Vac (Negative Wound Pressure) Therapy

Evidence table

Title: ***The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial.***						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3195 Level of evidence: () Study type: RCT Authors: Etoz et al. (2004)	<u>Total no. of patients:</u> Baseline = 24 NPWT-12 Control-12 In this study, wound closure was to be achieved by lesser surgical procedures. <u>Baseline characteristics:</u> Mean age: NPWT: 66.2 (54-77) years Control: 64.7 (56-74) years Mean Diabetic wound surface area NPWT: 109cm^2 Control: 94.8cm^2 There was no significant difference in groups regarding the initial wound surface area and ages (p>0.05) <u>Setting:</u>	<u>Inclusion:</u> Not mentioned <u>Exclusion:</u> Not mentioned	Negative pressure wound therapy (NPWT)(n=12) The diabetic foot ulcers were surgically debrided prior to initiation of treatment. During the healing process, the patients ambulated using walking sticks and/or wheelchairs.	Control-saline-moistened gauze dressing, (n- 12). Changed twice a day. The diabetic foot ulcers were surgically debrided prior to initiation of treatment. During the healing process, the patients ambulated using walking sticks and/or wheelchairs.	Every 48 hour until the wound beds approached nearly total coverage with granulation tissue without any inflammatory signs.	NPWT Mean diabetic wound surface area decreased from 109cm^2 to 88.6 cm^2 (20.4 cm^2, SD-11.7) Control Mean diabetic wound surface area decreased from 94.8cm^2 to 85.3 cm^2 (9.5 cm^2, SD-4.11) There was a significant difference in decrease rates. NPWT reduced the wound surface areas more effectively than moist gauze dressing (p- 0.032). Adverse events: No negative impact was seen on extremity functions and psychology of patients.

	Not mentioned					

Additional comments:

Randomisation was performed (method not stated). Blinding performed. Power calculation not used. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were not analysed as intention to treat.

Reference: Etoz, A, Kahveci, R Negative pressure wound therapy on diabetic foot ulcers. *Wounds: A Compendium of Clinical Research & Practice* 2007; 19: 250-255.

Title: ***Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. A multicenter randomised controlled trial..***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 1559 Level of evidence: () Study type: RCT Authors: Blume et al. (2008)	Total no. of patients: Baseline = 384 42 excluded 342-enrolled 335-analysed(7 –no treatment received) NPWT-169 AMWT- 166 Baseline characteristics: No statistically significant demographic differences existed between treatment arms. Setting: 37 diabetic foot and wound clinics and hospitals.	Inclusion: Diabetic adults ≥18 years with a stage 2 or 3 (Wagner's scale), calcaneal, dorsal, or plantar foot ulceration ≥2cm^2 in area after debridement, adequate blood perfusion. Exclusion: Patients with recognised active Charcot disease or ulcers resulting from electrical, chemical, or radiation burns and those with collagen vascular disease, ulcer malignancy, untreated osteomyelitis, or cellulitis, uncontrolled hyperglycaemia (AIC >12%) or inadequate lower extremity perfusion, ulcer with normothermic or hyperbaric oxygen therapy, concomitant medications such as corticosteroids, immunosuppressive	Negative pressure wound therapy using vacuum-assisted closure (NPWT, n= 169) Dressings changed every 48-72h All patients received off-loading as deemed necessary.	Control- advanced ,moist wound therapy (AMWT, n- 166) All patients received off-loading as deemed necessary.	Weekly for first 4 weeks (day 28), then every other week until day 112 or ulcer closure by any means. Patients achieving ulcer closure were followed at 3 and 9 months.	Efficacy Complete ulcer closure during ATP(active treatment phase) NPWT- 73/169 AMWT-48/166 The NPWT group proportion was significantly (p-0.007) greater for complete closure than the AMWT group. Relative risk- 73/169 ÷ 48/166 = 1.5 Complete ulcer closure after ATP NPWT- 73/120 AMWT-48/120 For patients completing the ATP, analysis significantly (p- 0.001) confirmed that a greater percentage of NPWT-treated ulcers achieved ulcer closure than AMWT-treated ulcers. Relative risk- 73/120 ÷ 48/120 = 1.52 Kaplan Meier median time to complete ulcer closure: NPWT- 96 days (95% CI 75-114, p- 0.001) AMWT- could not be estimated.

<table>
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<td></td>
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<td>medications, or chemotherapy; recombinant or autologous growth factors products; skin and dermal substitutes within 30 days of study start; or use of any enzymatic debridement, pregnant or nursing mothers.</td>
<td></td>
<td></td>
<td></td>
<td>
>75% Ulcer closure (p- 0.044)

NPWT-106/161
AMWT- 85/166

Relative risk- 106/161 ÷ 85/166 = 1.21

Kaplan Meier median time to 75% ulcer closure:

NPWT- 58 days (95% CI 53-78, p- 0.014)
AMWT- 84 days (95% CI 58-89)

Ulcer area

NPWT= -4.32cm^2
AMWT= -2.53cm^2

Safety

Table 1: Results of safety analysis (6 months)

<table>
<tr><td></td><td>NPWT</td><td>AMWT</td></tr>
<tr><td>n</td><td>169</td><td>166</td></tr>
<tr><td>Secondary amputation</td><td>7</td><td>17</td></tr>
<tr><td>Oedema</td><td>5</td><td>7</td></tr>
<tr><td>Wound infection</td><td>4</td><td>1</td></tr>
<tr><td>Cellulitis</td><td>4</td><td>1</td></tr>
<tr><td>Osteomyelitis</td><td>1</td><td>0</td></tr>
<tr><td>Infected skin ulcer</td><td>1</td><td>2</td></tr>
</table>

Significantly (p-0.035) fewer amputations were observed in the NPWT patients compared with AMWT patients. In all other categories, no significant differences were observed.
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</tr>
<tr>
<td colspan="7">Additional comments:</td>
</tr>
</table>

Randomisation was performed (method not stated). Blinding performed. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.

Reference: Blume, PA, Walters, J, Payne, W, Ayala, J, Lantis, J Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008; 31: 631-36.

Title: ***Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial..***						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 11715 Level of evidence: () Study type: RCT Authors: Williams et al. (2005)	<u>Total no. of patients:</u> Baseline = 162 NPWT-77 Control-85 All patients received off-loading therapy, preventatively and therapeutically, as indicated. <u>Baseline characteristics:</u> There were no statistically significant differences in the demographic char-acteristics of the patients. <u>Setting:</u> 18 centres (diabetic foot and wound clinics in private and academic health-science centres)-USA	<u>Inclusion:</u> People aged 18 years or older, presence of a wound from a diabetic foot amputation to the transmetatarsal level of the foot, evidence of adequate perfusion, and wounds with University of Texas grade 2 or 3 in depth. <u>Exclusion:</u> Patients with active Charcot arthropathy of the foot, wounds resulting from burns, venous insufficiency, untreated cellulitis, or osteomyelitis (after amputation), collagen vascular disease, malignant disease in the wound, or uncontrolled hyperglycaemia, treatment with corticosteroids, immunosuppressive drugs, or chemotherapy, previous VAC therapy in the past 30 days, present or previous treatment with growth factors, normothermic therapy, hyperbaric	Negative pressure wound therapy (NPWT)(n=77) Delivered through the VAC system and dressings changed every 48 h	Control- moist wound therapy with alginates, hydrocolloids, foams, or hydrogels. Dressing changes occurred every day.	Day 0, 7, 14, 28, 42, 56, 84, and 112	Wound closure (16 weeks) NPWT-43/77 Control-33/85 A greater proportion of patients had healed achieved complete closure during the 16 week assessment in the NPWT group compared to the control group (p-0.040). Relative risk- 43/77 ÷ 33/85 = 1.43 Time (median) to achieve 75-100% granulation in patients with 0-10% granulation at baseline NPWT- 42 days (40-56) Control-84 days (57-112), p-0.002. Time (median) to achieve 75-100% granulation in patients with 0-25% granulation at baseline NPWT- 42 days (14-56) Control-82 days (28-112), p-0.010 Relative risk ratio for second amputation was 0.244 (95% CI, 0.05-1.1) indicating that patients treated with NPWT were only a quarter as likely as control patients to need a second amputation. Adverse events: 40 (52%) patients assigned to receive NPWT and 46 (54%) patients assigned to receive control

		medicine, or bioengineered tissue products in the past 30 days.				treatment had one or more adverse event during the study but this was not significant (p- 0.875). Relative risk- 40/77 ÷ 46/85 = 0.96 9 in NPWT had a treatment-related adverse event 11 in control group had a treatment-related adverse event Relative risk- 9/77 ÷ 11/85 = 0.90
Additional comments: Randomisation was performed (neither patients nor investigators were masked to the randomised treatment assignment). Blinding performed. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Williams, DT, Maegele, M, Gregor, S, Peinemann, F, Sauerland, S, Chantelau, E, Armstrong, DG, Lavery, LA Negative pressure therapy in diabetic foot wounds... Armstrong DG, Lavery LA et al. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet 2005;366:1704-10. *Lancet* 2006; 367: 725-28.

Skin Grafts

<table>
<tr><td colspan="7">Title: Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective randomised, clinical trial.</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr><td>ID: 8456

Level of evidence: ()

Study type: RCT

Authors: Pham et al. (1999)</td><td><u>Total no. of patients:</u>
Baseline = 33
Skin equivalent-16
Control-17

Ulcers in both groups that did not heal by study week 5 were covered with a layer of saline-moistened gauze and a layer of conforming gauze bandage for weeks 6-12.

<u>Baseline characteristics:</u>
Demographic data were comparable between the two groups with no significant differences.
Baseline observations were generally similar between skin equivalent and control groups.

<u>Setting:</u>
Deaconess-Joslin Foot Centre</td><td><u>Inclusion:</u>
Patients with diabetes with full thickness (>1cm^2 but <16cm^2) ulcers on the foot, 18-80 years old, without active Charcot's disease, had dorsalis pedis and posterior tibial pulses, HbA1C >6% but <12%.

<u>Exclusion:</u>
Patients with clinical infection at the study ulcer site, clinically significant lower-extremity ischemia, ulcer of a non-diabetic pathophysiology, patients with significant medical conditions that wound impair wound healing, and patients whose ulcers responded to saline-moistened gauze during the screening period.</td><td>Skin equivalent (n- 16) treatment for 12 weeks

Proper wound care, including extensive debridement and weight offloading was provided to all participants.</td><td>Control-woven gauze kept moist by saline (n-17)for 12 weeks.

Proper wound care, including extensive debridement and weight offloading was provided to all participants.</td><td>Weekly from study 0 to week 12.</td><td>Efficacy analysis

Table 1: Complete wound closure (at 12 weeks)

<table>
<tr><td colspan="4">Frequency of complete closure</td></tr>
<tr><td>Treatment</td><td colspan="2">% healed</td><td>P value</td></tr>
<tr><td>Graft skin</td><td colspan="2">75 (12/16)</td><td><0.05</td></tr>
<tr><td>control</td><td colspan="2">41 (7/17)</td><td></td></tr>
<tr><td colspan="4">Kaplan-Meier estimate of time (days) to complete closure</td></tr>
<tr><td></td><td>Minimum</td><td>Medium</td><td>Maximum</td></tr>
<tr><td>Graft skin</td><td>7</td><td>38.5</td><td>85</td></tr>
<tr><td>control</td><td>14</td><td>91</td><td>91</td></tr>
</table>

The difference in median time to healing was shown to be significantly in favour of the skin equivalent-treated group (p-0.01).

Relative Risk - 12/16 ÷ 7/17 = 1.83</td></tr>
<tr><td colspan="7"><u>Additional comments:</u>
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.</td></tr>
</table>

Reference: Pham, HT, Rosenblum, BI, Lyons, TE, Giurini, JM, Chrzan, JS, Habershaw GM, ea Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective, randomized, clinical trial. *Wounds: A Compendium of Clinical Research and Practice* 1999; 11: 79-86.

Title: ***Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage.***

<table>
<tr><th>Level of Evidence</th><th>Patient Population/ Characteristics</th><th>Selection/Inclusion criteria</th><th>Intervention</th><th>Comparison</th><th>Follow-up</th><th>Outcome and Results</th></tr>
<tr>
<td>ID: 8753

Level of evidence: ()

Study type: RCT

Authors: Puttirutvong et al. (2004)</td>
<td><u>Total no. of patients:</u>
Baseline = 80
Meshed skin graft-36
Ordinary split thickness skin graft-17

The thighs were used for donor site of skin graft. Dressing changed every day.

<u>Baseline characteristics:</u>

Demographic data were comparable between the two groups with no significant differences. Baseline observations were generally similar between skin equivalent and control groups.

<u>Setting:</u>
Deaconess-Joslin Foot Centre</td>
<td><u>Inclusion:</u>
Patients with FBS 150-200 mg%, haematocrit ≥30% and rare bacterial colonisation (<10^5 micro-organisms/g tissue)

<u>Exclusion:</u>

Patients with clinical infection at the study ulcer site, clinically significant lower-extremity ischemia, ulcer of a non-diabetic pathophysiology, patients with significant medical conditions that wound impair wound healing, and patients whose ulcers responded to saline-moistened gauze during the screening period.</td>
<td>Meshed skin graft (n- 38)</td>
<td>Control- Ordinary split thickness skin graft (n- 42)</td>
<td>Weekly for 6 months.</td>
<td>Complete healing duration

Meshed skin graft – 19.84 ± 7.37 days
Ordinary split thickness skin graft- 20.36 ± 7.21 days (p-0.282)

Table 1:the efficacy of treatment
<table>
<tr><th></th><th colspan="2">Meshed skin graft</th><th colspan="2">Ordinary split thickness skin graft</th></tr>
<tr><th></th><th>Cases</th><th>%</th><th>Cases</th><th>%</th></tr>
<tr><td>Excellent</td><td>19</td><td>50</td><td>17</td><td>40.5</td></tr>
<tr><td>Good</td><td>12</td><td>31.6</td><td>18</td><td>42.9</td></tr>
<tr><td>Fair</td><td>7</td><td>18.4</td><td>5</td><td>11.9</td></tr>
<tr><td>Poor</td><td>0</td><td>0</td><td>2</td><td>4.8</td></tr>
</table>
Excellent- skin grafts epithelised or healed 95% within 14 days with a smooth scar
Good- skin grafts epithelised or healed 95% within 21days/hypertrophic scar subsided within 6 months
Fair- skin grafts epithelised or healed 95% within 21days/prone to abrasion from minor trauma/minor infected wounds/obvious hypertrophic scar after 6 months
Poor- skin grafts epithelised or healed 95% within 28days/keloid/contracture of toes or joints/recurrent ulcer.

Relative Risk (excellent) - 19/38 ÷ 17/42 = 1.23
Relative Risk (excellent and good) - 31/38 ÷ 35/42 = 0.98
Relative Risk (excellent, good, and fair) - 38/38 ÷ 40/42 = 1.05

Adverse events:
The cosmetic results in both groups were very satisfactory at 6 months.</td>
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<tr><td colspan="7"><u>Additional comments:</u>
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were not analysed as intention to treat.</td></tr>
</table>

Reference: Puttirutvong, P Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage. *Journal of the Medical Association of Thailand* 2004; 87: 66-72.

Title: Grafts Skin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers . A prospective randomized multicenter clinical trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 11258 Level of evidence: () Study type: RCT Authors: Veves et al. (2001)	<u>Total no. of patients:</u> Baseline = 277 69 excluded Graftskin-112 Control- 96 Ulcers in both groups that did not heal by study week 5 were covered with a layer of saline-moistened gauze and a layer of petrolatum and wrapped with a layer of Kling for study weeks 6-12. <u>Baseline characteristics:</u> At baseline, the two groups were similar regarding demographics, type and dura-tion of diabetes, and ulcer size and duration. <u>Setting:</u> 24 centres-USA	<u>Inclusion:</u> Type 1. or 2 diabetes, age 18-80 years, HbA_{1c} between 6 and 12%, and full-thickness neuropathic ulcers (excluding the dorsum of the foot and the calcaneus). The ulcer was required to be of ≥2 weeks duration and the post-debridement ulcer size had to be between 1 and 16 cm^2-. All patients were also required to have dorsalis pedis and posterior tibial pulses. <u>Exclusion:</u> Clinical infection at the studied ulcer site, clinically significant lower-extremity ischemia, active Charcot's disease, and an ulcer that was of a non-diabetic pathophysiology (e.g., rheumatoid, radiation-related, and vasculitis-relaied ulcers). Patients with significant medical conditions that would impair wound healing were also excluded from the study. These conditions included liver disease, aplastic anaemia, scleroderma, malignancy, and treatment with immunosuppressive agents or steroids. Patients whose ulcere responded lo saline-	Graftskin (n-112, its a living human skin equivalent) Standard state-of-the-art adjunctive therapy, which included extensive surgical debridement and adequate fool off-loading, was provided in both groups.	Control- saline moistened gauze (n-96). Standard state-of-the-art adjunctive therapy, which included extensive surgical debridement and adequate fool off-loading, was provided in both groups.	Weekly from study day 0 until 12weeks. Then once a month for 3 months for safety evaluations.	By the end of the study, complete wound healing was achieved in 63 (56%) Graftskin-treated patients—a significantly higher rate when compared with 36 (38%) control subjects (P = 0.0042). Relative Risk- 63/112 ÷ 36/96 = 1.50 The odds ratio for complete healing for a Graftskin-treated ulcer compared with a control-treated ulcer was 2.14 (95% CI 1.23-3.74). The Kaplan-Meier median time to complete closure was 65 days for Graftskin—significantly lower than the 90 days observed in the control group (P = 0.0026). The estimated hazard ratio indicated that an average patient treated with Graftskin had a 1.59-fold better chance for closure per unit lime than a patient treated with the active control (95% CI 1.26-2.00). Secondary end points Between study day 0 and study week 12, both Graftskin and active control groups showed statistically significant improve-ment in undermining, maceration, exu-date, granulation, eschar, and fibrin slough. A statistically significant difference was seen between the two treatment groups

		moistened gauze during the screening period, as defined by a 30% decrease in the size of the ulcer, were not entered into the study.				with regard lo maceration (P < 0.05), exudate (P < 0.05), and eschar (P < 0.05). Ulcer recurrence At 6 months, the incidence of ulcer recurrence was similar in the two groups, with 5.9% (3 of 51) in the Graflskin group and 12.9% (4 of 31) in the active control group (NS). Relative Risk- 3/51 ÷ 4/31 = 0.45 Adverse events Because of adverse events, six Graftskin-treated and nine control-treated patients withdrew before completion of the study. Relative Risk (non specific adverse events)- 35/112 ÷ 46/96 = 0.65 Relative Risk (withdrawal due to adverse events-non specific) = 6/112 ÷ 9/96 = 0.57
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Veves, A, Falanga, V, Armstrong, DG, Sabolinski, ML Graftskin, a human skin equivalent, is effective in the management of neuropathic diabetic foot ulcers. *Diabetes Care* 2001; 24: 290-295.

Title: Use of Dermagraft, a Cultured Human Dermis, to Treat Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3855 Level of evidence: () Study type: RCT Authors: Gentzkow et al. (1996)	Total no. of patients: Baseline = 25 Dermagraft- 12 Control-13 Baseline characteristics: No significant differences were observed in any of these factors Setting: 5 institutions	Inclusion: The patients had IDDM or NIDDM under reasonable control. HbA_{Ic} was measured, and patients could not have had more than one episode of hospitalization during the previous 6 months due to hyperglycemia, hypoglycemia, or ketoacidosis. 2) Diabetic ulcers of the plantar surface or heel were included; ulcers of nondiabetic origin were excluded. 3) The ulcer had to be a full-thickness defect >1 cm^2. 4) The foot had to have circulation adequate for healing. 5) The patient had to be able to complete a 12-week trial and could not be pregnant. Exclusion: Medications known to interfere with healing (e.g., corticosteroids, immunosuppressives, or cytotoxic agents) were excluded.	Dermagraft Group A (n-12) One piece of Dermagraft applied weekly for a total of eight pieces and eight applications, plus control treatment. Group B (n-14) Two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment. Group C(n-11) One piece of Dcrmagraft applied every 2 weeks for a total of four pieces and four applications, plus control treatment. All patients received debridement, dressings, and pressure relief.	Group D (n-13) (Control group): conventional therapy and wound-dressing techniques using saline moistened gauze All patients received debridement, dressings, and pressure relief.	Weekly for 12weeks.	Percentage of wounds achieving complete closure and 50% closure The percentage of patients who achieved complete wound closure by week 12 was significantly higher in group A than in the control group (50.0, 21.4, 18.2, and 7.7% in groups A, B, C, and D, respectively; P = 0.03 for group A vs. D). Relative Risk (A vs. D)- 6/12 ÷ 1/13 = 6.5 A dose response was observed; that is, the percentage of patients achieving complete wound closure by week 12 increased with increasing Dermagraft dosage (group A > group B > group C). Time to complete wound closure Median time to complete wound closure was 12 weeks in group A and >12 weeks in the remaining groups. Percentage of wounds achieving 50% closure In group A, 75% of patients achieved 50% wound closure by week 12, compared with 50.0, 18.2, and 23.1% in groups B, C, and D, respectively. Relative Risk (A vs. D)- 9/12 ÷ 3/13 = 3.24 For group A, the difference was statistically significant compared with the control group (P« 0.017). Time to 50% closure Median time to 50% closure was significantly faster, 2.5 weeks in group A, compared with >12 weeks in the control group (P = 0.0047). Wound volume In group A, the median percentage decrease in volume was 88.9% at week 12 versus no decrease in group D (P = 0.017). Adverse events No patients in this study experienced an adverse device effect. Incidences of specific intercurrent

						events were low. Relative Risk - 2/12 ÷ 3/13 = 0.72
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Gentzkow, GD, Iwasaki, SD, Hershon, KS, Mengel, M, Prendergast, JJ, Ricotta, JJ, Steed, DP, Lipkin, S Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996; 19: 350-354.

Title: HYAFF 11 -Based Autologous Dermal and Epidermal Grafts in the Treatment of Noninfected Diabetic Plantar and Dorsal Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 2034 Level of evidence: () Study type: RCT Authors: Caravaggi et al. (1996)	Total no. of patients: Baseline = 82 3 excluded Hyalograft-43 Control- 36 IN CASE OF WOUND INFECTION DURING THE STUDY PERIOD, AN APPROPRIATE ANTIBIOTIC THERAPY WAS PRESCRIBED. Baseline characteristics: AT BASELINE THE TWO GROUPS WERE SIMILAR IN REGARD TO CLINICAL CHARACTERISTICS. Setting: 6 centres-Italy	Inclusion: TYPE 1 OR TYPE 2 DIABETES, AN ULCER >2 cm^2 ON PLANTAR SURFACE OR DORSUM OF THE FOOT WITHOUT SIGNS OF HEALING FOR 1 MONTH, WAGNER SCORE 1-2, $TcPO_2$ ≥30 MMHG, AND ANKLE BRACHIAL PRESSURE INDEX (ABPI) ≥ 0.5. Exclusion: ULCERS WITH CLINICAL INFECTION, EXPOSED BONE, OSTEOMYELITIS, INABILITY TO TOLERATE AN OFF-LOADING CAST, AND POOR-PROGNOSIS DISEASES. AFTER 15 DAYS OF SCREENING (APPLICATION OF STANDARD DRESSING, I.E., AT VISIT 1) ALL PATIENTS WITH AN ULCER AREA <1 CM' WERE EXCLUDED FROM THE STUDY.	THE TREATMENT GROUP WITH AUTOLOGOUS FIBROBLASTS ON HYALOGRAFT 3D GRAFTS (N = 43). ALL ULCERS WERE SUBJECTED TO AN AGGRESSIVE AND EXTENSIVE DEBRIDEMENT TO REMOVE NE-CROTIC TISSUE AND TO CONTROL INFECTION.	CONTROL GROUP WITH NON-ADHERENT PARAFFIN GAUZE (N = 36) ALL ULCERS WERE SUBJECTED TO AN AGGRESSIVE AND EXTENSIVE DEBRIDEMENT TO REMOVE NE-CROTIC TISSUE AND TO CONTROL INFECTION.	Weekly until ulcer healed or 11 weeks, whichever came first.	Complete wound healing (ITT analysis) COMPLETE WOUND HEALING WAS ACHIEVED IN 65.3% OF THE TREATMENT GROUP ULCERS VERSUS 49.6% OF THE CONTROL GROUP ULCERS (P = 0.191, LOG-RANK TEST). Relative Risk- 28/43 ÷ 18/36 = 1.31 THE KAPLAN-MEIER MEDIAN TIME FOR COMPLETE ULCER HEALING WAS 57 AND 77 DAYS FOR THE TREATMENT AND CONTROL GROUPS, RESPECTIVELY. Complete wound healing (per-protocol analysis to assess robustness of the outcomes) COMPLETE WOUND HEALING WAS ACHIEVED IN 63.7% (N- 35)OF THE TREATMENT GROUP ULCERS VERSUS 50% (N- 26) OF THE CONTROL GROUP ULCERS (P = 0.332, LOG-RANK TEST) WITH A MEDIUM TIME FOR COMPLETE ULCER HEALING OF 59 DAYS FOR THE TREATMENT GROUP AND >77 DAYS FOR THE CONTROL GROUP. Relative Risk- 22/35 ÷ 13/26 = 1.27 SECONDARY EFFICACY PARAMETERS: SECONDARY EFFICACY PARAMETERS (PRESENCE OF

						FIBROUS SLOUGH, NECROTIC TISSUE, GRANULATION TISSUE, MACERATION, EXUDATE, ODOUR, INFECTION, AND PAIN SYMPTOMATOLOGY) WERE ANALYZED, AND BOTH groups showed an improvement in these parameters, the treatment group showed greater improvement than the control group as far as exudate presence. Adverse events TWENTY-TWO ADVERSE EVENTS WERE REPORTED FROM THE 82 RANDOMIZED PATIENTS (26.8%). THESE EVENTS WERE EQUALLY DISTRIBUTED BETWEEN THE TWO GROUPS. OF THESE, 17 (10 IN THE CONTROL GROUP AND 7 IN THE TREATMENT GROUP) WERE CLASSIFIED AS SERIOUS ADVERSE EVENTS. WITHDRAWAL DUE TO ADVERSE EVENTS (ULCER RELATED) Relative Risk- 3/43 ÷ 6/36 = 0.41
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Caravaggi, C, De, GR, Pritelli, C, Sommaria, M, Dalla, NS, Faglia, E, Mantero, M, Clerici, G, Fratino, P, Dalla, PL, Mariani, G, Mingardi, R, Morabito, A HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. *Diabetes Care* 2003; 26: 2853-59.

Title: The Efficacy and Safely of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers. Results of a prospective randomized trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6909 Level of evidence: () Study type: RCT Authors: Marston et al. (2003)	Total no. of patients: Baseline = 245 Dermagraft- 130 Control- 115 STUDY ULCERS WERE STRATIFIED INTO ONE OF TWO GROUPS ACCORDING TO ULCER SIZE: GROUP 1, ≥1 TO ≤2 CM^2; GROUP 2, >2 TO ≤20 CM^2 Baseline characteristics: THERE WERE NO STATISTICALLY SIGNIFICANT DIFFERENCES WITH RESPECT TO ANY DEMOGRAPHIC CHARACTERISTICS BETWEEN THE TWO GROUPS. Setting: 35 centres-USA	Inclusion: • PATIENT IS >18 YEARS OLD • PATIENT HAS TYPE I OR II DIABETES • PATIENT'S ULCER HAS BEEN PRESENT FOR A MINIMUM OF 2 WEEKS UNDER THE CURRENT INVESTIGATOR'S CARE • PATIENT'S FOOL ULCER IS ON THE PLANTAR SURFACE OF IHE FOREFOOT OR HEEL AND 2=1,0 CM^2 IN SIZE AT DAY 0 • PATIENT'S ULCER EXTENDS THROUGH THE DERMIS AND INTO SUBCUTANEOUS TISSUE BUT WITHOUT EXPOSURE OF MUSCLE, TENDON, BONE, OR JOINL CAPSULE • PATIENT'S WOUND IS FREE OF NECROTIC DEBRIS AND APPEARS LO BE MADE UP OF HEALTHY VASCULARIZED TISSUE • PATIENT HAS ADQEQUALE CIRCULATION LO THE FOOT AS EVIDENCED BY A PALPABLE PULSE Exclusion: • GANGRENE IS PRESENT ON ANY PART OF THE AFFECTED FOOL • PATIENT'S ULCER IS OVER A CHARCOT DEFORMITY • ULCER TOTAL SURFACE AREA IS >20 CM^2 • PATIENT'S ULCER HAS DECREASED OR INCREASED IN SIZE BY 50% OR MORE DURING	DERMAGRAFT (A BIOENGINEERED DERMAL SUBSTITUTE, N-130) STUDY ULCERS RECEIVED SHARP DEBRIDEMENT AND SALINE-MOISTENED GAUZE DRESSINGS. IN ADDITION, PATIENTS RECEIVED OFF-WEIGHT BEARING INSTRUCTIONS.	CONTROL GROUP CONVENTIONAL THERAPY (N- 115) IT CONSISTED OF WOUND DRESSINGS (CON-SISTED OF A NONADHERENT INTERFACE, SALINE-MOISTENED GAUZE TO FILL THE ULCER) DRY GAUZE, AND ADHESIVE FIXATION SHEETS (HYPAFIX). STUDY ULCERS RECEIVED SHARP DEBRIDEMENT AND SALINE-MOISTENED GAUZE DRESSINGS. IN ADDITION, PATIENTS RECEIVED OFF-WEIGHT BEARING INSTRUCTIONS.	WEEKLY UNTIL COMPLETE WOUND CLOSURE OR THE PATIENT REACHED THE WEEK 12 VISIT WITHOUT HEAL-ING.	Efficacy: Complete Wound Closure at 12 weeks THE RESULTS SHOWED THAT TREATMENT WITH DERMAGRAFL PRODUCED A SIGNIFICANTLY GREATER PROPORTION (30%) OF HEALED ULCERS COMPARED WITH THE CONTROL GROUP (18%) (P-0.023). Relative Risk- 39/130 ÷ 21/115 = 1.66 THE DERMAGRAFT-TREATED GROUP HAD A SIGNIFICANTLY FASTER TIME TO COMPLETE WOUND CLOSURE THAN THE CONTROL GROUP (P — 0.04). BY WEEK 12, THE MEDIAN PERCENT WOUND CLO-SURE FOR THE DERMAGRAFT GROUP WAS 91% COMPARED WITH 78% FOR THE CONTROL GROUP (P = 0.044). Adverse events THE OVERALL INCIDENCE OF ADVERSE EVENTS WAS COMPARABLE BETWEEN THE DERMAGRAFT GROUP (67%) AND THE CONTROL GROUP (73%). Relative Risk- 87/130 ÷ 84/115 = 0.92 THE NUMBER OF PATIENTS WHO DEVELOPED STUDY ULCER-RELATED ADVERSE EVENTS (I.E., LOCAL WOUND INFECTION, OSTEOMYELITIS, AND CELLULITIS) WAS SIGNIFICANTLY LOWER IN THE DERMAGRAFT-TREATED PATIENTS (19%) THAN IN THE CONTROL PATIENTS (32%; P = 0.007) Relative Risk (ulcer related)- 31/130 ÷ 49/115 = 0.56 Surgical Interventions in Ulcers

		THE SCREENING PERIOD • SEVERE MALNUTRITION IS PRESENT AS EVIDENCED BY ALBUMIN <2.0 • PATIENT'S RANDOM BLOOD SUGAR READING IS >450 MG/DL • URINE KETONES ARE NOTED LO BE "SMALL, MODERATE, OR LARGE" • PATIENT HAS A NONSTUDY ULCER ON THE STUDY FOOT THAT IS LOCATED WITHIN 7.0 CM OF THE STUDY ULCER AT DAY 0 • PATIENT IS RECEIVING ORAL OR PARENTERAL CORTICOSTEROIDS, IMMUNOSUPPRESSIVE OR CYTOTOXIC AGENTS, COUMADIN, OR HEPARIN • PATIENT HAS A HISTORY of BLEEDING DISORDER • PATIENT HAS AIDS OR IS HIV-POSITIVE • CELLULITIS, OSTEOMYELITIS, OR OTHER EVIDENCE OF INFECTION IS PRESENT EXCLUDED FROM THE STUDY.				Relative Risk (ulcer related)- 13/163 ÷ 22/151 = 0.54
Additional comments: Randomisation was performed. Blinding performed (single). Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Marston, W, Foushee, K, Farber, M Prospective randomized study of a cryopreserved, human fibroblast-derived dermis in the treatment of chronic plantar foot ulcers associated with diabetes mellitus. *14th Annual Symposium on Advances Wound Care and Medical Research Forum on Wound Repair* 2001.

Title: A Metabolically Active Human Derma! Replacement for the Treatment of Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: Level of evidence: () Study type: RCT Authors: Naughton et al. (1997)	Total no. of patients: Baseline = 281 Group 1- 142 Group 2- 139 All patients were screened. Baseline characteristics: Not mentioned Setting: 20 investigational centres-USA	Inclusion: PATIENTS WITH NEUROPATHIC FULL-THICKNESS PLANTAR SURFACE FOOT ULCERS OF THE FOREFOOT OR HEEL, ≥1.0CM^2 IN SIZE. Exclusion: Initial rapid healing in response to standard care during the screening period.	Group 2(n-139) Treated with conventional therapy plus applications of Dermagraft on day 0 and weeks 1,2,3,4,5,6, and 7.	GROUP 1(N-142) TREATED WITH CONVENTIONAL THERAPY WHICH INCLUDED DEBRIDEMENT, INFECTION CONTROL, SALINE MOISTENED GAUZE DRESSINGS AND STANDARDISED OFF WEIGHTING.	Weekly until week 12 and then 4 weekly until week 32	Efficacy: Healing at week 12 Group 1- 31.7% Group 2- 38.5% Relative Risk- 54/139 ÷ 45/142= 1.21 Time to healing (mean) Group 1- 28 weeks Group 2- 13 weeks Recurrence of ulcers Ulcers recurred in a comparable minority of both groups, it is noteworthy that Dermagraft tended to delay recurrence Medial time to recurrence Dermagraft- 12 weeks Control-7 weeks Adverse events No safety problems were identified, and no significant differences were found between Dermagraft and control patients in the occurrence of wound infections or other intercurrent events.
Additional comments: Randomisation was performed. Single Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Naughton, G, Mansbridge, J, Gentzkow, G A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. *Artificial Organs* 1997; 21: 1203-10.

Growth Factors

Section 1: Granulocyte-colony stimulating factors (G-CSF)

Title: Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections (Cochrane review)					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: Study type: Systematic review Authors: Cruciani et al. (2009)	People with diabetes who have a foot infection, including infected ulcers, cellulitis, osteomyelitis, deep abscess. Where possible, wound severity was reported according to the Wagner classification system The studies varied considerably in design and quality. For instance, de Lalla (2001) included only patients with limb-threatening infections, all of whom had osteomyelitis, whilst Yonem (2001) enrolled only patients with mild infections. Most of the studies included patients with foot cellulitis; Viswanathan (2003) and Kastenbauer (2003) enrolled patients with foot ulcers graded 2 or 3 on the Wagner scale, while Yonem (2001) included only patients with grade 1 or 2, and de Lalla (2001) patients with grade 3 or 4.	All randomised controlled trials (RCTs) that investigated the therapeutic effects of G-CSF in people with a diabetic foot infection. Studies were included only if they compared the effects of treatment as usual (e.g. antibiotic treatment for infection, surgery, pressure relief, wound care) with that of treatment as usual plus adjunctive G-CSF therapy, such that the G-CSF therapy is the only systematic treatment difference between trial arms. Review content assessed as up-to-date: 15 March 2009. The methodological strength of each study was appraised using a standard risk of bias checklist for the following criteria: • sequence generation; • allocation concealment; • blinding; • incomplete outcome data/completeness of follow-up • selective reporting of outcomes; • ITT analysis • other bias. The clinical characteristics of the diabetic foot infections varied, but the level of severity described among the	Intervention: G-CSF given subcutaneously, intramuscularly or intravenously plus treatment as usual. Control: treatment as usual with or without placebo. One study (de Lalla 2001) used lenograstim, the glycosylate human recombinant G-CSF, while the other studies used filgrastim, a non-glycosylate. Studies with filgastrim used a daily dose of 5 µg/kg, with dose reduction based on neutrophil count. Lenogastrin was administered at a daily dose of 263 µg (one vial). By contrast, the duration of G-CSF administration varied from 7 to 21 days, thus accounting for a wide range (from 2114 to 5523 µg) in the total G-CSF dose administered . Systemic antibiotics were administered in all the trials. A combination of intravenous clindamycin and ciprofloxacin (followed by oral route if necessary) was given in three trials (de Lalla 2001; Yonem 2001; Kastenbauer 2003); a combination of four intravenous antibiotics (ceftazidime, amoxicillin,	Range from 10 days to 6 months. <u>*5 studies:*</u> Gough (1997): unclear de Lalla (2001): 6 months Yonem (2001): unclear Kastenbauer (2003): 10 days Viswanathan (2003): unclear	Meta-analyses were carried out where there are two studies or more. *Resolution of infection* (2 studies; study period: unclear; total 80 participants): RR = 2.75 (95%CI: 1.05 to 7.20) *Infection status - improvement*[a] (4 studies; study period: range 10 days to 6 moths; total 140 participants): RR = 1.40 (95%CI: 1.06 to 1.85) [a]*improvement = eradication or some eradication of pathogen (through swab or tissue culture) but still have persistent signs (pain, swelling, erythema).* *Healing of wounds* (2 studies; study period: unclear; total 79 participants): RR = 9.45 (95%CI: 0.54 to 164.49) *Overall surgical interventions* (5 studies; study period: range 10 days to 6 moths; total 164 participants): RR = 0.37 (95%CI: 0.20 to 0.68) *Number of amputation* (5 studies; study period: range 10 days to 6 moths; total 167 participants): RR = 0.41 (95%CI: 0.18 to 0.95)

		studies varied from relatively mild (Yonem 2001; Viswanathan 2003) to severe (de Lalla 2001). Initial antibiotic therapy was apparently uniformly parenteral, but regimens and duration of therapy also varied considerably. The inclusion and exclusion criteria, clinical characteristics monitored, and end-points for therapy also differed.	flucloxacillin, and metronidazole) was given in one study (Gough 1997); the antibiotic regimen consisted of intravenous ofloxacin andmetronidazole in the remaining study (Viswanathan 2003). The studies employed different G-CSF preparations, at different dosages, and for different durations. Even the several studies that gave filgrastim used products made in different laboratories.		*Adverse events (side effects of G-CSF)* (3 studies; study period: range 10 days to 6 moths; total 117 participants): RR = 5.59 (95%CI: 0.71 to 44.05) *Days with systemic antibiotics* (3 studies; study period: range 10 days to 6 moths; total 107 participants): MD = -0.27 (95%CI: -1.30 to 0.77) *Days of hospital stay* (2 studies; study period: unclear; total 50 participants): MD = 2.75 (95%CI: 1.05 to 7.20)
Additional comments: Good quality systematic review. The generation of the randomisation process was unclear in 3 studies. Allocation concealment was unclear in 3 studies. There were 3 blinded placebo-controlled studies and 2 open-labelled studies. 2 studies were reported to be patient-blinded; blinding of investigators was reported in 3 other placebo-controlled studies; blinding of the outcome assessor was reported in 1 study and not stated or unclear in the remaining studies. No information about the blinding of the data analyst were available from any of the studies.					

Reference: Cruciani Mario AU: Lipsky Benjamin Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. *Cochrane Database of Systematic Reviews: Reviews* 2009; Issue 3.

Section 2: Recombinant Human Platelet-Derived Growth Factor (rhPDGF)

Title: Efficacy of Recombinant Human Platelet-Derived Growth Factor (rhPDGF) Based Gel in Diabetic Foot Ulcers: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study in India					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 4435 Study type: RCT Authors: Hardikar et al. (2005)	Total no. of patients = 113 Treatment = 58 Control = 55 <u>Mean age (SD)</u> Control = 54.5 (9.9) Treatment = 54.7 (9.0) <u>Males/females</u> Control = 40 (69%)/18 (31%) Treatment = 40(73%)/15 (27%) <u>Target ulcer surface area (mean cm^2) (SD)</u> Control = 13.7 (11.2) Treatment = 11.9 (9.9) <u>Duration of ulceration (mean weeks) (SD)</u> Control = 19.8 (39.8) Treatment = 25.5 (31.9) <u>Setting:</u> 8 sites, mostly public	<u>Inclusion:</u> Patients either with type 1 or 2 diabetes mellitus, were aged > 18 years but < 80 years and had at least 1 but less than 3 full-thickness chronic neuropathic ulcers of at least 4 weeks duration on the lower extremity. Only ulcers categorized as stage III or stage IV, as defined by the Wound, Ostomy, and Continence Nurses Society," and those with infection control as determined by a wound evaluation score were considered for inclusion. If multiple ulcers were present, the largest ulcer was taken as the target ulcer, and the size of ulcer was restricted to an area of 1-4Ocm1 <u>Exclusion:</u> Patients with arterial venous ulcers or those with ulcers caused by osteomyelitis or burns; if they had poor nutritional status (serum total proteins <6.5g/dL), persistent infection, life-threatening concomitant diseases, deformities like Charcot foot, chronic renal insufficiency (serum creatinine >3mg/dL), uncontrolled hyperglycemia (HbAlc >12%), history of corticosteroids or	<u>Treatment:</u> A 0.01% gel containing 100ng of rhPDGF-BB/g + standard wound care <u>Control:</u> Standard wound care only. The wounds were covered with thin 1.5mm layers of gel and covered with moist saline gauze. Standard wound care = regimen consisting of appropriate sharp surgical debridement, daily ulcer cleaning and dressing, and offloading (eg, crutches or wheelchair) or, in cases where possible, complete bed rest. Treatment group = 5 withdrawn due to concomitant illness and lost to follow-up Control group = 13 withdrawn	10 weeks and 20 weeks	Complete healing of ulcers: At 10 weeks: Treatment = 39/55; Control = 18/58 At 20 weeks: Treatment = 47/55; Control = 31/58 Mean healing time (days): At 10 weeks: Treatment = 46 days; Control = 61 days $p < 0.001$ At 20 weeks: Treatment = 57 days; Control = 96 days $p < 0.01$ The use of systemic antibiotics was found to contribute to increased healing percentages. In the treatment group, use of antibiotics increased the healing rate from 59% to 78%, while in the control group, antibiotic use increased the healing rate from 22.7% to 36%. Withdrawal due to adverse events was also similar at about 4% in the treatment group

	hospitals, in India.	immunosuppressant use, or any known hypersensitivity to the gel components. Women of childbearing age and pregnant or nursing women who were not taking contraceptives or not willing to use them were also excluded.	due to concomitant illness and lost to follow-up		and 5% in the control group. Nearly half of the adverse events were due to ulcer-related events, such as infection and osteomyelitis. No erythematous rashes or hypersensitivity to the gel or excipients was noted in any of the patients.
Additional comments: No details on randomisation methods; no mention of allocation concealment; no mention of blinding methods					

Reference: Hardikar, JV, Reddy, YC, Bung, DD, Varma, N, Shilotri, PP, Prasad ED, ea Efficacy of recombinant human platelet-derived growth factor (rhPDGF) based gel in diabetic foot ulcers: a randomized, multicenter, double-blind, placebo-controlled study in India. *Wounds: A Compendium of Clinical Research and Practice* 2005; 17: 141-52.

Title: Integrating the Results of Phase IV (Postmarketing) Clinical Trial With Four Previous Trials Reinforces the Position that Regranex (Becaplermin) Gel 0.01% Is an Effective Adjunct to the Treatment of Diabetic Foot Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 9181 Study type: RCT Authors: Robson et al. (2005)	Total no. of patients = 146 Treatment = 74 Control = 72 Baseline characteristics were generally comparable between groups. The mean duration of diabetes mellitus in the Regranex Gel 0.01% group (17.9 years) was slightly longer than that in the standardized therapy group (14.7 years). The median ulcer at baseline was similar in the two treatment groups (1.5 and 1.6 cm2).	Inclusion: • Be 18 years of age or older; if female, must be practicing birth control. • Have documented wound etiology resulting from complications of diabetes mellitus. • Have at least one chronic nonhealing cutaneous full thickness diabetic neuropathic foot ulcer between 1.7-12 cm2area, 4-52 weeks duration, on the plantar aspect of the forefoot (midarch forward) and free of necrotic and infected tissue postdebridement. • Have a supine TcP02 > 30 mmHg on the dorsum of the target ulcer foot; an ulcer tissue biopsy with < 1 x 105organisms/g of tissue and no beta hemolytic streptococci. • Be willing and able to comply with the protocol. Exclusion: • Have the target ulcer other than on the plantar surface forward of the mid-arch; and a known hypersensitivity to any of the study drug components; have a malignant disease at the ulcer site; osteomyelitis confirmed by bone biopsy • Have a target ulcer < 1.7 or > 12 cm2 post-debridement. • Have more than one diabetic ulcer on the same foot as the target ulcer; more than three chronic wounds on the same extremity as the target ulcer; have thermal, electrical, chemical, or radiation wounds at the site of the target ulcer. • Have wounds resulting from large vessel arterial insufficiency, venous insufficiency, or necrobiosis lipoidica.	Treatment: Regranex Gel 0.01% with the Adaptic dressing + standardized good wound care Control: Adaptic dressing + standardized good wound care. The dosage of Regranex Gel 0.01% was determined by study personnel on a weekly basis by multiplying the greatest length of the target ulcer by the greatest width. In addition to the once daily dressing changes, standardized good	20 weeks	Complete wound healing at 20 weeks: Treatment = 31/74 Control = 25/72 p = 0.316 Of the patients who achieved complete healing, there was evidence for preferential healing of target ulcers with baseline areas less than 1.46 cm2 in favour of patients treated with Regranex Gel 0.01% (p = 0.0286).

		• Have significant metabolic, rheumatic, collagen vascular disease, chronic renal insufficiency, or chronic severe liver disease. • Have received any investigational drug, Procuren solution, or prior Regranex Gel 0.01% usage within the past 30 days. • Have a preexisting disease or condition that could interfere with evaluation of the effectiveness of Regranex Gel 0.01% or be adversely affected by Regranex Gel 0.01%. • Be receiving any systemic corticosteroids, immunosuppressive agents, radiation, or chemotherapy or revascularization surgery in the past 6 weeks; exposed bone or tendon, or presence of Charcot foot; or severe pitting limb edema.	wound care procedures (maintenance of a clean moist environment, infection control, non-weightbearing regimen, and debridement) were followed.		
Additional comments: No details on randomisation methods; no mention of allocation concealment; only sing-blinded (investigator).					

Reference: Robson, MC, Payne, WG, Garner, WL, Biundo, J, Giacalone, VF, Cooper, DM, Ouyang, P Integrating the results of phase IV (postmarketing) clinical trial with four previous trials reinforces the position that Regranex (becaplermin) Gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. *Journal of Applied Research* 2005; 5: 35-45.

Title: Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (Becaplermin) in patients with chronic neuropathic diabetic ulcers					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 11667 Study type: RCT Authors: Wieman et al. (1998)	Total no. of patients = 382 Treatment 100ug/g = 124 Treatment 30ug/g = 132 Control (placebo gel) = 127 <u>Treatment 100ug/g</u> Male/female = 82/41 Mean age (SD) = 57 (11.5) Mean ulcer duration (wks) (SD) = 46 (54.7) Mean ulcer size (cm^2) (SD) = 2.6 (3.41) <u>Treatment 30ug/g</u> Male/female = 82/50 Mean age (SD) = 58 (11.3) Mean ulcer duration (wks) (SD) = 56 (80.3) Mean ulcer size (cm^2) (SD) = 2.6 (2.69)	<u>Inclusion:</u> Patients > 19 years of age with type 1 or type 2 diabetes. Patients had at least one full thickness (stage III or IV, as defined in the International Association of Enterostomal Therapy guide to chronic wound staging, chronic ulcer of the lower extremities. Target ulcers had to be present for at least 8 weeks despite previous treatment. <u>Exclusion:</u> Patients were excluded if 1) osteomyelitis affecting the area of the target ulcer was present, 2) after debridement, the target ulcer area (estimated by multiplying length by width) was <1 cm2 or >40 cm2, or 3) the sum of the areas of all ulcers present exceeded 100 cm2. Patients with ulcers resulting from any cause other than	<u>Treatment:</u> (Regranex Gel 0.01%) Becaplermin gel 100 ug/g or Becaplermin gel 30 ug/g, plus standard wound care <u>Control:</u> Placebo gel plus standard wound care Patients were instructed to apply a continuous thin layer of gel to the entire ulcer area once daily, preferably when the dressing was changed in the evening. Standardized regimen of good wound care = complete sharp debridement of ulcers to remove callus, fibrin, and	20 weeks then 3 months	Complete wound healing at 20 weeks: Treatment 100ug/g = 61/124 Treatment 30ug/g = 48/132 Control (placebo gel) = 44/127 Discontinuation because of treatment related adverse effects: Treatment 100ug/g = 11/124 Treatment 30ug/g = 13/132 Control (placebo gel) = 10/127 Discontinuation: Placebo gel 30 100

	Control (placebo gel) Male/female = 91/36 Mean age (SD) = 58 (11.8) Mean ulcer duration (wks) (SD) = 46 (52.1) Mean ulcer size (cm^2) (SD) = 2.8 (4.14) Before randomization, the target ulcer was sharply debrided to remove all nonviable tissue and callus. Any infection or cellulitis present before debridement had to be well controlled before randomization. Setting: Multicentres (23 sites in the U.S.)	diabetes (e.g., electrical, chemical, or radiation insult) and patients with cancer were excluded. Additional exclusion criteria included concomitant diseases (e.g., connective tissue disease), treatment (e.g., radiation therapy), or medication (e.g., corticosteroids, chemotherapy, or immunosuppressive agents) that would present safety hazards or interfere with evaluation of the study medication. Women who were pregnant, nursing, or of childbearing potential and not using either an intrauterine device or oral contraception were excluded. All patients gave their written informed consent before study entry.	necrotic tissue was an important component of good wound care and was performed by investigators during clinic visits if necessary. Good wound care also consisted of twice-daily dressing changes (moist saline), off-loading of pressure from the affected area, and adequate control of infection if present		Reason for discontinuation Lost 10 follow up 2 1 1 AE 13 17 13 Noncompliance 3 4 3 Protocol violation 3 2 2 Other 3 4 2 Total discontinuations 24 28 21 Patients completing study* 103 104 102 Treatment failures 7 17 10
Additional comments: No details on randomisation methods; no mention of allocation concealment; no mention of blinding methods					

Reference: Wieman, TJ, Smiell, JM, Su, Y Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; 21: 822-27.

Title: Sodium Carboxymethylcellulose Aqueous-Based Gel vs. Becaplermin Gel in Patients with Non-healing Lower Extremity Diabetic Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 2584 Study type: RCT Authors: D'Hemecourt et al. (2005)	Total no. of patients = 172 NaCMC gel = 70 Becaplermin gel 100 ug/g = 34 Control = 68 <u>Treatment NaCMC gel</u> Male/female = 49/21 Mean age (SD) = 59 (13.02) Mean ulcer duration (wks) (SD) = 52.8 (60.92) Mean ulcer size (cm^2) (SD) = 3.2 (2.75) <u>Treatment 100ug/g</u> Male/female = 24/10 Mean age (SD) = 58.5 (11.9) Mean ulcer duration (wks) (SD) = 20 (14.39) Mean ulcer size (cm^2) (SD) = 2.4 (2.02) <u>Control (good wound care)</u> Male/female = 54/14 Mean age (SD) = 59 (11.29) Mean ulcer duration (wks) (SD) = 42 (42) Mean ulcer size (cm^2) (SD) = 3.5 (3.53) <u>Setting:</u> Multicentres (10 sites), US.	<u>Inclusion:</u> Patients 19 years of age or older with type 1 or type 2 diabetes mellitus. Patients had at least one full-thickness (Stage 3 or 4), chronic diabetic ulcer of the lower extremity that had been present for at least eight weeks prior to the study. A target area between 1.0 and 10.0 cm2 post-debridement was required. <u>Exclusion:</u> Patients were excluded if (1) osteomyelitis affecting the area of the target ulcer was present, (2) after debridement, the target ulcer area (measured by multiplying length by width) was < 1 cm2 or > 10 cm3, or (3) they had more than three chronic ulcers present at baseline. Patients with ulcers resulting from any cause other than diabetes (e.g. electrical, chemical, or radiation insult), or patients with cancer at the time of enrolment were excluded. Additional exclusion criteria included use of concomitant medications known to affect wound healing (e.g. corticosteroids, chemotherapy, or immunosuppressive agents). Women who were pregnant or nursing, or of childbearing potential and not using an acceptable method of birth control were excluded.	<u>Treatment:</u> NaCMC gel plus good wound care Becaplermin gel 100 ug/g plus good wound care <u>Control:</u> Good wound care alone In the treatment groups, a thin layer of the corresponding gel was applied once daily at the morning dressing change for a maximum of 20 weeks or until the target ulcer was completely healed. Good wound care = included sharp debridement of ulcers to remove calluses, fibrin, and necrotic tissue. Debridement was performed by investigators at Visit 2 and throughout the study as necessary; and also included wet-to-moist saline-soaked gauze dressing changes every 12 hours, off-loading of pressure, and systemic control of infection if present.	20 weeks	Complete wound healing at 20 weeks: NaCMC gel = 25/70 Becaplermin gel 100 ug/g = 15/34 Control = 15/68 Discontinuation because of treatment related adverse effects: NaCMC gel = 8/70 Becaplermin gel 100 ug/g = 5/34 Control = 16/68 At least 1 treatment related adverse effect: NaCMC gel = 57/70 Becaplermin gel 100 ug/g = 22/34 Control = 48/68 Good wound care alone (n = 68) / NaCMC gel (n = 70) / Becaplermin gel 100 ug/g (n = 34) Withdrew: 21 (31) / 11(16) / 9(26) AE: 16(24) / 8(11) / 5(15) Lost to follow-up: 1(1) / 2(3) / 2(6) Patient choice: 3(4) / 0(0) / 1(3) Other: 1(1) / 1(1) / 1(3) A treatment-emergent AE was defined as an adverse event not present at baseline or if present at baseline, one which worsened in frequency or severity as the study progressed.

Additional comments: No details on randomisation methods; no mention of allocation concealment; only evaluator-blinded.

Reference: d'Hemecourt, PA, Smiell, JM, Karim, MR Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower extremity diabetic ulcers. *Wounds: A Compendium of Clinical Research & Practice* 1998; 10: 69-76.

Section 3: Human Epidermal Growth Factor

Title: Human Epidermal Growth Factor Enhances Healing of Diabetic Foot Ulcers					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 10951 Study type: RCT Authors: Tsang et al. (2003)	127 patients were screened Total no. of patients randomised = 61 0.02% [wt/wt] hEGF = 21 0.04% [wt/wt] hEGF = 21 Control =19 <u>Treatment 0.02% [wt/wt] hEGF</u> Male/female = 13/8 Mean age (SD) = 68.76 (10.45) Mean ulcer duration (wks) (SD) = 8.24 (5.55) Mean ulcer size (cm^2) (SD) = 2.78 (0.82) <u>Treatment 0.04% [wt/wt] hEGF</u> Male/female = 6/15 Mean age (SD) = 62.24 (13.68) Mean ulcer duration (wks) (SD) = 11.48 (14.68) Mean ulcer size (cm^2) (SD) = 3.4 (1.1) <u>Control</u> Male/female = 10/9 Mean age (SD) = 64.37 (11.67) Mean ulcer duration (wks) (SD) = 12 (15.47) Mean ulcer size (cm^2) (SD) = 3.48 (0.82) Between September 2000 and August	<u>Inclusion:</u> 1) ulcer with grade I or 13, as defined by the Wagner Classification; 2) ulcer located below the ankle, and 3) ulcer with adequate perfusion, as indicated by an ankle-brachial index (ABI) ≥ 0.7. <u>Exclusion:</u> Patients were excluded if they had very poor sugar control (HbA, c > 12%) or had ulcers with severity equal to or greater than grade III. In the second consultation, we excluded patients whose ulcers healed >25% with conventional foot ulcer care.	<u>Treatment:</u> • 0.02% [wt/wt] hEGF plus Actovegin 5%cream plus standard wound care • 0.04% [wt/wt] hEGF plus Actovegin 5%cream plus standard wound care <u>Control:</u> Actovegin 5% cream plus standard wound care Actovegin is a protein free calf blood extract manufactured by NYCOMED Austria The cream under study was applied locally and covered with sterile gauze. Patients were instructed to continue with the normal daily saline dressing, combined with local application of the cream. Standard wound care consisted of debridement of necrotic tissue and reduction of callus. Antibiotics were prescribed	12 weeks and 24 weeks	<u>Wound completely healed (12 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 12/19 Treatment 0.04% [wt/wt] hEGF = 20/21 Control = 8/19 <u>Wound completely healed (24 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 17/19 Treatment 0.04% [wt/wt] hEGF = 20/21 Control = 17/19 <u>Amputation (24 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 2/19 Treatment 0.04% [wt/wt] hEGF = 0/21 Control = 2/19

	2002 Diabetes Ambulatory Care centre, China		based on clinical judgment or on positive wound bacterial cultures.		
Additional comments: No mention of allocation concealment; no mention of blinding methods; no report of adverse events.					

Reference: Tsang, MW, Wong, WK, Hung, CS, Lai, KM, Tang, W, Cheung, EY, Kam, G, Leung, L, Chan, CW, Chu, CM, Lam, EK Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; 26: 1856-61.

Title: Efficacy of topical epidermal growth factor in healing diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 579 Study type: RCT Authors: Afshari et al. (2005)	Total no. of patients = 50 Treatment ECF = 30 Control = 20 Treatment ECF Male (%) = 72.7% Mean age (SD) = 56.9 (12.7) Mean ulcer duration (days) (SD) = 42.9 (38.4) Mean ulcer size (mm^2) (SD) = 87.5 (103.2) Infection = 21/30 Control Male (%) = 53.3% Mean age (SD) = 59.7 (12.3) Mean ulcer duration (days) (SD) = 59.7 (55.5) Mean ulcer size (mm^2) (SD) = 103.4 (147.8) Infection = 12/20 Between October 1998 and September 2001 Tehran's Doctor Shariati University Hospital	Inclusion: Ulcer with Grade I or II, as defined by the Wagner Classification Ulcer with adequate perfusion, as indicated by an ankle-brachlal index (ABI) and ultrasound. Exclusion criteria not reported.	Treatment: 1 mg EGF plus 1000 mg of 1 % silver sulfadiazine in a hydrophilic base plus standard wound care Control: 1000 mg of 1 % silver sulfadiazine in a hydrophilic base plus standard wound care Patients in both the EGF and placebo groups had their wounds washed with normal saline and dressed every day Wound dressing consisted of sterile gau/e and adhesive tape only No disinfecting solution, such asbetadine, was used. EGF or placebo was applied once a day, every day, for 28 consecutive days, at the time of wound dressing.	4 weeks	Treatment = 7/30 Control = 2/20 Mean hospital stay (days, SD): Treatment = 29.6 (20.95) Control = 28.9 (15.1)
Additional comments:					

No details on randomisation methods; no mention of allocation concealment; assessor blinded only; no report of adverse events exclusion criteria not reported.

Reference: Afshari, M, Larijani, B, Fadayee, M, Darvishzadeh, F, Ghahary, A, Pajouhi, M, Bastanhagh, MH, Baradar-Jalili, R, Vassigh, AR Efficacy of topical epidermal growth factor in healing diabetic foot ulcers. *Therapy* 2005; 2: 759-65.

Title: Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 3327 Study type: RCT Authors: Fernandez-Monntequin et al. (2009)	Total no. of patients = 149 rhEGF 75 ug = 53 rhEGF 25 ug = 48 Control = 48 <u>Treatment rhEGF 75 ug:</u> Male/female = 28/25 Median age (IQR) = 63 (55-69) Median duration of ulcer (wks) (IQR) = 4.3 (2.9-10.3) Median ulcer size (cm^2) (IQR) after initial debridement = 28.5 (10.4-42.8) <u>Treatment rhEGF 25 ug:</u> Male/female = 21/27 Median age (IQR) = 65.5 (56-72) Median duration of ulcer (wks) (IQR) = 4.3 (2.6-8.3) Median ulcer size (cm^2) (IQR) after initial debridement = 20.1 (11-34) <u>Control:</u> Male/female = 27/21 Median age (IQR) = 64 (51-70) Median duration of ulcer (wks) (IQR) = 4.9 (3.3-12.9) Median ulcer size (cm^2) (IQR) after initial debridement = 21.8 (8.8-34.6)	<u>Inclusion:</u> Patients (type 1 or 2 diabetes) >18 years old were included if they had a Wagner's grade 3 or 4 DFU, >1 cm^2 <u>Exclusion:</u> Revascularisation surgery possibility (for ischaemic ulcers), haemoglobin <100 g/l, uncompensated chronic diseases such as heart failure signs, diabetic coma or ketoacidosis and renal failure (creatinine >200mg/dl), malignancies, psychiatric or neurological diseases that could impair proper reasoning for consent, immune-suppressor drugs or corticosteroids use, pregnancy and nursing.	<u>Treatment (injection):</u> rhEGF 75 ug plus standard wound care rhEGF 25 ug plus standard wound care <u>Control:</u> Standard wound care Treatment injected intralesionally, 3 times per week on alternate days. rhEGF was presented as a lyophilised powder containing 75 or 25 u,g per vial (Heberprot-P*, Heber Biotec, Havana). Both doses and placebo vials (containing all components of the formulation except EGF) were indistinguishable. Standard good wound care = ulcers were sharply debrided, gangrenous and necrotic tissue removed (toe disarticulation or transmeta tarsal amputation if necessary) and saline-moistened gauze dressing used. The affected area was pressure off-loaded by bed rest during the hospital period and appropriate footwear afterwards. Metabolic control was strictly followed. Broad-spectrum antibiotics were used if	2 weeks	<u>More than 50% wound reduction (2 weeks):</u> rhEGF 75 ug = 44/53 rhEGF 25 ug = 34/48 Control = 19/48 <u>Adverse events:</u> *Pain at the administration site:* rhEGF 75 ug = 13/53 rhEGF 25 ug = 13/48 Control = 20/48 *Burning sensation:* rhEGF 75 ug = 12/53 rhEGF 25 ug = 10/48 Control = 14/48 *Shivering:* rhEGF 75 ug = 17/53 rhEGF 25 ug = 8/48 Control = 2/48 <u>Lost to follow-up:</u> rhEGF 75 ug = 2/53 rhEGF 25 ug = 3/48 Control = 2/48

	20 centres throughout all Cuban provinces		needed to clear infections before intra-lesional injections started.		
Additional comments: No details on randomisation methods; no mention of allocation concealment; code was opened after 2 weeks, if no response, patients on placebo or 25 ug EGF were offered to continue treatment unblinded with 25 or 75 ug.					

Reference: Fernandez-Montequin, JI, Valenzuela-Silva, CM, Diaz, OG, Savigne, W, Sancho-Soutelo, N, Rivero-Fernandez, F, Sanchez-Penton, P, Morejon-Vega, L, Artaza-Sanz, H, Garcia-Herrera, A, Gonzalez-Benavides, C, Hernandez-Canete, CM, Vazquez-Proenza, A, Berlanga-Acosta, J, Lopez-Saura, PA, Cuban Diabetic Foot Study Group Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. *International Wound Journal* 2009; 6: 432-43.

Title: A Phase III Study to Evaluate the Safety and Efficacy of Recombinant Human Epidermal Growth Factor (REGEN-D™ 150) in Healing Diabetic Foot Ulcers					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 11327 Study type: RCT Authors: Viswanathan et al. (2006)	Total no. of patients = 57 Treatment = 29 Control = 28 *Patients' baseline characteristics not reported.* Multicenter (3 centres) in India.	Inclusion: Target ulcers were no less than 2 cm^2 and no more than 50 cm^2 in area. Healthy men or women between the ages of 18 and 65 years at the time of consent were included. Women had to be of non-child bearing potential (eg, surgically sterilized) or, if of child bearing potential, must have had a negative pregnancy test, must have used adequate contraceptive precautions and must have agreed to continue such precautions up to Week 15. Included patients had controlled diabetes mellitus (type 1 and 2) and foot ulcers. Ulcers that remained open without healing for more than 2-3 weeks (irrespective of the ambulatory treatment administered) were included. Patients had to have ankle brachial index (ABI) readings of ≤ 0.75. Exclusion: Patients with ≥ Grade III Wagner classification diabetic foot ulcers; with life-threatening or serious cardiac failure, gastrointestinal, hepatic, renal, endocrine, hematological, or immunologic disorder; hypertension Grade III; known case of hypersensitivity to the incipient(s); uncontrolled diabetes mellitus (type 1 or 2), diabetic ketoacidosis or coma; past history of current acute or chronic autoimmune disease; chronic alcohol abuse; those who were receiving or had received within 1 month prior to the initial visit any treatment known to impair wound healing including but not limited to corticosteroids, immunosuppressive drugs, cytotoxic agents, radiation therapy, and chemotherapy; use of any marketed,	Treatment: Topical rhEGF gel Control: Placebo gel (water base) No mention of standard good wound care The visit at Day 0 constituted the study medication administration day. The study drug was provided in a gel base to allow for even application (topically) on the ulcer using a sterile cotton swab. This was done twice daily until the wound healed or until the end of Week 15, whichever was earlier Patients were also given oral and intravenous antibiotics	15 weeks	Complete wound healing (15 weeks): Treatment = 25/29 Control = 14/28

		investigational, or herbal medicine or non-registered drug for wounds or burns in the past 6 months; clinically relevant abnormal hematology or biochemistry values; evidence of systemic or local infection; treatment with a dressing containing any other growth factors or other biological dressings within 30 days prior to the screening visit; or participation in another clinical study within 30 days prior to the screening visit or during the study.	for prevention of infection. The antibiotics used were regular antibiotics prescribed for patients with diabetes and foot ulcers		
Additional comments: Randomisation method and allocation concealment were reported; double-blinded (patients and investigators); but no ITT and baseline characteristics not reported.					

Reference: Viswanathan, V, Pendsey, S, Sekar, N, Murthy, GSR A phase III study to evaluate the safety and efficacy of recombinant human epidermal growth factor (REGEN-D 150) in healing diabetic foot ulcers. *Wounds: A Compendium of Clinical Research and Practice* 2006; 18: 186-96.

Section 4: Transforming Growth Factor β2

Title: Effects of Transforming Growth Factor β2 on Wound Healing in Diabetic Foot Ulcers: A Randomized Controlled Safety and Dose-Ranging Trial					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 9180 Study type: RCT Authors: Robson et al. (2002)	Total no. of patients = 177 TGF-β2 0.05 ug/cm^2 = 43 TGF-β2 0.5 ug/cm^2 = 44 TGF-β2 5.0 ug/cm^2 = 44 Placebo = 22 Standard care alone = 24 *TGF-β2 0.05 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (11) Mean ulcer duration (wks) (SD) = 51 (64) Mean ulcer size (cm^2) (SD) = 2.1 (3.1) *TGF-β2 0.5 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (12) Mean ulcer duration (wks) (SD) = 59 (74) Mean ulcer size (cm^2) (SD) = 2.7 (3.6) *TGF-β2 5.0 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (8) Mean ulcer duration (wks) (SD) = 54 (72) Mean ulcer size (cm^2) (SD) = 2.7 (3.5) *Placebo:* Male/female (%) = 82/18 Mean age (SD) = 60 (10) Mean ulcer duration (wks) (SD) = 41 (47) Mean ulcer size (cm^2) (SD) = 2.7 (3.0) *Standard care alone:* Male/female (%) = 92/8 Mean age (SD) = 55 (9) Mean ulcer duration (wks) (SD) = 59 (103) Mean ulcer size (cm^2) (SD) = 2.1 (1.9) Between December 1995 and October 1998	Inclusion: Patients who were at least 18 years of age, had diabetes mellitus and a neuropathic ulcer present for at least 8 weeks on the plantar surface of the forefoot, toes, metatarsals, or dorsum of the fool. After debridement, the ulcer must have been between 1 cm^2 and 20 cm^2 in area and full thickness without exposed bone or tendon; have had adequate peripheral arterial circulation as determined by an ankle/brachial index between 0.7 and 1.3, or a transcutaneous oxygen pressure measurement on the foot of 30 mm Hg or more. Exclusion: Those who had radiographically documented osteomyelitis, clinical infection of the ulcer, use of systemic steroids within the previous 30 days, HgAc greater than 13%, serum creatinine greater than 2.5 mg/dL or serum albumin less than 2 mg/dL.	Treatments: TGF-β2 0.05 ug/cm^2 sponge TGF-β2 0.5 ug/cm^2 sponge TGF-β2 5.0 ug/cm^2 sponge Controls: Placebo collagen sponge Standard care alone All patients who received sponges also received standard care. Standard care = sharp debridement, coverage with non-adherent dressing, and weight off-loading from the affected fool Dressing changes and additional sponge placements were required twice weekly. If, however, clinical infection of the ulcer or osteomyelitis was observed, treatment was suspended and the infection was treated according to best judgment of the physician. If the infection resolved within the 20 week intervention period, treatment could be resumed.	21 weeks	Complete wound healing (week 21): TGF-β2 0.05 ug/cm^2 = 25/43 TGF-β2 0.5 ug/cm^2 = 25/44 TGF-β2 5.0 ug/cm^2 = 27/44 Placebo = 7/22 Standard care alone = 17/24 Median time to wound closure (weeks)[compared to placebo]: TGF-β2 0.05 ug/cm^2 = 16, p = 0.133 TGF-β2 0.5 ug/cm^2 = 12, p = 0.085 TGF-β2 5.0 ug/cm^2 = 13, p = 0.03 Placebo = not reported Standard care alone = 9, p = 0.009 **IQR not reported.* *Uncertainty regarding the report on adverse events (the figures did not match)* 38 patients lost to follow-up.

	15 centres in the United States				
Additional comments: Randomisation method and allocation concealment were reported; double-blinded (patients and investigators).					

Reference: Robson, MC, Steed, DL, McPherson, JM, Pratt, BM Effects of transforming growth factor ÇY2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. *Journal of Applied Research* 2002; 2: 133-46.

Hyperbaric Oxygen Therapy

Title: Hyperbaric oxygen therapy for chronic wounds (Cochrane review)					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: Study type: Systematic review Authors: Kranke et al. (2003)	The baseline characteristics of patients entering these trials varied. 2 trials measured and reported Wagner Grades of the ulcers at baseline, but included different subsets of patients: 1 trial included people with Wagner grade 2, 3, 4; 1 trial included only patients with grade 0, 1, 2. Of the other 2 trials, 1 included any diabetic patient with a chronic foot lesion; whilst 1included patients with lesions present for more than 6 weeks where the ulcers were between 1 and 10 cm in diameter. Both these trials are likely to have included patients with a broad range of Wagner grades and in such cases, particularly where trials are small, imbalance across treatment arms for wound size or severity is highly likely	Inclusion: RCTs that compared the effect on chronic wound healing of treatment with HBOT with no HBOT: Any person in any health care setting with a chronic wound associated with diabetes mellitus. Chronic wounds were defined as described in the retrieved papers (prolonged healing or healing by secondary intention), but must have had some attempt at treatment by other means prior to the application of HBOT. Compared wound care regimens which included HBOT with similar regimens that excluded HBOT. Exclusion criteria: 1 trial specifically excluded patients for whom vascular surgical procedures were planned. Review content assessed as up-to-date: 13 October 2003. Quality assessment by the five-point Oxford-Scale (Jadad 1996): Randomisation Double-blinding Description of withdrawals Each of which, if present, is given a score of 1. Further points are available for description of a reliable randomisation method and use of a placebo (modified for our analysis to include a sham HBOT session). The scores are totalled as an estimate of overall quality of reporting. Missing data	4 trials were included in the systematic review. Treatment: HBOT + standard care HBOT administered in a compression chamber between pressures of 1.5ATA and 3.0ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. Treatment periods ranged from 2 weeks to 6 weeks. Control: Standard care alone 2 trials employed a sham treatment in the control group, on the same schedule as the HBOT group. The other 2 trials did not employ a sham therapy. The comparator group was diverse, any standard treatment regimen designed to promote wound healing was accepted. The salient feature of the comparison group was that these measures had failed before enrolment in the studies. 1 trial did not specify any comparator, 2 trials described a comprehensive and specialised multidisciplinary wound management program to which HBOT was added for the active arm of the trial, and 1 specified a	Treatment period: Doctor (1992) = 4 wks Faglia (1996) = 6 wks Lin (2001) = 30 days Abidia (2003) = 6 wks The follow-up periods varied between trials: Doctor (1992) = *followed patients to discharge from hospital* Faglia (1996) = *followed patients to discharge from hospital* Lin (2001) = 30 days Abidia (2003) = 1 year Faglia (1996) and Abidia (2003) = both had 2 lost to follow-up.	Complete wound healing (end of treatment – 6 weeks): Treatment = 7/9; Control = 4/9 RR = 1.75 (95%CI: 0.78 to 3.93) Complete wound healing (at 6 months follow-up): Treatment = 6/9; Control = 4/9 RR = 1.50 (95%CI: 0.63 to 3.56) Complete wound healing (at 1 year follow-up): Treatment = 8/9; Control = 4/9 RR = 2.00 (95%CI: 0.93 to 4.30) Major amputation: Treatment = 8/60; Control = 19/58 RR = 0.41 (95%CI: 0.19 to 0.86) Minor amputation: Treatment = 6/24; Control = 2/24 RR = 2.60 (95%CI: 0.68 to 10.01) 2 trials (Doctor 1992; Abidia 2003) stated explicitly that there were no complications or adverse events as a result of HBOT. The other 2 trials simply did not report on adverse events or complications of therapy in either arm.

	at entry into the trial.	As ITT was not conducted in some of the trials, missing data was imputed using the worst-case scenario.	surgical and dressing regimen common to both arms.		

Additional comments:
Good quality systematic review.
The study samples were small and the quality of the studies varied. Allocation concealment was unclear in 3 studies.
Standard care was not clearly described in some studies. Also, it is not clear if the surgical decision to amputate was made while blinded to treatment allocation, and this is an important potential source of bias and thus a threat to validity of these results.
No report of adverse events.

Reference: Kranke Peter AU: Bennett Michael Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database of Systematic Reviews: Reviews* 2004; Issue 1.

Title: Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 5583 Study type: RCT Authors: Kessler et al. (2003)	Total no. of patients = 28 (1 withdrawn with no ITT) Treatment = 14; Control = 13 Treatment: Male/female = 10/4 Mean age (SD) = 60.2 (9.7) Mean diabetes duration (years) (SD) = 18.2 (13.2) Mean ulcer size (cm^2) (SD) = 2.31 (2.18) Control: Male/female = 9/4 Mean age (SD) = 67.6 (10.5) Mean diabetes duration (years) (SD) = 22.1 (13.1) Mean ulcer size (cm^2) (SD) = 2.82 (2.43) January 1999 to January 2000 Hospital in France.	Inclusion: Type 1 and 2 diabetic patients admitted to the ward for chronic foot ulcers (Wagner grade 1, 2 and 3). Ulcers depth <2mmfor at least 3 months despite the stabilization of glycemia, the absence of clinical local infection, and satisfactory off-loading measures. Exclusion: Gangrenous ulcers with severe sepsis; severe arteriopathy; emphysema, proliferating retinopathy, claustrophobia.	Treatment: HBOT + standard care Control: Standard care alone Treatment = two 90min daily session of 100% O_2 breathing in a multi-place hyperbaric chamber pressurized at 2.5 ATA; for 5 days a week for 2 consecutive weeks. Standard care = each patient was asked to keep weight off the affected foot. Each patient was provided with an orthopaedic device to remove mechanical stress and pressure at the site of the ulcer during walking; the optimization of metabolic control required subcutaneous insulin administration. Antibiotics were given to patients with chronic infection.	2 weeks treatment with 1 month follow-up (2 weeks in hospital; 2 weeks as outpatient)	Complete wound healing (4 weeks): Treatment = 2/14; Control = 0/13 Reduction of ulcer surface area (4 weeks)(% with SD): Treatment = 61.9% (23.3%) Control = 55.1% (21.5%), p > 0.05.

Additional comments:
No mention of allocation concealment; only investigator-blinded; no ITT.

Reference: Kessler, L, Bilbault, P, Ortega, F, Grasso, C, Passemard, R, Stephan, D, Pinget, M, Schneider, F Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; 26: 2378-82.

Title: Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 2982 Study type: RCT Authors: Duzgun et al. (2008)	Total no. of patients = 100 Treatment = 50 Control = 50 <u>Treatment:</u> Male/female = 37/13 Mean age (SD) = 58.1 (11.03) Mean diabetes duration (years) (SD) = 16.9 (6.24) <u>Control:</u> Male/female = 27/23 Mean age (SD) = 63.3 (9.15) Mean diabetes duration (years) (SD) = 15.88 (5.56) January 2002 to December 2003 A teaching and research hospital, Turkey.	<u>Inclusion:</u> Consecutive diabetes patients who were admitted to the emergency surgical department; at least 18 years of age; had a foot wound that had been present for at least 4 weeks despite appropriate local and systemic wound care. <u>Exclusion:</u> Those considered would have contraindications to HBOT such as untreated pneumothorax; COPD; history of otic surgery; URTI; febrile state; history of idiopathic convulsion; hypoglycaemia; current use of corticosteroid, amphetamine, catecholamine or thyroid hormone.	<u>Treatment:</u> HBOT + standard care <u>Control:</u> Standard care alone Treatment = administered at a maximum working pressure of 20 ATA, using a unichamber pressure room employing a volume of $10m^3$ at 2 to 3 ATA for 90mins. Treatment was administered as 2 session per day, alternating throughout the course of therapy, which typically extended for a period of 20 to 30 days. Standard care = daily wound care including dressing changes and local debridement at bedside or in the operating room, as well as amputation when indicated. Infection controls were carried out by clinical follow-up and by performing culture-antibiograms of surgically obtained specimens to determine appropriate antibiotic therapy.	20 to 30 days	<u>Complete wound healing (without any surgical interventions) (30 days):</u> Treatment = 33/50; control = 0/50 <u>Required surgical interventions to achieve wound coverage (surgical debridement, amputation, use of a flap or skin graft):</u> Treatment = 8/50; control = 50/50 <u>Amputation (all):</u> Treatment = 4/50; control = 41/50 <u>Amputation (distal):</u> Treatment = 4/50; control = 24/50 <u>Amputation (proximal):</u> Treatment = 0/50; control = 17/50
<u>Additional comments:</u> No mention of lost to follow-up or ITT.					

Reference: Duzgun, AP, Satir, HZ, Ozozan, O, Saylam, B, Kulah, B, Coskun, F Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *Journal of Foot & Ankle Surgery* 2008; 47: 515-19.

Title: Randomised controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcer					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 6307 Study type: RCT Authors: Leslie et al. (1988)	Total no. of patients = 28 Treatment = 12; control = 16 <u>Treatment:</u> Male/female = 6/6 Mean age (SD) = 52.8 (8.6) Mean ulcer duration (weeks) (SD) = 6.4 (6.2) Previous amputation = 7/12 <u>Control:</u> Male/female = 10/6 Mean age (SD) = 46.2 (8.5) Mean ulcer duration (weeks) (SD) = 6.2 (7.8) Previous amputation = 5/16 1 April 1983 to 31 July 1985 Rancho Los Amigos Medical Centre Ortho-Diabetes Service, US.	<u>Inclusion:</u> A diagnosis of diabetes; a well demarcated foot ulcer, circular or elliptical in shape; located at or below the level of the ankle, and with no visible bone exposure; the patient was considered to be a candidate for a 2-week trial of conservative therapy and was not deemed to require urgent surgical amputation, according to the attending physician; there was absence of gangrene, crepitation, severe ischemia, and persistent fever > 100^{o}F. <u>Exclusion:</u> None reported.	<u>Treatment:</u> THO + standard care <u>Control:</u> Standard care alone Treatment = two daily 90mins sessions with the topical hyperbaric leg chamber; provided 100% oxygen at pressures that cycled between 0 and 30 mmHg every 20 second. Standard care = treated for 2 weeks with intravenous antibiotics, wet to dry local dressings, and bed rest.	2 weeks	<u>Reduction in ulcer size (at 2 weeks) from baseline:</u> Treatment = 45.6% (SD: 23.4%) Control = 35.6% (SD: 23%) p > 0.05 <u>Reduction in ulcer depth (at 2 weeks) from baseline:</u> Treatment = 75.8% (SD: 23.4%) Control = 67.3% (SD: 23.5%) p > 0.05
<u>Additional comments:</u> No mention of allocation concealment; only investigator-blinded; no mention of lost to follow-up or ITT.					

Reference: Leslie, CA, Sapico, FL, Ginunas, VJ, Adkins, RH Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care* 1988; 11: 111-15.

Other Adjunctive Therapies

Evidence table

Title: A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 2933 Level of evidence: () Study type: RCT Authors: Driver et al. (2006)	<u>Total no. of patients:</u> Baseline = 129 57-excluded Intention to treat-72 PRP-40 Control-32 Because the results of the ITT analyses did not seem to reflect previous clinical outcomes, the study sponsor commissioned an independent audit to ensure study compliance with Good Clinical Practices (GCP) at the investigative sites. Excluded from both groups-32 PRP per protocol-19 Control per protocol- 21 <u>Baseline characteristics:</u> In the intent-to-treat (ITT) population, the mean and standard deviations (SD) for age, HgA_{1c}, wound area, and volume in the two treatments were not significantly different. No significant differences in patient demographics, wound distribution, or ulcer location were observed between the two treatment groups. <u>Setting:</u> 14 investigative sites-USA	<u>Inclusion:</u> Persons with type 1 or type 2 diabetes between the ages of 18 and 95 with an ulcer of at least 4-weeks* duration, hemoglobin AIC <12, index foot ulcer located on the plantar, medial, or lateral aspect of the foot (including all toe surfaces), and wound area (length x width) measurement between 0.5 cm^3 and 20 cm^2, inclusive, wounds located under a Charcot deformity had to be free of acute changes and must have undergone appropriate structural consolidation. The index ulcer had to be clinically noninfected and full-thickness without exposure of bone, muscle, ligaments, or tendons (University of Texas Treatment-Based Diabetic Foot Classification System: Grade 1 A), the limb had to have adequate perfusion. <u>Exclusion:</u> Patient currently enrolled in another investigational device or drug trial or previously enrolled (within last 30 days) in investigative research of a	Platelet rich plasma gel (PRP, n- 40) All patients completed a 7-day screening-period. This included initial excision/debridement, baseline wound measurements and evaluation, and application of the control saline gel to the wound.	Control- Normal saline gel (n-32) All patients completed a 7-day screening-period. This included initial excision/debridement, baseline wound measurements and evaluation, and application of the control saline gel to the wound.	Weekly up to week 12.	ITT group In the ITT group, 13 out of 40 patients (32.5%) in the PRP gel and nine out of 32 patients (28.1%) in the control group had completely healed wounds after 12 weeks (*P* = 0.79). Relative risk- 13/40 ÷ 9/32 = 1.16 (0.57-2.35) Efficacy outcomes: Healed In the PP dataset, 13 of 19 (68.4%) patients in PRP gel and 9 out of 21 (42.9%) patients in the control group healed (P- 0.125). Relative risk- 13/19 ÷ 9/21 = 1.59 Time to healing: The Kaplan-Meier median time to complete closure was 45 days for PRP gel compared to 85 days for control (log-rank test, *P* - 0.126). Follow-up Of the 40 patients in the PP dataset, 22 with healed wounds participated in the 12-week follow-up phase; of those, 1 in the PRP gel group had a wound that reopened.

	(wound care physicians' and podiatrists' offices, outpatient wound care centres, a university-based college of podiatric medicine clinic, Veteran's Administration wound care clinics, and an Army hospital limb preservation program).	device or pharmaceutical agent Ulcer decreased >50% in area during 7-day screening period; Ulcer is due to non-diabetic aetiology; Patient's blood vessels are non-compressible for ABI testing; Evidence of gangrene in ulcer or on any part of the foot; Patient has radiographic evidence consistent with diagnosis of acute Charcot foot; Patient is currently receiving or has received radiation or chemotherapy within 3 months of randomization; Topical, oral, or IV antibiotic/antimicrobial agents or medications have been used within 2 days (48 hours) of randomization; Patient has received growth factor therapy (e.g., autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix) within 7 days of randomization; Screening serum albumin level <2.5 g/dL; Screening haemoglobin <10.5 mg/dl Screening platelet count < 100 x 109/L; Patient is undergoing renal dialysis, has known immune insufficiency, known abnormal platelet activation disorders -i.e., gray platelet syndrome, liver disease, active cancer (except remote basal cell of the skin), eating/nutritional, hematologic, collagen vascular disease, rheumatic disease, or bleeding				None of the control-treated patients' wounds re-opened; this difference was not statistically significant. Adverse events 122 adverse events occurring after randomization, 60 (49%) were in the PRP gel group and 62 (51%) in the control group. Relative risk- 0.96 Of the 122 adverse events after randomization, 23 were classified as serious adverse events; 6 occurred in the PRP gel group and 17 in the control group. All serious adverse events were unlikely or unrelated to device usage as defined by the investigators

		disorders; History of peripheral vascular repair within the 30 days of randomization; Patient has known or suspected osteomyelitis; Surgical correction (other than debridement) required for ulcer to heal; Index ulcer has exposed tendons, ligaments, muscle, or bone; Patient is known to have a psychological, developmental, physical, emotional, or social disorder, or any other situation that may interfere with compliance with study requirements and/or healing of the ulcer; History of alcohol or drug abuse within the last year prior to randomization; Patient has inadequate venous access for blood draw ; Patient has a religious or cultural conflict with the use of platelet gel treatment; Patients whose wounds reduced in area by >50% during the screening period were not randomized to treatment and discontinued from any further study participation because they appeared to be able to heal without more advanced intervention.				
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Driver, VR, Hanft, J, Fylling, CP, Beriou, JM, Autologel Diabetic Foot Ulcer Study Group A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy/wound management* 2006; 52: 68-70, 72, 74.

Title: Electric Stimulation as an Adjunct to Heal Diabetic Foot Ulcers: A Randomized Clinical Trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 8394 Level of evidence: () Study type: RCT Authors: Peters et al. (2001)	<u>Total no. of patients:</u> Baseline = 40 *Electrical stimulation-20* *2 withdrew* *Control-20* *3 withdrew* <u>Baseline characteristics:</u> No significant differences were noted between the treatment and the placebo groups as far as age, gender, glycosylated hemoglobin, peak plantar pressure, duration of diabetes, initial wound area, and neuropathy were concerned. <u>Setting:</u> University medical centre.	<u>Inclusion:</u> All wounds were classified as grades 1A-2A using the University of Texas Diabetic Wound Classification System. All patients had a transcutaneous oxygen tension greater than 30mmHg <u>Exclusion:</u> Soft tissue or bone infection, malignancy, or any cardiac conductivity disorder.	Electrical stimulation (n-20) It was delivered via the Micro-Z$^{TM\,c}$, a small 5.5 x 6cm electric simulation device, that delivers current via a microcomputer to a Dacron-mesh silver nylon stocking. A dose of 50V with 80 twin peak monophase pulses per second was delivered for 10 minutes. This was followed by 10 minutes of 8 pulses per second of current. Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Placebo-used an active electric stimulation unit but did not deliver any current (n-20) Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Weekly until week 12	Healed 13 (65%) of the patients healed in the electric stimulation treatment group, 7 (35%) healed in the group that received a sham unit (p-0.058). Relative risk- 13/20 ÷ 7/20 = 1.86 (0.94- 3.7) Rate of Wound Healing and the Average time until wounds healed There was no significant difference in the rate of wound healing and the average time until wounds healed among treatment and placebo groups. The total change in ulcer cross-sectional area was 86.2%versus 71.4% in treatment and control groups, respectively, over the 12-week duration of the study. Among patients who healed, the average healing times for patients with an electric stimulation unit and a placebo unit were 6.8 ± 3.4 weeks and 6.9 ± 2.8 weeks, respectively.
<u>Additional comments:</u> Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Peters, EJ, Lavery, LA, Armstrong, DG, Fleischli, JG Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. *Archives of Physical Medicine & Rehabilitation* 2001; 82: 721-25.

Title: The management of neuropathic ulcers of the foot in diabetes by shock wave therapy.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 7455 Level of evidence: () Study type: RCT Authors: Moretti et al. (2009)	Total no. of patients: Baseline = 30 *ESWT-15* *Control-15* Baseline characteristics: There were no significant differences between the two groups in terms of demographics and clinical data. Setting: Diabetic ambulatory of endocrinology unit of university of Bari-Italy.	Inclusion: Neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months with an area wider than 1 cm^2, age 30-70 years, a diameter of the lesion between 0.5 and 5 cm and type 1 diabetes mellitus with insulin treatment for at least 5 years prior. Patients also should have had peripheral neuropathy, ankle-brachial index > 0.7 and palpation of the dorsalis pedis and posterior tibial arteries. Exclusion: Peripheral vascular disease, coronary bypass, pregnancy, coagulation diseases or history of neoplasia or other conditions, based on the principal investigator's clinical judgment.	External shock wave therapy (ESWT) plus standard therapy (n-15) The treatment lasted just 1 or 2 minutes. The protocol consisted of 3 sessions (every 72 hours), with 100 pulses per 1 cm^2 of wound delivered at each session at a flux density of 0.03mJ/mm^2 using a electromagnetic lithotripter (MINILITH SL1). Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Control-standard therapy consisting of therapeutic footwear, debridement and dressing and treatment of infection (n-15). Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	For 20 weeks	Healing The proportions of ulcers that healed in 20 weeks in the A and B groups were 53.33% and 33.33%, respectively. Relative risk- 8/15 ÷ 5/15 = 1.60 (0.68-3.77) Healing times For the ulcers that healed during the 20-week period, the healing times were 60.8 +/- 4.7 days (mean +/- DS) in group ESWT and 82.2 +/- 4.7 days (mean +/- DS) in control group patients ($p < 0.001$). Re-epithelisation A significant difference was observed in the index of the re-epithelization between the two groups, with values of 2.97 +/- 0.34 mm^2/die (mean +/- DS) in the ESWT group and 1.30 +/- 0.26 mm^2/die (mean +/- DS) in the control-group ($p < 0.001$). Adverse events All patients of both groups completed the study and attended all control visits. No significant differences emerged between the two groups with regard to treatment complications. One patient in each group developed local signs of infection
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Moretti, B, Notarnicola, A, Maggio, G, Moretti, L, Pascone, M, Tafuri, S, Patella, V The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC Musculoskeletal Disorders* 2009; 10: 54.

<table>
<tr><td colspan="7">Title: Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study.</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr><td>ID: 9032

Level of evidence: ()

Study type: RCT

Authors: Reyzelman et al. (2009)</td><td><u>Total no. of patients:</u>
Baseline = 93
7 excluded
Am therapy-47
1 patient withdrew
Control-39

<u>Baseline characteristics:</u>

No statistically significant differences in demographic, ulcer location and pre-treatment ulcer variables were observed between treatment groups.

<u>Setting:</u>
Multicentre-11 sites</td><td><u>Inclusion:</u>
Patients who were 18 years of age or older, with a diagnosis of type 1 ortype 2 diabetes, a University of Texas (UT) grade 1 or 2 diabetic foot ulcer ranging in size from 1 to 25 cm^2, absence of infection, adequate circulation.

<u>Exclusion:</u>
Patients who were in poor metabolic control (HgAlc greater than 12%; within the previous 90 days) were excluded, as were patients with serum creatinine levels of 3-0 mg/ dl or greater. Patients with sensitivity to gentamycin, cefoxilin, linocmycin, polymyxin B or vancomycin also were excluded because of the broth composition in which the AM is processed. Additional exclusion criteria included non re-vascuiarable surgical sites, ulcers probing to bone (UT grades 3A to D), and wounds treated with biomedical or topical growth factors within the</td><td>Study group received a single application of a human acel-lular dermal regenerative tissue matrix graft (n-46)

All patients underwent debridement and off loading.</td><td>Control group received standard-of-care wound management consisting of moist-wound therapy with alginates, foams, hydrocolloids or hydrogels at the discretion of the treating physician (n-39)

All patients underwent debridement and off loading.</td><td>Weekly until complete epithcli-alisation occurred or 12 weeks</td><td>Complete healing:
Of the patients completing the clinical trial, complete healing occurred in 32 (69.6%) of the 46 patients in the study group and 18(46.2%) of the 39 patients in the control group.

Relative risk- 32/46 ÷ 18/39 = 1.50 (1.02-2.22)

There was a statistically significant difference in proportion of healed ulcers between the treatment groups (P = 0.0289, OR – 2.7). Based on the odds ratio, the odds of healing in the study group were 2.7 times higher than in the control group.

Table1: Comparison of time to complete healing of ulcers that healed on or before 12 weeks between treatment groups

<table>
<tr><td></td><td colspan="2">Time to complete healing</td></tr>
<tr><td></td><td>Study group (n-32)</td><td>Control group (n-18)</td></tr>
<tr><td>Mean</td><td>5.7</td><td>6.8</td></tr>
<tr><td>Median</td><td>4.5</td><td>7.0</td></tr>
<tr><td>Standard deviation</td><td>3.5</td><td>3.3</td></tr>
<tr><td>Range</td><td>1.0-12.0</td><td>2.0-12.0</td></tr>
</table>
No statistically significant difference in mean time to wound healing was observed between treatment groups.

A statistically significant difference in non healing rate was calculated between treatment groups (P = 0.0075). At the 12-week endpoint, the non healing rate of 53.8% in the control group was</td></tr>
</table>

		previous 30 days.				significantly higher than the 30.4% non healing rate observed in the study group. After adjusting for ulcer size at presentation (following Cox proportional hazards model), there was a statistically significant difference in non healing rate between treatment groups (P — 0-0233). The corresponding adjusted hazard ratio of 2-0 (95% CI, 1-0-3-5) indicated that the probability of healing is approximately two times greater in the study group than in the control group. Adverse events: A total of 6 occurred in both groups (3-study group, 3-control)
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. All parameters were analysed as intention to treat. Confounding not mentioned. Power calculation mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Reyzelman, A, Crews, RT, Moore, JC, Moore, L, Mukker, JS, Offutt, S, Tallis, A, Turner, WB, Vayser, D, Winters, C, Armstrong, DG Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *International Wound Journal* 2009; 6: 196-208.

Title: Randomized Clinical Trial Comparing OASIS Wound Matrix to Regranex Gel for Diabetic Ulcers**.**

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 7857 Level of evidence: () Study type: RCT Authors: Niezgoda et al. (2005)	Total no. of patients: Baseline = 98 73 completed treatment assigned OASIS-50 37 completed treatment Regranex-48 36 completed treatment. Patients whose wounds were not healing by the 12th week were given the option to cross over to the other treatment arm; in other words, OASIS-	Inclusion: Patients were age 18 or older Type 1 or type 2 diabetes, 1 to 48 cm^2 in ulcer size, Extends through both the epidermis and dermis, Grade I, Stage A {University of Texas classification), month and nonhealing Viable wound bed with granulation tissue. Exclusion: Exposed bone, tendon, or fascia, clinically defined	OASIS wound matrix (n-50) with standard care *All patients underwent debridement, off loading and regularly cleansed.*	Regranex gel (Growth factor-PDGF, n-48) with standard care *All patients underwent debridement, off loading and regularly cleansed.*	Weekly for 12 weeks and then final 6 month visit.	Healing At the end of the 12-week treatment period, 49% (I8/37) of patients receiving OASIS Wound Matrix were considered healed versus 28% (10/36) of patients receiving daily treatment with Regranex Gel (P- 0.055) Relative risk- 18/37 ÷ 10/36 = 1.75 (0.94-3.26) Subgroup analysis Table 1: INCIDENCE OF HEALING AT 12 WEEKS Healed (%) / Not healed (%) Alt patients / OASIS / 18 (49) / 19

	treated patients could receive Regranex Gel and vice versa. Baseline characteristics: Patient demographics and baseline values were similar for both groups on all values measured. Setting: *9 outpatient institutions- USA and Canada*	and documented severe arterial disease, history of radiation therapy to ulcer site, Ulcer of nondiabetic pathophysiology, Receiving corticosteroids or immune suppressive, History of collagen vascular disease, Malnutrition (albumin <2.5 g/dl), Known allergy to porcine-derived products, Known hypersensitivity to any component of Regranex Gel (e.g. parabens), Religious or cultural objection to the use of porcine products, Uncontrolled diabetes (A1C>12%, Previous organ transplant, Ulcer clinically infected, Signs of cellulitis, osteomyelitis, necrotic or avascular ulcer bed, Undergoing haemodialysis, Insufficient blood supply to the ulcer ($TcPO_2$ <30 mm Hg or toe-brachial index <0.70), Active Charcot or sickle cell disease, Received treatment with any other investigational drug or device within the last 30 days, Unable to comply with the procedures described in the protocol, Enrolled in a clinical evaluation for another investigational wound care device or drug				<table><tr><td>*(p- 0* .055)</td><td></td><td></td><td>(51)</td></tr><tr><td></td><td>Regranex</td><td>10 (28)</td><td>26 (72)</td></tr><tr><td>Planter ulcers (P- 0.014)</td><td>OASIS</td><td>14 (52)</td><td>13 (48)</td></tr><tr><td></td><td>Regranex</td><td>3 (14)</td><td>18 (86)</td></tr><tr><td>Type 1 diabetes (P- 1.000)</td><td>OASIS</td><td>6 (33)</td><td>12 (67)</td></tr><tr><td></td><td>Regranex</td><td>2 (25)</td><td>6 (75)</td></tr><tr><td>Type *2* diabetes *(P- 0* .034)</td><td>OASIS</td><td>12 (63)</td><td>7 (37)</td></tr><tr><td></td><td>Regranex</td><td>8 (29)</td><td>20 (71)</td></tr></table> Of the patients with type 1 diabetes, 33% (6/18) of OASIS-treated patients healed versus 25% (2/8) of Regranex Gel-treated patients (P = 1). Of the patients with type 2 diabetes, 63% (12/19) of patients treated with OASIS healed versus 29% (8/28) of patients treated with Regranex Gel (P = .034). Of the patients with plantar ulcers, 52% (14/27) of OASIS-treated patients healed versus 14% (3/21) of Regranex Gel-treated patients (P- 0.014) Time to healing No significant difference was found in the mean time to healing between treatment groups (67 days for the OASIS group and 73 days for the Regranex Gel group, P- 0.245)

A Cox proportional hazards regression model showed an improved trend of healing for the OASIS group. This model indicates that at 7 weeks, patients in the OASIS group were approximately twice as likely to heal as those in the Regranex group.

Covariate analysis
Covariate analyses of interest revealed significant differences in healing proportions between treatment group after adjusting for type 1 and type 2 diabetes (P-0.030) and ulcer location (P-0.026).

Recurrence of ulcers
Table 2: RESULTS AT 6-MONTH FOLLOW-UP (n = 37)

	OASIS	Regranex
Total patients seen at follow up	19	18
Patients healed at 12 weeks	8	6
Patients remaining healed at 6 months	6	4
% Recurrence-	25%	33%

Approximately half (37) of the 73 patients were seen at a 6-month or later follow-up visit. Ulcers from 14 of these 37 patients had healed within the 12-week study period; 10 remained healed at the follow-up visit.
Relative risk- 0.79 (0.29-2.12)

Adverse events
A total of 27 study-relevant events were reported for all patients, 17 for the OASIS group and 10 for the Regranex Gel group.
Relative risk- 17/50 ÷ 10/48 = 1.63

Between the 2 treatment groups, no significant

						differences were found in the proportion of patients experiencing complications/adverse events.
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Niezgoda, JA, Van Gils, CC, Frykberg, RG, Hodde, JP Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Advances in Skin & Wound Care* 2005; 18: t-66.

Title: Effect of Dalteparin on Healing of Chronic Foot Ulcers in Diabetic Patients With Peripheral Arterial Occlusive Disease. **A prospective, randomized, double-blind, placebo-controlled study.**

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 5365 Level of evidence: () Study type: RCT Authors: Kalani et al. (2003)	Total no. of patients: Baseline = 87 2 dropped out *Delteparin-43* *Placebo-42* *All patients underwent debridement, off loading. Dressings and antibiotic treatment as and when required.* Baseline characteristics: Baseline characteristics of the treatment groups were compa-rable. Setting: Department of Endocrinology and Diabe-tology, Karolinska Hospital ; the Department of Medicine, University Hospital, Lund ; the Diabetes Center, Sahlgrenska University Hospital, Goteborg; and the	Inclusion: Patient with diabetes, chronic foot ulcers and PAOD (peripheral arterial occlusive disease), foot ulcer duration of more than 2 months, ulcer stage 1 and 11 according to the Wagner classification (7), toe/arm blood pressure index ≤0.6, and treatment with a daily dose of *75* mg aspirin for at least four weeks before randomization. Exclusion: Vascular reconstruction or angioplasty performed less than 3 months before randomization, renal insufficiency defined as a serum creatinine level ≥200 p.mol/1, and treatment with anticoagulants.	Dalteparin-0.2 ml (fragmin, 25,000 units/ml) for maximum of 6 months (n-43)	Placebo-0.2ml of physiologic saline for maximum of 6 months (n-42)	For 6 months	Table 1: Ulcer outcome in 85 diabetic patients with PAOD and chronic foot ulcers, randomly assigned lo treatment with dalteparin or placebo The ulcer outcome—including healing with intact

	Dalteparin	Placebo
n	43	42
Healed (with intact skin)	14 (33)	9(21)
Improved (ulcer area decreased ≥50%)	15(35)	11 (26)
Unchanged (decreased or increased ulcer area <50%)	7(16)	9(21)
Impaired (increased ulcer area ≥50%)	5(12)	5(12)
Amputation (above/below ankle)	2(5)	8(19)

	Department of Medicine, University Hospital, Umea, Sweden.					skin; improved, unchanged, or impaired ulcer area; and amputation— was significantly (P = 0.042) improved by Dalteparin treatment compared with placebo. More patients healed with intact skin in the Dalteparin group (n -14) compared with the placebo group (n = 9; NS). Relative risk- 14/43 ÷ 9/42 = 1.57 Reduced ulcer ≥50% in area A total of 15 patients reduced the ulcer area ≥50% in the dalteparin group compared with 11 in the placebo group (NS). Relative risk- 15/43 ÷ 11/42 = 1.35 The percentage decrease in ulcer area was the same in the dalteparin group (73%) as in the placebo group (75%). Healing times There was no significant difference in mean healing time between the dalteparin group (17 ± 8; 8-26 weeks |min-max) and the placebo group (16 ± 7; 8-26 weeks [min-max). Biochemical variables There were no significant differences in haemoglobin concentration, leukocyte count, and serum concentrations of hsCRP, S-AA, albumin, and creatinine between the treatment groups at cither baseline or study termination, respectively, nor were there any significant changes within the treatment groups between study termination and baseline Amputations There were four times more amputations in the placebo group (n= 8) than in the Dalteparin group (n = 2; NS)

						Relative risk- 2/43 ÷ 8/42 = 0.24
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Kalani, M, Apelqvist, J, Blomback, M, Brismar, K, Eliasson, B, Eriksson, JW, Fagrell, B, Hamsten, A, Torffvit, O, Jorneskog, G Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2003; 26: 2575-80.