores in the EMT groups were significantly greater than the reduction in the control group.[71] In one trial, 68% (13/19) of all patients were reported to have experienced adverse events, none leading to study withdrawal.[71] These included moderate-to-severe headaches (2 EMT patients) and sensations of heat, tingling, and "needles and pins" in the limbs (3 patients in each group). Adverse events were not reported in the second trial but 2 of 7 patients not included in the analyses (both in the EMT group) were withdrawn from the study, one after suffering an allergic reaction to medications and one after being diagnosed with rheumatoid arthritis.[70] One study reported no deaths;[70] the second reported no deaths in the EMT group.[71]

Hyberbaric Oxygen

We identified one small double-blinded trial evaluating HBOT for the treatment of venous leg ulcers.[72] Patients were allocated to either HBOT or air at 2.5 ATA for 90 minutes for five days a week for a total of 30 treatments over 6 weeks. The authors reported 100% compliance with the treatment sessions. Patients also continued their pre-study treatment regimen. The trial of 16 patients was conducted in Sweden and included eight men and eight women. Infection status at baseline was not reported. All patients had "normal" ABI values. The median age was 67 years (range 42 to 75). All patients had chronic (greater than 1 year duration), non-diabetic ulcers that ranged from 20.9 to 307.0 cm^2 in size in the HBOT group (8 patients) and 22.1 to 196.9 cm^2 in size in the sham (air) group (8 patients). The trial satisfactorily met the four study quality domains and was therefore considered good quality. Study details are presented in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

No ulcers were reported healed at post-treatment (week 6). Within 12 weeks after the post-treatment assessment (i.e., week 18), two patients (25%) in the HBOT group had healed ulcers and none in the sham group. Five patients were not available for evaluation at this time-point, three in the sham group and two in the HBOT group. Both of the healed ulcers were initially among the smallest, measuring less than 40 cm^2 at baseline. No definition of healing was provided.[72]

Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

No secondary outcomes were reported.

Summary of Key Question 2

We identified 20 trials of nine different advanced ulcer care therapies for patients with venous ulcers: collagen, biological dressings, biological skin equivalents, keratinocytes, platelet-rich plasma, silver products, intermittent pneumatic compression therapy, electromagnetic therapy, and hyperbaric oxygen therapy. Sixteen of twenty studies compared an advanced therapy to standard therapy.

Primary Outcomes

For collagen, platelet-rich plasma, intermittent pneumatic compression therapy, and hyperbaric oxygen therapy, no eligible studies reported a significant improvement in the number of ulcers healed. Strength of evidence was low for each of those comparisons with only one trial for each advanced wound care therapy (see Executive Summary Table 2). For biological dressings, we found low strength of evidence of improved healing compared with standard care (55% versus 34% healed). The biological skin equivalent Apligraf significantly increased healed ulcers compared to compression bandaging in one trial (63% versus 49%) but the strength of evidence was low. In two trials, Dermagraft was not significantly better than compression bandaging. One trial comparing a keratinocyte product to standard care found improved healing versus standard care although a second trial found no difference. The pooled risk ratio was significant with healing in 38% versus 24% (RR=1.57, 95% CI 1.16-2.11; p=0.003). Two trials of keratinocyte

therapies found no difference in ulcer healing when compared to another advanced wound care therapy. Silver creams improved healing in two studies (one comparing silver cream to standard care and one comparing silver cream to a copper-based cream) while three studies of silver dressings found mixed results (significant benefit in one study of silver dressing compared to non-silver dressing and no differences in two studies with non-silver or alternative silver dressings as the comparator). Strength of evidence was low for these outcomes. Two trials of electromagnetic therapy found mixed results; strength of evidence was low.

Few studies reported time to ulcer healing. Two studies of the biological skin equivalent Apligraf found shorter time to ulcer healing as did the study comparing a keratinocyte product to standard care. Two other keratinocyte studies reported no significant differences in time to ulcer healing as did a study comparing a silver dressing to a non-silver dressing. Strength of evidence was low for these comparisons. Two studies of silver products reported higher global assessment outcomes in the silver groups; a study of electromagnetic therapy reported no difference between groups. Only studies of electromagnetic therapy reported patient activity levels; one finding no difference between treatment groups and one noting improvements pre- to post-treatment.

Secondary Outcomes

The most commonly reported secondary outcomes were ulcers infected during treatment (8 studies), ulcer recurrence (7 studies), and pain (9 studies). The collagen treatment study reported fewer ulcers infected in the collagen group. No other study reported a difference between treatment groups. The biological dressings study reported fewer recurring ulcers in the active treatment group compared to standard care. No other differences were reported. One of the EMT studies reported a significant reduction in pain from baseline to 30 days in patients receiving EMT. Other studies reporting pain found no differences between treatment groups. No studies reported amputation, revascularization or other surgery, time to recurrence, or need for home care. Two studies reported hospitalization and one reported quality of life with no difference between treatment arms in the studies. No significant differences were observed in all-cause mortality, study withdrawals due to adverse events, or allergic reactions to treatment.

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Table 17. Strength of Evidence – Advanced Wound Care Therapies for Venous Ulcers

Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Collagen	Standard care	Percentage of ulcers healed	1 (73)	One fair quality RCT found no significant differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Dressings	Standard care with compression bandage	Percentage of ulcers healed	1 (120)	One fair quality study found biological dressing (OASIS) more effective at 12 weeks but not 6 months versus standard care.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Skin Equivalents [BSE] - *Dermagraft*	Standard care with compression bandage	Percentage of ulcers healed	2 (44)	Data from two small trials (fair quality) found *Dermagraft* was not more effective than standard care.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Skin Equivalents [BSE] - *Apligraf*	Standard care with compression bandage	Percentage of ulcers healed	1 (275)	One large fair quality trial found significant improvement with *Apligraf* versus standard compression therapy.	Low
		Mean time to ulcer healing		Significant improvement with *Apligraf* versus standard compression therapy.	Low
Keratinocyte Therapy	Standard care with compression bandage	Percentage of ulcers healed	2 (418)	Keratinocyte therapy was more effective than standard care (RR=1.57, 95% CI 1.16 to 2.11, I^2=0%). The trials were rated fair quality.	Moderate
		Mean time to ulcer healing		Inconsistent results, one trial found a significant difference versus standard care and one found no difference between groups.	Low
Keratinocyte Therapy (*Cryopreserved*)	Advanced therapy control (*Lyophilized keratinocytes)*	Percentage of ulcers healed	1 (50)	One poor quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		No difference between groups.	Low
Keratinocyte Therapy	Advanced therapy control *(Pneumatic compression)*	Percentage of ulcers healed	1 (27)	One fair quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Platelet-Rich Plasma	Placebo	Percentage of ulcers healed	1 (86)	One fair quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient

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Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Silver, Dressings	Controls *(non-silver dressing, ionic silver vs. lipido-colloid silver)*	Percentage of ulcers healed	3 (536)	Inconsistent results from two fair quality trials, one found a significant difference versus non-silver dressing and one found no difference. One fair quality trial found no difference between two silver dressing groups.	Low
		Mean time to ulcer healing	2 (250)	Two fair quality trials; one found no significant difference between silver and non-silver dressings; one did not report significance	Low
Silver, Cream/ Ointment	Controls *(placebo, non-adherent dressing, standard care)*	Percentage of ulcers healed	3 (199)	One fair quality trial found significant benefit compared to standard care; one fair and one good quality trail found no benefit compared to placebo or standard dressing	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Silver, Cream	Placebo, tri-peptide copper cream	Percentage of ulcers healed	1 (86)	One three-armed trial of fair quality trial found silver more effective than tri-peptide copper cream but not placebo.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Intermittent Pneumatic Compression (IPC)	Unna's boot dressing	Percentage of ulcers healed	1 (53)	One fair quality trial found no significant difference between groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Electromagnetic Therapy (EMT)	Sham	Percentage of ulcers healed	2 (56)	Inconsistent results between trials. Study quality was fair.	Low
		Mean time to ulcer healing	1 (37)	Comparable between groups.	Low
Hyperbaric Oxygen Therapy (HBOT)	Sham	Percentage of ulcers healed	1 (16)	One good quality trial found no significant difference between groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient

*Number of ulcers evaluated for the primary outcome.
The evidence is rated using the following grades: (1) high strength indicates further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate strength denotes further research may change our confidence in the estimate of effect and may change the estimate; (3) low strength indicates further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence is unavailable or does not permit a conclusion.

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KEY QUESTION #3. What are the efficacy and harms of therapies for arterial ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Overview of Studies

We identified one trial of advanced wound care for ulcers attributed to arterial insufficiency,[73] seven trials of advance wound care for lower extremity ulcers of mixed etiology,[74-80] and one trial of advanced wound care for amputation ulcers[81,82] (Table 18).

The study of arterial ulcers compared a biological skin equivalent to standard care. Forty-eight percent of the included ulcers were located on the forefoot, 7% were located on the heel, and 45% were partial open foot amputations (transmetatarsal level).

The studies of mixed ulcer etiologies included 3 studies of biological dressings, 3 studies of silver products, and 1 trial of negative pressure wound therapy. The ulcers were described only as leg ulcers in 4 studies. One study included lower leg extremity ulcers (foot and ankle). In one study, 97% of the ulcers were located on the lower leg and 3% on the ankle or foot.

The trial of amputation ulcers compared negative pressure wound therapy to standard care in patients with partial foot amputation wounds.

No trials of collagen, keratinocytes, platelet-derived growth factors, platelet-rich plasma, pneumatic compression therapy, electromagnetic therapy, hyperbaric oxygen therapy, topical oxygen therapy, or ozone-oxygen therapy were identified that addressed Key Question #3.

Arterial Ulcers

Biological Skin Equivalent

We identified a single RCT of 31 patients that evaluated the use of Apligraf in arterial ulcers following revascularization surgery.[73] This study, based in the United States, was of fair quality. The source of funding was not reported. The mean age of the study participants was 70 years and 77% were male. Race/ethnicity was not reported. All study ulcers were 2.0 cm^2 or larger with an average ulcer size of 4.8 cm^2 at baseline. Ulcer duration was not reported. Participants were patients with ischemic ulcers who had successfully undergone revascularization surgery (ABI <0.5 pre-surgery, >0.7 post-surgery) within 60 days of entering the trial. Patients were followed until ulcer closure or up to 6 months after randomization. A single application of Apligraf was used in 21 patients (10 had a meshed graft and 11 had unmeshed graft) and was compared to 10 patients receiving twice-daily moist dressing changes (considered standard care). Additional study information is presented in Appendix D, Table 1.

Primary Outcomes (Appendix D, Table 2)

Statistically significant improvements in the incidence of complete ulcer healing were seen for the Apligraf group at weeks 8, 12, and 24. At 12 weeks, 86% of Apligraf patients and 40% of control patients had completely healed ($p<0.01$). At 6 months, complete healing occurred

in 100% of the Apligraf group and 75% of the controls. A significant benefit in median time to closure was also seen for Apligraf (7 weeks versus 15 weeks for standard care, p=0.002).[73] Patients in the treatment group also received continuous Unna boot dressing changes until the skin equivalent graft matured (around 5 weeks, on average). As there was no internal control for the additional dressing, more frequent ulcer checks, and recommendation for off-loading in the treatment group, the effect of ancillary therapies could not be measured.

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Table 18. Overview of Therapies for Arterial Ulcers, Mixed Lower Extremity Ulcers, and Amputation Wounds

Study, year	N Randomized	Treatment	Product	Comparator	Healed ulcers	Mean time to ulcer healing	Global assessment	Return to daily activities	Ulcers infected during treatment	Amputation	Revascularization/ surgery	Recurrence	Time to Recurrence	Pain/discomfort	Hospitalization	Required home care	Quality of life	Withdrawals due to adverse events	Patients with ≥ 1 adverse event	All-cause mortality	Allergic reactions to treatment
Arterial Ulcers																					
Chang 2000[73]	31	BSE	Apligraf	Standard	+	+			-			-						-	-	-	
Mixed Lower Extremity Ulcers																					
Brigido 2006[74]	28	Col	Graftjacket	Sharp debridement + Curasol gel	+	±			-										-		
Romanelli 2007[75]	54	BD	OASIS	Hyaluronic acid dressing	+									+				-	-	-	
Romanelli 2010[76]	50	BD	OASIS	Standard	+	+			-					-				-	-	-	
Jørgensen 2005[77]	129	Silver foam dressing	Contreet	Non-silver foam dressing	-									-			-		-		
Miller 2010[78]	281	Silver dressing	Multiple products	Cadexomer iodine dressing	-	-													-		
Fumal 2002[79]	17	Silver cream		Standard		-															
Vuerstaek 2006[80]	60	NPWT	V.A.C	Standard	-	+			-			-	-	+/-			-		-	-	
Amputation Wounds																					
Armstrong 2005, Apelqvist 2008[81,82]	162	NPWT	V.A.C.	Standard	+	+			↓	-					-				-		

BD – Biological Dressing; BSE – Biological Skin Equivalent; Col – Collagen; NPWT – Negative Pressure Wound Therapy
+ Treatment group better than comparator ($p < 0.05$)
- Treatment group demonstrated no significant benefit
↓ Treatment group worse than comparator
± Significance could not be determined

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Secondary Outcomes (Appendix D, Tables 3, 4, and 5)

Three localized, indolent ulcer infections were reported in the Apligraf group with no infections in the control group. The difference between groups was not significant. There was also no difference between treatment groups in ulcer recurrence. No differences between groups were reported for adverse events, withdrawals due to adverse events, or all-cause mortality.[73]

Studies of Mixed Ulcer Types

Collagen

One fair quality trial (n=28) compared a collagen product (Graftjacket) to standard care.[74] Study characteristics and outcomes data are reported in Appendix D, Tables 1 to 5. The mean age of the patients was 64 years. Gender, ulcer size, and ulcer duration were not provided but it was reported that patient age and ulcer size were similar for the two treatment groups at baseline. Patients were required to have a palpable/audible pulse in the affected lower extremity; patients with infected ulcers were excluded. Standard care included off-loading but compliance was not reported. A significantly higher percentage of healed ulcers was found in the Graftjacket group compared to standard care (86% versus 29%, p=0.01). No difference was observed in mean time to ulcer healing. Number of ulcers infected during treatment and number of patients experiencing adverse events also did not differ between the collagen and standard care groups.

Biological Dressings

Two randomized controlled trials evaluated biological dressings (OASIS) in patients with mixed (arterial or venous) or non-specific chronic lower-extremity ulcers.[75,76] One study comparing a biological dressing with another advanced therapy (hyaluronic acid dressing) was of poor quality[75] and one study comparing a biological dressing with standard care was of fair quality.[76] Neither study included a run-in period with standard care or reported on compliance with therapy or antibiotic use. Both trials excluded patients with infected wounds and ABI less than 0.6. One study reported mean age (63 years);[75] in both studies 48% of the patients were male. Mean ulcer size was 6 cm^2 in one study[75] and 24.4 cm^2 in the other.[76] Mean ulcer durations were similar (7.8 and 7.1 weeks). The studies reported no differences between treatment arms at baseline. Study characteristics and outcomes data are presented in Appendix D, Tables 1 to 5.

Both studies reported a significantly higher percentage of ulcers healed by study completion for the biological dressing compared to either another advanced wound therapy (81% versus 46%, $p<0.001$)[75] or standard care (80% versus 65%, $p<0.05$).[76] One study reported time to complete ulcer healing finding a significantly shorter mean time to ulcer healing with biological dressing compared to standard care (5.4 weeks versus 8.3 weeks, p=0.02).[76] One study reported no difference between a biological dressing and standard care in ulcers infected during treatment.[76] Both studies reported on pain. One found a significant reduction in pain in the biological dressing group compared to another advanced wound therapy;[75] the second reported no difference between biological dressing and standard care.[76] No significant differences in withdrawals due to adverse events, patients experiencing adverse events, or all-cause mortality were observed (no events in either treatment group in either study).

Silver Products

Three fair quality studies reported on the use of silver products for patients with mixed ulcer types. One study included 129 patients with chronic venous or mixed venous/arterial ulcers of at least 2 cm^2 (with no decrease in area of greater than 0.5 cm in the past 4 weeks), ABI of 0.65 or higher, and signs of infection.[77] Median age was 74 years and 36% of the patients were male. Median ulcer size was 6.4 cm^2 and median ulcer duration was 1.1 years. Patients were treated with a silver-releasing foam dressing or a similar dressing without silver. The second study included 281 patients with venous and mixed ulcers with a diameter of 15 cm or less.[78] All patients had clinical signs of infection and an ABI of 0.6 or higher; patients with a diagnosis of diabetes were excluded. Approximately 20% of the patients required antibiotics. Seventy-four percent of the ulcers were venous. One group received a silver-based dressing and the other group received an iodine-based dressing. Compression bandaging was part of the treatment for both groups and compliance with compression was monitored. Mean age of the participants was 80 years with 41% male. The mean ulcer size was 705 mm^2 and mean ulcer duration was 54 weeks. There was a significant difference in baseline ulcer size between the silver dressing group (597 mm^2) and the iodine dressing group (912 mm^2). The third study enrolled 17 patients with at least 2 chronic leg ulcers.[79] Patients with infection, diabetes, or arterial occlusion were excluded. Mean age of the participants was 55 years; other baseline characteristics were not reported. Two similar looking ulcers on each patient were randomly assigned to treatment with silver sulfadiazine cream or standard care for 6 weeks.

The two studies reporting healed ulcers found no significant difference between a silver-releasing foam dressing and a similar dressing without silver (9.6% versus 8.8% at 4 weeks)[77] or a silver dressing and an iodine dressing (64% versus 63% at 12 weeks).[78] The study comparing silver and iodine dressings also reported no significant difference in days to healing.[78] The third study did not report healed ulcers but did report a non-significant difference in time to healing (15 weeks for silver-treated ulcers, 16 weeks for standard care).[79] One study looked at subgroups.[78] There was no difference in number of ulcers healed with silver or iodine dressings for "young" ulcers (less than 12 weeks), "old" ulcers (more than 12 weeks), "small" ulcers (3.6 cm^2 or smaller), or "large" ulcers (greater than 3.6 cm^2).[78] Decrease in pain during the treatment period and quality of life were found to be similar in patients treated with silver-releasing foam dressing compared to non-silver foam dressing.[77] Two studies reported adverse events. The percentages of patients with adverse events (silver dressing versus iodine dressing)[78] or device-related adverse events(silver-releasing foam dressing versus non-silver foam dressing)[77] did not differ. Additional information about these studies is presented in Appendix D, Tables 1 to 5.

Negative Pressure Wound Therapy

One study of NPWT compared to standard care included venous ulcers (43%), mixed venous and arterial ulcers (13%), and microangiopathic ulcers (43%).[80] The study was of fair quality. Patients with infected ulcers or an ABI of less than 0.6 were excluded. The median age of the participants was 72 years, 23% were male, the median ulcer surface area was 38 cm^2, and the median ulcer duration was 7.5 months. Although not significant, mean ulcer area differed between groups by 10 cm^2 at baseline. Patients were hospitalized for chronic leg ulcers at the time of enrollment and remained hospitalized until complete healing. They were mobile for

hygiene only. Antibiotics were allowed as needed (approximately 3.5% of patients at baseline). Patients in the NPWT group received treatment (125 mmHg permanent negative pressure) until granulation tissue covered 100% of the surface and secretion was minimal. They then underwent skin graft transplantation, 4 days of negative pressure therapy, and standard ulcer care until complete healing. The standard care group was treated with either hydrogel or alginate dressings and compression bandage therapy until granulation followed by skin graft transplantation and additional compression therapy.

Complete healing occurred in 96% of patients in both the NPWT and standard care groups. The time to complete healing was shorter in the NPWT group (median of 29 days versus 45 days in the standard care group, p=0.0001). After adjustment for ulcer area, smoking, baseline infection signs, history of ulcers, use of angiotensin-converting enzyme inhibitors, and use of anticlotting therapy, the time to healing remained significantly shorter in the NPTW group than in the standard care group (HR=3.2, 95% CI 1.7 to 6.2, p<0.001). Time to preparation of the ulcer for skin graft transplantation was also shorter in the NPTW group (median of 7 days versus 17 days in the standard care group, p=0.005) and remained shorter after adjustment for baseline factors (HR=2.4, 95% CI 1.2 to 4.7, p<0.01). Ulcer recurrence was similar between the groups (52% NPWT, 42% standard care) but skin graft survival was significantly better in the NPWT group (83% versus 70%, p=0.01). Quality of life scores increased over time with no differences between groups. Pain scores decreased over time and at week 5 and beyond, were significantly lower in the NPWT group. Most ulcers in the NPWT group were healed by that point. There were no differences between NPWT and standard care in infection, mortality, percentage of patient who experienced an adverse event, or percentage of patients who reported pain as an adverse event. More detailed study characteristics and outcomes are presented in Appendix D, Tables 1 to 5.

Amputation Wounds

We identified one good quality study that compared NPWT to standard wound therapy in 162 patients with partial diabetic foot amputation wounds.[81,82] Patients with severely infected wounds or inadequate blood supply were excluded. Standard care included off-loading, as needed; compliance was not reported. The mean age of the patients was 59 years and 81% were male. The mean wound size was 20.7 cm^2 and mean duration was 1.5 months. The percentage of healed wounds (56% versus 39%, p=0.04) was higher and the time to healing was shorter (median days: 56 versus 77, p=0.005) in the NPWT group compared to standard care. A second amputation was required by 3% of the NPWT group and 11% of the standard care group (RR=0.23, 95% CI 0.05 to 1.1, p=0.06). Adverse events were reported for 52% of the NPWT group and 54% of the standard care group (p=0.88) with infections most common (17% in the NPWT group, 6% in the standard care group, p=0.04).[81] An analysis of resource utilization among patients in the study who were treated for a minimum of 8 weeks (n=135) found similar hospital stays with means of 10.6 and 9.9 inpatient days in the NPWT and standard care groups, respectively. The overall number of procedures performed (e.g., debridement, dressing changes, grafts) was significantly higher in the standard care group (mean of 120 procedures versus 43 in the NPWT group, p<0.001). There were also significantly more outpatient visits in the standard care group (mean of 11 visits versus 4 in the NPWT group, p<0.05).[82] Appendix D, Tables 1 to 5 contain more details about the study.

Summary of Key Question 3

For arterial ulcers, one small, fair quality study found that a biological skin equivalent, may improve the incidence and rate of complete ulcer healing when used on ischemic foot ulcers following revascularization surgery. Other outcomes did not differ significantly from standard care. The effects of ancillary therapies or baseline patient characteristics were not explored in the study. We found no RCTs that included any of the other therapies of interest exclusively in patients with arterial lower extremity ulcers.

In seven studies of mixed ulcer types, collagen and biological dressings were found to improve ulcer healing; silver products and negative pressure wound therapy did not. There were mixed results for time to ulcer healing and, overall, no differences between investigational treatment and control on other outcomes. The studies were of poor to fair quality.

One good quality study of ulcers associated with partial foot amputation showed a benefit of NPWT with respect to healed ulcers and mean time to healing. There were significantly more infections in the NPWT group but the incidence of other adverse events did not differ between the NPWT and standard care groups.

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SUMMARY AND DISCUSSION

Chronic lower extremity ulcers are a common and serious health problem. A wide range of standard treatment approaches to achieve ulcer healing are used (e.g., off-loading, compression, leg elevation etc.) based on patient and ulcer factors and provider preferences. While many ulcers heal completely within several weeks, a significant portion either do not heal or increase in size, depth, and severity. These chronic ulcers can result in considerable clinical morbidity and health care costs.

Many types of advanced wound care therapies exist but all represent considerably greater product costs compared to standard therapy. These costs may be justified if they result in improved ulcer healing, reduced morbidity, fewer lower extremity amputations, and improved patient functional status. In addition to the treatment selected, many potential factors contribute to the success or failure of the ulcer healing process including ulcer etiology; ulcer area, depth, duration, and location; patient comorbid conditions; and patient compliance with the treatment protocol. Much of the existing research on advanced wound care therapies has attempted to minimize the influence of many of these factors by limiting enrollment to patients with ulcers of a particular size, including only patients with adequate circulation, and excluding patients taking certain classes of medications.[83,84] Furthermore, many of the trials are industry sponsored (55% of the studies included in our review) and the role of the sponsor is typically not stated, definitions of "chronic" ulcers vary widely, and few studies are of sufficient duration to assess whether healing is maintained.[84,85]

Our systematic review of randomized controlled trials found discouragingly low strength evidence regarding the effectiveness and comparative effectiveness of advanced wound care therapies for treatment of lower extremity ulcers. This was primarily due to the fact that for each ulcer type (diabetic, venous, or arterial) individual categories of advanced wound care therapies were only evaluated in a few studies, often in highly selected populations, and frequently had conflicting findings. Furthermore, within each category of wound care therapies several different types of interventions were used making it difficult to determine if results were replicable in other studies or generalizable to broader clinical settings. Additionally, most studies compared advanced wound care therapies to standard care or placebo. Therefore there is little comparative effectiveness research evaluating one advanced wound care therapy to another. It has been noted that standard care is an inappropriate comparator for studies of advanced therapy since patients have likely already failed standard care.[86,87] For arterial ulcers we identified only a single study of any advanced wound care therapy (and this was compared to standard care) despite the clinical importance of arterial ulcers.

However, based on the available findings we conclude that for patients with diabetic chronic ulcers, there is moderate strength of evidence that the biological skin equivalent Apligraf and negative pressure wound therapy improve healing compared to standard care. There is low strength evidence that advanced wound care therapies improved the percentage of ulcers healed compared to standard care for the following therapies: collagen (notably Graftjacket), the biological skin equivalent Dermagraft, platelet-derived growth factors, silver cream, and hyperbaric oxygen therapy but results were not uniform for any treatment group. Most beneficial effects were derived from single or few studies so we recommend caution regarding translating

these findings of effectiveness into broader clinical application. Pooled analyses were possible for several therapies and demonstrated a significant improvement in ulcer healing compared to standard care for Apligraf (a biological skin equivalent), platelet-derived growth factors, and negative pressure wound therapy; no improvement was observed for Dermagraft (a biological skin equivalent). Few studies compared one advanced treatment to another but in those studies, no differences in percentage of ulcers healed were found between the two treatment arms. For time to ulcer healing, the pattern of findings was similar and strength of evidence was low for all treatment comparisons reporting that outcome. No studies reported a significant difference in adverse events for any treatment comparison.

Findings for venous ulcers were similar. Although some individual trials of biological dressings (notably OASIS), biological skin equivalents (Apligraf), keratinocytes, silver cream and dressing, and electromagnetic therapy noted significant benefit of the therapy in percentage of ulcers healed compared to standard care, overall the results for each therapy were mixed. In pooled analyses only keratinocytes resulted in significantly better healing compared to standard care. Strength of evidence was moderate for the benefit of keratinocyte therapy and low for the other therapies. Few studies of venous ulcers compared two advanced therapies and, where reported, typically found no differences. Time to ulcer healing was reported infrequently. No advanced wound care therapy was observed to result in an increase in adverse events.

We identified only one study of patients with arterial ulcers despite the clinical importance of this population. It is possible that patients with arterial disease were included in the studies of diabetic ulcers or venous ulcers (i.e., mixed etiology). In one study of patients with non-healing lower extremity ulcers or amputation wounds following a revascularization procedure, Apligraf increased ulcer healing and decreased time to healing compared to standard care with no difference in adverse events.

For amputation wounds, one study of negative pressure wound therapy versus standard care found significantly better healing with no difference in adverse events.

Despite finding benefits of some therapies compared to standard care, the methodological quality of individual studies reviewed was predominantly fair or poor. Common factors limiting the quality were inadequate allocation concealment, no blinding (including no blinding of outcome assessment), failure to use intention-to-treat analysis methods, and failure to adequately describe study dropouts and withdrawals. With methodological flaws, few trials reporting, and heterogeneity in the comparators, study duration, and how outcomes were assessed, the overall strength of evidence was low. While a wide range of patients were enrolled in studies most were older than age 60 years, male, of white race, likely compliant with treatment protocols, and possessed ulcers that were relatively small as measured by surface area. However, authors rarely reported outcomes by patient demographic, comorbidity or ulcer characteristics. Therefore, we found insufficient evidence to guide clinicians and policy makers regarding whether efficacy differs according to patient demographics, comorbid conditions, treatment compliance, or activity level.

APPLICABILITY AND COST EFFECTIVENESS

It is not well known how outcomes reported in studies of selected populations will translate to daily practice settings including in Veterans Health Administration facilities. There is evidence of good success in ulcer healing with strict adherence to off-loading for diabetic ulcers and compression therapy for venous ulcers.[88-91] The patients enrolled in trials were likely more compliant than typical patients and received very close monitoring. Therefore, results from these studies may overestimate benefits and underestimate harms in non-study populations.

Our review was limited to studies of FDA approved products. We excluded studies with wounds of multiple etiologies (e.g., vascular, pressure, trauma, surgery) if they did not report results by etiology. We also excluded studies if they did not report our primary outcomes of healed wounds or time to complete healing. Many studies report change in ulcer size but the clinical benefit of change in ulcer size has not been established.[92]

Furthermore, we did not conduct cost effectiveness analyses or assess additional costs of care associated with chronic ulcers. Despite the high costs of advanced wound care therapies it is possible that they may be cost effective or even cost saving if found to improve ulcer healing; reduce ulcer associated morbidity, hospitalizations, medical care and amputations; and improve functional status and quality of life. Based on our findings from randomized controlled trials the decision of if, when, and in whom to use advanced wound care therapies as well as the type of advanced wound care therapy selected is difficult. Additionally, because little comparative effectiveness research exists to guide choices, decisions may be based on other factors including wound care product cost, ease of use, and patient and provider preferences (the latter also influenced by personal experience with ulcer and patient characteristics).

RECOMMENDATIONS FOR FUTURE RESEARCH

Our review highlights several much needed areas for future research. Most studies compared an advanced therapy to either standard ulcer care or placebo treatment. Few studies (10 of the 35 eligible studies of diabetic ulcers, 4 of the 20 eligible studies of venous ulcers, and none for arterial or mixed ulcers) directly compared two advanced therapies. Furthermore, few studies provided a run-in period with carefully monitored standard care to exclude patients for whom carefully monitored standard care would obviate the need for advanced therapy. Therefore, additional randomized trials of advanced wound care therapies versus standard care are needed to replicate or refute current findings. Comparative effectiveness research is also needed to evaluate the relative benefits and harms of different advanced wound care therapies. In both effectiveness and comparative effectiveness research, the sample sizes should be adequate to report specific outcome reporting according to key patient and ulcer characteristics including age, race, gender, and ulcer size, location, and depth. We note below the limitations of the existing research by type of ulcer and therapy assessed.

Of the studies of diabetic ulcers included in this review, only two focused on biological dressings (using different products) and two on platelet-rich plasma. We identified no studies of topical oxygen or electromagnetic therapy. No studies reported on return to daily activities or the need for home care related to ulcer treatment and only one study reported quality of life or

hospitalization. The need for amputation or revascularization and the incidence of and time to ulcer recurrence require further investigation. The majority of studies described the ulcers as diabetic foot ulcers with only six providing greater detail about ulcer location. Future research should report healing by ulcer location. Future research should also examine microvascular disease to more clearly distinguish diabetic ulcers from arterial ulcers.

For venous ulcers, we identified only one study of the following advanced wound care therapies: collagen, biological dressings, platelet rich plasma, intermittent pneumatic compression, and hyperbaric oxygen therapy. There were no studies of platelet-derived growth factors or typical oxygen. We found no studies that reported on amputations, time to ulcer recurrence, or need for home health care related to the ulcer. One study reported hospitalization, one study reported quality of life, and two studies reported return to work or daily activities.

We identified only one study of patients with arterial disease requiring advanced wound care following revascularization. Only this study and one other included patients with partial foot amputations with delayed healing. Neither of these studies reported on return to daily activities, pain, quality of life, or need for home health assistance related to the wound. There is a paucity of research on advanced wound care therapies in patients with strictly arterial disease.

In addition to specific topics needing further research, several organizations have outlined overall methodological standards for future research of wound healing therapies (see Appendix E). The standards focus on study design, patient population, comparators, outcomes and outcome assessment, and potential sources of bias. Randomized trials, with allocation concealment and, at a minimum, blinding of third-party outcomes assessors, are recommended. The patient population should be appropriate for the treatment being studied and exclusion criteria should be minimal to enhance generalizability. Endpoints should be selected based on the purpose of the intervention (i.e., closure versus preparation for surgery) and adequate follow-up should be included to confirm healing. Dropouts and study withdrawals should be documented, including withdrawals due to ulcer deterioration. Additional research, conducted in accordance with the standards, is needed to establish the safety and efficacy of advanced wound care therapies. Finally, future research is needed to determine the effectiveness, comparative effectiveness and harms of advanced wound care therapies as used in general clinical practice settings (e.g., vascular and dermatology clinics) where patients may have more severe and larger ulcers, greater comorbidities, or increased difficulty with treatment compliance.

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