APPENDIX D. EVIDENCE TABLES

Table 1. Study Characteristics Table

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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