Appendix G: Full evidence tables – review questions 11 – 16

G.11 Review question 11 full evidence tables

G.11.1 New included studies

Table 1: Clay 2004

<table>
<tr><td>Reference</td><td>Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89</td></tr>
<tr><td>Study type & aim</td><td>Prospective, open label, randomised controlled trial (RCT) to evaluate the efficacy, tolerability and cost differences associated with using metronidazole plus ceftriaxone once daily with ticarcillin/ clavulanate every 6 hours in hospitalised older males with diabetic lower-extremity infections.</td></tr>
<tr><td>Number of participants & patient characteristics</td><td>Total number of participants: Out of the 70 participants randomly assigned using a computer-generated schedule to one of two treatment groups. 36 participants received metronidazole plus ceftriaxone (MTZ/CTX)and 34 participants in received ticarcillin/clavulanate (T/C).
Inclusion criteria: Eligible participants were adult hospitalised males aged 18 years or over with a diagnosis of type1 or type 2 diabetes and a clinical diagnosis of a diabetic lower-extremity infection (based on physical signs of infection).
Exclusion criteria: Exclusion criteria included: bone involvement, hypersensitivity to any of the study medications, receipt of an intravenous (IV) antibiotic for more than 24 hours before study enrolment, presence of neutropenia or thrombocytopenia.
Patient characteristics: All participant baseline demographics in both the MTZ/CTX and T/C groups were generally well matched. The following table shows baseline characteristics of the treatment group

<table>
<tr><td></td><td>Metronidazole plus ceftriaxone (n=36)</td><td>Ticarcillin/ clavulanate (n=34</td><td>P</td></tr>
</table>
</td></tr>
</table>

Reference	**Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89**

Age,mean (SD), years	65 (11.5)	62 (9.9)	0,292
Male no (%)	36 (100)	34 (100)	1.000
Duration of diabetes mean, (SD), years	10.5 (7.9)	13.9 (9.8)	0.173
Creatine clearance, mean, (SD), mL/min	68.4 (28.5)	65.7 (23.4)	0.682
Comorbidities no. (%)			
Hypertension	18 (50)	21 (62)	0.347
Coronary artery disease	14 (39)	11 (32)	0.624
Peripheral artery disease	12 (33)	8 (24)	0.433
Hyperlipidemia	8 (22)	9 (26)	0.783
Diabetic neuropathy	7 (19)	6 (18)	1.000
Chronic renal insufficiency	4 (11)	3 (9)	1.000
Hypothyroidism	4 (11)	0 (0)	0.115
Diabetic retinopathy	3 (8)	2 (6)	1.000
Diabetic nephropathy	1 (3)	1 (3)	1.000
No. of comorbidities, mean (SD)	2.0 (1.6)	1.8 (1.4)	0.571
Site/ distribution of infection, no (%)			
Foot	12 (33)	13 (38)	0.804
Toe	4 (11)	9 (26)	0.129
Unilateral	8 (22)	5 (15)	0.543
Bilateral	3 (8)	0 (0)	0.240
Cellulitis (no distinct lesion)	14 (39)	9 (26)	0.315

Monitoring information & definitions	**Monitoring:** Treatment outcomes were determined at or before 96 hours after enrolment and at end of study therapy or discontinuation of intravenous antibiotic therapy **Primary outcome measures:** Treatment success was defined as at least 1 of the following measures of clinical stability or improvement at 96 hours: body temperature less than 100.6 F, normalisation of finger stick blood sugar concentration; improvement in wound staging; white blood cell count of less than 10,000/mm3 **Secondary outcome measures:** Patients completing less than 96 hours patients completing less therapy due to transfer to oral therapy were considered successful if it was noted on patient's chart. **Other outcomes:** Treatment failure at 96 hours was defined as worsening of initial signs and symptoms after receiving 1 dose of study medication; the change or addition of at least 1 more antibiotic to assigned regimen; occurrence of an adverse event that

<table>
<tr><td>Reference</td><td>Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89</td></tr>
<tr><td></td><td>required discontinuation of study drug.</td></tr>
<tr><td>Intervention</td><td>Participants in group 1 received 1g IV metronidazole plus 1g IV ceftriaxone once a day.</td></tr>
<tr><td>Comparator:</td><td>Participants in group 2 received 3.1g of IV ticarcillin/clavulanate every 6 hours.</td></tr>
<tr><td>Length of follow-up</td><td>After 96 hours of treatment with IV therapy</td></tr>
<tr><td>Outcome measures & effect sizes</td><td>At 96 hours treatment success was achieved in 31 patients (86%) in the MTZ/CTX group and 28 patients (82%) in the T/C group. The distribution of criteria for treatment success or failure did not differ between the treatment groups. The following table shows results for clinical endpoi. Values are mean (SD).
<table>
<tr><th></th><th>Metronidazole plus ceftriaxone</th><th>Ticarcillin/clavulanate</th><th>P (between groups)</th></tr>
<tr><td>Temperature (F)
Baseline
Final</td><td>
98.9 (1.6)
98.2 (0.8)</td><td>
98.2 (1.2)
98.2 (0.9)</td><td>
0.063
0.883</td></tr>
<tr><td>White blood cell count cells /mm3
Baseline
Final</td><td>
10.3 (4.2)
8.6 (3.0)</td><td>
9.1 (3.2)
8.3 (2.9)</td><td>
0.187
0.643</td></tr>
<tr><td>Finger stick blood sugar mg/dL
Baseline
Final</td><td>
160.6 (83.8)
167.6 (72.6)</td><td>
159.8 (59.5)
162.1 (54.9)</td><td>
0.971
0.723</td></tr>
<tr><td>Creatine clearance Ml/min
Baseline
Final</td><td>
68.4 (28.5)
64.5 (25.9)</td><td>
65.7 (23.4)
70.6 (21.4)</td><td>
0.682
0.414</td></tr>
</table>
</td></tr>
</table>

Reference	**Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89**
Study location	Study carried out at a veterans affairs medical centre in the USA
Authors conclusion	MTZ/CTX was as well tolerated and effective as T/C in the treatment of diabetic lower-extremity infections in older adult males
Source of funding	Roche pharmaceuticals
Comments	

Table 2: Schaper 2012

Reference	**Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.**
Study type & aim	Data from a subset of patients with diabetic foot infections (DFI) included in the RELIEF trial. The RELIEF trial was a multicentre, prospective double-blind, RCT to compare the efficacy and safety of 2 antibiotic regimens
Number of participants & patient characteristics	**Total number of participants:** A total of 233 patients with a DFI were randomised. 206 of these (110 receiving moxifloxacin; 96 receiving Piperacillin/Tazobactam) were eligible for the per protocol (PP) analysis, which was the population at test of cure. **Inclusion criteria:** Eligible participants were men and women aged 18 years or over with a diagnosis of a complicated bacterial skin & skin structure infection of less than 21 days duration, requiring hospitalisation and parenteral antibiotic treatment of 48 hours or more. The data subset required all patients had to have a DFI of moderate to severe infection intensity (based on PEDIS grade 2-4). **Exclusion criteria:** Patients who had received therapy with a topical or systemic antimicrobial for more than 24 hours in the previous 7 days were excluded **Patient characteristics:** There were no significant differences between the patient demographics in either treatment group. The table below shows the baseline demographics for participants in each treatment group

	Moxifloxacin (n=110)	**Piperacillin/Tazobactam (n=96)**
Sex, male, n(%)	61 (55)	69 (71)
Mean age, years (SD)	58.9 (10.2)	59.5 (10.1)
Mean BMI kg/m2 (SD)	28.9 (5.7)	28.6 (4.7)
Temperature >38 C, n (%)	98 (89.1)	79 (82.3)

Reference	Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.		
	Mean WBC, 10/L (SD)	10.0 (4.0)	9.3 (3.8)
	Mean HbA1C % (SD)	9.7 (2.5)	9.0 (2.1)
	Mean CRP mg/L (SD)	8.3 (8.8)	8.7 (8.4)
	Mean PCT ng/ml (SD)	0.2 (0.3)	0.2 (0.6)
	Peripheral neuropathy, n (%) Vibration perception test- negative Light pressure test (plantar surface of heel) negative	 44 (41.5) 52 (49.5)	 48 (51.6) 44 (47.8)
	Peripheral arterial disease, n (%)	72 (65.5)	68 (70.8)
	ABI <0.9	46 (41.8)	42 (43.8)
	Absent or barely palpable dorsalis pedis & posterior tibialis pulses	66 (60.0)	63 (65.6)
	Infection type, n (%) Community acquired Hospital acquired	 96 (87.3) 14 (12.7)	 87 (90.6) 9 (9.4)
	Mean time since occurrence of symptoms, days (SD)	9.5 (5.4)	9.2 (5.6)
	Pre-therapy antibiotic use, n (%)	9 (8.2)	8 (8.3)
	Mean lesion area cm2 (SD)	46.9 (66.4)	33.1 (48.5)
	Deepest tissue layer infected, n (%) Dermis Subcutaneous fat Fascia, muscle	 10 (9.1) 12 (10.9) 88 (80.0)	 6 (6.3) 4 (4.2) 86 (89.6)
	Type of surgery during first 48 hours, n (%) No surgery Abscess drainage Local debridement Extensive debridement Primary closure Amputation	 32 (29.1) 28 (25.5) 21 (19.1) 32 (29.1) 12 (10.9) 51 (46.4)	 24 (25.0) 31 (32.3) 17 (17.7) 38 (39.6) 8 (8.3) 33 (34.4)

Reference	**Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.**

Graft surgery	0 (-)	1 (1.0)
Removal of infected bone area	21 (19.1)	19 (19.8)
Revascularisation	1 (0.9)	1 (1.0)
Necrectomy	0 (-)	1 (1.0)
University of Texas wound classification, n (%)		
Grade 0 (infected)	0 (-)	1 (1.1)
Grade 0 (Ischaemic)	1 (0.9)	0(-)
Grade I (infected)	4 (3.7)	1 (1.1)
Grade I (Ischaemic)	11 (10.3)	8 (8.5)
Grade II (infected)	16 (15.0)	14 (14.9)
Grade II (Ischaemic)	45 (42.1)	43 (45.7)
Grade III (infected)	9 (8.4)	2 (2.1)
Grade III (Ischaemic)	21 (19.6)	25 (26.6)
Wilson score, mean (SD)	100.6 (21.9)	103.5 (22.5)
Risk class I, n (%)	5 (4.5)	4 (4.2)
Risk class II, n (%)	20 (18.2)	8 (8.3)
Risk class III, n (%)	34 (30.9)	33 (34.4)
Risk class IV, n (%)	51 (46.4)	51 (53.1)
Baseline PEDIS infection score all patients n (%)		
2 (Mild)	14 (13.1)	8 (8.5)
3 (Moderate)	87 (81.3)	81 (86.2)
4 (Severe)	6 (5.6)	5 (5.3)
Baseline PEDIS infection score before amputation n (%)		
2 (Mild)	1 (2.0)	0 (0.0)
3 (Moderate)	47 (92.2)	31 (93.9)
4 (Severe)	3 (5.9)	2 (6.1)

Monitoring information & definitions	**Monitoring:** Treatment outcomes were assessed during treatment (days 3-5), at the end of treatment (EOT; 7-21 days after inclusion) and at test of cure (TOC 14-21 days after EOT)

<table>
<tr><td>Reference</td><td>Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.</td></tr>
<tr><td></td><td>Primary outcome measures: The primary efficacy variable was response at TOC. Photographs of lesions were taken at each assessment.
Secondary outcome measures: Safety assessment was based on physical examination, vital signs, ECG, adverse events, and standard laboratory tests throughout study.
Other outcomes: Clinical cures or successes were patients considered to be cured at TOC.</td></tr>
<tr><td>Intervention</td><td>400mg sequential IV / oral moxifloxacin (MOX) plus matching placebo 3 times a day</td></tr>
<tr><td>Comparator:</td><td>875/125mg IV Piperacillin/Tazobactam 3 times a day followed by oral amoxicillin/ clavulanate (PIP/TAZ/AMC) 2 times a day</td></tr>
<tr><td>Length of follow-up</td><td>Treated for a minimum of 7 days and maximum of 21 days</td></tr>
<tr><td>Outcome measures & effect sizes</td><td>Clinical cure rates were similar between treatment groups at TOC
Cure rate for the PP population: MOX =76.4%; PIP/TAZ/AMC= 78.1%; 95%CI-14.5%, 9.0%
Cure rate for ITT/ safety population MOX= 69.9%; PIP/TAZ/AMC= 69.1% 95%CI-12.4%, 12.1%

The table below shows the clinical success separated by disease severity scoring system for the PP population. P<0.05 in all cases (based on Cochran-Mantel-Hantzel test
<table>
<tr><td></td><td>Moxifloxacin n/N (%)</td><td>Piperacillin/tazobactum/ amoxicillin clavulanate n/N (%)</td></tr>
<tr><td>Texas wound classification</td><td></td><td></td></tr>
<tr><td>Grade 0</td><td>0/1 (0)</td><td>1/1 (100)</td></tr>
<tr><td>Infected</td><td></td><td>1/1 (100)</td></tr>
<tr><td>Ischaemic</td><td>0/1 (0)</td><td></td></tr>
<tr><td>Grade I</td><td>11/15 (73.3)</td><td>7/9 (77.8)</td></tr>
<tr><td>Infected</td><td>3/4 (75.0)</td><td>1/1 (100)</td></tr>
<tr><td>Ischaemic</td><td>8/11 (72.7)</td><td>6/8 (75.0)</td></tr>
<tr><td>Grade II</td><td>45/61 (73.8)</td><td>47/57 (82.5)</td></tr>
<tr><td>Infected</td><td>12/16 (75.0)</td><td>14/14 (100)</td></tr>
<tr><td>Ischaemic</td><td>33/45 (73.3)</td><td>33/43 (76.7)</td></tr>
<tr><td>Grade III</td><td>25/30 (83.3)</td><td>18/27 (66.7)</td></tr>
<tr><td>Infected</td><td>9/9 (100)</td><td>2/2 (100)</td></tr>
<tr><td>Ischaemic</td><td>16/21 (76.2)</td><td>16/25 (64.0)</td></tr>
<tr><td>PEDIS infection score classification (prior to surgery)</td><td></td><td></td></tr>
<tr><td>2 (Mild)</td><td>12/14 (85.7)</td><td>6/8 (75.0)</td></tr>
</table></td></tr>
</table>

Reference	**Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.**

3 (Moderate) 4 (Severe)	66/87 (75.9) 3/6 (50.0)	64/81 (79.0) 3/5 (60.0)
Wilson classification Risk class I Risk class II Risk class III Risk class IV	 4/5 (80.0) 15/20 (75.0) 30/34 (88.2) 35/51 (68.6)	 4/4 (100) 7/8 (87.5) 28/33 (84.8) 36/51 (70.6)

Overall the proportion of patients with bacteriological clinical success was similar for each treatment group (MXF 71.7% vs. PIP/TAZ-AMC 71.8%; 95%CI -16.9%, 10.7%)

The following table shows bacteriological success both overall and by key organism for each treatment group.

	Moxifloxacin n/N (%)	Piperacillin/tazobactum/ amoxicillin clavulanate n/N (%)
Microbiologically valid population	66/92 (71.7)	61/85 (71.8)
ITT population with organisms	69/102 (67.6)	62/96 (64.6)
Staphylococcus aureous Methicillin- susceptible Methicillin- resistant	 43/53 (81.1) 8/11 (72.7)	 39/57 (68.4) 10/12 (83.3)
Streptococcus pyogenes	3/3 (100)	2/2 (100)
Enterococcus faecalis	19/30 (63.3)	20/29 (69.0)
Escherichia coli ESBL- producing Non-ESBL- producing	 1/1 (100) 6/8 (75.0)	 1/1 (100) 8/11 (72.7)
Bacteroides fragiles	3/3 (100)	¾ (75.0)

The total number of patients experiencing an adverse event (AE) was comparable between the Moxifloacin (38:30.9%) and Piperacillin/Tazobactam (35: 31.8%) groups. The table below shows the overview of treatment-emergent adverse events and the most frequent adverse events (>3)for the ITT/safety population

Reference	**Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.**

Event	Moxifloxacin n (%)	Piperacillin/tazobactum/ amoxicillin clavulanate n (%)	P value
Adverse Event (AE) Diarrohea Gangrene Nausea Blood creatine increased Creatine renal clearance decreased	38 (30.9) 1 (0.8) 2 (1.6) 2 (1.6) 3 (2.4) 3 (2.4)	35 (31.8) 4 (3.6) 3 (2.7) 3 (2.7) 1 (0.9) 1 (0.9)	0.89
Electrocardiogram QT prolonged	3 (2.4)	1 (0.9)	
Pyrexia	1 (0.8)	3 (2.7)	
Abscess limb	0 (-)	3 (2.7)	
Insomnia	3 (2.4)	2 (1.8)	
Hypertension	5 (4.1)	1 (0.9)	
Drug related AE Premature discontinuation due to AE	12 (9.8) 5 (4.1)	11 (10.0) 2 (1.8)	1.00 0.45
Serious AE Drug related SAE Premature discontinuation due to SAE	13 (10.6) 2 (1.6) 2 (1.6)	10 (9.1) 0 (0.0) 0 (0.0)	0.83
Deaths	3 (2.4)	1 (0.9)	0.62

Study location	Multinational (Netherlands, UK, France, Germany, Belgium, USA
Authors conclusion	Moxifloxacin showed favourable safety and efficacy profiles in management of a DFI
Source of funding	Not reported
Comments	

Table 3: Saltoglu 2010

<table>
<tr><td>Reference</td><td>Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.</td></tr>
<tr><td>Study type & aim</td><td>A prospective open-label RCT to compare efficacy and safety of Piperacillin/Tazobactam and imipenem/Cilastatin for treatment of severe diabetic foot infections</td></tr>
<tr><td>Number of participants & patient characteristics</td><td>Total number of participants: Out of 68 eligible participants, 64 took part. 2 of these patients discontinued treatment so 62 overall remaining participants completed the study (30 received Piperacillin/Tazobactam; 32 received imipenem/Cilastatin
Inclusion criteria: Hospitalised adults aged 18 years or over with a clinical diagnosis of moderate to severe diabetic lower extremity infection (based on Wagner grades 2-4)
Exclusion criteria: Treatment with any potentially effective antibiotic in the previous 48hours; hypersensitivity to any study medications; epilepsy; psychiatric illness; pregnancy or lactation
Patient characteristics: Baseline characteristics were comparable in terms of age, sex, duration of diabetes, size of ulcer, and other clinical findings. The table below shows the demographic and clinical characteristics of patients.
<table>
<tr><th></th><th>Piperacillin/Tazobactam (n=30)</th><th>Imipenem/Cilastatin (n=32)</th><th>P value</th></tr>
<tr><td>Age, median (range years</td><td>58.3 (47-72)</td><td>58.5 (37-80)</td><td>0.942</td></tr>
<tr><td>Sex, n (%)
Female
Male</td><td>
11 (36.7)
19 (63.3)</td><td>
12 (37.5)
20 (62.5)</td><td>0.945</td></tr>
<tr><td>Co-morbidity, n (%)</td><td>20 (66.7)</td><td>22 (68.8)</td><td>0.810</td></tr>
<tr><td>Duration of diabetes, median, (range) years</td><td>13.5 (3-30)</td><td>10.5 (0-30)</td><td>0.063</td></tr>
<tr><td>Prior antibiotic usage, median (range), days</td><td>21 (14-42)</td><td>24 (14-45)</td><td>0.431</td></tr>
<tr><td>Prior hospitalisation, n (%)</td><td>15 (50)</td><td>10 (31.3)</td><td>0.213</td></tr>
<tr><td>Anti diabetic usage before hospitalisation, n, (%)
Oral anti-diabetics
Insulin</td><td>
14 (46.7)
16 (53.3)</td><td>
18 (56.3)
12 (37.5)</td><td>0.300</td></tr>
<tr><td>Wagner class, n (%)</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Reference	**Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.**

Class 2 **Class 3** **Class 4**	5 (16.7) 15 (50) 10 (33.3)	4 (12.5) 19 (59.4) 9 (28.1)	0.751
Width of ulcer, median (range), mm	32.5 (20-50)	30 (5-50)	0.847
Depth of ulcer, median (range), mm	25 (15-35)	20 (2-35)	0.103
Duration of infection, median (range), days	30 (7-50)	40.5 (3-120)	0.693
Ulcer duration before therapy, median, (range), days	40.5 (3-120)	30 (7-150)	0.926
Type of infection, n (%) **Osteomyelitis** **Deep soft tissue infection/infected ulcer**	 22 (73.3) 8 (26.7)	 26 (81.2) 6 (18.8)	 0.05
Presence of ischaemia	5 (16.7)	7 (21.8)	
Duration of therapy, median (range) days	21 (14-42)	24 (14-45)	0.431
Microbiologically documented infection, n (%)	24 (80)	25 (78.1)	1.000
Vacuum Assisted Closure treatment, n (%)	3 (10)	4 (12.5)	1.000

Monitoring information & definitions	**Monitoring:** Clinical cure was defined as complete resolution of presenting signs and symptoms. Clinical improvement and failure were defined as partial improvement (or regression) respective of presenting signs and symptoms. On days 1, 7, 14 and 28 of treatment patients were followed with haematological, biochemical, erythrocyte sedimentation rate and C-reactive protein values. Microbiological responses were assessed by obtaining cultures at days 4-7 and at end of therapy. **Primary outcome measures:** The primary end-point was the clinical response to the antibiotic s being tested. A cure was recorded as the complete regression of signs and symptoms such as purulent discharge, erythema, or induration that were present before treatment commenced.

<table>
<tr><td>Reference</td><td>Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.</td></tr>
<tr><td></td><td>Secondary outcome measures: Secondary end-points included relapse rate at the end of 2 months
Other outcomes:</td></tr>
<tr><td>Intervention</td><td>4.5g IV Piperacillin/Tazobactam 3 times a day</td></tr>
<tr><td>Comparator:</td><td>500mg IV imipenem/ Cilastatin 4 times a day</td></tr>
<tr><td>Length of follow-up</td><td>Treatment was planned for 14 days. All patients were followed for 2 months after discharge</td></tr>
<tr><td>Outcome measures & effect sizes</td><td>A successful clinical response was seen in 14 (46.7%) patients receiving Piperacillin/Tazobactam and in 9 (28.1%) patients receiving imipenem/ Cilastatin (RR:1.6; 95%CI 0.84-3.25, p= 0.130)
The table below shows the micro-organisms isolatedin each study group (n, %)
<table>
<tr><th></th><th>Piperacillin/Tazobactam (n=0)</th><th>Imipenem/cilastain (n=32)</th><th>P value</th></tr>
<tr><td>Total Gram positive
Total Gram negative</td><td>20 (66.6)
23 (76.6)</td><td>18 (56.2)
28 (87.5)</td><td>0.400
0.264</td></tr>
<tr><td>Susceptible Gram positive</td><td>18/20 (90)</td><td>17/18 (94.4)</td><td>0.607</td></tr>
<tr><td>Susceptible Gram negative</td><td>23/23 (100)</td><td>28/28 (100)</td><td>1.000</td></tr>
<tr><td>Streptococcus spp</td><td>4 (13.3)</td><td>4 (12.5)</td><td></td></tr>
<tr><td>Streptococcus areus</td><td>1 (3.3)</td><td>4 (12.5)</td><td>0.305</td></tr>
<tr><td>Coagulase negative staphylococcus</td><td>11 (36.7)</td><td>4 (12.5)</td><td>0.053</td></tr>
<tr><td>Enterococcus spp
Enterococcus faecalis
Enterococcus avium
Enterococcus faecium</td><td>
3 (10)
1 (3.3)
11 (36.7)</td><td>
3 (9.4)
2 (6.3)
1 (3.1)</td><td>
0.736</td></tr>
<tr><td>Eschericia coli</td><td>3 (10)</td><td>4 (12.5)</td><td>1.000</td></tr>
<tr><td>Pseudomonas aeruginosa</td><td>7 (23.3)</td><td>6 (18.8)</td><td>0.759</td></tr>
<tr><td>Acinetobactar baumanni</td><td>0 (0)</td><td>3 (9.4)</td><td>0.238</td></tr>
<tr><td>Marganella morganii</td><td>4 (13.3)</td><td>3 (9.4)</td><td>0.238</td></tr>
<tr><td>Proteus spp</td><td>1 (3.3)</td><td>4 (12.5)</td><td>1.000</td></tr>
<tr><td>Klebsiella spp</td><td>2 (6.7)</td><td>2 (6.2)</td><td>0.998</td></tr>
<tr><td>Enterobacter cloaca</td><td>2 (6.7)</td><td>2 (6.2)</td><td>1.000</td></tr>
</table></td></tr>
</table>

Reference	**Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.**

Citrobacter freundii	2 (6.7)	0 (0)	0.230
Gram negative nonfermentive bacilli	0 (0)	1 (3.1)	1.000
Other	2 (6.7)	3 (9.4)	0.789
No micro organism isolated	6 (20)	7 (21.9)	

Side effects were reported in 9 participants (30%) of the group receiving Piperacillin/Tazobactam and 3 participants (9.4%) of the group receiving imipenem/Cilastatin. The table below shows the clinical response, side effects and surgical interventions in each study group

	Piperacillin/Tazobactam (n=30)	**Imipenem/cilastain (n=32)**	**P value**
Clinical response	14 (46.7)	9 (28.1)	0.130
Relapse	0/14	2/9 (2.2)	0.058
Microbiological response			
Complete response	23/24 (95.8)	24/25 (96)	1.000
Partial response	1/24 (4.2)	1/25 (4)	
Surgical intervention			
None	3 (10)	4 (12.5)	0.739
Debridement	5 (16.7)	4 (12.5)	
Ray resection	4 (13.3)	2 (6.3)	
Amputation	18 (60)	22 (68.8)	
Side Effects			
Total	9 (30)	3 (9.4)	0.055
Hepatoxicity	5 (16.7)	1 (3.1)	
Nephrotoxicity	6 (20)	1 (3.1)	
Hematological side effects	2 (6.7)	-	
Other (nausea)	-	1 (3.1)	

Study location	Turkey
Authors conclusion	Piperacillin/Tazobactam was superior to imipenem/Cilastatin in terms of clinical response rate to treatmentof moderate to

Reference	**Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.**
	severe diabetic foot infections. The difference was not statistically significant
Source of funding	Not reported
Comments	

Table 4: Siami 2001

<table>
<tr><td>Reference</td><td>Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.</td></tr>
<tr><td>Study type & aim</td><td>A randomised, investigator blind, multicentre, parallel group trial to evaluate the efficacy and safety of clinafloxacin vs. a regimen of Piperacillin/Tazobactam and optional vancomycin in hospitalised patients with complicated skin and skin structure infections (SSTIs).</td></tr>
<tr><td>Number of participants & patient characteristics</td><td>Total number of participants: Out of a total of 409 patients randomised to treatment with either clinafloxacin (n=213) or Piperacillin/Tazobactam (n=196, participants with a diabetic foot infection included 42 patients in the clinafloxacin treatment group and 34 in the Piperacillin/Tazobactam treatment group.
Inclusion criteria: Eligible participants were adult patients with severe or limb-threatening SSTIs serious enough to require hosp italisation. Patients with an aetiology and diagnosis of spontaneous infection or a diabetic foot infection were included
Exclusion criteria: Exclusion criteria included pregnancy or breast-feeding, significant hepatobiliary or renal dysfunction, immunodeficiency conditions, risk of convulsive disorders, hypersensitivity to study medications, septic shock, infected burns or decubitus ulcers, osteomyelitis and major amputation. Patients were not allowed to have been treated with more than a single dose of antibacterial therapy for the current SSTI or had the infected site treated with a topical antibiotic within 24 hours prior to baseline collection of culture. Patients were not allowed to have had any other investigational drug in the 7 days prior to entry in the study or received treatment with any other investigational drug in the 4 weeks prior to randomisation.
Also excluded were patients taking corticosteroids, requiring concomitant topical antimicrobial therapy for an SSTI and patients known to have SSTI pathogens resistant to study medication.
Patient characteristics: The table below shows the baseline patient characteristics.
<table>
<tr><th rowspan="2">Characteristic</th><th colspan="2">No (%) of patients in treatment group</th></tr>
<tr><th>Clindamycin (n=213)</th><th>Piperacillin/Tazobactam (n=196)</th></tr>
<tr><td>Gender
Male</td><td>
152 (71.4)</td><td>
142 (72.4)</td></tr>
</table>
</td></tr>
</table>

Reference	**Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.**
	Female: 61 (28.6) / 54 (27.6) Race White or Caucasian: 137 (64.3) / 135 (68.9) Black: 44 (20.7) / 34 (17.3) Asian: 4 (1.9) / 1 (0.5) Other: 28 (13.1) / 26 (13.3) Median age (range): 52 (18-86) / 54 (19-92) Baseline diagnosis Spontaneous infection: 84 (40.4) / 84 (42.9) Wound infection: 83 (40.0) / 73 (37.2) Diabetic foot infection: 42 (19.7) / 34 (17.3) Other: 2 (0.9 / 5 (2.6)
Monitoring information & definitions	**Monitoring:** Dosoing of the IV and oral courses was not to exceed more than 14 days combined. Pathogens were assessed at test of cure (TOC; days 6 to 14 post therapy) and at long term follow up (days 21 to 35 post therapy). **Primary outcome measures:** The primary efficacy parameter was the clinical cure rate and by-pathogen microbiological eradication rates (determined at TOC) **Secondary outcome measures:** Secondary efficacy parameter was the clinical cure rate and by-pathogen microbiological eradication rates (determined at long term follow up). Development of resistance, amputation rate and survival rate **Other outcomes:** Cure was defined as remission of signs and symptoms of baseline infection; failure was defined as absence of remission.
Intervention	Clindamycin 200mg IV every 12 hours plus placebo infusions every 12 hours switched to 200mg oral clinafloxacin every q12 hours after 3 days
Comparator:	3.375g IV Piperacillin/Tazobactam every 6 hours plus vancomycin (only if MRSA suspected) switched to 500mg oral amoxicillin/clavulanate every 8 hours
Length of follow-up	TOC 6 to14 days post therapy Long term follow up 21 to 35 days post therapy
Outcome measures & effect sizes	Median duration of treatment was 13 days in both groups. Clinical cure rates were similar between those treated with clinafloxacin (68.8%) and those treated with Piperacillin/Tazobactam (65.2%). Microbiological eradication rates were equivalent between treatment groups (61.5% in the clinafloxacin treated group;57.2% in the Piperacillin/Tazobactam treated greoup). The table below shows clinical cure and microbiological eradication rates at TOC. **Infection** | **No/total (%)** | **95%CI** | **P**

Reference	**Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.**

	Clinafloxacin	**Piperacillin/Tazobactam**		
Clinical cure				
All patients	99/144 68.8)	88/135 (65.2)	-7.5%, 14.6%	0.423
Spontaneous	44/58 (75.9)	44/61 (72.1)		
Wound	40/57 (70.2)	32/49 (65.3)		
Diabetic foot	15/29 (51.7)	12/25(48.0)		
Microbiological eradication				
All patients	152/247 (61.5)	139/243 (57.2)	-4.4%, 13.0%	0.500
Spontaneous	48/69 (69.6)	56/77 (72.7)		
Wound	72/105 (68.6)	68/119 (57.1)		
Diabetic foot	32/73 (43.8)	15/47 (31.9)		

The majority of adverse events were mild to moderate. 82 (39%) patients in the clinafloxacin treated group with drug-related adverse events compared to 57 (30%) treated with Piperacillin/Tazobactam (p=0.050)

The table below shows the most frequent adverse events during treatment

Adverse event	**Clinafloxacin (n=210) n (%)**	**Piperacillin/Tazobactam (n=190) n (%)**
Photosensitivity reaction	22 (10.5)	0 (0.0)[a]
Headache	17 (8.1)	7 (3.7)
Constipation	16 (7.6)	11 (5.8)
Nausea	16 (7.6)	23 (12.1)
Vomitting	12 (5.7)	5 (2.6)
Insomnia	11 (5.2)	9 (4.7)
Diarrhea	8 (3.8)	22 (11.6)[a]
Rash	7 (3.3)	3 (1.6)
[a] statistically different p=0.05)		

Study location	
Authors conclusion	Clinafloxacin monotherapy was as equivalent in effectiveness to therapy with Piperacillin/Tazobactam plus optional vancomycin in treating hospitalised patients with severe SSTIs
Source of funding	Not reported

Reference	**Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.**
Comments	

Table 5: Vick-fragoso 2009

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**
Study type & aim	A multicentre, randomised open-label, parallel group trial to examine the clinical and microbiological efficacy of moxifloxacin compared to amoxicillin/clavulanate
Number of participants & patient characteristics	**Total number of participants:** Out of a total of 804 participants enrolled, 406 received moxifloxacin treatment and 397 received amoxicillin/clavulanate. Out of these, 315 participants in the moxifloacin group comprised the efficacy-valid per protocol (PP) population and 167 were microbiologically valid. 317 participants in the amoxicillin/clavulanate group comprised the PP population for efficacy, with 172 participants in this group were microbiologically valid. **Inclusion criteria** Patients aged 18 years or over with a CSSSI at 1 site only were eligible for enrolment. If they required systemic antimicrobial therapy. CSSSIs were prospectively defined as diabetic foot infections, necrotising fasciitis, post surgical wound infection , complicated cellulitis, complicated erysipelas, major abscess of the skin, infection of traumatic lesion and infected ulcer. **Exclusion criteria:** Patients with a diagnosis of mild to moderate SSSIs, secondary infected burns, atopic dermatitis or eczema were excluded. Also excluded were pregnant or nursing women with severe life threatening diseases, people with a life expectancy of less than 2 months, end stage liver cirrhosis, severe renal impairment requiring dialysis and septic shock. Other exclusions were patients with neutropenia or at AIDS stage 1 or 2. Patients with known congenital or sporadic syndromes of QTc prolongation or taking concomitant medication. Patients with hypersensitivity to fluoroquinolones and beta-lactams **Patient characteristics:** Overall, the baseline demographic characteristics for the PP population were comparable between treatment groups, although there were significantly more men in the amoxicillin/clavulanate group (p=0.05). The table below shows baseline and demographic characterisics

Characteristic	**ITT population**			**PP population**		
	Moxifloxacin (n=406)	**Amoxicillin/ clavulanate (n=397)**	**P value**	**Moxifloxacin (n=315)**	**Amoxicillin/ clavulanate (n=317)**	**P value**
Mean (SD) age (years)	52.1 (18.0)	51.0 (18.2)	0.39	51.8 (18.0)	51.1 (18.3)	0.72
Male, n (%)	237 (58.4)	250 (63.0)	0.17	173 (54.9)	198 (62.5)	0.05

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**						
	Indication, n (%)						
	Abscess	135 (33.3)	126 (31.7)		98 (31.1)	93 (29.3)	13 (4.1)
	Necrotising fasciitis	36 (8.9)	18 (4.5)		22 (7.0)	13 (4.1)	
	Surgical wound infection	13 (3.2)	18 (4.5)		9 (2.9)	63 (19.9)	
	Diabetic foot infection	63 (15.5)	71 (17.9)		49 (15.6)	63 (19.9)	
	Complicated erysipelas	114 (28.1)	111 (28.0)		101 (32.1)	95 (30.0)	
	Infected traumatic lesion	26 (6.4)	26 (6.5)		21 (6.7)	19 (6.0)	
	Infected ischaemic ulcer	7 (1.7)	8 (2.0)		6 (1.9)	4 (1.3)	
	Complicated cellulitis	12 (3.0)	19 (4.8)		9 (2.9)	17 (5.4)	
	Comorbid condition, n (%)						
	Peripheral vascular	138 (34.0)	122 (30.7)	0.91	131 (41.6)	103 (32.5)	0.02
	Diabetes mellitus	159 (39.2)	143 (36.0)	0.33	124 (39.4)	115 (36.3)	0.46

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**
	Cardiac: 52 (12.8) / 45 (11.3) / 0.38 / 49 (15.6) / 33 (10.4) / 0,06 Respiratory: 50 (12.3) / 37 (9.3) / 0.59 / 41 (13.0) / 31 (9.8) / 0.21 Renal: 34 (8.4) / 29 (7.3) / 0.18 / 34 (10.8) / 28 (8.8) / 0.43 Cancer: 19 (4.7) / 20 (5.0) / 0.60 / 19 (6.0) / 19 (6.0) / 1.00 Immunologic: 4 (1.0) / 2 (0.5) / 0.87 / 15 (4.8) / 12 (3.8) / 0.56 IV drug user: 2 (0.5) / 0 (-) / 0.69 / 2 (0.6) / 0 (-) / 0.25
Monitoring information & definitions	**Monitoring:** Patients had to receive the study drug for at least 3 days (if clinical failure) or at least 5 days (to be classed a success). 3 study populations were evaluated: the intention to treat (ITT) population included all patients receiving at least 1 drug. The per protocol (PP) population comprised patients in ITT population with fully documented CSSSI diagnostic criteria, at least 80% compliance to treatment, no protocol violations and no essential missing data. The microbiologically evaluable(MBE) population were all patients in the PP population with causative organisms identified at baseline and a microbiological evaluation at TOC. **Primary outcome measures:** The primary endpoint was clinical response at test of cure (TOC) for the PP population **Secondary outcome measures:** Secondary endpoints were clinical response at TOC for the ITT population,and clinical response at TOC per indication. A secondary bacteriological eradication success rate was also defined at TOC for the PP/ITT population. **Other outcomes:**
Intervention	400mg IV moxifloxacin once daily for 3 days followed by 400mg oral moxifloxacin for 7-21 days
Comparator:	1000mg/200mg IV amoxicillin/clavulanate 3 times a day for at least 3 days followed by 500mg/125mg amoxicillin/clavulanate oral 3 times a day for 7-21 days.
Length of follow-up	14-28 days
Outcome measures & effect sizes	There was no difference in the overall duration of treatment or duration of IV therapy between treatment groups. The mean no of days on study medication was 13.5 ± 4.8 days for moxifloxacin; 14.1 ± 4.1 for ampoxicillin/clavulanate. Mean length of time on IV therapy was 6.2 ± 4.1 days moxifloxacin; 6.6 ± 3.9 days for amoxicillin/clavulanate. Duration of treatment was dependent on diagnosis; for diabetic foot infection 14.1 ± 5.5 days for moxifloxacin; 15.2 ± 5.4 days amoxicillin/clavulaanate). Clinical success rate at TOC for the PP population were not significantly different between treatment groups.80.6% (254/315)

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**

for moxifloxacin compared to 84.5% (268/317) for amoxicillin/clavulanate 95%CI -9.41, 2.18. For the ITT population results were also supported 72.7% (295/406) for moxifloxacin; 74.8% (297/397) for amoxicillin/clavulanate 95%CI-7.56, 4.31.

The table below shows clinical success rates at TOC by indication in the PP and ITT populations

Patient population	**Clinical success rate n/N (%)**		**95% CI for difference in success rate**
	Moxifloxacin	**Amoxicillin/clavulanate**	
PP population			
Abscess	92/98 (93.9)	82/93 (88.2)	-2.4, 13.8
Necrotising fasciitis	11/22 (50.0)	7/13 (53.8)	-39.2, 31.6
Surgical wound infection	8/9 (88.9)	12/13 (92.3)	-29.9, 23.1
Diabetic foot infection	25/49 (51.0)	42/63 (66.7)	-34.0, 2.7
Infection of ischaemic ulcer	2/6 (33.3)	4/4 (100)	-100.0, -25.3
Complicated erysipelas	91/101 (90.1)	90/95 (94.7)	-12.0, 2.8
Infection of traumatic lesion	17/21 (81.0)	16/19 (84.2)	-27.3, 20.8
Complicated cellulitis	8/9 (88.9)	15/17 (88.2)	-26.2, 27.6
ITT population			
Abscess	106/135 (78.5)	92/126 (73.0)	-4.9, 15.9
Necrotising fasciitis	16/36 (44.4)	8/18 (44.4)	-28.8, 28.8
Surgical wound infection	11/13 (84.6)	14/18 (77.8)	-21.6, 35.3
Diabetic foot infection	30/63 (47.6)	43/71 (60.6)	-29.8, 4.0
Infection of ischaemic ulcer	2/7 (28.6)	4/8 (50.0)	-73.2, 30.3
Complicated erysipelas	102/114 (89.5)	100/111 (90.1)	-8.6, 7.3

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**

Infection of traumatic lesion	17/26 (65.4)	20/26 (76.9)	-36.4, 13.4
Complicated cellulitis	11/12 (91.7)	16/19 (84.2)	-16.0, 30.9

There was no significant difference in bacteriological success rate at TOC for the PP/MBE population. Moxifloxacin (127/167, 76%); amoxicillin/clavulannate (140/172, 81.4%) (95%CI-12.96, 4.41, p=0.59)

Both treatments were generally well-tolerated and there were no significant differences of overall incidence of adverse events between groups. The table below shows adverse events for the ITT population

Adverse event	**Moxifloxacin (n=406)**	**Amoxicillin/clavulanate (n=397)**	**P value**
Overall incidence n(%)	211 (52.0)	190 (47.9)	0.27
Any cardiac disorder	12 (3.0)	12 (3.0)	1.00
Drug related adverse event n (%)	72 (17.7)	64 (16.1)	0.57
Diarrhea	7 (1.7)	10 (2.5)	0.47
Headache	6 (1.5)	5 (1.3)	1.0
Nausea	9 (2.2)	3 (0.5)	0.14
Vomiting	4 (1.0)	6 (1.5)	0.54
GGT increased	7 (1.7)	5 (1.3)	0.77
AST increased	6 (1.5)	4 (1.0)	0.75
Serious adverse events n (%)	57 (14.0)	45 (11.3)	0.28
Any cardiac disorder	5 (1.2)	5 (1.3)	1.00
Drug related serious adverse event n (%)	6 (1.5)	3 (0.8)	0.06
Any cardiac disorder	0	0	1.00
Discontinuation to adverse event n (%)	25 (6.1)	15 (3.8)	0.15
Deaths during study n (%)	8 (2.0)	3 (0.8)	0.22
Deaths after last visit n (%)	5 (1.2)	5 (1.3)	1.00

Reference	**Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.**
Study location	74 centres worldwide
Authors conclusion	Treatment with sequential IV/oral moxifloxacin monotherapy once daily is clinically comparable to IV/oral amoxicillin/clavulanate 3 times daily in the management of CSSSIs.
Source of funding	Bray
Comments	

Table 6: Lipsky 2012

Reference	**Lipsky,B.A. Kuss,M. Edmonds,M. Reyzelman,A. Sigal,F. (2012) Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial.Journal of the American Podiatric Medical Association 102 (4) 323-32.**
Study type & aim	A multi-centre, open label, randomised controlled pilot study to determine the safety and benefit of adding daily application of a gentamicin collagen sponge to standard care would improve the resolution of infection in patients with diabetic foot infections of moderate severity.
Number of participants & patient characteristics	**Total number of participants:** 56 patients were eligible for participation. 38 patients were randomised to the treatment group and 18 to the control group. Of these, 23 patients in the treatment group and 10 patients in the control group completed the study. **Inclusion criteria:** Patients aged between 18 and 80 years with a single site, diabetic foot infection were eligible for inclusion. A moderately infected ulcer was defined by the Infectious Diseases Society of America guideline criteria. **Exclusion criteria:** Patients were excluded if the ulcer could not be completely covered with a 10 x q10cm gentamicin collagen sponge. Also excluded were patients who had received antimicrobial therapy in the previous 2 weeks. Patients with ischaemia of the lower limb were also excluded **Patient characteristics:** Baseline characteristics were not significantly different between treatment arms although in the ITT group baseline scores of wound severity were significantly higher in the treatment group compared to control (median, 17 vs. 12, p=.011) The table below shows baseline demographic characteristics

Parameter	Treatment group (n=36)	Control group (n=18)
Age (years)		
Mean (SD)	57.9 (11.47)	54.7 (12.80)
Median (range)	58.0 (24-80)	54.5 (29-81)

<table>
<tr><td>Reference</td><td colspan="3">Lipsky,B.A. Kuss,M. Edmonds,M. Reyzelman,A. Sigal,F. (2012) Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial.Journal of the American Podiatric Medical Association 102 (4) 323-32.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Sex no (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>23 (60.5)</td><td>15 (83.5)</td></tr>
<tr><td>Female</td><td>15 (39.5)</td><td>3 (196.7)</td></tr>
<tr><td>Race no (%)</td><td></td><td></td></tr>
<tr><td>American Indian or Alaskan Native</td><td>1 (2.6)</td><td>0</td></tr>
<tr><td>Black</td><td>4 (10.5)</td><td>13 (16.7)</td></tr>
<tr><td>Native Hawaiian or other Pacific Islander</td><td>1 (2.6)</td><td>0</td></tr>
<tr><td>White</td><td>32 (84.2)</td><td>15 (83.3)</td></tr>
<tr><td>Ethnicity no (%)</td><td></td><td></td></tr>
<tr><td>Hispanic or Latino</td><td>12 (31.6)</td><td>5 (27.8)</td></tr>
<tr><td>Not Hispanic or Latino</td><td>26 (68.4)</td><td>13 (72.2)</td></tr>
<tr><td>BMI</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>32.38 (6.5000)</td><td>32.67 (5.795)</td></tr>
<tr><td>Median (range)</td><td>32.30 (21.1-44.8)</td><td>31.70 (23.7-45.1)</td></tr>
</table>
</td></tr>
<tr><td>Monitoring information & definitions</td><td colspan="3">Monitoring: Patients were assessed at day 7 of treatment, day 10, 14 and day 21. Patients received treatment for up to 28 days. Test of cure was assessed 14 days after all antibiotic treatment was stopped. End of treatment was assessed at 28-40 days post therapy.
Primary outcome measures: The primary efficacy end point was the percentage of patients with a clinical outcome of cure on day 7.
Secondary outcome measures: Secondary efficacy end points were percentage of patients with a clinical outcome of cure on all other days than day 7. Percentage of patients with a positive clinical response, percentage of patients with pathogen eradication at each time point, time to clinical cure, time to clinical response and time to eradication of pathogens.
Other outcomes: Safety evaluations included summaries of the incidence and severity of adverse events</td></tr>
<tr><td>Intervention</td><td colspan="3">Daily topical application of the gentamicin collagen sponge (10 x 10cm sponge with 200mg gentamicin sulphate in combination with standard antibiotic therapy (daily oral or IV dose of 750ml Levoflaxacin).</td></tr>
<tr><td>Comparator:</td><td colspan="3">Placebo collagen sponge plus daily oral or IV dose of 750ml Levoflaxacin.</td></tr>
<tr><td>Length of follow-up</td><td colspan="3">14 days.</td></tr>
<tr><td>Outcome measures & effect sizes</td><td colspan="3">At TOC patients in the treatment group had a significantly higher rate of clinical cure than in the control group (22/22 vs. 7/10, p=0.024). The treatment group also had a non-significantly higher clinical cure rate at the end of treatment visit than the control (24/26 vs. 7/10 , p=0.119)</td></tr>
</table>

Reference	**Lipsky,B.A. Kuss,M. Edmonds,M. Reyzelman,A. Sigal,F. (2012) Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial.Journal of the American Podiatric Medical Association 102 (4) 323-32.**
	The proportion of patients with baseline pathogen eradication on day 3 was significantly higher in the treatment group compared to the control (20/26 vs. 1/8, p<0.001). This continued to show a significant increase at each point of assessment (p≤0.038). Out of the 56 patients enrolled, 16 patients experienced at least 1 adverse event during the study. Adverse events were similar for the treatment group (11/38) compared to control group (5/18). There was 1 discontinuation due to an adverse event and no deaths occurred during the study.
Study location	USA
Authors conclusion	Topical application of the gentamicin collagen sponge seems safe and may improve clinical and microbiological outcomes of patients with diabetic foot infections of moderate severity.
Source of funding	Not reported.
Comments	

Table 7: File 1983

Reference	**File, Jr and Tan,J.S. (1983) Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections) American Journal of Medicine 75 (2 A) 100-105.**
Study type & aim	Single-blind randomised comparative design to compare the clinical efficacy and safety of cefoxitin vs. cefoxitin and amdinocillin in the treatment of soft tissue infections.
Number of participants & patient characteristics	**Total number of participants:** Out of the 45 participants randomly entered into the study using a computer generated randomised table, 41 patients were evaluable. 21 were treated wiith cefoxitin alone and 20 were treated with the combination of cefoxitin plus amdinocillin. **Inclusion criteria:** Eligible participants were hospitalised adult patients with clinical evidence of bacterial soft tissue infection. Most patients had diabetes mellitus and for the majority of patients infection was localised to the lower extremities. **Exclusion criteria:** Patients were excluded if they were allergic to penicillins or cephalosporins, or if they required other antibiotics during the stud period. **Patient characteristics: is.** Patient in each group were similar in terms of sex age and diagnosis. The table below shows baseline patient demographics.

<table>
<tr><td>Reference</td><td>File, Jr and Tan,J.S. (1983) Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections) American Journal of Medicine 75 (2 A) 100-105.</td></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Cefoxitin</th><th>Cefoxitin & Amdinocillin</th></tr>
<tr><td>Total number of patients</td><td>21</td><td>20</td></tr>
<tr><td>Percent female</td><td>33</td><td>25</td></tr>
<tr><td>Mean age</td><td>57</td><td>55</td></tr>
<tr><td>Infection site</td><td></td><td></td></tr>
<tr><td>Leg</td><td>2</td><td>4</td></tr>
<tr><td>Foot</td><td>16</td><td>15</td></tr>
<tr><td>Hand</td><td>2</td><td>_</td></tr>
<tr><td>Face</td><td>1</td><td>_</td></tr>
<tr><td>Abdominal wall</td><td>_</td><td>1</td></tr>
<tr><td>Number with diabetes</td><td>12</td><td>13</td></tr>
<tr><td>Number with osteomyelitis</td><td>3</td><td>4</td></tr>
<tr><td>Number requiring incision and drainage</td><td>6</td><td>7</td></tr>
<tr><td>Number requiring amputation</td><td>4</td><td>2</td></tr>
<tr><td>Mean dose (g/day)</td><td></td><td></td></tr>
<tr><td>Cefoxitin</td><td>6.4</td><td>7.2</td></tr>
<tr><td>Amdinocillin</td><td>_</td><td>3.3</td></tr>
<tr><td>Mean duration of therapy (days)</td><td>14.1</td><td>13.4</td></tr>
</table>
</td></tr>
<tr><td>Monitoring information & definitions</td><td>Monitoring: Clinical evaluation and bacterial cultures were obtained prior to start of therapy, on day 3 of therapy, periodically during therapy and at end of treatment
Primary outcome measures: Satisfactory symptomatic response was defined as cure (disappearance of all presenting signs and symptoms
Secondary outcome measures: Satisfactory bacteriological response was eradication of a pathogen at end of therapy
Other outcomes: Unsatisfactory clinical response was defined as no appreciable change or worsening of symptoms at end of therapy. Bacterial persistence was defined as continued presence of pathogen at end of therapy.</td></tr>
<tr><td>Intervention</td><td>Participants in the combined group received 1-2g g IV cefoxitin every 4 to 6 hours plus 10mg/kg IV amdinocillin every 6 hours.</td></tr>
<tr><td>Comparator:</td><td>Participants in the comparator group received 1-2g g IV cefoxitin every 4 to 6 hours.</td></tr>
<tr><td>Length of follow-up</td><td>Length of follow up varied.</td></tr>
<tr><td>Outcome measures &</td><td>A satisfactory symptomatic response occurred in 71 % of patients treated with cefoxitin and 90% of patients treated with the</td></tr>
</table>

Reference	**File, Jr and Tan,J.S. (1983) Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections) American Journal of Medicine 75 (2 A) 100-105.**
effect sizes	combination therapy. Bacteriologic results were similar for patients treated with cefoxitin or combination therapy (65% and 83% of all isolates eradicated).
Study location	Study carried out in a city hospital in Ohio, USA
Authors conclusion	The combination of amdinocillin and cefoxitin was effective in mixed soft tissue infections including diabetic foot infections.
Source of funding	Not reported
Comments	

Table 8: Bradsher 1984

Reference	**Bradsher, T and Snow, J.M. (1984) Ceftriaxone treatment of skin and soft tissue infections in a once daily regimen, American Journal of Medicine 77 (4) 63-67.**
Study type & aim	A randomised trial to compare the efficacy and safety of ceftriaxone daily and cefazolin daily in hospitalised adults with skin and soft tissue infections.
Number of participants & patient characteristics	**Total number of participants:** A total of 84 patients were enrolled in the study. 42 received ceftriaxone and 42 received cefazolin **Inclusion criteria:** Eligible participants were hospitalised adults with a suspected serious bacterial infection of the skin and soft tissue. **Exclusion criteria:** Patients who had received antibiotics in the previous 72 hours or patients with renal failure, pregnancy, lactation, neutropenia or significant penicillin hytpersensitivity. **Patient characteristics:** The two treatment groups were comparable with respect to race and sex and there were no major differences in terms of underlying illnesses. The table below shows the baseline demographics for participants in each treatment group

	Ceftriaxone (n=42)	**Cefazolin (n=42)**
Sex Male Female	 27 15	 18 24
Mean age, years	57	54
Race		

	Black White	25 17	24 18
	Number with underlying illness	30	29
	Mean dose (mg/kg) negative	15.4	48.5

Monitoring information & definitions

Monitoring: Treatment outcomes were assessed during treatment. Patients were monitored daily for signs.

Primary outcome measures: Patients were considered cured if there was resolution of signs and symptoms of infection.

Secondary outcome measures: Patients were monitored daily for signs of toxicity.

Other outcomes:

Intervention

1g every 6 hours or 1g every 8 hours (depending on treatment site) l IV or IM cefazolin

Comparator:

1g ceftriaxone (IV or IM) once a day

Length of follow-up

Follow up 7 days

Outcome measures & effect sizes

Clinical cure without surgery was noted in 21/42 (50% of patients treated with ceftriaxone and 25/42 (60%) patients treated with cefazolin

The table below shows clinical responses to cephalosporin therapy

	Ceftriaxone n (%)	**Cefazolin n (%)**
Clinical cure	21 (50)	25 (60)
Cure with surgery	13 (31)	7 (17)
Clinical improvement	7 (17)	5 (12)
Failure	1 (2)	5 (12)

Based on patients with a diabetic foot infection eradication of pathogens was achieved in 4/10 patients treated with cefazolin and 6/10 patients treated with ceftriaxone.

12/42 patients treated with ceftriaxone and 13/42 patients treated with cefazolin experienced a minor adverse event during therapy.

The table below shows possible cephalosporin adverse events

Adverse effect	**Ceftriaxone**	**Cefazolin**
Eosinophilia	7	5
Thrombocytosis	2	0
Leukopenia	0	1
Elevated transaminase	2	1
Rash	0	3

	Diarrohea	1	3
Study location	2 hospitals in USA		
Authors conclusion	Ceftriaxone appears to be an effective agent when given once daily as therapy for many skin and soft tissue infections		
Source of funding	Not reported		
Comments			

Table 9: Lauf 2014

Reference	**Lauf, L., Ozsvár, Z., Mitha, I., Regöly-Mérei, J., Embil, J. M., Cooper, A., ... & Maroko, R. (2014). Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagnostic microbiology and infectious disease, 78(4), 469-480.**
Study type & aim	A randomised trial to compare the efficacy and safety of parenteral (intravenous [IV] tigecycline (150 mg once-daily) versus 1 g once-daily iv ertapenem ± vancomycin for the treatment of diabetic foot infections with and without osteomyelitis
Number of participants & patient characteristics	**Total number of participants:** A total of 944 subjects were enrolled in the study. 477 patients received tigecycline and 467 received ertapenem treatment **Inclusion criteria:** hospitalised men and women aged 18 years or older with diabetes mellitus who had a foot infection that did not extend above the knee. PEDIS infection grade from 2 to 4 and a perfusion grade from 1 to 2. In addition the infection had to be of acute onset or a worsening within 14 days prior to the screening visit. **Exclusion criteria:** Patients who had received more than 48 hours of prior antibiotic unless considered a prior treatment failure. Infections categorised as necrotising faciitis, crepitant cellulitis, wet gangrene, gas gangrene, ecthyma gangrenosum or which involved implanted prosthetic material or devices that were not to be removed, or infection known or suspected to be caused by a pathogen known to be resistant to either study drug. Severely impaired arterial supply to any portion of the the affected foot or requiring anticipated complete resection or amputation of the infected anatomical site within 1 month were also excluded along with patients: undergoing hemodialysis, hemofiltration, peritoneal dialysis or plasmapherisis; contraindication or hypersensitivity to any of the study treatments, were neutropenic or receiving immunosuppressive therapy, creatinine clearance of less than 30 mL/min, any significant hepatic disease, a known or suspected infection other than diabetic foot which would require treatment with a systemic antibacterial agent, and pregnant or lactating women. **Patient characteristics:** The two treatment groups were comparable with respect to age, weight and sex and there were no major differences in terms of underlying illnesses. The table below shows the baseline demographics for participants in each treatment group

		Tigecycline (n=477)	**Ertapenem ± vancomycin (n=467)**
	Sex Male Female	 300 177	 315 152
	Mean age, years	59.6 ± 11.8	59.2 ± 11.4
	Type of diabetes Type 1 Type 2	 65 412	 68 399
	PEDIS infection grade 2 3 4	 244 187 46	 228 187 52
	Prior antibiotic failure	100	93
	Prior amputation at site of infection	82	80
	Bacteremia	19	24
	Osteomyelitis	76	41
Monitoring information & definitions	**Monitoring:** Subjects had a test of cure assessment of cure or failure within the appropriate timeframe (12 to 92 days after the last dose for those without osteomyelitis) (25-27 weeks for subjects in the substudy arm with osteomyelitis). **Primary outcome measures:** Patients were considered cured if there had been resolution of signs and symptoms of infection such that no further antibiotic therapy was required. **Secondary outcome measures:** Safety assessment included a physical examination and 12 lead ECG at baseline, day 3, last day of study medication and at the test of cure assessment. **Other outcomes:** The non-inferiority of tigecycline to ertapenem ± vancomycin was evaluated for clinical response by using the lower limit of a 2-sided 95% confidence interval that must be not less than 10% for non-inferiority.		
Intervention	150 mg once-daily, parenteral intravenous [IV] tigecycline		
Comparator:	1 g once-daily intravenous [IV] ertapenem ± vancomycin		
Length of follow-up	Follow up was at the test of cure assessment: (12 to 92 days after the last dose for those without osteomyelitis) (25-27 weeks for subjects in the substudy arm with osteomyelitis).		
Outcome measures & effect sizes	Clinical cure was noted in 316/408 (77.5%) of patients treated with tigecycline and 334/405 (82.5%) patients treated with ertapenem ± vancomycin in the clinically evaluable population of patients with diabetic foot infections. Clinical failure was noted in 92/408 (22.5%) of patients treated with tigecycline and 71/405 (17.5%) patients treated with ertapenem ± vancomycin in the clinically evaluable population of patients with diabetic foot infections.		

Clinical cure was noted in 12/38 (31.6%) of patients treated with tigecycline and 13/24 (54.2%) patients treated with ertapenem ± vancomycin in the substudy of clinically evaluable patients with osteomyelitis

In the clinically modified intention to treat population:

Clinical cure was noted in 340/476 (71.4%) of patients treated with tigecycline and 363/466 (77.9%) patients treated with ertapenem ± vancomycin in the intention to treat study of patients with diabetic foot infections.

Clinical failure was noted in 117/476 (24.6%) of patients treated with tigecycline and 86/466 (18.5%) patients treated with ertapenem ± vancomycin in the intention to treat study of patients with diabetic foot infections.

Clinical cure was noted in 19/53 (35.8%) of patients treated with tigecycline and 21/33 (63.6%) patients treated with ertapenem ± vancomycin in the substudy of intention to treat patients with osteomyelitis

Amongst the intention to treat population tigecycline failed the test for noninferiority in terms of clinical cure rate (P=0.129 [adjusted], P=0.120 [non adjusted])

Adverse events amongst the primary study population: events from first dose through last day of treatment.
***Significant P=<0.001
**Significant P=<0.01
*Significant P=<0.05

Adverse effect	**Tigecycline** (primary study) n=477	**Ertapenem ± Vancomycin** (primary study) n=467
Any adverse event	339***	266
Fever	19	15
Headache	23	19
Pain	18	12
Hypertension	34	35
Diarrhoea	54	46
Nausea	190***	39
Vomiting	118***	22

Anemia	10	14
Hypoglycaemia	34	24
SGOT increased (serum glutamic oxaloacetic transaminase)	15	19
SGPT increased (serum glutamic pyruvic transaminase)	15	18
Osteomyelitis	22	11
Insomnia	15*	4
Study withdrawals due to adverse events	10*	2
Drug discontinuations due to adverse events	42	27

Adverse events amongst the substudy population (osteomyelitis): events from first dose through last day of treatment.

***Significant P=<0.001

**Significant P=<0.01

*Significant P=<0.05

Adverse effect	**Tigecycline** (substudy) n=76	**Ertapenem ± Vancomycin** (substudy) n=41
Any adverse event	67	26
Fever	8	4
Headache	3	1
Pain	7	5
Hypertension	2	5
Diarrhoea	21	5
Nausea	37	7
Vomiting	33	3
Anemia	4	4
Hypoglycaemia	16	-
SGOT increased (serum glutamic oxaloacetic transaminase)	5	2

	SGPT increased (serum glutamic pyruvic transaminase)	4	2
	Osteomyelitis	3	1
	Insomnia	3	1
	Study withdrawals due to adverse events	5	6
	Drug discontinuations due to adverse events	11	1
Study location	119 investigational sites in 30 countries		
Authors conclusion	The 150 mg once-daily regimen of tigecycline evaluated in this trial did not meet the criteria for noninferiority when compared to ertapenem ± vancomycin in the primary study of patients with diabetic foot infections. Higher rates of nausea and vomiting were observed for tigecycline in this trial than in other phase 3 trials, with higher discontinuation rates for these adverse effects.		
Source of funding	Wyeth research, Pfizer Inc		
Comments			

G.11.2 Included from CG119

Title: Antibiotic Therapy for Diabetic Foot Infections: Comparison of Two Parenteral-to-Oral Regimens.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6489 Level of evidence: () Study type: RCT Authors: Lipsky et al. (1997)	<u>Total no. of patients:</u> Baseline = 108 Ofloxacin regimen-55 8 excluded Final number-47 Aminopenicillin regimen-53 12 excluded Final number- 41 Any patient for whom culture of the admission specimen was sterile or yielded pathogens that were resistant to the study drugs	<u>Inclusion:</u> Patients who had diabetes mellitus and a foot infection that required antibiotic therapy, as evidenced by purulent drainage, erythema, and swelling, and who were 18 years of age or older. <u>Exclusion:</u> Patients who had evidence	Ofloxacin—400 mg of ofloxacin intravenously that was changed when appropriate to 400 mg of ofloxacin orally every 12 hours. Metronidazol	Aminopenicillin— 1-2 g of ampicillin/0.5-1 g of sulbactam intravenously every 6 hours that was changed when appropriate to 500 mg of amoxicillin/125 mg of clavulanic acid	Third to seventh day or until therapy was completed	Therapy resulted in a cure or in improved conditions for 85% of the evaluable ofloxacin recipients and for 83% of the evaluable aminopenicillin recipients. Cured or improved condition / Failed / Total Ofloxacin: 40 / 7 / 47 Aminopenicillin: 34 / 7 / 41 Total: 74 / 14 / 88 **Cured-** disappearance of all signs and

	or who developed osteomyelitis (as diagnosed by the investigator) during treatment with the study drugs was withdrawn from the study. The total duration of therapy was to be 14 to 28 days, as clinically indicated. <u>Baseline characteristics:</u> There were no statistically significant differences in the demographic characteristics of the patients randomized to receive the two thera-peutic arms. The severity of infections was, on average, nearly identical in the two treatment groups. <u>Setting:</u> 12 centres across United States	of osteomyelitis, usually suspected because of clinical, laboratory, and plain radiograph findings, or who had an infection known to be caused by a microorganism resistant to any of the study drugs, were allergic to any of the study drugs or related compounds, were grossly underweight, had a seizure or major psychiatric disorder, were pregnant or nursing, were undergoing renal dialysis, or were likely to die during the study. Patients who had received potentially effective antimicrobial therapy within 48 hours before presentation. Those patients who required a second systemic antimicrobial for any reason other than as defined below or who were receiving a topical antimicrobial at .the site of infection	e was added if patient not improving(for improved coverage of anaerobic bacteria) to the ofloxacin regimen.	orally every 8 hours. Gentamicin, trimethoprims ulfamethoxazol e, or another agent (for broader coverage of gram-negative bacilli) to the aminopenicilli n regimen.		symptoms associated with active infection **Improved**- incomplete abatement of the signs or symptoms **Failed**- no improvement during therapy **Relative Risk- 40/47 ÷ 34/41 = 1.02** The mean number of pathogens isolated from cultures of wound specimens taken at the time of enrolment of the evaluable patients was 1.6 (range, 0-7). Cultures of specimens obtained while the patients were receiving therapy yielded an average of 0.2 isolate. While those of specimens taken after completion of therapy yielded a mean of 0.1 isolate. **Microbiological outcomes:** | | Cured or partially cured | Failed | To tal | |---|---|---|---| | Ofloxacin | 39 | 8 | 47 | | Aminope nicillin | 36 | 5 | 41 | | Total | 75 | 13 | 88 | **Cured**- eradication of the original pathogen(s) **Partially cured**- eradication of some but not all of the original pathogens **Failed-** persistence of the original pathogen(s). **Relative Risk- 39/47 ÷ 36/41 = 0.94** **Eradication of Gram Positive)67%) and**

						Negative (27%) organisms Ofloxacin | Aminpenicillin | 33/47 | 38/43 | Positive 18/19 | 15/18 | Negative **Adverse events** Potential side effects were experienced by 36% of the ofloxacin recipients and 22% of the aminopenicillin recipients (not a statistically significant difference). Adverse event / No adverse event / Total Ofloxacin: 17 / 30 / 47 Aminopenicillin: 9 / 32 / 41 Total: 26 / 62 / 88 **Relative Risk- 17/47 ÷ 9/41 = 1.65**
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: Lipsky, BA, Baker, PD, Landon, GC, Fernau, R Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. *Clinical Infectious Diseases* 1997; **24:** 643-48.

Title: Use of Ampicillin/Sulbactam Versus Imipencm/Cilastatin in the Treatment of Limb-Threatening Foot Infections in Diabetic Patient.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 4151 Level of evidence: () Study	Total no. of patients: Baseline = 92 No. of events-97 1 excluded (exacerbation of gout) Final no. of events: 96 I/C- 48 infections in 46 patients	Inclusion: Requirement for hospitalization, age of ≥18 years, and presence of diabetes mellitus and limb-	Imipenem/cilastatin (I/C; 500 mg-IV every 6 hours)	Ampicillin/sulbactam (A/S; 3 g-IV every 6 hours) Doses were	Daily for first 6 days and then regularly until therapy was	**Table 1: Clinical and microbiological outcomes of antibiotic therapy, as assessed on day 5 of empirical therapy and at the conclusion of parenteral therapy.** No. of episodes per group in which

<table>
<tr>
<td>type:
RCT

Authors:
Grayson et al.
(1994)</td>
<td>A/S- 48 infections in 47 patients.

Patients' therapy was routine and consisted of bed rest, surgical drainage and debridement of infected ulcers and necrotic tissue, vigorous control of diabetes mellitus, and use of sterile wound dressings (gauze soaked with normal saline or one-quarter-strength povidone-iodine). When appropriate, arterial circulation of the lower limb was evaluated by non-invasive and arteriographic techniques. Surgery to improve the arterial circulation or amputation of unsalvageable tissues was performed at the discretion of the attending surgeon.

<u>Baseline characteristics:</u>

I/C
Mean age: 61 years
Duration of diabetes: 19 years

A/S
Mean Age: 59 years
Duration of diabetes: 20 years

The vast majority of patients had relatively acute infection or exacerbated chronic infection with prominent local signs of aggressive infection. Patients in the treatment groups were similar in regard to severity of diabetes and presence of peripheral vascular disease, sensory neuropathy, and renal</td>
<td>threatening infection involving the lower extremity (limb-threatening infection was defined by at least the presence of cellulitis, with or without ulceration or purulent discharge).

Also included were patients who had recently received antibiotic therapy but had failed to demonstrate clinical improvement and whose cultures revealed one or more pathogens were eligible

<u>Exclusion:</u>

Known hypersensitivity to β-lactam antibiotics; requirement for other concomitant antibiotic treatment; serum creatinine level of ≥3.5 mg/dL; pregnancy; illness so severe that the patient was likely to die within 48 hours; severe underlying disease that might interfere with evaluation of the therapeutic response; immune depression by virtue of underlying disease, prior organ transplantation, or immunosuppressive drug therapy; and current involvement in a clinical study of an investigational drug.</td>
<td>Doses were adjusted in patients with impaired renal function.

45 infections completed 20-dose regimen
2 infections-inadvertently received only 19 doses of study drug-both were clinically cured
1 infection-marked nausea and given 13 doses only.</td>
<td>adjusted in patients with impaired renal function.

45 infections completed 20-dose regimen
2 infections-added another antibiotic
1 infection-discharged after 4 days of therapy</td>
<td>completed.</td>
<td>
<table>
<tr><td></td><td colspan="4">indicated outcome was noted</td></tr>
<tr><td></td><td colspan="2">I/C (48 episodes)</td><td colspan="2">A/S (48 episodes)</td></tr>
<tr><td>Assessment</td><td>Day 5</td><td>End of therapy</td><td>Day 5</td><td>End of therapy</td></tr>
<tr><td>Clinical</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Cure</td><td>28</td><td>39</td><td>29</td><td>41</td></tr>
<tr><td>Improvement</td><td>17</td><td>0</td><td>18</td><td>0</td></tr>
<tr><td>Failure</td><td>3</td><td>3</td><td>1</td><td>6</td></tr>
<tr><td>Indeterminate</td><td>0</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>Microbiological</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Eradication</td><td>17</td><td>32</td><td>20</td><td>36</td></tr>
<tr><td>Partial eradication</td><td>18</td><td>3</td><td>15</td><td>5</td></tr>
<tr><td>Persistence</td><td>7</td><td>2</td><td>6</td><td>3</td></tr>
<tr><td>Superinfection</td><td>0</td><td>2</td><td>0</td><td>3</td></tr>
<tr><td>Indeterminate</td><td>6</td><td>4</td><td>7</td><td>1</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Upon completion of definitive parenteral therapy, cure was achieved in 81% of episodes treated with A/S and 85% of those treated with 1/C (difference in cure rates, 4%; *95%* confidence interval, -11 % to 19%).

<table>
<tr><td></td><td>Cure</td><td>No cure</td><td>Total</td></tr>
<tr><td>I/C</td><td>41</td><td>7</td><td>48</td></tr>
<tr><td>A/S</td><td>39</td><td>9</td><td>48</td></tr>
<tr><td>Total</td><td>80</td><td>16</td><td>96</td></tr>
</table>

Relative Risk- 41/47 ÷ 39/41 = 1.07

Microbiological outcomes:

<table>
<tr><td></td><td>Eradication</td><td>No eradication</td><td>Total</td></tr>
</table>
</td>
</tr>
</table>

	impairment. The sites and severity of infection, including the frequency of osteomyelitis, were similar for both treatment groups. Setting: Not mentioned					

I/C	36	12	48
A/S	32	16	48
Total	68	28	96

Relative Risk- 36/47 ÷ 32/41 = 0.98

Eradication of Gram Positive and Negative organisms

Imipenem/cilastatin	Ampicillin/sulbactam	
14/47	21/45	Gram positive alone
0/47	0/45	Gram negative alone

Osteomyelitis:

Underlying osteomyelitis was associated with 11 of the 14 failures (six infections treated with A/S and five with I/C).

However, among all patients, osteomyelitis was not associated with failure to eliminate soft-tissue infection; at the end of therapy, treatment failure was noted in 11 (19%) of the 59 infections in patients with osteomyelitis and three (8%) of the 37 infections in patients without osteomyelitis (p= 0.26).

Recurrence of infection after average 1 year follow up:

Recurrence of infection at the original site was noted in 9 of 39 assessable patients treated with A/S and 8 of 41 assessable patients who received I/C.

Adverse events:

	No. (%) of patients with adverse reactions

Adverse reactions	I/C (48 episodes)	A/S (48 episodes)
Significant	7 (15)	9 (19)
Moderate/possible	8 (17)	6 (13)
Mild/unlikely	1 (2)	2 (4)
Total	16	16

Significant- a severe reaction necessitating with-drawal of the study agent or specific treatment
Moderate- a reaction that did not necessitate withdrawal of the study agent or specific treatment
Mild- an event uncertainly associated with the study drug
The total incidence of adverse reactions was similar in both treatment groups

Additional comments:
Because pathogen identification and antimicrobial susceptibility testing is frequently not complete for 5 days in cases of polymicrobial infection, the initial 5 days or 120 hours of study therapy were considered to be the period of empirical therapy. A clinical and microbiological assessment was made at the end of empirical therapy. A final assessment of treatment outcome was made at the end of iv antimicrobial therapy.
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: Grayson, ML, Gibbons, GW, Habershaw, GM, Freeman, DV, Pomposelli, FB, Rosenblum, BI, Levin, E, Karchmer, AW Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients.[Erratum appears in Clin Infect Dis 1994 Oct;19(4):820]. *Clinical Infectious Diseases* 1994; **18:** 683-93.

Title: Prospective, Randomized Comparison of Ampicillin/Sulbactam and Cefoxitin for Diabetic Foot Infections.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3174 Level of evidence: ()	Total no. of patients: Baseline = 36 Cefoxitin- 18 Ampicillin/sulbactam- 18 No other antimicrobials were	Inclusion: At least Grade 1 foot infection and had not received successful antimicrobial therapy within the previous four-day period, as noted by	Cefoxitin-2 g every six hours Therapy was given for at least 5 days	Ampicillin/sulbactam — 3 g every six hours Therapy was	Daily until therapy was stopped	**Table: Clinical outcomes**

	Cefoxitin	Ampicillin/sulbactam

Study type: RCT Authors: Erstad et al. (1997)	administered during hospitalization, unless a patient failed to respond to the study antimicrobial therapy within forty-eight hours, in which case the patient was withdrawn from the investigation**.** <u>Baseline characteristics:</u> There were no significant differences in the baseline characteristics of the patients in the two groups on study entry <u>Setting:</u> University medical centre-Southern Arizona	clinical improvement. <u>Exclusion:</u> Known hypersensitivity to penicillins or cephalosporins, a calculated creatinine clearance less than 15 mL/minute, a recent history of drug or alcohol abuse, or a concomi-tant infection at a site other than the foot that required additional antimicrobials. Patients were also excluded if they were terminally ill, neu-tropenic (neutrophil count <1500/m^3), pregnant, or breastfeeding.	but maximum duration was left to discretion of attending surgeon.	given for at least 5 days but maximum duration was left to discretion of attending surgeon.		<table><tr><td>Cured</td><td>7</td><td>1</td></tr><tr><td>Improvement</td><td>9</td><td>14</td></tr><tr><td>Treatment failures</td><td>2</td><td>3</td></tr><tr><td>Total</td><td>18</td><td>18</td></tr></table> **Cured**- complete alleviation of signs and symptoms of infection **Improvement**- partial alleviation of signs and symptoms of infection **Failure**- no improvement **Relative Risk- 7/18 ÷ 1/18 = 7.05** There was a significant difference (P-0.03) between treatment groups with more patients in the cefoxitin group classified as cured. However, there was no significant difference in treatment outcome between the ampicillin/sulbactam (15/17) and cefoxitin (16/17) groups when both cure and improvement were considered. **Relative Risk- 15/18 ÷ 16/18 = 0.94** Similarly, there was no significant difference between groups in the proportion of patients who had changes in clinical signs and symptoms from baseline (just prior to study medication administration) to the end of therapy.

						Duration of Hospitalisation The mean (range) duration of hospitalization was 21.1 (6.0-58.0) days in the ampicillin/sulbactam group and 12.1 (4.0-39.0) days in the cefoxitin group. **Bacteriologic evaluation:** 6 patients in the ampicillin/sulbactam group and 11 patients in the cefoxitin group were evaluable for bacteriologic outcome (ie, these patients had culturable material from the infected site prior to initiating the study antimicrobial). Eradication of the causative organisms occurred in all patients in the ampicillin/sulbactam group 6/6 (100%) compared with 8/11 (73%) patients in the cefoxitin group. **Adverse events:** Most adverse events were of minor clinical importance, gastrointestinal disturbances being particularly common in both the ampicillin/sulbactam and the cefoxitin groups (39% and 33% of patients, respectively). **Relative Risk- 6/18 ÷ 7/18 = 0.86**
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were analysed as intention to treat. Ten patients in the ampicillin/sulbactam group and 7 patients in the cefoxitin group had failed outpatient antimicrobial therapy prior to hospital admission. Most of the patients in the former group had received ciprofloxacin (at least 6 patients), and patients in the latter group had received a variety of antimicrobial agents. Three patients did not complete the five-day course of antimicrobial therapy, although all were included in the intention-to-treat analysis.						

Reference: Erstad, BL, McIntyre, J Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. *Vascular Surgery* 1997; **31:** 419-26.

Title: ***An Open-Label, Randomized Study Comparing Efficacy and Safety of Intravenous Piperacillin/Tazobactam and Ampicillin/Sulbactam for Infected Diabetic Foot Ulcers*****.**

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 4446 Level of evidence: () Study type: RCT Authors: Harkless et al. (2005)	<u>Total no. of patients:</u> Baseline = 314 P/T- 155 Modified all-treated (MAT)- 139 A/S- 159 Modified all-treated - 150 MAT-population comprised of all patients who received at least one dose of study drug and did not have any osteomyelitis. Standard wound care, including off-loading, sharp debridement of devitalized tissue, and moist dressings, were followed during the study, and the one-time use of a topical antiseptic was allowed after a surgical procedure or debridement. <u>Baseline characteristics:</u> Overall, patients' demographic characteristics, baseline diagnoses, wound classes and ulcer locations, and concomitant diseases were similarly distributed in the two	<u>Inclusion:</u> Adult patients with diabetes mellitus and open infected foot ulcers that met the University of Texas Grade IB, ID, IIB, or IID classification of foot ulcers , have at least one full- or partial-thickness infected ulcer at or below the ankle. Patients were also required to have purulent drainage or two of the following: Erythema, local edema, fluctuance, induration, increased local warmth, or fever. <u>Exclusion:</u> Pregnancy or lactation; anticipated amputation of the infected area within two months; conditions requiring concurrent topical antibiotics to the ulcer site or any other systemic antibacterials during the study period; creatinine clearance less than 40 mL/min; conditions requiring	I.V. piperacillin /tazobactam (P/T) (4 g/0.5 g q8h). Doses adjusted in patients with renal function in both groups.	I.V. ampicillin/ sulbactam (A/S- 2 g/1 g q6h). Patients with MRSA or methicillin-resistant *Staphylococcus epidermidis* (MRSE) present as part of a polymicrobial infection were also given vancomycin at 1 g ql2h	Day 4, day 7, at the end of treatment visit, and at the test-of-cure visit (occurred within 14-21 days of completion of therapy)	The rates of clinical success(defined as cure or improvement for the patient-level clinical response) in the MAT population between treatment groups were: 71.2% of the patients in the piperacillin/tazobactam group and 66.7% of the patients in the ampicillin/sulbactam group. **Relative Risk- 99/139 ÷ 100/150 = 1.07** There were no substantial differences in clinical success rates when results were compared by age, gender, race, or smoking status. **Eradication of Gram Positive and Negative organisms** **Adverse events:**

	Clinical success	No clinical success	Total
P/T	99	40	139
A/S	100	50	150
Total	199	90	289

P/T	Ampicillin/sulbactam	
51/65	46/64	Gram positive
6/7	0/0	Gram negative

	treatment groups. Setting: Regional areas in United States	immunosuppressive drug treatments; gangrene or severely impaired arterial supply to any portion of the affected foot; hypersensitivity to penicillins, /S-lactamase inhibitors, or vancomycin; presence of organisms known or suspected to be resistant to either study drug; renal insufficiency requiring renal replacement therapy; osteomyelitis; or thrombocytopenia. A patient could be withdrawn from the study for noncompli-ance, adverse events, investigator belief that withdrawal was in the best interest of the patient, patient choice, lack of efficacy, patient loss to follow-up, or death. Additionally, patients who had infections caused by organisms resistant to randomized treatment were withdrawn from the study.				<table><tr><th>Adverse event</th><th>P/T (n=155)</th><th>A/S (n=159)</th></tr><tr><td>With at least 1 adverse event</td><td>117</td><td>105</td></tr><tr><td>With at least 1 treatment related adverse event</td><td>29</td><td>21</td></tr><tr><td>With at least 1 serious adverse event</td><td>42</td><td>46</td></tr></table>**Relative Risk- 29/155 ÷ 21/159 = 1.41** The majority of adverse events were mild-to-moderate in severity, and the incidence and severity of all adverse events and treatment-related adverse events were comparable between the two groups.
Additional comments: Randomisation was performed. Open-labelled. Power calculation used. Allocation concealment not mentioned. Confounding mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Harkless, L, Boghossian, J, Pollak, R, Caputo, W, Dana, A, Gray, S, Wu, D An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. *Surgical Infections* 2005; **6:** 27-40.

Title: ***Treatment of hospitalised patients with complicated skin and structure infections: double-blind, randomised, multicentre study of piperacillin-tazobactam versus ticarcillin-clavulanate***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 10637 Level of evidence: () Study type: RCT Authors: Tan et al. (1993)	<u>Total no. of patients:</u> A patient was considered evaluable if each of the following criteria was met: a pretherapy pathogen susceptible to either study drug was present, susceptibility data for at least one pathogen were available, no other antibacterial agents were administered concomitantly during the study, there were at least 5 days of treatment with the study medication (to qualify for a favourable outcome), and the patient underwent at least one post-therapy follow-up (to qualify for a favourable outcome). For an unfavourable outcome, at least 3 days of therapy were required. Surgical debridement or drainage was allowed and was accepted as an integral part of patient management. <u>Baseline characteristics:</u>	<u>Inclusion:</u> Patients 16 years of age and older with complicated skin or skin structure infections like ischemic or diabetic foot infec-tions, present with purulent drainage or collection and at least three of the following: temperature greater than 38°C, peripheral leukocyte count greater than 10,000/mm^3 with greater than 5% immature neutrophils, local erythema, local swelling, tenderness, pain, or fluctuance. <u>Exclusion:</u> Known or suspected hypersensitivity to beta-lactam antibiotics or {3-lactamasc inhibitors; moderate to severe renal dysfunction; evidence of active liver disease; peripheral granulocyte counts of <l,000/mm^3 or platelet counts of <50,000/mm^3; receipt of more than two doses of another antibacterial agent within 72 h prior to enrolment;	Dosed every 6 h with pipcracillin-tazobactam (P/T), 3 g and 375 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms.	Dosed every 6 h with ticarcillin-clavuianatc (T/C), 3 g and 100 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms.	Patients were evaluated for their clinical responses to therapy daily for the duration of treatment in the hospital, at 24 to 72 h after the completion of therapy (early follow-up), and at 10 to 14 days after the completion of therapy (late follow-up).	Table: Clinical responses at endpoint for evaluable patients. Outcome / P/T / T/C / p value Cured/improved / 12 / 7 / 0.90 Unfavourable / 6 / 10 / total / 18 / 17 / Relative Risk- 12/18 ÷ 7/17 = 1.62 Adverse Events: Data not extractable for patients with diabetic foot infection.

	The distribution of patients by race and sex was comparable between the two treatment arms and the mean ages among all treated patients were similar. Differences in the distributions of clinical diagnoses were not significant between the two treatment arms. Setting: 20 centers	receipt of another investigational drug within 1 month prior to enrolment; active or treated leukaemia; AIDS; the need for haemodialysis, peritoneal dialysis, plasmapheresis, or haemoperfusion; osteomyelitis contiguous with a skin or skin structure infection; potential requirement for amputation of the infected area; pressure ulcer infections of greater than 2 weeks' duration {because of the. known difficulty in eradicating organisms from chronic decubitus ulcers); and a concomitant infection other than the skin and skin structure infection.				
Additional comments: Randomisation was performed. Blinding performed. Power calculation used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Tan, JS, Wishnow, RM, Talan, DA, Duncanson, FP, Norden, CW Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. *Antimicrobial Agents & Chemotherapy* 1993; **37:** 1580-1586.

Title: Treatment of diabetic foot infection: an open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 1702 Level of	Total no. of patients: Baseline = 46	Inclusion:	Piperacillin 3000 mg QID in combination	Imipenem/cilastatin (I/C)- 500 mg QID	Every 3 days and after completion of	Efficacy: Table: Assessment of clinical response to

<table>
<tr>
<td>evidence:
()

Study type:
RCT

Authors:
Bouter et al. (1996)</td>
<td>I/C- 22 (1 excluded due to being included twice)

I/C-21

P/LC- 24

The minimum length of treatment required for evaluability was at least 10 days. Antibiotic therapy was discontinued if the patient's clinical condition worsened after 72 h and questions were raised about the appropriateness of therapy.

In case of chronic osteomyelitis, antibiotic therapy was continued with oral quinolone (ciprofloxacin 500 mg BID or ofloxacin 400 mg BID) and/or clindamycin 600 mg TID depending on culture results.

<u>Baseline characteristics:</u>

The two study populations were similar with regard to age, sex, type of diabetes mellitus and associated conditions.

The two study groups were comparable in terms of baseline severity.

<u>Setting:</u></td>
<td>Diabetic foot lesions, Wagner Stages II, III or IV, and have an ankle/brachial index (AB1) of at least 0.45.

<u>Exclusion:</u>

Patients known to be hypersensitive to any of the study drugs or who had received antimicrobial therapy known or presumed effective against the infecting pathogens within 48 h preceding initiation of treatment were excluded from the study. Patients with a high probability of death within 48 h were also excluded from the study as were patients known to be infected with Xanthomonas maltophilia other microorganisms known or presumed resistant to the study drugs.</td>
<td>with clindamycin 600 mg (P/CL)-TID

Dosages reduced in patients with renal or liver function impairment.</td>
<td>Dosages reduced in patients with renal or liver function impairment.</td>
<td>antibiotic therapy.</td>
<td>treatment with imipcncm/cilastalin or the combination of piperacillin with clindamycin

<table>
<tr><th>Clinical outcome</th><th>Imipenem/ cilastatin (n-21)</th><th>Piperacillin/ clindamycin (n-24)</th></tr>
<tr><td>Cured</td><td>4</td><td>6</td></tr>
<tr><td>Improved</td><td>16</td><td>12</td></tr>
<tr><td>Failed</td><td>0</td><td>2</td></tr>
<tr><td>Died</td><td>1</td><td>4</td></tr>
</table>

In the IC study population, four (19.0%) patients were considered to be clinically cured, 16 (76.2%) improved. No patients were classified as a clinical failure.

In the PCL study population, six (25.0%) patients were considered to be clinically cured, 12 (50.0%) improved. Two patients (8.3%) were classified as a clinical failure due to persistence or aggravation of clinical signs of infection

Relative Risk$_{cured}$- 6/24 ÷ 4/21 = 1.31

Relative Risk$_{cured\ and\ improved}$ -18/24 ÷ 20/21 = 0.79

Bacteriological response:

Table 2: Assessment of bacteriological response to treatment with imipenem/ cilastatin or the combination of piperacillin with clindamycin

<table>
<tr><th>Bacteriological outcome</th><th>Imipenem/ cilastatin (n = 20)</th><th>Piperacillin/ clindamycin (n = 23)</th></tr>
<tr><td>Eradication</td><td>9</td><td>16</td></tr>
<tr><td>Partial eradication</td><td>3</td><td>1</td></tr>
<tr><td>Failure</td><td>1</td><td>3</td></tr>
</table>
</td>
</tr>
</table>

	Bosch McdiCentre, Den Bosch and the Eemland Hospital, Amersfoort, The Netherlands.					

Superinfection	4	3
Relapse	3	0

In the IC treatment group eradication of baseline pathogens was in 9 and partial eradication in 3 patients. 1patient was considered to be a bacteriological failure.

In the PCL patient group antibiotic treatment resulted in eradication of baseline pathogens in 16 patients. 3 patients were classified as a bacteriological failure.

Relative Risk- 16/24 ÷ 9/21 = 1.56

Adverse Events:

Table: Adverse events reported during treatment with miipcnem/cilastatin or the combination of piperacillin with clindamycin

Adverse event	Imipenem/ cilastatin (n-21)	Piperacillin/ clindamycin (n-24)
Yes	3	12
No	18	12

Significantly more patients treated with PCL than patients treated with IC experienced side effects that were probably related to the study drugs ($P < 0.05$).
Relative Risk- 12/24 ÷ 3/21 = 3.50

Additional comments:
Randomisation was performed. Blinding performed. Power calculation not mentioned. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.

Reference: Bouter, KP, Visseren, FLJ, Van Loenhout, RMM, Bartelink, AKM, Erkelens, DW, Diepersloot, RJA Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. *International Journal of Antimicrobial Agents* 1996; 7: 143-47.

Title: *Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-Clavulanate.*

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6518 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2007)	Total no. of patients: Baseline = 607 306 randomised to moxifloxacin 311 to P/T-A/C ITT (intention-to treat)-127 63 to moxifloxacin 64 to P/T-A/C Efficacy valid population(EVP)-78 37- moxifloxacin 41- P/T-A/C ITT- and safety populations were defined as all randomized patients who received at least one dose of study medication The efficacy-valid population consisted of patients who met the entry criteria, had an investigator-defined DFI, received study medication for the minimum duration (2 days if a clinical failure and >5 days if a clinical cure), received no non-study systemic or topical antibiotic agent for >72h prior to enrolment and had no protocol violations that would have influenced treatment efficacy.	Inclusion: At least 18 years of age, with a cSSSI (complicated skin and skin structure infections). Each enrolled patient had to have al least three of the following signs or symptoms of wound infection: drainage or discharge, erythema, fluctuance, localized heat or warmth, pain or tenderness, swelling or induration, fever, leucocyiosis or >15% immature neutrophils on peripheral blood smear. The investigators only enrolled patients with an infection of sufficient severity to require hospitalization and iv antimicrobial therapy. Exclusion: Excluded patients who had received antibiotic therapy for >24h within 3 days prior to study enrolment or those who needed concomitant systemic antibiotic therapy for treatment of other infections. We also excluded patients with a DFI who had suspected or	IV therapy for at least 3 days with moxifioxacin (400 mg/day). Then switched to oral therapy with moxifloxacin 400 mg/day	piperacillin-tazobactam (P/T) (3.0 g/0.375 g every 6 h) for at least 3 days. Then switched to amoxicillin-clavulanate (A/C)suspension 800 mg every 12 h	Patients were evaluated regularly until 10-42 after completing the study therapy.	Efficacy Table 1: Clinical cure rates at the TOC (test-of cure) visit (10-42 days post-therapy) in the efficacy-valid population DFI definition: Per investigator (efficacy valid population) — Moxifloxacin: 25/37 — P/T-A/C: 25/41 — p-value: 0.54 DFI definition: ITT — Moxifloxacin: 28/63 — P/T-A/C: 25/64 — p-value: 0.54 Relative Risk (EVP)- 25/37 ÷ 25/41 = 1.10 Relative Risk (ITT)- 28/63 ÷ 25/64 = 1.14 Bacteriologic response Bacteriologic eradication rates for the microbiologically-valid population at TOC for patients in the moxifloxacin(n-29) and comparator (n-32)treatment arms were not statistically significantly different overall (69% versus 66%, P = 1.00). Relative Risk (EVP)- 20/29 ÷ 21/32 = 1.05 Eradication of Gram positive and Negative organisms Moxifioxacin | P/T

	Patients in the microbiologically-valid population consisted of those in the efficacy-valid population with one or more causative organism(s) identified at enrolment. Baseline characteristics: There were no statistically significant differences between patients in the two treatment groups in their demographic or clinical characteristics at baseline for all variables Setting: 68 centres in 6 countries.	documented osteomyelitis, unless the infected bone was fully or partially resected and any residual soft tissue infection could be adequately treated with study drug for < 14 days.				<table><tr><td>Gram positive aerobes</td><td>24/27</td><td>27/42</td></tr><tr><td>Gram positive anerobes</td><td>0/1</td><td>¾</td></tr><tr><td>Gram negative aerobes</td><td>2/7</td><td>8/12</td></tr><tr><td>Gram negative anerobes</td><td>1/3</td><td>3/6</td></tr></table> Adverse events: Table 2: Adverse events by treatment group <table><tr><td></td><td>Moxifloxacin N= 63</td><td>P/T-A/C N= 64</td></tr><tr><td>Any adverse event</td><td>52</td><td>42</td></tr><tr><td>Drug-related adverse event</td><td>20</td><td>8</td></tr><tr><td>Serious adverse effect</td><td>15</td><td>15</td></tr><tr><td>Study drug discontinued due to adverse event</td><td>8</td><td>7</td></tr></table> Almost a quarter of patients experienced a serious adverse event, and in ~11% this led to their study drug being discontinued prematurely. More patients in the moxifioxacingroup than in the comparator group experienced a drug-related adverse event (28 versus 8). No severe drug-related adverse events occurred in any patient in the moxifioxacin

						group, compared with two that occurred in patients in the comparator group. Relative Risk (ITT)- 52/63 ÷ 42/64 = 1.26
Additional comments: Randomisation was performed. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Giordano, P, Choudhri, S, Song, J Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. *Journal of Antimicrobial Chemotherapy* 2007; **60:** 370-376.

Title: Treating Foot Infections in Diabetic Patients: A Randomized, Multicenter, Open-Label Trial of Linezolid versus Ampidllm-Sulbactam/ Amoxicillin-Clavulanate.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6504 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2004)	Total no. of patients: Baseline = 371 Linezolid- 241 After exclusion Linezolid- 203 A/S and A/C- 120 After exclusion A/S and A/C- 108 Patients with presumed osteomyelitis were allowed to be enrolled if the investigator believed 4 weeks of antibiotic therapy was sufficient for treatment. Patients received twice-daily dressing changes (which consisted of any sterile nonadherent type selected by the investigator) and periodic debridement, as needed throughout the study.	Inclusion: Men and women (age, ≥18 years) with diabetes mellitus, a foot infection (cellulitis, paronychia, infected ulcer, deep soft-tissue infection, septic arthritis, abscess, or osteomyelitis) were potentially eligible. Exclusion: If they had critical ischemia of the affected limb, if they had a wound with prosthetic materials or devices; if they had an infection requiring >28 days of antibiotic treatment; or if they had a wound with extensive gangrene. Patients were also	Linezolid (600 mg ql2 h either iv or per oral)	ampicillin-sulbaclam (A/S, 1.5-3 g q6h iv}, or amoxicillin-clavulanate (A/C, 500-875 mg every 8-12 h per oral).	The test-of-cure evaluation was conducted 15-21 days after treatment was completed	Efficacy Table 1: Clinical cure rates for the intent-to-treat population, by selected parameters.

	No. of patients cured/ No. of patients assessed(%)*	
	Linezolid (n- 241)	Aminopenicillin / β lactamase inhibitor (n-=120)
Overall	165/203 (81)	77/108 (71)
Type of infection**		
Infected ulcer	131/161 (81)	57/84 (68)
Cellulitis	68/86 (79)	40/54 (74)
Deep soft-tissue infection	20/32 (63)	8/14 (57)
Paronychia	11/12 (92)	9/11 (82)

	Baseline characteristics: There were no significant differences between the 2 treatment groups at baseline with respect to demographic characteristics, medical histories, findings of physical examination, and results of laboratory tests. Setting: 45 sites in 8 countries.	excluded if they had received potentially effective antibiotic therapy for >72 h in the week before enrollment, if they needed additional treatment with antibiotics not tested in our study, if they had an absolute neutrophil count of <500 cells/mm^3, if they were pregnant or lactating, or if they had a history of hypersensitivity to linezolid, penicillin, or vancomycin.				<table><tr><td>Abscess</td><td>5/5 (100)</td><td>1/1 (100)</td></tr><tr><td>Osteomyelitis</td><td>27/44 (61)</td><td>11/16(69)</td></tr><tr><td>Route of initial treatment</td><td></td><td></td></tr><tr><td>Intravenous</td><td>41/53 (77)</td><td>15/22 (68)</td></tr><tr><td>Oral</td><td>124/150 (83)</td><td>62/86 (72)</td></tr></table> *- Excludes patients with indeterminate and missing outcomes **- Patients could have had >1 baseline diagnosis. There was no statistically significant difference between the treatment groups in the overall clinical cure rate. When analyzed by primary diagnosis, however, statistically significantly more patients with an infected ulcer in the linezolid arm were clinically cured than in the aminopenicillin//3-lactamase inhibitor arm (81% vs. 68%, respectively; 95% CI, 1.9-25.2; P = .018). Clinical outcomes were similar between treatment groups among patients with cellulitis, deep soft-tissue infection, paronychia, abscess, and osteomyelitis. Relative Risk (overall)- 165/203 ÷ 77/108 = 1.14 Relative Risk (infected ulcer)- 131/161 ÷ 57/84 = 1.20 Relative Risk (Osteomyelitis)- 27/44 ÷ 11/16 = 0.89 Adverse events: Linezolid group No. of patients- 64 Patients who discontinued therapy- 18 Aminopenicillin / β lactamase inhibitor

						No. of patients- 12 Patients who discontinued therapy- 4 Overall, significantly fewer patients experienced a drug-related adverse event in the aminopenicillin/β-laclamase inhibitor groups than in the linezolid group (12 [10%] of 120 patients vs. 64 [27%] of 241 patients, respectively; P = .001), but the frequencies of drug-related events leading to drug discontinuation were comparable (4 [3%] of 120 patients vs. 18 [8%] of 241 patients, respectively; P - 0.16) Treatment-related adverse events occurred in 55% and 53% of patients in the linezolid and aminopenkillin/ /J-lactamase inhibitor groups, respectively (P = .82) Events were generally mild to moderate in intensity and of limited duration. Relative Risk- 64/241 ÷ 12/120 = 2.65
Additional comments: Randomisation (ratio 2:1) was performed. Open-labelled. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Itani, K, Norden, C, Linezolid Diabetic Foot Infections Study Group Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. *Clinical Infectious Diseases* 2004; **38:** 17-24.

Title: Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results

<table>
<tr>
<td>ID: 6512

Level of evidence: ()

Study type: RCT

Authors: Lipsky et al. (2005)</td>
<td><u>Total no. of patients:</u>
Baseline = 133
103-clinically evaluable
47-Daptomycin
56-comparator

For suspected or proven polymicrobial infection, the investigator was allowed to add aztreonam to cover gram-negative bacteria or metronidazole lo cover obligate anaerobic bacteria, at his or her discretion.

<u>Baseline characteristics:</u>

Patients in the daptomycin and comparator groups were statistically equivalent with respect to all noted baseline variables, including mean age (60 and 63 years), sex (54% and 54% male) and race (80% and 78% white), respectively.

<u>Setting:</u>
134 sites in the United States, Europe. South Africa, Australia, and Israel</td>
<td><u>Inclusion:</u>

Eligible patients were those with diabetes between the ages of 18 and 85 years who required hospitalization for an infected ulcer that was known or suspected (based on a Gram-stained smear) to be caused by a Gram-positive organism.
<u>Exclusion:</u>

Patients with minor or superficial skin infections, uncomplicated cellulitis, myositis, multiple infected ulcers at distant sites, infected third-degree burn wounds, osteomyelitis, known bacleraemic shock, hypotension, or any disorder that could interfere with the treatment evaluation were excluded. Other exclusions were pregnancy, infection due to an organism known to be resistant lo any study drug before study entry, body weight less than 40kg, history of hypersensitivity reaction lo any study drug, need for haemodialysis or peritoneal dialysis, impaired renal function (creatinine clearance less than 30ml7min). immunosuppression, serum creatine phosphoki-nase (CPK) more than 50% above the upper limit of normal, or the use of any 3-hydroxy-3-metlwlghitaryl coenzyme reductase inhibitor (statin) drugs. Patients were also</td>
<td>Daptomycin [4mg/kg every 24h intravenously (iv) over 30min]</td>
<td>Vancomycin 1 g every 12h iv over 60min or a semi-synthetic penicillin (nafcillin. oxacillin, cloxacillin or llucloxa-cillin, per the investigator's choice) given in equally divided doses totalling 4-12g/day iv].</td>
<td>Patients were assessed at 'end-of-therapy' (i.e. within 3 days of the last dose of study drug); 'test-of-cure' (i.e. within 6-20 days after completing the study drug); and 'post-study' (i.e. within 20-28 days after completing the study drug).</td>
<td>Table 1: Clinical success rates for patients with infected diabetic ulcers by antibiotic treatment group (clinically evaluable population).

<table>
<tr><td>Comparator group</td><td>Daplomycin*

(n=47)</td><td>Comparator

(n= 56)</td></tr>
<tr><td>Pooled</td><td>66.0 (31/47)</td><td>70.0 (39/56)</td></tr>
<tr><td>Semi-synthetic penicillin</td><td>64.0 (16/25)</td><td>70.4 (19/27)</td></tr>
<tr><td>Vancomycin</td><td>71.4 (10/14)</td><td>69.0 (20/29)</td></tr>
</table>
*-Pre-randomization assignment unavailable in 8 subjects

The overall clinical success rate was 66% for patients treated with daptomycin and 70% for patients treated with a comparator agent (95% CI, -14.4-21.8).

Relative Risk(? Methodology)- 31/47 ÷ 39/56 = 0.95

Looking at individual comparators, the clinical success rates for patients randomized to daptomycin versus a semi-synthetic penicillin were 64.0% and 70.4%, respectively.

Relative Risk- 16/25 ÷ 19/27 = 0.91

Whereas for those randomized to daptomycin versus vancomycin rates were 71.4% and 69.0%,</td>
</tr>
</table>

		excluded if they had received more than 24h of systemic antibiotic therapy for the infected ulcer within the previous 48 h.				respectively. None of these differences was statistically significant. **Relative Risk- 10/14 ÷ 20/29 = 1.03** **Adverse events:** The most common events in both groups were gastrointestinal; most adverse events were deemed unrelated to the study medications, were of mild to moderate intensity, and rarely required that the drug be discontinued. Of the 56 adverse events that were possibly or probably related to treatment, 37 (66%) occurred in the 72 patients in the comparator group, and 19 (34%) occurred in the 61 patients in the dapto-mycin group. **Relative Risk(? Methodology)- 19/61 ÷ 37/72 = 0.60**
Additional comments: Randomisation was performed but partially.. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Lipsky, BA, Stoutenburgh, U Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. *Journal of Antimicrobial Chemotherapy* 2005; **55:** 240-245.

Title: *Ertapenem Versus Piperacillin/Tazobactam for Diabetic Foot Infections (SIDESTEP):* Prospective/Randomized, Controlled, Double-Blinded, Multicentre Trial

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6511 Level of evidence: () Study	Total no. of patients: Baseline = 586 295- ertapenem 289- clinical MITT (modified-intention-to-treat) 244- microbiological MITT	Inclusion: Presented with diabetes mellitus (type 1 or type 2, controlled by diet or medications) and a foot infection that did not extend above the knee and required	Intravenous ertapenem (1 g bolus, followed by a saline placebo every 6 h for three additional doses).	Intravenous piperacillin/tazobactam (P/T-3-375 g every 6 h).	Day 5 of intravenous therapy, at the time of discontinuation of intravenous therapy (DCIV), at the time of discontinuation of any subsequent oral	The proportion of patients with a favourable clinical response at the DCIV timepoint, adjusted for baseline severity, was 94% (213 of 226) for the ertapenem group and 92% (202 of 219) for the piperaciliin/lazobaclam group.

type: RCT Authors: Lipsky et al. (2005)	226 DCIV clinically evaluable 206-FUA clinically evaluable 151-microbiologically evaluable 291-P/T 285-clinical MITT 226-mocrobiological MITT 219-DCIV clinically evaluable 196-FUA clinically evaluable 135-microbiologically evaluable Investigators sharply debrided any wounds that had callus or devitalized tissue at baseline, and whenever necessary during the study. To ensure adequate antibiotic coverage for potentially antibiotic resistant Enlerococcus spp and meticillin-resistant S aureus (MRSA), investigators could administer vancomycin to patients in either treatment group if these organisms were known or suspected pathogens. After 5 days of intravenous therapy, the investigator could elect to switch patients in either group to oral antibiotic therapy with amoxicillin/ clavulanic acid (875/125 mg every 12 h). <u>Baseline characteristics:</u> The baseline characteristics—including details of peripheral neuropathy, palpable pedal pulses, and wound severity—of those randomized, which were similar between groups. At baseline, we stratified patients with the University of Texas Diabetic Wound Classification.	intravenous antibiotics. All patients had purulent drainage or at least three other indicators of infection. <u>Exclusion:</u> Patients who had infections that were: mild and did not require parenteral antibiotic therapy; known at entry to be caused by pathogens resistant to either study drug; predominantly caused by thermal bums; categorised as necrotising fasciitis; known or suspected to be associated with underlying osteomyelitis, complicated by indwelling foreign or prosthetic material; or associated with gangrenous tissue that could not be adequately removed by surgical debridement. We also excluded women who were pregnant, nursing, or fertile and not using contraception, as well as patients with: a history of a serious reaction to any β lactam antibiotic; a need for any additional concomitant systemic antibacterial agent other than the study drug(s) or vancomycin; diabetes or impaired glucose tolerance that was secondary; arterial perfusion insufficiency of the affected limb, requiring a revascularisation procedure; any rapidly progressive or terminal illness; a requirement for dialysis; immunosuppression of any cause; or receiving corticosteroid therapy {2=40 mg prednisone daily or its equivalent). Laboratory variables for which patients were excluded were:			antibiotic therapy, and at the follow-up assessment (FUA) 10 days after the last dose of study antibiotic therapy (intravenous or oral).	Relative Risk- 213/226 ÷ 202/219 = 1.02 At the 10-day FUA timepoint, the clinical response rate, adjusted for baseline severity, was 87% (180 of 206) in the ertapenem group and 83% (162 of 196) in the piperacillin/tazobactam group. Relative Risk- 180/206 ÷ 162/196 = 1.06 Among the 574 patients in the more conservative MITT analysis (those who received at least one dose of study drug, with patients with missing or indeterminate outcomes considered treatment failures), the proportion with a favourable clinical response at the 10-day FUA was 71% (206 of 289) and 66% {188 of 285), respectively (treatment difference 5%, 95% CI —2-6 to 12-5). Relative Risk- 206/289 ÷ 188/285 = 1.08 None of these differences between treatment groups is significant. Table1: Rate of favourable clinical response at 10-day FUA, by baseline stratum and wound classification Ertapenem (n=206) / P/T (n=196) Moderate 127/142 / 129/135 Severe 53/64 / 43/61 Grade 0 2/2 / 5/5(Grade 1 125/140 / 114/130 Grade 2 43/51 / 33/48 Grade 3 10/13 / 10/l3

	Stratum I patients had a relatively superficial wound with or without ischemia (grade 0 or 1, stages B or D), and Stratum II patients had a deeper wound (grades 2 or 3, stages B or D). <u>Setting:</u> USA	markedly abnormal liver function tests; haemalocril of less than 25%, haemoglobin of less than 8 g/L, platelet count of less than 75 OOO/mm^1; or coagulation test results more than 1.5 times the upper limit of normal (unless on anticoagulant therapy). Finally, we excluded patients who had been treated for more than 24 h with systemic antibiotic therapy likely to be effective for their infection within the 72 h before study screening, unless there was clinical evidence of treatment failure with an associated deep-tissue culture that yielded pathogen(s).				<table><tr><td>Stage B</td><td>172/195</td><td>156/187</td></tr><tr><td>Stage D</td><td>8/11</td><td>6/9</td></tr></table> Clinical cure rates were generally similar between treatment groups for patients with either moderate or severe infections, and for every stage and grade. There was a trend towards lower success rates with deeper wounds (moving from grade 0 to grade 3}, and patients with an ischemic limb (stage D) generally had lower clinical success rates than patients with adequate perfusion (stage B). Microbiological outcome: Among individuals with a positive wound culture, 358 of 384 (93%) isolates were known or presumed to be eradicated in those in the ertapenem group compared with 271 of 336 (81%) in the piperacillin/tazobactam group (difference 12-5%, 95% CI 7-2-18-8). Relative Risk- 358/384 ÷ 271/336 = 1.16 Adverse Events: Most adverse events were unrelated to the study drugs. 137 (47%) patients on ertapenem and 136 (47%) on piperacillin/tazobactam had at least one adverse event during parenteral therapy. There were no significant differences between treatment groups in drug-related adverse events (n=44 [15%] for ertapenem; n=57 [20%] for piperacillin/tazobactam) Relative Risk- 44/295 ÷ 57/291 = 0.76
<u>Additional comments:</u> Randomisation was performed. Open-labelled. Power calculation used. Allocation concealment mentioned. Confounding mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Armstrong, DG, Citron, DM, Tice, AD, Morgenstern, DE, Abramson, MA Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. *Lancet* 2005; **366:** 1695-703

Title: ***Treatment and Long-Term Follow-Up of Foot Infections in Patients with Diabetes or Ischemia: A Randomized, Prospective, Double-Blind Comparison of Cefoxitin and Ceftizoxime***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 4914 Level of evidence: () Study type: RCT Authors: Hughes et al. (1987)	Total no. of patients: Baseline = 63 Ceftizoxime – 33 (5 unevaluable) Cefoxitin- 30 (5-unevaluable) Some patients, after completing the study, received oral antibiotics for variable lengths of time at the discretion of their physician. Baseline characteristics: Evaluable patients were similar with regard to age, sex, duration of therapy, and associated conditions. Setting: 2 Veterans Administration medical centers (VAMC)	Inclusion: (1) a history or clinical evidence of peripheral arterial insufficiency or diabetes mellitus; (2) isolation of bacterial organisms from wound, soft tissue, or bone; (3) two or more signs of infection, including local heat, drainage, erythema, or temperature greater than 38 °C. Exclusion: Excluded for previous penicillin or cephalosporin allergy, rapidly progressive underlying disease, concomitant infection, or antibiotic therapy effective against the bacterial isolates within three days preceding initiation of-the study.	Ceftizoxime, up to 4 gm IV every eight hours. Dosages of study medication were reduced for patients with renal dysfunction. Placebo infusions were given at appropriate intervals to patients in the ceftizoxime group to maintain double-blind conditions.	Cefoxitin, up to2 gm IV every four hours. Dosages of study medication were reduced for patients with renal dysfunction.	Every 3 days. Subsequent follow-up evaluations were made after 3, 6, 9, and 12 months.	**Table 1: Clinical responses** Number with Satisfactory Clinical Response/ Total Number Treated Ceftizoxime / Cefoxitin All evaluable patients: 23/28 / 17/25 Osteomyelitis: 10/14 / 8/12 Soft tissue infections: 13/14 / 9/13 Infections associated with bacteremia: 0/1 / 1/4 Satisfactory clinical responses were observed in 82% of patients treated with ceftizoxime and 68% of patients treated with cefoxitin. **Relative Risk- 23/28 ÷ 17/25 = 1.20** Treatment of osteomyelitis with either agent was particularly encouraging, being only slightly less successful than treatment of soft tissue infections. Infections associated with bacteremia frequently were clinically unsatisfactory. There was no significant difference between responses of patients with peripheral vascular disease alone and responses of diabetics with or without apparent peripheral vascular disease.

						The in vitro susceptibilities of selected bacterial isolates are 161 of 185 (87%) isolates tested were susceptible to ceftizoxime and 148 of 183 (81%) were susceptible to cefoxitin. **Long term Follow up** **3 months** After three months of follow-up, six patients in each group had relapses of infection at the same site, which required parenteral antibiotics. **12 months** After 12 months, of 23 patients who initially had satisfactory clinical responses to ceftizoxime, eight were free of infection (at the same site), nine had relapsed, two had died of unknown causes, and four had failed to return for follow-up. Seventeen patients had initially satisfactory clinical responses to cefoxitin. After 12 months, seven remained free of infection, eight had relapsed, and two had not returned for follow-up. Five of 12 patients with soft tissue infections and two of 11 with osteomyelitis were known to have satisfactory long-term outcomes. **Adverse events** Adverse effects were observed in 16/33 (48%) patients receiving ceftizoxime and in 19/30 (63%) patients receiving cefoxitin. These consisted

						mostly of minor laboratory abnormalities, which resolved with discontinuation of therapy. **Relative Risk- 16/33 ÷ 19/30 = 0.76**
Additional comments: Randomisation (Computer-generated Code) was performed. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Hughes, CE, Johnson, CC, Bamberger, DM, Reinhardt, JF, Peterson, LR, Mulligan, ME, Gerding, DN, George, WL, Finegold, SM Treatment and long-term follow-up of foot infections in patients with diabetes or ischemia: a randomized, prospective, double-blind comparison of cefoxitin and ceftizoxime. *Clinical Therapeutics* 1987; **10:** Suppl-49.

Title: Outpatient management of uncomplicated lower-extremity infections in diabetic patients.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: HTA paper Level of evidence: () Study type: RCT Authors: Lipsky et al. (1990)	Total no. of patients: Baseline = 56 I= 27 C= 29 At the initial evaluation, lesions were cleaned with half-strength hydrogen peroxide, debrided mechanically and covered with a gauze dressing. Baseline characteristics: Mean ± SEM age: I: 59.4 ± 2.3 years C: 62.7 ± 2.4 years Patients with an ulcerated lesion: I: 24/27 (89%) C: 27/29 (93%) Setting: Washington State Veterans Affairs Medical Centre	Inclusion: non-limbthreatening lower extremity infections. Clinically infected lesions were defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, induration, fluctuance, drainage Exclusion: Systemic or topical antimicrobial therapy within the preceding 2 weeks, presence of systemic toxicity, an infection that was immediately threatening to life or limb, patient unable to perform daily wound care, history of nonadherence with outpatient treatment, unwilling to return for outpatient visits, allergy to study drugs.	I (n = 27 patients): Clindamycin 300 mg orally, four times daily for 2 weeks.	C (n = 29 patients): Cephalexin 500 mg orally, four times daily for 2 weeks	**Not mentioned.**	**Results at 2 weeks** **Complete healing:** I: 10/25 (40%) C: 9/27 (33%) **Relative Risk- 10/25 ÷ 9/27 = 1.21** **Improved lesions:** I: 14/25 (56%) C: 18/27 (67%) **Relative Risk- 14/25 ÷ 18/27 = 0.83** **Lesions not improved:** I: 1/25 (4%) C: 0/27 (0%)

						Adverse effects: I: 1 patient had mild Diarrhoea C: 2 patients had mild nausea and diarrhoea No tests of statistical significance reported
Additional comments: Randomisation was performed (method not stated). Blinding performed. 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: Lipsky BA, Pecoraro RE, Larson SA et al. (1990) Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Archives of Internal Medicine 150: 790-7.

G.12 Review question 12 full evidence tables

Table 10: Edmonds 2009

Bibliographic reference	**Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. *The international journal of lower extremity wounds*, *8*(1), 11-18.**
Study type	Randomised control trial
Study quality	Summary Population: United Kingdom, European Union, Australia. participants did not exactly match population of interest as people with Charcot foot were excluded, as were participants with any signs of infection. Intervention: Apligraf Comparison: Standard therapy Outcome: Complete healing, wound closure, adverse events 1. Has an appropriate method of randomisation been used? Unclear method of randomisation 2. Was there adequate concealment of allocation? Allocation was adequately concealed in a sealed envelope 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar for demographics, duration of diabetes and duration of target ulcer. No P values were provided for other potential differences at baseline. 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received standard care. The Apligraf group could have additional applications if required. Otherwise participants were seen at similar intervals. The mean number of debridements between the two treatment groups was similar. 5. Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6. Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? An intention to treat analysis was performed in those who had been randomised and received at least one treatment. After randomisation 7 were lost to the apligraf group and 3 were lost control group. No participants were lost to follow up in the

Bibliographic reference	**Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. *The international journal of lower extremity wounds*, *8*(1), 11-18.**
	treatment group and 1 was lost in the control group following treatment. 8. Did the study have an appropriate length of follow up? Follow up was appropriate (3 months) 9. Did the study use a precise definition of outcome? A precise definition of outcome was used (see below) 10. Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11. Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participants exposure to the intervention. 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. Trial was terminated prematurely by the study sponsor with unclear reasons. Unclear source of funding The author has also been reimbursed by Organogenesis, Inc. Manufacturer of Apligraf for attending conferences and has received an honoraria for providing clinical expertise in meetings with regulatory agencies.
Number of patients	Randomised= 72 Treatment group= 33 Control group = 42
Patient characteristics	Patients taken from: United Kingdom, European Union, Australia Inclusion: Aged 18-80 years Written informed consent Ulcer of primarily neuropathic origin, limited to plantar region, through the dermis without sinus tract, tendon capsule or bone exposure. Present at least 2 weeks at the date of screening. Surface area between 1 and 16 cm^2. Maximum of two ulcers on target foot. Not infected. Diminished sensation. Diabetic type 1 or type 2

Bibliographic reference	**Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. *The international journal of lower extremity wounds*, *8*(1), 11-18.**

Adequate vascular supply to target extremity
Available to visit outpatient department for 6.5 months
Can tolerate extensive debridement
Can follow strict offloading requirements

Exclusion:
Active Charcot foot or inactive Charcot foot that cannot be properly off loaded
Ulcers of non-neuropathic origin
Evidence of skin cancer within or adjacent to target ulcer site
Osteomyelitis
Infected target ulcers
Clinically significant medical conditions that would impair wound healing
Pregnancy
Females of childbearing potential who are not practicing medically approved forms of contraception or are rhesus-D negative.
Receiving or having received within the last four weeks: systemic corticosteroids; immunosuppressive agents; chemotherapy or radiotherapy.
Investigational drug, device or biologic within 8 weeks prior to the study
History of any skin graft at the target ulcer site within the past 12 weeks
History of drug or alcohol abuse
Uncooperative or non-compliant patients
Any other condition that in the opinion of the investigator would render the patient ineligible

Baseline characteristics:

Characteristics	Apligraf group	Control group
n	33	39
Age, y	56.4 ± 11.6	60.6 ± 9.8
Male/female	29/4	33/6
Weight, kg	98.1	97.9
Height, cm	177.9 ± 7.7	177.5 ± 10.0
Duration of diabetes, y	15.7 ± 9.2	16.0 ± 9.1
Type of diabetes Type 1	 16 (48.5%)	 13 (33.3%)

Bibliographic reference	**Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. *The international journal of lower extremity wounds*, *8*(1), 11-18.**
	Type 2 — 17 (51.5%) — 26 (66.7%) Duration of target ulcer, y Median — 1.1 — 1.2 Range — 0.1-8.0 — 0.0-7.0 Ulcer size Median — 2.50 — 2.25 Range — 0.8–9.3 — 0.5–10.0
Intervention	Apligraf placed directly on the bed of the target ulcer. Then a primary, nonadherent dressing. Secondary dressing then applied to the site. Standard care was consistent with international treatment guidelines and comprised of sharp debridement, saline-moistened dressings and a non-weight bearing regimen.
Comparison	Control group received the same primary and secondary dressings without the Apligraf. As well as standard care.
Length of follow up	Length of follow up was 3 months
Location	United Kingdom, European Union, Australia
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Kaplan-Meier curves were provided but not reported here. Time to complete wound healing showed a trend to shorter time in the Apligraf group compared to the control group during the 12 week treatment period (P=0.059) however this is non-significant. Healing was defined as full epithelialization with no drainage. Incidence to complete healing by 12 weeks: Apligraf treatment group: 17 of 33 participants Control group: 10 of 38 participants P value= 0.049 i.e. significant difference Rates and extent of amputation: No data provided on rates and extent of amputation Length of stay: No data provided on length of stay

Bibliographic reference	**Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. *The international journal of lower extremity wounds*, *8*(1), 11-18.**
	Health related quality of life: No data provided on health related quality of life Adverse events: Number of non-fatal serious adverse events (definition consistent with International Conference on Harmonisation guidelines) During treatment phase: Apligraf treatment group: 4 of 33 participants Control group: 5 of 38 1 additional apligraf participant received a fatal myocardial infarction non-attributable to the treatment. During follow up phase: Apligraf treatment group: 4 of 33 participants Control group: 3 of 38 participants None of the adverse events were thought attributable to the Apligraf treatment
Source of funding	Unclear source of funding
Comments	

Table 11: Abidia 2003

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
Study type	Randomised control trial
Study quality	Summary Population: United Kingdom

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
	Intervention: Hyperbaric oxygen therapy Comparison: Standard therapy (air) Outcome: Complete healing, quality of life 1) Has an appropriate method of randomisation been used? Acceptable method of randomisation was used (randomisation code) 2) Was there adequate concealment of allocation? Allocation was concealed using sealed envelopes 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? In the treatment group 1 participant was withdrawn and 1 was withdrawn in the control group. Groups were comparable for availability of outcome data 8) Did the study have an appropriate length of follow up? Follow up was appropriate all outcomes (1 year) 9) Did the study use a precise definition of outcome? Precise definitions of outcomes were used (see below). 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
Number of patients	Randomised= 18 Treatment group= 9 Control group = 9
Patient characteristics	Patients taken from: United Kingdom Inclusion: Ulcer 1–10 cm in maximum diameter. Non-healing despite optimum medical management for more than 6 weeks since presenting. Occlusive arterial disease confirmed by ankle brachial pressure index <0.8 (or great toe-brachial pressure index <0.7 if calf muscles were incompressible) HbA1c <8.5% Exclusion: Patients for whom vascular surgery, angioplasty or thrombolysis was planned Baseline characteristics:

Characteristics	Hyperbaric Oxygen group	Control group
n	9	9
Age, y	72 ± 12.6	70 ± 6.6
Male/female	2:1	1:2
Body Mass Index	26 ± 7	29 ± 4
Insulin therapy	4/8	5/8
Duration of diabetes, y	15.7 ± 9.2	16.0 ± 9.1
Type of diabetes	Not provided	Not provided
Smokers	1/8	2/8
Ulcer size at baseline	Not provided	Not provided
Neuropathy (biothesiometer)	47 ± 16.2	55 ± 13.7
Previous amputation Minor Major	 1/8 0/8	 2/8 0/8
Previous ulcers	3/8	4/8

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
	HbA1c | Not provided | Not provided No significant differences observed
Intervention	Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute for 90 minutes daily, 5 days per week, totalling 30 sessions. Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection.
Comparison	Air given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute for 90 minutes daily, 5 days per week, totalling 30 sessions. Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection.
Length of follow up	Length of follow up was 1 year
Location	United Kingdom
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: At 6 weeks follow up Complete healing defined as complete epithelialisation of ulcer evident. Hyperbaric treatment group: 5 of 8 participants Control group: 1 of 8 participants Non-significant At 6 months follow up Complete healing defined as complete epithelialisation of ulcer evident. Hyperbaric treatment group: 5 of 8 participants Control group: 2 of 8 participants Non-significant

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
	At 1 year follow up Complete healing defined as complete epithelialisation of ulcer evident. Hyperbaric treatment group: 5 of 8 participants Control group: 0 of 8 participants P value = 0.026 i.e. significant difference Rates and extent of amputation: Major Hyperbaric treatment group: 1 of 8 participants Control group: 1 of 8 participants Minor Hyperbaric treatment group: 1 of 8 participants Control group: 0 of 8 participants Length of stay: No data provided on length of stay Mean number of visits for dressing of study ulcer: Hyperbaric treatment group: 33.75 (±62) Control group: 136.5 (±126) Health related quality of life: Depression score as defined by the HAD scale: Improvement in the depression score was significant in both groups Hyperbaric treatment group: P=0.011 Control group: P= 0.023 Only the control group had significant improvement in anxiety score: P=0.042

Bibliographic reference	**Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... & McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery*, *25*(6), 513-518.**
	General health and vitality as defined by the SF–36 score: Hyperbaric treatment group: P=0.012 Control group: P= 0.018 Significant improvement in both groups Overall there were found to be no significant improvements in quality of life measures greater than those already seen in patients in the control group as measured by the SF–36 and HADS. Adverse events: Outcomes for adverse events were not reported
Source of funding	Unclear source of funding
Comments	

Table 12: Ma 2013

Bibliographic reference	**Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.*Ostomy/wound management*, *59*(3), 18-24.**
Study type	Randomised control trial
Study quality	Summary Population:China Intervention: Hyperbaric oxygen therapy Comparison: Standard therapy: offloading, debridement, dressings Outcome: TcPO2 and ulcer area 1) Has an appropriate method of randomisation been used? Acceptable method of randomisation was used (randomisation table) 2) Was there adequate concealment of allocation?

Bibliographic reference	**Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.*Ostomy/wound management*, *59*(3), 18-24.**
	Patient allocation was not concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included offloading, aggressive debridement and regular dressing. Patients with suspected infection however, received silver impregnated dressing. Antibiotic therapy was also given if there were signs of infection. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no loss to follow up among those randomised. Groups were comparable for availability of outcome data 8) Did the study have an appropriate length of follow up? Follow up needed to be longer to gain the useful outcome of complete healing. Follow up was only 2 weeks. 9) Did the study use a precise definition of outcome? Unclear definition of complete ulcer healing. Poor definition of serious adverse events. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. Standardised photography was used to measure wound area. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention on only two occasions (day 7 and day 14). Investigators were not blinded on day 0. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 36 Treatment group= 18 Control group = 18
Patient characteristics	Patients taken from: China

Bibliographic reference	**Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.*Ostomy/wound management*, *59*(3), 18-24.**

Inclusion:
Diagnosis of diabetes mellitus
At least one full thickness wound below the ankle (Wagner grade III or less) for > 3 months
History of receiving standard care for >2 months
Normal palpation of arterial pulses at lower extremities
Normal lower limb Doppler scan results
TcPO2 > 30 mm Hg at the dorsum of the foot
No abnormal Xray findings that may be indicative of chronic bone infection

Exclusion:
Wounds classified as more severe than Wagners grade III
TcPO2 at the dorsum of the foot <30 mm Hg
Upper respiratory infection
Emphysema
History of thoracic surgery
Malignant disease
Middle ear barotraumas
Pregnancy
Smoking or abstention for <1 month

Baseline characteristics:

Characteristics	Hyperbaric Oxygen group	Control group
n	18	18
Age, y	59.8 ± 6.5	60.4 ± 5.6
Male/female	11:7	12/6
Body Mass Index	29.18 ± 2.18	29.48 ± 1.45
Insulin therapy	16	17
Duration of diabetes, y	24.8 ± 16.9	23.1 ± 16.6
Type of diabetes	Type 1: 3 Type 2: 15	Type 1: 2 Type 2: 16
Smokers	Not reported	Not reported
Ulcer size at baseline	4.21± 0.99	4.35 ± 1.04

<table>
<tr><td>Bibliographic reference</td><td>Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.Ostomy/wound management, 59(3), 18-24.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Ulcer duration (months)</td><td>11.3 ± 8.5</td><td>14.3 ± 11.6</td></tr>
<tr><td>Neuropathy (biothesiometer)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Coronary artery disease</td><td>4</td><td>5</td></tr>
<tr><td>Renal impairment</td><td>4</td><td>2</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>
11
7</td><td>
9
9</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III</td><td>
4
4
10</td><td>
5
6
7</td></tr>
</table>

No significant differences observed (P values provided)</td></tr>
<tr><td>Intervention</td><td>Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute, twice a day for 90 minutes, 5 days per week, for 2 weeks (20 treatment sessions).

Wound care was standardised for all patients and included offloading, aggressive debridement and dressing. Antibiotic therapy was given if there were signs of infection. Silver impregnated dressings were used if infection were suspected</td></tr>
<tr><td>Comparison</td><td>Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection.</td></tr>
<tr><td>Length of follow up</td><td>Length of follow up was 12 weeks</td></tr>
<tr><td>Location</td><td>China</td></tr>
<tr><td>Outcomes measures and</td><td>Cure rates of foot ulcer resulting from diabetes:</td></tr>
</table>

Bibliographic reference	**Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.*Ostomy/wound management*, *59*(3), 18-24.**
effect size	At 6 weeks follow up Complete healing unclear definition Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant At 12 weeks follow up Complete healing unclear definition Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant Rates and extent of amputation: At 6 weeks follow up Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant At 12 weeks follow up Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant Length of stay: No data provided on length of stay Health related quality of life: No data provided Adverse events:

Bibliographic reference	**Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer.*Ostomy/wound management*, *59*(3), 18-24.**
	Serious complications such as death, amputation, barotraumatic otitis, dizziness, seizures, pneumothorax. Clearer definition not provided. At 6 weeks follow up Serious adverse events Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant At 12 weeks follow up Serious adverse events Hyperbaric treatment group: 0 of 8 participants Control group: 0 of 8 participants Non-significant
Source of funding	Research funding from Subei People's Hospital of Yangzhou University
Comments	

Table 13: Londahl 2010

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
Study type	Randomised control trial (the HODFU study)
Study quality	Summary Population: Sweden Intervention: Hyperbaric oxygen therapy Comparison: Standard therapy: offloading, debridement, dressings and hyperbaric air Outcome: Complete healing, Quality of life, amputation, death, adverse reactions 1) Has an appropriate method of randomisation been used? Randomisation was done in blocks of 10. Patients were stratified based on arterial toe blood pressure 2) Was there adequate concealment of allocation? Clear allocation concealment with sealed envelopes used 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline. No significant differences reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included revascularisation, offloading, aggressive debridement, regular dressing, metabolic control and regular attendance at the multidisciplinary diabetes foot clinic. Unclear wound dressing methods. Antibiotic therapy was also given if there were signs of infection. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Groups were comparable for availability of outcome data. They were also comparable for the number that withdrew following randomisation: 11 in the treatment group and 8 in the placebo arm. Intention to treat analysis was used. 8) Did the study have an appropriate length of follow up? Follow up was of an appropriate length (1 year)

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
	9) Did the study use a precise definition of outcome? There was a precise definition of ulcer healing and other outcomes 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 94 Treatment group= 49 Placebo group = 45
Patient characteristics	Patients taken from: Sweden Inclusion: Diabetes At least one full thickness wound below the ankle for > 3 months Previously treated in a diabetes clinic for a period of no less than 2 months Adequate distal perfusion or nonreconstructable peripheral vascular disease Resolved acute phase infection of the foot Exclusion: Contraindications for hyperbaric treatment (severe obstructive pulmonary disease, malignancy, untreated thyrotoxicosis) Current drug or alcohol misuse Vascular surgery in the lower limbs in the past 2 months

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
	Participation in another study Suspected poor compliance Baseline characteristics:

Characteristics	Hyperbaric Oxygen group	Control group
n	49	45
Age, y, median	69 (37-95)	68 (28-86)
Male/female	27:22	29:16
Body Mass Index	Not reported	Not reported
Insulin therapy (%)	90	91
Duration of diabetes, y	20 (1-63)	23 (3-54)
Type of diabetes (%)	Type 1: 24 Type 2: 76	Type 1: 42 Type 2: 58
Smokers	22	29
Ulcer size at baseline cm^2	3.1 (0.6-55)	2.8 (0.6-39)
Ulcer duration (months)	9 (3-44)	10 (3-39)
Nephropathy (%)	90	80
Congestive heart failure (%)	35	27
Neuropathy	Not reported	Not reported
Previous amputation (%) Minor Major	 32 14	 47 7
Previous ulcers	Not reported	Not reported
HbA1c	7.8	8.1
Mobility (%) Walking with support Walking without support wheelchair	 38 43 18	 31 44 24

<table>
<tr><td>Bibliographic reference</td><td>Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes care, 33(5), 998-1003.

Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. Diabetic Medicine, 28(2), 186-190.

Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. Journal of clinical nursing, 18(14), 1975-1985.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Wagner Classification (%)
Grade I
Grade II
Grade III
Grade IV
Grade V</td><td>
0
24
51
24
0</td><td>
0
27
62
11
0</td></tr>
<tr><td>Previous vascular surgery (%)</td><td>57</td><td>49</td></tr>
</table>

No significant differences observed</td></tr>
<tr><td>Intervention</td><td>Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.5 atmospheres absolute, daily for 85 minutes, 5 days per week, for 8 weeks (40 treatment sessions).
Wound care was standardised for all patients and included revascularisation, offloading, aggressive debridement, regular dressing, metabolic control and regular attendance at the multidisciplinary diabetes foot clinic. Unclear wound dressing methods. Antibiotic therapy was also given if there were signs of infection.</td></tr>
<tr><td>Comparison</td><td>Air given in a multi-place chamber via hood at a pressure of 2.5 atmospheres absolute, daily for 85 minutes, 5 days per week, for 8 weeks (40 treatment sessions).
Wound care was standardised for all patients and included revascularisation, offloading, aggressive debridement, regular dressing, metabolic control and regular attendance at the multidisciplinary diabetes foot clinic. Unclear wound dressing methods. Antibiotic therapy was also given if there were signs of infection.</td></tr>
<tr><td>Length of follow up</td><td>Length of follow up was 1 year</td></tr>
<tr><td>Location</td><td>Sweden</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Cure rates of foot ulcer resulting from diabetes:</td></tr>
</table>

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
	An ulcer was considered healed when it was completely covered by epithelial regeneration and remained so until the next visit in the study. Wagner grade IV ulcers were considered healed when gangrene had separated and the ulcer below was completely covered by epithelial regeneration. Intention to treat analysis was used. At 1 year follow up (intention to treat analysis) Complete healing Hyperbaric treatment group: 25 of 48 participants Control group: 12 of 42 participants Significant difference (P=0.03) Number needed to treat= 4.2 At 1 year follow up (per protocol analysis analysis) Complete healing Hyperbaric treatment group: 23 of 38 participants Control group: 10 of 37 participants Significant difference (P=0.009) Number needed to treat= 3.1 More data is available in graph form regarding healing rates at 1, 2, 3, 6, 9 and 12 months between hyperbaric oxygen treatment and placebo should this be required for decision making or meta-analysis. Rates and extent of amputation: At 1 year follow up Major amputation Hyperbaric treatment group: 3 of 49 participants Control group: 1 of 45 participants

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**

At 1 year follow up
Minor amputation
Hyperbaric treatment group: 4 of 49 participants
Control group: 4 of 45 participants

Length of stay:
No data provided on length of stay

Health related quality of life:
Data provided via the paper by Londahl et al (2011) which included only participants that had completed 36 out of the 40 treatment sessions. All patients self reported quality of life in an SF-36 questionnaire both before therapy and at the 12 month follow up mark:

	Treatment group (n=23)			Placebo group (n=10		
SF 36 domain	Baseline	12 month	P value	Baseline	Follow up	P value
Physical functioning	40 ± 5	41 ± 6	Ns	32 ± 9	50 ± 9	Ns
Bodily Pain	30 ± 8	61 ± 8	<0.05	323 ± 14	70 ± 12	Ns
Role limitation due to physical health	62 ± 6	66 ± 5	Ns	48 ± 10	67 ± 10	Ns
General health	55 ± 4	54 ± 4	Ns	43 ± 6	46 ± 11	Ns
Vitality	55 ± 4	61 ± 4	Ns	52 ± 8	58 ± 10	Ns
Social function	72 ± 5	84 ± 4	Ns	66 ± 6	81 ± 10	Ns
Role limitation	65 ± 8	87 ± 6	<0.05	53 ± 16	67 ± 14	Ns

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**

due to emotional health						
Role limitation due to mental health	78 ± 4	80 ± 3	Ns	66 ± 6	71 ± 9	Ns
Physical health summary score	31 ± 2	33 ± 2	Ns	30 ± 4	38 ± 4	Ns
Mental health summary score	50 ± 3	55 ± 2	Ns	47 ± 3	48 ± 5	Ns

Adverse events:

At 1 year follow up
Death (fatal outcome)
Hyperbaric treatment group: 1 of 49 participants
Control group: 3 of 45 participants
Relation between hyperbaric oxygen therapy and the death cannot be excluded (multiple organ failure)

During treatment period (8 weeks)
Hypoglycaemia
Hyperbaric treatment group: 2 of 49 participants
Control group: 4 of 45 participants
Non-significant

During treatment period (8 weeks)

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
	Barotraumatic otitis Hyperbaric treatment group: 1 of 49 participants Control group: 0 of 45 participants During treatment period (8 weeks) Pain (due to not equalising air pressure through eustacian tube) Hyperbaric treatment group: 2 of 49 participants Control group: 2 of 45 participants These patients had a myringotomy performed During treatment period (8 weeks) Treatment related dizziness Hyperbaric treatment group: 1 of 49 participants Control group: 0 of 45 participants During treatment period (8 weeks) Worsening of cataracts Hyperbaric treatment group: 1 of 49 participants Control group: 0 of 45 participants During treatment period (8 weeks) Oxygen toxicity Hyperbaric treatment group: 0 of 49 participants Control group: 0 of 45 participants During treatment period (8 weeks)

Bibliographic reference	**Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes care*, *33*(5), 998-1003.** **Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine*, *28*(2), 186-190.** **Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *Journal of clinical nursing*, *18*(14), 1975-1985.**
	Seizures Hyperbaric treatment group: 0 of 49 participants Control group: 0 of 45 participants During treatment period (8 weeks) Pneumothorax Hyperbaric treatment group: 0 of 49 participants Control group: 0 of 45 participants
Source of funding	Supported by unrestricted grants from Thelma Zoegas foundation, Region Skane foundation and the medical faculty of Lund University
Comments	

Table 14: Faglia 1996

Bibliographic reference	**Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes care*, *19*(12), 1338-1343.**
Study type	Randomised control trial
Study quality	Summary Population: Italy. Only diabetic patients with full thickness gangrene (Wagner IV) or abscess (Wagner III). Subjects with less deep ulcers were also admitted if the ulcer was large and infected and showed defective healing in 30 days of outpatient therapy. Intervention: Hyperbaric oxygen therapy. (participants only received 8 sessions on this occasion)

Bibliographic reference	**Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes care*, *19*(12), 1338-1343.**
	Comparison: Standard therapy: offloading, debridement, dressings, empirical broad spectrum antibiotic therapy for all participants and optimisation of glucose control. The need for percutaneous transluminal angioplasty or bypass graft was assessed in certain patients. Outcome: Amputations, TcPO2 1) Has an appropriate method of randomisation been used? An acceptable method of randomisation was used (random number table) 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed. 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included orthopaedic devices for the feet, debridement and dressing up to twice a day. All patients received empirical antibiotic therapy 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Two participants were lost to follow up among those randomised. Groups were comparable for availability of outcome data 1 person was lost to each group. 8) Did the study have an appropriate length of follow up? Follow up appears to be variable between participants depending on length of hospital stay. Attempts were made to account for this by reporting rates. 9) Did the study use a precise definition of outcome? Clear definition of amputation. Unfortunately the paper only provides the mean number of days of hospital stay and the number of amputations that were performed in this time. Total number of days of hospital stay can be confounded by whether a participant has had an amputation or not. 10) Was a valid and reliable method used to determine that outcome? Unclear if valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention.

<table>
<tr><td>Bibliographic reference</td><td>Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes care, 19(12), 1338-1343.</td></tr>
<tr><td></td><td>12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)</td></tr>
<tr><td>Number of patients</td><td>Randomised= 70
Treatment group= 36
Control group = 34</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: Italy

Inclusion:
Only diabetic patients with full thickness gangrene (Wagner IV) or abscess (Wagner III). Subjects with less deep ulcers were also admitted if the ulcer was large and infected and showed defective healing in 30 days of outpatient therapy.

Baseline characteristics: No significant P values reported

<table>
<tr><td>Characteristics</td><td>Hyperbaric Oxygen group</td><td>Control group</td></tr>
<tr><td>n</td><td>35</td><td>33</td></tr>
<tr><td>Age, y</td><td>61.7 ± 10.4</td><td>65.6 ± 9.1</td></tr>
<tr><td>Male/female</td><td>27/8</td><td>21/12</td></tr>
<tr><td>Obesity</td><td>9</td><td>9</td></tr>
<tr><td>Insulin therapy</td><td>21</td><td>22</td></tr>
<tr><td>Duration of diabetes, y</td><td>16 ± 10</td><td>19 ± 9</td></tr>
<tr><td>Type of diabetes</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Smokers</td><td>11</td><td>12</td></tr>
<tr><td>Ulcer size at baseline</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ulcer duration (months)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Neuropathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Coronary artery disease</td><td>14</td><td>15</td></tr>
<tr><td>Renal impairment</td><td>4</td><td>9</td></tr>
<tr><td>Retinopathy
Background
Proliferant</td><td>
12
13</td><td>
13
9</td></tr>
<tr><td>Previous amputation</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes care, 19(12), 1338-1343.</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>Minor
Major</td><td>6
0</td><td>10
0</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c
Baseline
discharge</td><td>
9.3 ± 2.5
7.1 ± 1.5</td><td>
8.5 ± 2.3
6.6 ± 1.2</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>
0
4
9
22</td><td>
0
5
8
20</td></tr>
<tr><td>Total hospital stay</td><td>43.2 ± 31</td><td>50.8 ± 32</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Patients breathed pure oxygen in a multiplace hyperbaric chamber, pressurised with air, with a soft helmet. Pressure was 2.5 absolute atmosphere in the first phase and 2.4-2.2 in the second phase, daily for 90 minutes. (8 sessions total)
Wound care was standardised for all patients and included orthopaedic devices for the feet, debridement and dressing up to twice a day. All patients received empirical antibiotic therapy</td></tr>
<tr><td>Comparison</td><td colspan="3">Wound care was standardised for all patients and included orthopaedic devices for the feet, debridement and dressing up to twice a day. All patients received empirical antibiotic therapy</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Length of follow up was variable, unclear if length was adequate</td></tr>
<tr><td>Location</td><td colspan="3">Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Cure rates of foot ulcer resulting from diabetes:
No data provided

Rates and extent of amputation:
Data must be calculated from total hospital stay mean data and number of amputations:</td></tr>
</table>

Bibliographic reference	**Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes care*, *19*(12), 1338-1343.**
	Major amputations Number of amputated limbs Hyperbaric treatment group: 3 of 35 participants Control group: 11 of 33 participants Number of salvaged limbs Hyperbaric treatment group: 32 of 35 participants Control group: 22 of 33 participants Minor amputations Forefoot Hyperbaric treatment group: 5 of 35 participants Control group: 4 of 33 participants Toe Hyperbaric treatment group: 16 of 35 participants Control group: 8 of 33 participants No amputation Hyperbaric treatment group: 11 of 35 participants Control group: 10 of 33 participants Length of stay: Mean total length of hospital stay was Hyperbaric treatment group: 43.2 ± 31 days Control group: 50.8 ± 32 days Mean length of hospital stay till major amputation was

Bibliographic reference	**Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes care*, *19*(12), 1338-1343.**
	Hyperbaric treatment group: 57.6 ± 24 days Control group: 72.8 ± 59 days Health related quality of life: No data provided Adverse events: No data provided
Source of funding	Unclear source of funding
Comments	

Table 15: Gentzkow 1996

Bibliographic reference	**Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes care*, *19*(4), 350-354.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Dermagraft, a cultured human dermis. Comparison: Standard therapy: pressure relief, debridement, dressings. Outcome: treatment completion, wound closure, treatment completion, recurrence 1) Has an appropriate method of randomisation been used? An acceptable method of randomisation was used 2) Was there adequate concealment of allocation? Patient allocation was concealed in sealed envelopes 3) Were the groups comparable at baseline for all major confounding/prognostic factors?

Bibliographic reference	**Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes care*, *19*(4), 350-354.**
	Groups were reported similar at baseline although the control group were significantly younger of age. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included sharp debridement, saline moistened gauze dressing and pressure relief. The study took place across 5 institutions however dressings were standardised. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. (single blind) 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Groups were comparable for availability of outcome data 1 person was lost to each group. Intention to treat analysis was used. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (12 weeks). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing. Full epithelialisation was required. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 50 Group A: one piece of dermagraft applied weekly for a total of 8 pieces and eight applications, plus control treatment.= 12 Group B : two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment= 14 Group C: one piece of dermagraft applied every 2 weeks for a total of four pieces and four applications, plus control treatment= 11 Group D (control) conventional therapy and wound-dressing techniques.= 13
Patient characteristics	Patients taken from: Italy

Bibliographic reference	**Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes care*, *19*(4), 350-354.**
	Inclusion: Type 1 or 2 diabetes Full thickness ulcer > 1cm² Free of necrotic tissue or infection at randomisation and suitable for skin graft Circulation adequate for healing Able to complete a 12 week course Exclusion: More than one episode of hospitalisation within the previous 6 months due to hyperglycaemia, hypoglycaemia or ketoacidosis Ulcers of non-diabetic origin Exposed bone, tendon or joint Medications known to interfere with healing pregnant Baseline characteristics: P values reported statistically significant for the differences for age between groups. Control group had a younger age.

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes care, 19(4), 350-354.</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><th>Characteristics</th><th>Dermagraft A</th><th>Dermagraft B</th><th>Dermagraft C</th><th>Control group</th></tr>
<tr><td>n</td><td>12</td><td>14</td><td>11</td><td>13</td></tr>
<tr><td>Age, y</td><td>62.7</td><td>66.2</td><td>62.7</td><td>53.8</td></tr>
<tr><td>Male/female</td><td>8/4</td><td>11/3</td><td>7/4</td><td>9/4</td></tr>
<tr><td>Body Mass Index</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Type of diabetes type2/type1</td><td>5/7</td><td>5/9</td><td>2/9</td><td>3/10</td></tr>
<tr><td>Smokers</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ulcer size at baseline (cm²)</td><td>2.2</td><td>2.3</td><td>3.3</td><td>1.9</td></tr>
<tr><td>Ulcer duration (weeks)</td><td>50.4</td><td>40.7</td><td>43.2</td><td>87.0</td></tr>
<tr><td>Neuropathy</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Coronary artery disease</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Renal impairment</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Retinopathy</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c</td><td>8.0</td><td>8.2</td><td>8.4</td><td>9.1</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td rowspan="3">Intervention</td><td colspan="2">Group A: one piece of dermagraft applied weekly for a total of 8 pieces and eight applications, plus control treatment.= 12</td></tr>
<tr><td colspan="2">Group B : two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment= 14</td></tr>
<tr><td colspan="2">Group C: one piece of dermagraft applied every 2 weeks for a total of four pieces and four applications, plus control treatment= 11</td></tr>
<tr><td>Comparison</td><td colspan="2">Group D (control) conventional therapy and wound-dressing techniques.= 13</td></tr>
</table>

Bibliographic reference	**Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes care*, *19*(4), 350-354.**
	Wound care was standardised for all patients and included sharp debridement, saline moistened gauze dressing and pressure relief. The study took place across 5 institutions however dressings were standardised.
Length of follow up	Length of follow up was12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Wound closure at 12 weeks Full epithelialisation (calculated from percentages provided Dermagraft treatment A: 6 of 12 participants Dermagraft treatment B: 3 of 14 participants Dermagraft treatment C: 2 of 11 participants Control group D: 1 of 13 participants P=0.03 (for A vs D) i.e. significant difference. Wound closure at 12 weeks Median time to full epithelialisation Dermagraft treatment A: 12 weeks Dermagraft treatment B: >12 weeks Dermagraft treatment C: >12 weeks Control group D: >12 weeks Data also available for 50% closure times and completion. Rates and extent of amputation: No data provided Length of stay: No data provided

Bibliographic reference	**Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes care*, *19*(4), 350-354.**
	Health related quality of life: No data provided Adverse events: Infection development Dermagraft treatment A: 2 of 12 participants Dermagraft treatment B: 4 of 14 participants Dermagraft treatment C: 3 of 11 participants Control group D: 3 of 13 participants
Source of funding	Advanced Tissue Sciences, Inc. provided financial support
Comments	

Table 16: Veves 2001

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Graftskin, a human skin equivalent. Comparison: Standard therapy: offloading, debridement, moist saline gauze dressings.

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
	Outcome: complete wound healing 1) Has an appropriate method of randomisation been used? An acceptable method of randomisation was used. Computer generated randomisation schedule. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors. Some important variable were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included debridement, regular dressing changes and offloading. Within the treatment group participants could receive different amounts of Graftskin applications as required. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? A large proportion of participants were excluded after randomisation (69), normally exclusion takes place before randomisation, this may increase opportunity for the introduction of bias. Following exclusion groups were comparable for availability of outcome data 22 people were lost to each group, however none were lost in either group with regards to primary outcome. Intention to treat analysis was used. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (3 months). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing and adverse reactions. Full epithelialisation was required with no wound drainage. 10) Was a valid and reliable method used to determine that outcome?

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
	A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 277 Treatment group= 112 Control group= 96
Patient characteristics	Patients taken from: USA Inclusion: Type 1 or 2 diabetes Age 18-80 years HbA1c between 6 and 12% Full thickness neuropathic ulcers ≥2 weeks duration Postdebridement ulcer size between 1 and 16 cm^2 Dorsalis pedis and posterior tibialis pulses audible by doppler Exclusion: Dorsum of foot and calcaneus ulcers Clinical infection at the ulcer site Significant lower extremity ischaemia

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**

Active Charcot's disease

Ulcer of non-diabetic pathophysiology

Significant medical conditions that would impair healing (liver disease, aplastic anaemia, scleroderma, malignancy, and treatment with immunosuppressive agents or steroids.

Participants whose ulcers responded to treatment with saline moistened gauze.

Baseline characteristics: Study reports no differences in baseline characterisitics.

Characteristics	Graftskin	Control
n	112	96
Age, y	58 ± 10	56 ± 10
Male/female	88/24	74/22
Body Mass Index	30.9 ± 6.54	33.1 ± 7.72
Ethnicity (Caucasian/African-american/Hispanic)	77/20/14	67/14/13
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type2/type1	5/7	5/9
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	2.97 ± 3.10	2.83 ± 2.45
Ulcer duration (months)	11.5 ± 13.3	11.1 ± 12.5
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported

<table>
<tr><td>Bibliographic reference</td><td>Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. Diabetes Care, 24(2), 290-295.

Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..

Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c</td><td>8.6 ± 1.5</td><td>8.6 ± 1.6</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Graftskin applied directly over the ulcer site. The site was then covered with a layer of saline moistened tegapore. The wound was then dressed at participants in the graftskin group could have Graftskin reapplied at study weeks 1–4 for a maximum of 5 applications if required.

Wound care was standardised for all patients and included debridement, regular dressing changes and offloading. Full dressing changes were performed at weeks 1,2,3 and 4. Secondary dressings were changed daily. Patients received customised sandals for offloading.</td></tr>
<tr><td>Comparison</td><td>Wound care was standardised for all patients and included debridement, regular dressing changes and offloading. Full dressing changes were performed at weeks 1,2,3 and 4. Secondary dressings were changed daily. Patients received customised sandals for offloading.

In both groups if ulcers were not healed by week 5, dressings were changed twice daily.</td></tr>
<tr><td>Length of follow up</td><td>Length of follow up was 3 months</td></tr>
</table>

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 3 months Full epithelialisation Treatment group : 63 of 112 participants Control group: 36 of 96 participants P=0.0042 i.e. significant difference. Odds ratio: 2.14 (95% confidence interval= 1.23–3.74) Kaplan Meier median time to complete closure was: Treatment group : 65 days Control group: 90 days P=0.0026 i.e. significant difference. A graph of percentage wounds closed by study day is available in the study but not otherwise reported here. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life:

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
	No data provided Adverse events: Wound infection Treatment group : 12 of 112 participants Control group: 13 of 96 participants P=0.67 i.e. no significant difference. Cellulitis Treatment group : 10 of 112 participants Control group: 8 of 96 participants P=1.00 i.e. no significant difference. Osteomyelitis Treatment group : 3 of 112 participants Control group: 10 of 96 participants P=0.04 i.e. significant difference. Amputations on study limb Treatment group : 7 of 112 participants Control group: 15 of 96 participants P=0.028 i.e. significant difference. Reulceration within first 6 months

Bibliographic reference	**Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. *Diabetes Care*, *24*(2), 290-295.** **Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..** **Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.**
	Treatment group : 3 of 112 participants Control group: 4 of 96 participants P=0.42 i.e. no significant difference.
Source of funding	Organogenesis provided financial support (Canton, MA)
Comments	

Table 17: Marston 2003

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Dermagraft Comparison: Standard therapy: pressure relief (unmonitored), debridement, moist saline gauze dressings. Outcome: complete wound healing, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**
	3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors. Some important variable were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included debridement, moist saline dressing and pressure relieving footwear, however patients were allowed to remain ambulatory. Treatment took place at 35 centres across the USA therefore potential for differences in standard of care. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Forty-six participants withdrew before the end of the study. Unclear how many were lost to each group however data was available for the primary outcome for all participants. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (12 weeks). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing and adverse reactions. Full epithelialisation was required with no wound drainage. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely) Participants were also stratified depending on the size of ulcer at baseline: from 1-2 cm^2 and >2–20 cm^2
Number of patients	Randomised= 245 Treatment group= 130 Control group= 115
Patient characteristics	Patients taken from: USA

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**

Inclusion:
Type 1 or 2 diabetes
Age ≥18 years
Ulcer present for a minimum of 2 weeks
Patients foot ulcer is on the plantar surface of the forefoot or heel and ≥1.0 cm² at baseline
Patients ulcer extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone or joint capsule
Patients wound is free of necrotic debris and appears to be healthy vascularised tissue
Patient has adequate circulation to the foot as evidenced by a palpable pulse.

Exclusion:
Gangrene
Ulcer over Charcot deformity
Ulcer total surface >20 cm²
Patients ulcer has decreased or increased in size by 50% or more during the screening period
Severe malnutrition as evidenced by albumin <2.0
Patients random blood sugar >450 mg/dl
Urine ketones, small moderate or large
Patient has a non study ulcer located within 7.0 cm of the study ulcer
Patient is receiving oral or parenteral corticosteroids, immunosuppressive or cytotoxic agents, Coumadin or heparin
Patient has AIDS or is HIV positive
Cellulitis, osteomyelitis or other evidence of infection present

Baseline characteristics: Study reports no differences in baseline characterisitics.

Characteristics	Dermagraft	Control
n	130	115
Age, y	55.8	55.5
Male/female	90/40	91/24
Body Mass Index	Not reported	Not reported
Ethnicity (Caucasian/non-caucasian)	90/40	87/28
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**
	<table><tr><td>Type of diabetes type1/type2</td><td>32/98</td><td>27/88</td></tr><tr><td>Smokers</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Ulcer size at baseline (cm²)</td><td>2.31</td><td>2.53</td></tr><tr><td>Ulcer duration (weeks)</td><td>41</td><td>67</td></tr><tr><td>Neuropathy</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Coronary artery disease</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Renal impairment</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Retinopathy</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Previous amputation Minor Major</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr><tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Mobility Walking with support Walking without support</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Wagner Classification Grade I Grade II Grade III Grade IV</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr></table>
Intervention	Dermagraft application and standard care Wound care was standardised for all patients and included debridement, moist saline dressing and pressure relieving footwear, however patients were allowed to remain ambulatory.
Comparison	Wound care was standardised for all patients and included debridement, moist saline dressing and pressure relieving footwear, however patients were allowed to remain ambulatory.
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and	Cure rates of foot ulcer resulting from diabetes:

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**
effect size	Complete wound healing by 12 weeks Full epithelialisation Treatment group : 39 of 130 participants Control group: 21 of 115 participants P=0.023 i.e. significant difference. Bayesian probability of benefit: 98.4% Complete wound healing by 12 weeks for forefoot/toe ulcers Full epithelialisation Treatment group : 33 of 112 participants Control group: 20 of 102 participants P=0.065 i.e. significant difference. Complete wound healing by 12 weeks for heel ulcers Full epithelialisation Treatment group : 6 of 18 participants Control group: 1 of 13 participants P=0.10 i.e. no significant difference. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Wound infection

Bibliographic reference	**Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. *Diabetes Care*, *26*(6), 1701-1705.**
	Treatment group : 17 of 163 participants Control group: 27 of 151 participants P=0.073 i.e. no significant difference. Cellulitis Treatment group : 12 of 163 participants Control group: 14 of 151 participants P=0.547 i.e. no significant difference. Osteomyelitis Treatment group : 14 of 163 participants Control group: 13 of 151 participants P=1.000 i.e. no significant difference.
Source of funding	Advanced Tissue Sciences Inc. and Smith and Nephew, Inc. provided funding for this study
Comments	

Table 18: Hanft 2002

Bibliographic reference	**Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Dermagraft, human fibroblast-derived dermis Comparison: Control therapy consisted of sharp debridement, offloading, and sailine moistened gauze. Unclear how regularly dressings were changed. Outcome: complete wound healing, adverse events, time to complete wound closure 1) Has an appropriate method of randomisation been used?

Bibliographic reference	Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.
	Unclear method of randomisation was used 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients apart from intervention under study. Study took place in multiple centres however with potential for variable care. 5) Were participants receiving care kept blind to treatment allocation? Participants were not told to which group they were randomised however allocation would have been difficult to conceal 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? 5 participants did not complete the study however outcome data appears to be available for all participants. Unclear to which groups there was loss to follow up. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (12 weeks). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing and adverse reactions. Full epithelialisation was required with no wound drainage. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely) Participants were also stratified depending on the size of ulcer at baseline: from 1-2 cm^2 and >2–20 cm^2
Number of patients	Randomised= 28 Treatment group= 14 Control group= 14

Bibliographic reference	**Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.**
Patient characteristics	Patients taken from: USA Inclusion: Type 1 or type 2 diabetes with a plantar foot ulcer on the heel or forefoot (including the toes) with a plantar foot ulcer on the heel or forefoot (including the toes) Ulcer: ≥1 cm^2 and ≤20 cm^2 and the ulcer had not decreased or increased in size by 50% or more during the 2 week screening period Excluded: Tunnels, sinus tracts, cellulitis, osteomyelitis or signs of infection in the study ulcer In adequate circulation to the study foot: lack of palpable dorsalis pedis or posterior tibialis artery Ankle brachial pressure index of <0.7 Albumin <2.0 Random blood sugar >450 mg/dL Urine ketones were small, moderate or large Women pregnant or of childbearing potential and not using an acceptable form of birth control Baseline characteristics: Study reports no differences in baseline characterisitics.

Characteristics	Dermagraft	Control
N	24	22
Age, years	54.07 ± 15.62	58.21 ± 10.79
Male/female	13/1	13/1
Body Mass Index	29.95 ± 7.35	32.64 ± 9.21
Ethnicity (Caucasian/non-caucasian)	8/6	8/6
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	1/13	3/11
Smokers	4	2
Ankle-arm index	1.07 ± 0.20	1.10 ± 0.27
Ulcer size at baseline (> 2 cm^2)	11	11
Ulcer duration (weeks)	21.00 ± 18.20	80.79 ± 188.90
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported

<table>
<tr><th>Bibliographic reference</th><td colspan="3">Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Renal impairment</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Retinopathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c</td><td>7.95 ±2.50</td><td>7.96 ± 1.91</td></tr>
<tr><td>Mean hours non weight bearing</td><td>14.38 ± 5.24</td><td>15.99 ± 3.10</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="3">Dermagraft application and standard care. Up to 7 additional applications could be given.

Standard therapy consisted of sharp debridement, offloading, and sailine moistened gauze. Unclear how regularly dressings were changed.</td></tr>
<tr><td>Comparison</td><td colspan="3">Control therapy consisted of sharp debridement, offloading, and sailine moistened gauze. Unclear how regularly dressings were changed.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Length of follow up was 12 weeks</td></tr>
<tr><td>Location</td><td colspan="3">USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Cure rates of foot ulcer resulting from diabetes:

Patients with ulcers >6 weeks duration at baseline who achieved wound closure by week 12
Full epithelialisation with no drainage
Treatment group : 10 of 14 participants
Control group: 2 of 14 participants
P=0.003 i.e. significant difference.
Bayesian probability of benefit: 98.4%

Complete wound healing by 12 weeks for all participants</td></tr>
</table>

Bibliographic reference	Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.
	Full epithelialisation with no drainage Treatment group : 15 of 24 participants Control group: 6 of 22 participants Complete wound healing by 12 weeks for all participants with toe or forefoot ulcers Full epithelialisation with no drainage Treatment group : 7 of 10 participants Control group: 2 of 13 participants Complete wound healing by 12 weeks for all participants with heel ulcers Full epithelialisation with no drainage Treatment group : 3 of 4 participants Control group: 0 of 1 participants Time to complete wound closure results showed that participants in the treatment group had significantly faster complete wound closure than did control patients (P=0.0036) Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Number who experienced adverse events Unclear definition Treatment group : 14 of 24 participants

Bibliographic reference	Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.
	Control group: 16 of 22 participants Number who underwent surgical procedure for ulcers Unclear definition Treatment group : 1 of 24 participants Control group: 4 of 22 participants Cellulitis Unclear definition Treatment group : 1 of 24 participants Control group: 5 of 22 participants P=0.09 i.e. non-significant Infection Unclear definition Treatment group : 1 of 24 participants Control group: 2 of 22 participants P=0.6 i.e. non-significant Osteomyelitis Unclear definition Treatment group : 1 of 24 participants Control group: 4 of 22 participants P=0.178 i.e. non-significant
Source of funding	Advanced Tissue Sciences Inc. and Smith and Nephew, Inc. provided funding for this study
Comments	

Table 19: Zelen 2013

Bibliographic reference	**Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *International wound journal*, *10*(5), 502-507.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: amniotic membrane allograft. Comparison: Standard therapy: debridement, moist dressing and offloading footwear. Outcome: complete wound healing, adverse events, wound area reduction 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. Block randomisation 1:1 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors. Many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for control patients and included debridement, moist dressing and offloading footwear. Patients provided their own daily dressing changes after receiving instruction. Dressing changes in the treatment group took place weekly. There is potential for differences within standard care group for the quality of dressing care. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Twenty-five participants were enrolled; groups were comparable for outcome data available. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (6 weeks). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing and adverse reactions. Full epithelialisation. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was not used to determine outcome. Crude measure of wound area using ruler measurements. However method of attaining complete healing outcome was valid and reliable. 11) Were investigators kept blind to participant’s exposure to the intervention?

Bibliographic reference	**Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *International wound journal*, *10*(5), 502-507.**
	Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 25 Treatment group= 13 Control group= 12
Patient characteristics	Patients taken from: USA Inclusion: Type 1 or 2 diabetes Age ≥18 years Ulcer size >1 cm and <25 cm^2 Ulcer duration of ≥4 weeks No clinical signs of infection Serum creatinine <3.0 mg/dl HbA1c <12% Adequate circulation, dorsum transcutaneous oxygen test ≥30 mmHg Ankle brachial index between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of the effected leg Exclusion: Participating in another clinical trial Charcot foot Index ulcer probing to the bone Receiving chemotherapy or radiotherapy Known or suspected malignancy of current ulcer Autoimmune connective tissue disease Biochemical or topical growth factor for wound within previous 30 days Pregnant/breastfeeding

Bibliographic reference	**Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *International wound journal*, *10*(5), 502-507.**

Medication considered to be immune system modulators
Allergy to streptomycin or gentamycin

Baseline characteristics: Study reports no differences in baseline characterisitics.

Characteristics	Control	Amniotic membrane allograft
n	12	13
Age, y	61.7 ± 10.3	56.4 ± 14.7
Male/female	7/5	9/4
Body Mass Index	35.4 ± 6.6	30.4 ± 5.7
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	32/98	27/88
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	3.4 ± 2.9	2.6 ± 1.9
Ulcer duration (weeks)	16.4 ± 15.5	14.1 ± 13.0
Ulcer location Forefoot or digital Heel or midfoot	 7 5	 7 6
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I	Not reported	Not reported

Bibliographic reference	**Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *International wound journal*, *10*(5), 502-507.**
	Grade II Grade III Grade IV | | | Total hospital stay | Not reported | Not reported
Intervention	Application of dehydrated amniotic membrane allograft (EpiFix) following surgical debridement of all necrotic tissue followed by moisture retentive dressing and compression dressing. Repeat applications were applied at 2, 4, 6, 8 and 10 weeks. Offloading was implemented.
Comparison	Wound care was standardised for control patients and included debridement, moist dressing and offloading footwear. Patients provided their own daily dressing changes after receiving instruction. Dressing changes in the treatment group took place weekly.
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 4 weeks Full epithelialisation Treatment group : 10 of 13 participants Control group: 0 of 12 participants P=<0.001 i.e. significant difference. Complete wound healing by 6 weeks Full epithelialisation Treatment group : 12 of 13 participants Control group: 1 of 12 participants P=<0.001 i.e. significant difference. Rates and extent of amputation: No data provided

Bibliographic reference	**Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *International wound journal*, *10*(5), 502-507.**
	Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events Treatment group : 1 of 13 participants Control group: 4 of 12 participants P=0.547 i.e. no significant difference. Cellulitis Treatment group : 0 of 13 participants Control group: 2 of 12 participants P=0.547 i.e. no significant difference.
Source of funding	Unclear source of funding
Comments	

Table 20: Caravaggi 2003

Bibliographic reference	**Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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*, *26*(10), 2853-2859.**
Study type	Randomised control trial
Study quality	Summary

Bibliographic reference	**Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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*, *26*(10), 2853-2859.**
	Population: Italy Intervention: HYAFF 11- Based Autologous Dermal and Epidermal Grafts Comparison: Weekly assessment, aggressive debridement, wound infection control, adequate pressure relief. Outcome: complete wound healing, adverse events, wound closure, percentage healing 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. Randomisation list was held and generated by sponsor. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors. Many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included debridement, paraffin dressing and offloading footwear or pressure relief. Patients provided their own daily dressing changes after receiving instruction. Dressing changes in the both groups took place twice daily. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Intention to treat analysis was employed except for 2 excluded participants. 10 participants in the control group and 8 participants in the treatment group withdrew before completion of treatment. For one of the participants in the control group only “investigator decision” was given as reason for withdrawal. Before intention to treat analysis 3 participants were lost in the run up following randomisation. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (11 weeks). 9) Did the study use a precise definition of outcome? Clear definitions of wound closure/healing. Definition for severity of adverse events was unclear. Full epithelialisation was required for complete healing outcome. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome.

<table>
<tr><th>Bibliographic reference</th><th>Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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, 26(10), 2853-2859.</th></tr>
<tr><td></td><td>11) Were investigators kept blind to participant’s exposure to the intervention?
Investigators were not kept blind to participant’s exposure to the intervention.
12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)</td></tr>
<tr><td>Number of patients</td><td>Randomised= 82
Treatment group= 43
Control group= 36</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Type 1 or 2 diabetes
Ulcer ≥2 cm² on plantar surface or dorsum of the foot without signs of healing for 1 month
Wagner score 1–2
TcPO2 ≥30 mmHg
Ankle brachial pressure index ≥0.5

Exclusion:
Ulcers with clinical infection, exposed bone, osteomyelitis diagnosed by radiography, inability to tolerate offloading cast
Poor-prognosis diseases

Baseline characteristics: Study reports no differences in baseline characteristics. P values not provided.

<table>
<tr><td>Characteristics</td><td>Control</td><td>Treatment group</td></tr>
<tr><td>n</td><td>36</td><td>43</td></tr>
<tr><td>Age, y</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Male/female</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Body Mass Index</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (Caucasian/non-caucasian)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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*, *26*(10), 2853-2859.**

Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	3/33	2/14
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	Not reported	Not reported
Ulcer duration (weeks)	Not reported	Not reported
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index	0.73	0.7
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c	8.1 ± 2.25	7.9 ± 2.13
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Autologous fibroblasts on Hyalograft3D, this was grafted onto the debrided and cleansed wound and covered with a nonadherent paraffin gauze and secondary dressing. Second graft could be applied as required. 7–10 days after hyalograft3D grafting the ulcer received autologous keratinocytes grown on Laserskin that was covered and dressed as before. A second keratinocyte graft was permitted where required.
Comparison	Wound care was standardised for all patients and included debridement, paraffin dressing and offloading footwear or pressure relief. Patients provided their own daily dressing changes after receiving instruction. Dressing changes in the both groups took place twice daily.

Bibliographic reference	**Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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*, *26*(10), 2853-2859.**
Length of follow up	Length of follow up was 11 weeks
Location	Italy
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 11 weeks in the plantar ulcers Full epithelialisation Treatment group : 12 of 22 ulcers Control group: 10 of 20 ulcers P=1.00 i.e. no significant difference. The Kaplan-meier median time for complete closure of plantar ulcers was: Treatment group : 57 days Control group: 77 days Complete wound healing by 11 weeks in the dorsal ulcers Full epithelialisation Treatment group : 14 of 21 ulcers Control group: 5 of 16 ulcers P=0.049 i.e. significant difference. Odds ratio 4.44 (confidence interval 1.09–17.7 The Kaplan-meier median time for complete closure of dorsal ulcers was: Treatment group : 63 days Control group: 77 days Complete wound healing by 11 weeks for all ulcers Full epithelialisation Treatment group : 22 of 35 participants Control group: 13 of 26 participants

Bibliographic reference	**Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). 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*, *26*(10), 2853-2859.**
	P=0.332 i.e. no significant difference. The Kaplan-meier median time for complete closure of all ulcers was: Treatment group : 59 days Control group: >77 days Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events Treatment group : 11 of 43 participants Control group: 11 of 36 participants “Serious” adverse events (unclear) Treatment group : 7 of 43 participants Control group: 10 of 36 participants
Source of funding	Fidia Advanced Biopolymers
Comments	

Table 21: Uccioli 2011

Bibliographic reference	**Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *The international journal of lower extremity wounds*, *10*(2), 80-85.**
Study type	Randomised control trial
Study quality	Summary Population: Italy Intervention: Hyalograft-3D followed by Laserskin autograft Comparison: Standard therapy Outcome: Complete healing, wound area, adverse events 1. Has an appropriate method of randomisation been used? A computer generated randomisation method was used. 2. Was there adequate concealment of allocation? Allocation was adequately concealed in a sealed envelope. 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar for demographics and diabetes related risk factors. Area of ulcer was significantly larger for the treatment group, this was adjusted for in later results. No P values were provided for other potential differences at baseline. 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received standard care which included debridement and offloading. A paraffin gauze was used. 5. Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6. Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? An intention to treat analysis was performed in 160 participants who were not excluded and had returned to the investigation site after baseline visit. Data was available for all these participants. Initial number randomised was, however, 180. 8. Did the study have an appropriate length of follow up? Follow up was appropriate (18 months) 9. Did the study use a precise definition of outcome? A precise definition of outcome was used (see below)

Bibliographic reference	**Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *The international journal of lower extremity wounds*, *10*(2), 80-85.**
	10. Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11. Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participants exposure to the intervention. 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. Unclear source of funding
Number of patients	Randomised= 180 Treatment group= 80 Control group = 80
Patient characteristics	Patients taken from: Italy Inclusion: type 1 or 2 diabetes ulcer greater or equal to 2cm on the plantar or plantar marginal surface or dorsum of foot with no signs of healing for 1 month Wagner score 1 or 2 transcutaneous partial pressure of oxygen greater than or equal to 20mmHg ankle brachial pressure index greater or equal to 0.5 Exclusion: ulcers with clinical infection osteomyelitis inability to tolerate off loading for pressure relief peripheral vascularisation within 30 days before enrolment Baseline Characteristics:

Characteristics	Treatment group	Control Group

Bibliographic reference	**Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *The international journal of lower extremity wounds*, *10*(2), 80-85.**

N	37	47
Age, y	Not reported	Not reported
Male/female	Not reported	Not reported
Body Mass Index	Not reported	Not reported
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	5/32	4/43
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	10.02 ± 10.80	7.84 ± 9.15
Ulcer duration (weeks)	6.56 ± 4.97	8.37 ± 9.04
Ulcer location (dorsal/plantar)	25/52	30/50
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index	0.92 ± 0.17	0.89 ± 0.23
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	At baseline visits patients received dermal tissue-engineered Hyalograft 3D autografts; the graft was covered with non-adherent paraffin gauze and a secondary bandage of sterile cotton pads and gauze. Approximately 2 weeks later, the ulcer received the epidermal tissue-engineered autograft Laserskin covered and dressed in an identical manner. based on clinician judgement a

Bibliographic reference	**Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *The international journal of lower extremity wounds*, *10*(2), 80-85.**
	second autograft application was permitted. Both groups received standard care which included debridement and offloading
Comparison	Control group received covering with non-adherent paraffin gauze and a secondary bandage of sterile cotton pads and gauze. This could be changed daily depending upon the state of the wound bed. Both groups received standard care which included debridement and offloading
Length of follow up	Length of follow up was 18 months
Location	Italy
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Healing was defined as full epithelialization without exudates or eschar. Incidence to complete healing by 12 weeks: Two step grafting treatment group: 19 of 80 participants Control group: 17 of 80 participants P value= 0.85 i.e. no significant difference Incidence to complete healing by 20 weeks: Two step grafting treatment group: 40 of 80 participants Control group: 34 of 80 participants P value= 0.344 i.e. no significant difference mean time to complete healing Two step grafting treatment group: 50 days Control group: 58 days P value= 0.253 i.e. no significant difference Rates and extent of amputation:

Bibliographic reference	**Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *The international journal of lower extremity wounds*, *10*(2), 80-85.**
	No data provided on rates and extent of amputation Length of stay: No data provided on length of stay Health related quality of life: No data provided on health related quality of life Adverse events: Definition of adverse events unclear Incidence of adverse events by 12 weeks: Two step grafting treatment group: 18 of 84 participants Control group: 14 of 87 participants Incidence of serious adverse events by 12 weeks: Two step grafting treatment group: 7 of 84 participants Control group: 2 of 87 participants Incidence of infection by 12 weeks: Two step grafting treatment group: 13 of 84 participants Control group: 10 of 87 participants Incidence of adverse events by 18 months: Two step grafting treatment group: 1 of 51 participants Control group: 8 of 52 participants None of the adverse events were thought attributable to the graft treatment
Source of funding	Anika Therapeutics research grant
Comments	

Table 22: Agrawal 2009

Bibliographic reference	**Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.**
Study type	Randomised control trial
Study quality	Summary Population: India, only type 2 diabetics Intervention: Platelet derived growth factor gel Comparison: daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy. Outcome: complete wound healing, adverse events, percentage healing 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were not similar at baseline for all major confounding factors; participants in the treatment group were significantly younger and had larger ulcer sizes at baseline. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy. 5) Were participants receiving care kept blind to treatment allocation? Unclear if participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Five participants withdrew from the control group in the final week of study, no participants were lost to the treatment group. This could introduce attrition bias for outcomes in the final week of study. 8) Did the study have an appropriate length of follow up?

Bibliographic reference	**Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.**
	Follow up was appropriate (12 weeks). 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing 10) Was a valid and reliable method used to determine that outcome? Unclear if valid and reliable methods were used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 28 Treatment group= 14 Control group= 14
Patient characteristics	Patients taken from: India Inclusion: ≥30 years of age Apparent preference for participants ≤7.0% HbA1c Wagner grade I, II, III or IV Foot ulcer duration of >3 months Infection free Adequate lower limb blood supply as demonstrated on transcutaneous oxygen tension ≥30 mmHg Exclusion: Peripheral vascular disease Active neoplastic disease Active infection Immunosuppressive therapy in the preceding 3 months Liver disease

Bibliographic reference	**Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.**

Pulmonary tuberculosis
Thyroid disorder
Uraemia
Alcoholism
Renal insufficiency
Steroid or anticoagulant therapy
Undergoing vascular reconstruction

Baseline characteristics: Study reports significant differences in age and ulcer area. P values provided in study.

Characteristics	Control	Treatment group
n	14	14
Age, y	54.38 ± 8.77	56.24 ± 8.75
Male/female	9/5	10/4
Body Mass Index	26.70 ± 2.98	24.78 ± 3.09
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	10.69 ± 6.12	10.44 ± 5.08
Type of diabetes type1/type2	All type 2	All type 2
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	54.32 ± 45.16	28.72 ± 21.77
Ulcer duration (weeks)	Not reported	Not reported
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported
Neuropathy	14	12
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported

Bibliographic reference	**Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.**
	<table><tr><td>HbA1c</td><td>8.76 ± 0.98</td><td>8.83 ± 1.02</td></tr><tr><td>Mobility Walking with support Walking without support</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Wagner Classification Grade I Grade II Grade III Grade IV</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr></table>
Intervention	Platelet derived growth factor gel (rhPDGF) 0.01% at a dose of 2.2 µg/cm²/day. Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.
Comparison	Placebo gel given in the same manner as the rhPDGF Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.
Length of follow up	Length of follow up was 12 weeks
Location	India
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 1 week Unclear definition Treatment group : 2 of 14 participants Control group: 0 of 14 participants . Complete wound healing by 2 weeks

Bibliographic reference	Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.
	Unclear definition Treatment group : 3 of 14 participants Control group: 1 of 14 participants Complete wound healing by 3 weeks Unclear definition Treatment group : 5 of 14 participants Control group: 1 of 14 participants Complete wound healing by 5 weeks Unclear definition Treatment group : 6 of 14 participants Control group: 1 of 14 participants Complete wound healing by 12 weeks Unclear definition Treatment group : 9 of 14 participants Control group: 3 of 9 participants Overall P value= <0.001 i.e. significant difference Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events:

Bibliographic reference	Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.
	Fever or malaise Unclear definition Treatment group : 2 of 14 participants Control group: 0 of 14 participants P value= <0.20 i.e. non-significant Local pruritis or burning Unclear definition Treatment group : 3 of 14 participants Control group: 0 of 14 participants P value= <0.10 i.e. non-significant Neutrophilia Unclear definition Treatment group : 6 of 14 participants Control group: 0 of 14 participants P value= <0.01 i.e. significant Arthralgia or myalgia Unclear definition Treatment group : 1 of 14 participants Control group: 0 of 14 participants P value= <0.50 i.e. non-significant Allergic reaction Unclear definition Treatment group : 1 of 14 participants Control group: 0 of 14 participants P value= <0.50 i.e. non-significant

Bibliographic reference	**Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak "Use of a platelet derived growth factor gel in chronic diabetic foot ulcers" The Diabetic Foot Journal 2009, 12(2), 80-88.**
Source of funding	Unclear source of funding
Comments	

Table 23: Robson 2005

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
Study type	Randomised control trial
Study quality	Summary Population: USA, over many different sites and 5 different RCTs Intervention: Platelet derived growth factor gel Comparison: daily moist dressing changes, appropriate debridement, effective offloading and infection control Outcome: complete wound healing, adverse events, time to complete healing

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. Randomization was controlled by the sponsor in the case of Robson et al. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported to be generally comparable at baseline. The mean duration of diabetes mellitus in the in the Regranex Gel 0.01% group was longer than in the standardized therapy group. Many important variables were not reported. Also varying inclusion and exclusion critieria were employed between studies. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate infection control. However randomised controlled trials took place at different sites and often across multiple centres increasing the chance of variance in care given. Authors attempted to account for differences statistically in meta analysis. 5) Were participants receiving care kept blind to treatment allocation? Most studies were blinded, one study was unblinded. 6) Were the individuals administering care kept blind to treatment allocation? Most studies were blinded, one study was unblinded. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	available? Intention to treat analysis was applied across all studies. 5 total efficacy trials enrolled 1071 subjects 1065 of whom were considered intent-to-treat. 8) Did the study have an appropriate length of follow up? In all studies follow up was appropriate (20 weeks). 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing 10) Was a valid and reliable method used to determine that outcome? Unclear if valid and reliable methods were used 11) Were investigators kept blind to participant's exposure to the intervention? Most studies were blinded, one study was unblinded 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely) It should also be noted that this trial by Robson et al was stopped early due to poor accrual of participants. This, along with the fact that randomisation was controlled by the sponsor, shows that there was high industry infiltration in the study.

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
Number of patients	Randomised= 1071 Intent to treat= 1065 Standard therapy= 259 Vehicle gel group= 254 Becaplermin 30 µg/g group= 193 Becaplermin 100 µg/g group= 359
Patient characteristics	Patients taken from: USA Criteria below taken from Robson et al paper, which was the most recent paper and had the most extensive inclusion and exclusion criteria. Inclusion: 18 years of age or older If female, practising birth control Have documented wound etiology resulting from complications of diabetes mellitus Non-healing cutaneous full thickness diabetic neuropathic foot ulcer between 1.7–12 cm^2 in area, 4–52 weeks duration, on the plantar aspect of the forefoot and free of necrotic and infected tissue post debridement. Supine TcPO2 >30 mmHg on the dorsum of the target foot ulcer organisms/g of tissue

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	Have a ulcer tissue biopsy with <1 x 10^6 organisms/g of tissue and no beta haemolytic streptococci Exclusion: Target ulcer other than on the plantar surface forward of the midarch Pregnant female or nursing mother Known hypersensitivity to any of the study drug components Malignant disease at ulcer site Target ulcer <1.7 or >12 cm^2 postdebridement Have more than one diabetic foot ulcer on the same foot as the target ulcer Have more than three chronic wounds on the same extremity as the target ulcer Thermal, electrical, chemical or radiation wounds at the site of target ulcer Wounds resulting from large vessel arterial insufficiency, venous insufficiency or necrobiosis lipoidica Significant metabolic, rheumatic, collagen vascular disease, chronic renal insufficiency or chronic severe liver disease Osteomyelitis confirmed by bone biopsy Any investigational drug within the past 30 days Pre existing disease or condition that cound interfere with evaluation of effectiveness of Becaplermin gel Systemic corticosteroids, immunosuppressive agents, radiation or chemotherapy Revascularisation surgery in the past 6 weeks

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	Exposed bone or tendon Charcot foot Severe pitting oedema Baseline characteristics: Study reports significant differences in duration of diabetes

Characteristics	Standard therapy	Vehicle gel	Becaplermin 30 µg/g	Becaplermin 100 µg/g
n	259	254	193	359
Age, y	Not reported	Not reported	Not reported	Not reported
Male/female	Not reported	Not reported	Not reported	Not reported
Body Mass Index	Not reported	Not reported	Not reported	Not reported
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported	Not reported	Not reported
Insulin therapy	Not reported	Not reported	Not reported	Not reported
Duration of diabetes, y	14.7	Not reported	Not reported	17.9
Type of diabetes type1/type2	Not reported	Not reported	Not reported	Not reported
Smokers	Not reported	Not reported	Not reported	Not reported
Ulcer size at baseline (cm^2)	1.6	Not reported	Not reported	1.5

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**

Ulcer duration (weeks)	Not reported	Not reported	Not reported	Not reported
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported	Not reported
Coronary artery disease	Not reported	Not reported	Not reported	Not reported
Renal impairment	Not reported	Not reported	Not reported	Not reported
Retinopathy	Not reported	Not reported	Not reported	Not reported
Ankle Brachial Index	Not reported	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported	Not reported
Previous ulcers	Not reported	Not reported	Not reported	Not reported
HbA1c	Not reported	Not reported	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported	Not reported	Not reported
Wagner Classification Grade I Grade II	Not reported	Not reported	Not reported	Not reported

<table>
<tr><td>Bibliographic reference</td><td>Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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, 5(1).

Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair and Regeneration, 7(5), 335-346.

Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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, 21(5), 822-827.

Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plastic and reconstructive surgery, 117(7S), 143S-149S.

Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Grade III
Grade IV</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Becaplermin 100 µg/g gel plus adaptic dressing, once daily dressing changes

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate infection control.</td></tr>
<tr><td></td><td>Becaplermin 30 µg/g gel

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate infection control.</td></tr>
<tr><td>Comparison</td><td>Vehicle gel given as placebo in same manner as above gel

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate infection control.</td></tr>
<tr><td></td><td>Standard therapy

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective</td></tr>
</table>

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	offloading and appropriate infection control.
Length of follow up	Length of follow up was 20 weeks in all studies
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete healing by 20 weeks Definition of complete healing unclear Standard Therapy= 78 of 259 participants Vehicle gel group= 84 of 254 participants Becaplermin 30 µg/g gel group= 77 of 193 participants Becaplermin 100 µg/g gel group= 154 of 359 participants For becaplermin 100 µg/g gel vs standard therapy P value = 0.002 i.e. significantly different For becaplermin 100 µg/g gel vs vehicle gel P value = 0.015 i.e. significantly different

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	Kaplan Meier estimates of the number of days to healing were: Standard Therapy= 141 days Vehicle gel group= 141 days Becaplermin 30 µg/g gel group= 113 days Becaplermin 100 µg/g gel group= 100 days The authors of Robson et al felt that the results could be made more statistically robust by removing the outlying ulcers from the population i.e. those that were >10 cm² at baseline. By removing this subgroup the authors retained 95% of the population (n=1016) and attempted to make the populations more comparable. Results as follows: Complete healing by 20 weeks Definition of complete healing unclear Standard Therapy= 93 of 259 participants Vehicle gel group= 85 of 254 participants Becaplermin 30 µg/g gel group= 75 of 193 participants Becaplermin 100 µg/g gel group= 170 of 359 participants For becaplermin 100 µg/g gel vs standard therapy P value = 0.006 i.e. significantly different

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	For becaplermin 100 µg/g gel vs vehicle gel P value = 0.011 i.e. significantly different For becaplermin 100 µg/g gel vs becaplermin 30 µg/g gel P value = 0.327 i.e. not significantly different Kaplan Meier estimates of the number of days to healing were: Vehicle gel group= 141 days Becaplermin 100 µg/g gel group= 99 days Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events:

Bibliographic reference	**Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). 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*, *5*(1).** **Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair and Regeneration*, *7*(5), 335-346.** **Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely 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*, *21*(5), 822-827.** **Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plastic and reconstructive surgery*, *117*(7S), 143S-149S.** **Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.**
	Adverse events data was only available for 4 clinical trials reported by Smiell et al which reported treatment-emergent adverse events reported by ≥ 5% of patients. Treatment-emergent adverse events is only specifically reported for body systems affected and does not constitute useful outcomes. Serious adverse events Calculated from percentages Standard Therapy= 53 of 190 participants Vehicle gel group= 69 of 275 participants Becaplermin all doses group= 98 of 407 participants No P values provided.
Source of funding	Funding from Johnson and Johnson
Comments	

Table 24: Hardikar 2005

Bibliographic reference	**Hardikar, J. V., Reddy, Y. C., Bung, D. D., Varma, N., Shilotri, P. P., Prasad, E. D., ... & Suresh, K. R. (2005). 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, 17(6), 141-152.**
Study type	Randomised control trial
Study quality	Summary Population: India Intervention: Platelet derived growth factor gel Comparison: debridement, offloading dressing Outcome: complete wound healing, adverse events, time to complete healing 1) Has an appropriate method of randomisation been used? UNCLEAR 2) Was there adequate concealment of allocation? UNCLEAR 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported to be generally comparable at baseline. Unable to find table of baseline characteristics 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included offloading, debridement and wound dressing. However randomised controlled trials took place at different sites and often across multiple centres increasing the chance of variance in care given. 5) Were participants receiving care kept blind to treatment allocation? YES 6) Were the individuals administering care kept blind to treatment allocation? YES 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES Intention to treat analysis was applied across all studies. 8) Did the study have an appropriate length of follow up? In all studies follow up was appropriate (10 weeks). 9) Did the study use a precise definition of outcome? YES 10) Was a valid and reliable method used to determine that outcome? YES 11) Were investigators kept blind to participant's exposure to the intervention? YES 12) Were investigators kept blind to other important confounding and prognostic factors? YES
Number of patients	Randomised= 113 rhPDGF-BB gel group= 55 Placebo gel= 58

Bibliographic reference	**Hardikar, J. V., Reddy, Y. C., Bung, D. D., Varma, N., Shilotri, P. P., Prasad, E. D., ... & Suresh, K. R. (2005). 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, 17(6), 141-152.**
Patient characteristics	Patients taken from: India Inclusion: 18 years of age or older but ≤80 years Type 1 or type 2 diabetes mellitus At least 1 but less than 3 full thickness chronic neuropathic ulcers of at least 4 weeks duration in the lower extremity Stage III or IV ulcers (as defined by Wound, Ostomy and Continence Nurses Society Infection control as determined by a wound evaluation score Evidence of adequate perfusion Exclusion: Arterial venous ulcers Ulcers caused by osteomyelitis or burns Poor nutritional status Uncontrolled hyperglycaemia History of corticosteroids or immunosuppressant use Known hypersensitivity to gel components Women of childbearing age and preganant or nursing women not taking contreceptives. Baseline characteristics: Study reports no significant differences between groups but table of baseline characteristics not found
Intervention	0.01% gel containing 100 µg/g of rhPDGF-BB gel. Wound covered with 1.5 mm of the gel and covered with moist saline gauze, applied daily with a maximum treatment period of 20 weeks. Wound care was standardised for all patients and included offloading, debridement and wound dressing
Comparison	Vehicle gel given as placebo in same manner as above gel Wound care was standardised for all patients and included offloading, debridement and wound dressing

Bibliographic reference	**Hardikar, J. V., Reddy, Y. C., Bung, D. D., Varma, N., Shilotri, P. P., Prasad, E. D., ... & Suresh, K. R. (2005). 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, 17(6), 141-152.**
Length of follow up	Length of follow up was 20 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete healing by 10 weeks Wound closure with complete epithelialisation and no drainage or scab Placebo gel group= 18 of 58 participants rhPDGF 100 µg/g gel group= 39 of 55 participants Significant difference Kaplan Meier estimates of the number of days to healing were: Time to wound closure with complete epithelialisation and no drainage or scab Placebo gel group= 46 days rhPDGF 100 µg/g gel group= 61 days Significant difference Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events:

Bibliographic reference	**Hardikar, J. V., Reddy, Y. C., Bung, D. D., Varma, N., Shilotri, P. P., Prasad, E. D., ... & Suresh, K. R. (2005). 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, 17(6), 141-152.**
	Incidence of adverse events An unfavourable or abnormal finding that was not present at baseline, or, if present at baseline experienced increasing severity as treatment progressed Placebo gel group= 13% rhPDGF 100 µg/g gel group= 17% Incidence of withdrawal due to adverse events An unfavourable or abnormal finding that was not present at baseline, or, if present at baseline experienced increasing severity as treatment progressed Placebo gel group= 4% rhPDGF 100 µg/g gel group= 5%
Source of funding	Unclear funding
Comments	

Table 25: Jaiswal 2010

Bibliographic reference	**Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. *Indian Journal of Surgery*,*72*(1), 27-31.**
Study type	Randomised control trial
Study quality	Summary Population: India Intervention: Platelet derived growth factor gel Comparison: daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.

Bibliographic reference	**Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. *Indian Journal of Surgery*,*72*(1), 27-31.**
	Outcome: complete wound healing, adverse events, percentage healing 1) Has an appropriate method of randomisation been used? Computer generated numbers were used. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were not similar at baseline for all major confounding factors; participants in the treatment group were significantly more likely to have lower numbers of participants with moderate-severe pain compared to the control group (p=0.02). 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No loss to follow up was reported. All outcome data was reported for both groups. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (10 weeks). 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing 10) Was a valid and reliable method used to determine that outcome? Unclear if valid and reliable methods were used. Methods to record wound area were valid. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 50

<table>
<tr><th>Bibliographic reference</th><th>Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. Indian Journal of Surgery,72(1), 27-31.</th></tr>
<tr><td></td><td>Treatment group= 25
Control group= 25</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: India

Inclusion:
Type 1 or type 2 diabetes
Chronic ulcers of at least 4 weeks duration
IAET stage III and IV

Exclusion:
Ankle brachial pressure index <0.9

Baseline characteristics: Study reports significant differences in moderate to severe pain. P values not generally provided in study.

<table>
<tr><th>Characteristics</th><th>Control</th><th>Treatment group</th></tr>
<tr><td>n</td><td>25</td><td>25</td></tr>
<tr><td>Age, y</td><td>49.92 ± 18.89</td><td>56.20 ± 11.34</td></tr>
<tr><td>Male/female</td><td>23/2</td><td>19/6</td></tr>
<tr><td>Body Mass Index</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (Caucasian/non-caucasian)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, more than 10 y</td><td>9</td><td>8</td></tr>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Smokers</td><td>5</td><td>4</td></tr>
<tr><td>Ulcer size at baseline (cm²)</td><td>26.50 ± 2.507</td><td>29.96 ± 3.494</td></tr>
<tr><td>Ulcer duration (weeks) median</td><td>6</td><td>5</td></tr>
<tr><td>Ulcer location
Forefoot or digital
Heel or midfoot</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Neuropathy</td><td>8</td><td>11</td></tr>
<tr><td>Moderate to severe pain</td><td>17</td><td>9</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. Indian Journal of Surgery,72(1), 27-31.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Renal impairment</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Retinopathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ankle Brachial Index</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>1</td><td>1</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mobility
Impaired walking
Walking without support</td><td>20</td><td>15</td></tr>
<tr><td>IAET Classification
Grade I
Grade II
Grade III
Grade IV</td><td>

15
10</td><td>

16
9</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Platelet derived growth factor gel (rhPDGF) (PLERMIN) 0.01% applied once daily

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.</td></tr>
<tr><td>Comparison</td><td>KY Jelly (Ethnor) applied topically

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.</td></tr>
<tr><td>Length of follow up</td><td>Length of follow up was 10 weeks</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Cure rates of foot ulcer resulting from diabetes:</td></tr>
</table>

Bibliographic reference	**Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. *Indian Journal of Surgery*,*72*(1), 27-31.**
	Complete wound healing by 10 week Unclear definition Treatment group :15 of 25 participants Control group: 18 of 25 participants . Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Any side effects by 10 week Unclear definition Treatment group :0 of 25 participants Control group: 0 of 25 participants .
Source of funding	Unclear source of funding
Comments	

Table 26: Bhansali 2009

Bibliographic reference	**Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. *Diabetes research and clinical practice*, *83*(1), e13-e16.**
Study type	Randomised control trial
Study quality	Summary Population: India Intervention: Platelet derived growth factor gel Comparison: daily moist dressing changes, appropriate debridement, effective offloading Outcome: complete wound healing, adverse events, percentage healing 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline for all major confounding factors 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, and effective offloading with infection control 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no loss to follow up 8) Did the study have an appropriate length of follow up? Follow up was appropriate (150 days). 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing 10) Was a valid and reliable method used to determine that outcome? Unclear if valid and reliable methods were used 11) Were investigators kept blind to participant’s exposure to the intervention? Investigators were not kept blind to participant’s exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors?

Bibliographic reference	**Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. *Diabetes research and clinical practice*, *83*(1), e13-e16.**
	Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 20 Treatment group= 10 Control group= 10
Patient characteristics	Patients taken from: India Inclusion: Type 1 or type 2 diabetes >20 years of age At least 1 neuropathic plantar ulcer Wagners grade ≥2 without Xray evidence of osteomyelitis Ankle brachial pressure index of >0.9 Baseline characteristics: Study reports significant differences in age and ulcer area. P values provided in study.

Characteristics	Treatment group	Standard Care group
n	10	10
Age, y	51.7 ± 13.6	49.5 ± 8.8
Male/female	7/3	5/5
Body Mass Index	22.7 ± 2.8	25.29 ± 6.4
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	13.3 ± 5.9	13.6 ± 9.7
Type of diabetes type1/type2	1/9	1/9
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	18.1 ± 15.9	11.1 ± 9.3
Ulcer duration (>4 weeks)	8	8
Ulcer location Forefoot or digital	7	8

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. Diabetes research and clinical practice, 83(1), e13-e16.</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><td>Heel or midfoot</td><td>3</td><td>2</td></tr>
<tr><td>Neuropathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Coronary artery disease</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Renal impairment</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Retinopathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ankle Brachial Index
Right
Left</td><td>
1.03 ± 0.13
1.03 ± 0.13</td><td>
1.07 ± 0.10
1.10 ± 0.14</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>5</td><td>2</td></tr>
<tr><td>Previous ulcers</td><td>8</td><td>8</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="2">0.01% rh-platelet derived growth factor-BB (PLERMIN)

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.</td></tr>
<tr><td>Comparison</td><td colspan="2">Standard care

Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">Length of follow up was 150 days</td></tr>
</table>

Bibliographic reference	**Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. *Diabetes research and clinical practice*, *83*(1), e13-e16.**
Location	India
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Only geometric healing rates were provided, however time to complete (100% healing) was part of this data Time to complete wound healing Unclear definition. Treatment group : mean duration of healing 50.10 ± 23.38 days Control group: mean duration of healing 86.10 ± 30.71 days P value= 0.02 Time to complete wound healing Unclear definition. Treatment group : 100% healed by 90 days Control group: 100% healed by 150 days Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events Unclear definition. Treatment group : 0 participants

Bibliographic reference	**Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. *Diabetes research and clinical practice*, *83*(1), e13-e16.**
	Control group: 0 participants
Source of funding	Unclear source of funding, no conflicts of interest declared
Comments	

Table 27: Robson 1999

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Transforming Growth Factor ß2 Comparison: daily moist dressing changes, appropriate debridement, effective offloading Outcome: complete wound healing, adverse events, percentage healing, time to healing 1) Has an appropriate method of randomisation been used? Computer generated method of randomisation was used, carried out by sponsor. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline for all major confounding factors 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation except those in the standard care group 6) Were the individuals administering care kept blind to treatment allocation?

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
	Individuals administering care were blinded to treatment allocation except to those in the standard care group 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was significant loss to follow up of 38 participants by 3 months. There was no difference in loss to follow up between groups studied. 8) Did the study have an appropriate length of follow up? Follow up was appropriate (3 months). 9) Did the study use a precise definition of outcome? Precise definitions for wound closure were used. Full epithelialization with no breaks or drainage was required 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 177 Standardised care group= 24 placebo group= 22 growth factor 0.05 µg/cm²= 43 growth factor 0.5 µg/cm²= 44 growth factor 5.00 µg/cm²= 44
Patient characteristics	Patients taken from: India Inclusion: ≥18 years of age Diabetes mellitus Neuropathic ulcer present for at least 8 weeks on the plantar surface of the forefoot, toes, metatarsals or dorsum of the foot. Between 1–20 cm² in area following debridement Full thickness without exposed bone or tendonankle brachial pressure index between 0.7 and 1.3 or a transcutaneous oxygen

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**

pressure measurement on the foot of 30 mm Hg or more

Exclusion:
Radiographically confirmed osteomyelitis
Clinical infection of the ulcer
Use of systemic steroids within the previous 30 days
HbA1c > 13%
serum creatinine > 2.5 mg/dL
serum albumin <2 mg/dL

Baseline characteristics: Study reports no significant differences in age and ulcer area. P values not provided in study.

Characteristics	Standard care	placebo	growth factor 0.05 µg/cm²	growth factor 0.5 µg/cm²	growth factor 5.0 µg/cm²
n	24	22	43	44	44
Age, y	55	60	56	56	56
Male/female	92/8	82/18	77/23	77/23	77/23
Body Mass Index Height, cm Weight, kg	 182 104	 180 96	 177 99	 176 100	 178 102
Ethnicity (Caucasian/black/hispanic)	88/4/8	82/0/18	67/12/21	77/9/14	73/5/23
Insulin therapy	Not reported	Not reported	Not reported	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported	Not reported	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported	Not reported	Not reported	Not reported
Smokers	17	9	23	7	23
Ulcer size at baseline (cm²)	2.1	2.7	2.1	2.7	2.7
Ulcer duration (weeks) mean	59	41	51	59	54
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported	Not reported	Not reported
Coronary artery disease	Not reported	Not reported	Not reported	Not reported	Not reported
Renal impairment	Not reported	Not reported	Not reported	Not reported	Not reported

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**

Retinopathy	Not reported	Not reported	Not reported	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported	Not reported	Not reported
Previous ulcers	Not reported	Not reported	Not reported	Not reported	Not reported
HbA1c	Not reported	Not reported	Not reported	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported	Not reported	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported	Not reported	Not reported	Not reported
Total hospital stay	Not reported	Not reported	Not reported	Not reported	Not reported

Intervention	Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied
	Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied
	Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
Comparison	Standard care (unblinded) Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied
	Placebo collagen sponge Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied
Length of follow up	Length of follow up was 3 months
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure at 21 weeks Full epithelialisation Standardised care group= 17 of 24 (P value= 0.009 i.e. significant) placebo group= 7 of 22 growth factor 0.05 µg/cm²= 25 of 43 (P value= 0.046 i.e. significant) growth factor 0.5 µg/cm²= 25 of 44 (P value= 0.056 i.e. not significant) growth factor 5.00 µg/cm²= 27 of 44 (P value= 0.025 i.e. significant) P value= vs placebo sponge Time to complete wound healing (median, weeks) Full epithelialisation Standardised care group= 9 (P value= 0.009 i.e. significant) placebo group= NA growth factor 0.05 µg/cm²= 16 (P value= 0.133 i.e. not significant) growth factor 0.5 µg/cm²= 12 (P value= 0.085 i.e. not significant) growth factor 5.00 µg/cm²= 13 (P value= 0.030 i.e. significant)

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
	P value= vs placebo sponge Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Infection Unclear definition. Standardised care group= 21 placebo group= 32 growth factor 0.05 µg/cm²= 33 growth factor 0.5 µg/cm²= 16 growth factor 5.00 µg/cm²= 27 Skin ulcer Unclear definition. Standardised care group= 25 placebo group= 9 growth factor 0.05 µg/cm²= 14 growth factor 0.5 µg/cm²= 16 growth factor 5.00 µg/cm²= 27 Pain

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
	Unclear definition. Standardised care group= 4 placebo group= 18 growth factor 0.05 µg/cm²= 21 growth factor 0.5 µg/cm²= 16 growth factor 5.00 µg/cm²= 7 Cellulitis Unclear definition. Standardised care group= 17 placebo group= 18 growth factor 0.05 µg/cm²= 9 growth factor 0.5 µg/cm²= 18 growth factor 5.00 µg/cm²= 9 Peripheral oedema Unclear definition. Standardised care group= 17 placebo group= 0 growth factor 0.05 µg/cm²= 7 growth factor 0.5 µg/cm²= 9 growth factor 5.00 µg/cm²= 2 Vesiculobullous Rash Unclear definition. Standardised care group= 17 placebo group= 0 growth factor 0.05 µg/cm²= 5 growth factor 0.5 µg/cm²= 9 growth factor 5.00 µg/cm²= 7

Bibliographic reference	**Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In *3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France*.**
	Pharyngitis Unclear definition. Standardised care group= 0 placebo group= 14 growth factor 0.05 µg/cm²= 12 growth factor 0.5 µg/cm²= 7 growth factor 5.00 µg/cm²= 11
Source of funding	Genzyme Corporation
Comments	

Table 28: Richard 1995

Bibliographic reference	**Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care*, *18*(1), 64-69.**
Study type	Randomised control trial
Study quality	Summary Population: France Intervention: Topical human recombinant basic fibroblast growth factor (bFGF) Comparison: moist dressing, appropriate debridement, offloading (instruction) Outcome: complete wound healing, adverse events, rate of healing 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline for all major confounding factors

Bibliographic reference	**Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care*, *18*(1), 64-69.**
	4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and included moist dressing, appropriate debridement, offloading i.e. the instruction to keep totally non weight bearing. The first 6 weeks were as inpatients with daily applications 12 weeks as outpatient follow up with twice weekly applications 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was significant drop out and only 5 participants made it till the end of the study. Outcome data was provided for all participants. 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up was appropriate (18 weeks) 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 17 Treatment group= 9 Placebo group= 8
Patient characteristics	Patients taken from: India Inclusion: Diabetes mellitus

Bibliographic reference	**Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care*, *18*(1), 64-69.**

Typical, chronic, non healing, neuropathic ulcer on the plantar surface
Wagners grade I–III
Largest diameter >0.5 cm following debridement
Confirmed neuropathy

Exclude:
Significant peripheral vascular disease on Doppler wave form analysis
Active infection

Baseline characteristics: Study reports significant differences. P values not provided in study.

Characteristics	Placebo group	bFGF group
n	8	9
Age, y	63.6 ± 7.9	61.9 ± 10.0
Male/female	7/1	9/0
Body Mass Index	29.3 ±2.6	26.4 ±4.6
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	18.8 ± 9.5	20.9 ± 12.3
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	18.1 ± 6.2	18.0 ± 12.0
Ulcer duration (months)	27.9 ± 42.2	22.4 ± 27.9
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
Previous amputation	Not reported	Not reported

Bibliographic reference	**Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care*, *18*(1), 64-69.**
	Minor Major Previous ulcers: Not reported / Not reported HbA1c: 7.1 ± 1.7 / 7.9 ± 1.7 Mobility Walking with support Walking without support: Not reported / Not reported Wagner Classification Grade I: 1 / 2 Grade II: 4 / 4 Grade III: 3 / 3 Grade IV Total hospital stay: Not reported / Not reported
Intervention	Topical human recombinant basic fibroblast growth factor 5 µg/ml spray delivery Wound care was standardised for all patients and included moist dressing, appropriate debridement, offloading i.e. the instruction to keep totally non weight bearing. The first 6 weeks were as inpatients with daily applications 12 weeks as outpatient follow up with twice weekly applications
Comparison	Saline placebo spray delivery Wound care was standardised for all patients and included moist dressing, appropriate debridement, offloading i.e. the instruction to keep totally non weight bearing. The first 6 weeks were as inpatients with daily applications 12 weeks as outpatient follow up with twice weekly applications
Length of follow up	Length of follow up was 18 weeks
Location	France
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Only geometric healing rates were provided, however time to complete (100% healing) was part of this data

Bibliographic reference	**Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care*, *18*(1), 64-69.**
	Time to complete wound healing within 18 weeks Unclear definition. Treatment group : 3 of 9 Control group: 5 of 8 Median time to 100% healing could not be compared because of the few events Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Infection Unclear definition. Treatment group : 2 participants Control group: 2 participants
Source of funding	Farmitalia Carlo Erba Laboratory, Milano, Italy
Comments	

Table 29: Steed 1992

Bibliographic reference	**Steed, D. L., Goslen, J. B., Holloway, G. A., Malone, J. M., Bunt, T. J., & Webster, M. W. (1992). Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care*, *15*(11), 1598-1604.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: CT–102, homologous platelets containing multiple growth factors Comparison: moist dressing, aggressive debridement, offloading Outcome: complete wound healing, percentage volume/area reduction, 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were not similar at baseline for all major confounding factors. The treatment group had had a longer duration of diabetes mellitus (P=0.001). Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients within the same two clinics and moist dressing, aggressive debridement, offloading formed the basis of care. Wound dressings were changed every 12 hours. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no loss to follow up and outcomes were provided for all participants 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up was appropriate (20 weeks) 9) Did the study use a precise definition of outcome? Clear definitions for complete wound healing were used. 100% epithelialization with no or minimum drainage was required 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size 11) Were investigators kept blind to participant’s exposure to the intervention? Investigators were kept blind to participant’s exposure to the intervention.

<table>
<tr><th>Bibliographic reference</th><th>Steed, D. L., Goslen, J. B., Holloway, G. A., Malone, J. M., Bunt, T. J., & Webster, M. W. (1992). Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical versus placebo. Diabetes Care, 15(11), 1598-1604.</th></tr>
<tr><td></td><td>12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors.</td></tr>
<tr><td>Number of patients</td><td>Randomised= 13
Treatment group= 7
Placebo group= 6</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Diabetes mellitus
Neurotrophic ulcer of the lower extremity that had not healed after at least 8 weeks of standard treatment
Platelet count of ≥100,000/mm³
Supine periwound TcPO2 >30 mmHg

Exclude:
Active infection
Requiring antibiotic therapy

Baseline characteristics: Study reports significant differences. P values not provided in study.

<table>
<tr><td>Characteristics</td><td>CT-102 group</td><td>Placebo group</td></tr>
<tr><td>n</td><td>7</td><td>6</td></tr>
<tr><td>Age, y</td><td>58.7 ± 12.4</td><td>54.2 ± 12.9</td></tr>
<tr><td>Male/female</td><td>5/2</td><td>4/2</td></tr>
<tr><td>Body Mass Index</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (Caucasian/non-caucasian)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>26 ± 6.6</td><td>10.3 ± 5.9</td></tr>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Smokers</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Steed, D. L., Goslen, J. B., Holloway, G. A., Malone, J. M., Bunt, T. J., & Webster, M. W. (1992). Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care*, *15*(11), 1598-1604.**

Ulcer size at baseline (cm^2)	Not reported	Not reported
Ulcer duration (months)	17.08 ± 15.87	13.00 ± 14.37
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	51± 8.4	45 ± 7.4
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c	7.1 ± 1.4	7.5 ± 1.4
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	CT-102 applied to cotton gauze sponge and placed on wound Wound care was standardised for all patients within the same two clinics and moist dressing, aggressive debridement, offloading formed the basis of care. Wound dressings were changed every 12 hours.
Comparison	Placebo applied to cotton gauze sponge and placed on wound Wound care was standardised for all patients within the same two clinics and moist dressing, aggressive debridement,

Bibliographic reference	**Steed, D. L., Goslen, J. B., Holloway, G. A., Malone, J. M., Bunt, T. J., & Webster, M. W. (1992). Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care*, *15*(11), 1598-1604.**
	offloading formed the basis of care. Wound dressings were changed every 12 hours.
Length of follow up	Length of follow up was 20 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing within 20 weeks Complete epithelialization with no or little drainage. Treatment group : 5 of 7 Control group: 1 of 6 Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: No data provided
Source of funding	Curative technologies Inc.
Comments	

Table 30: Uchi 2009

Bibliographic reference	**Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.**
Study type	Randomised control trial
Study quality	Summary Population: Japan Intervention: basic fibroblast growth factor Comparison: moist dressing, debridement, offloading of target ulcer Outcome: cure rate, 75% or greater reductions, ulcer reduction, adverse events 1) Has an appropriate method of randomisation been used? Randomisation was computer generated. Participants were assigned to different groups depending on their telephone or fax. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients and comprised moist dressing, regular debridement (but not surgical) and offloading of target ulcer. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? 11 participants were lost following randomisation, 9 were lost following administration of treatment. 5 were lost to the 0.01% bFGF group, 3 were lost to the 0.001 bFGF group, and 4 were lost to the placebo group. In the treatment period, one participant appears to have been excluded from the efficacy analysis for the placebo group for the reason of having been cured. This seems inappropriate, Otherwise rates of loss to follow up seem similar between groups. 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up was appropriate (8 weeks) 9) Did the study use a precise definition of outcome? Clear definitions for complete wound healing and other outcomes were used. Complete epithelialization was required

Bibliographic reference	**Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.**
	10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 150 0.001% bFGF group= 48 0.01% bFGF group= 49 Placebo group= 51
Patient characteristics	Patients taken from: Japan Inclusion: Diabetes mellitus Ulcers 900 mm² or less, not reaching the periosteum (Wagners stage 2) Pulsation of dorsalis pedis or posterior tibialis Ankle brachial pressure index >0.9 Exclude: Malignant tumor History of hypersensitivity to bFGF Confirmed or suspected pregnancy Nursing women Women desiring pregnancy during the trial Oral administration or injection of adrenocortical steriod Baseline characteristics: Study reports significant differences. P values not provided in study.

Characteristics	Placebo	0.001% bFGF	0.01% bFGF

Bibliographic reference	Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.

n	51	48	49
Age, y	60.2	61.0	59.8
Male/female	37/14	32/16	35/14
Body Mass Index	Not reported	Not reported	Not reported
Ethnicity (Caucasian/non-caucasian)	Not reported	Not reported	Not reported
Insulin therapy	Not reported	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported	Not reported
Smokers	Not reported	Not reported	Not reported
Ulcer size at baseline (mm^2)	244.1 ± 218.3	269.2 ± 225.9	237.4 ± 211.5
Ulcer duration (months)	Not reported	Not reported	Not reported
Ulcer location Forefoot or digital Heel or midfoot	Not reported	Not reported	Not reported
Neuropathy (severe paraesthesia)	10	8	10
Coronary artery disease	Not reported	Not reported	Not reported
Renal impairment (dialysis)	7	7	6
Retinopathy	Not reported	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported
Previous ulcers	5	6	5
HbA1c	8.13 ± 2.12	8.18 ± 2.18	7.94 ± 2.03
Mobility Walking with support Walking without support	Not reported	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported	Not reported
Total hospital stay	Not reported	Not reported	Not reported

Bibliographic reference	**Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.**
Intervention	5 spray puffs of 0.001% bFGF once a day Wound care was standardised for all patients and comprised moist dressing, regular debridement (but not surgical) and offloading of target ulcer.
	5 spray puffs of 0.01% bFGF once a day Wound care was standardised for all patients and comprised moist dressing, regular debridement (but not surgical) and offloading of target ulcer.
Comparison	5 spray puffs of placebo once a day (0.0005% benzalkonium chloride in saline Wound care was standardised for all patients and comprised moist dressing, regular debridement (but not surgical) and offloading of target ulcer.
Length of follow up	Length of follow up was 8 weeks
Location	Japan
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing within 8 weeks Complete epithelialization 0.001% bFGF group= 27 of 47 participants 0.01% bFGF group= 30 of 45 participants Placebo group= 22 of 47 participants No significant differences observed between the three treatment groups Rates and extent of amputation: No data provided Length of stay: No data provided

Bibliographic reference	**Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.**
	Health related quality of life: No data provided Adverse events: Adverse events within 8 weeks Events with a possibility of causal relationship 0.001% bFGF group= 1 of 47 participants 0.01% bFGF group= 3 of 45 participants Placebo group= 3 of 47 participants None were severe Infection within 8 weeks 0.001% bFGF group= 0 of 47 participants 0.01% bFGF group= 1 of 45 participants Placebo group= 1 of 47 participants Pain at site within 8 weeks 0.001% bFGF group= 0 of 47 participants 0.01% bFGF group= 1 of 45 participants Placebo group= 2 of 47 participants Increased aminotransferases within 8 weeks 0.001% bFGF group= 1 of 47 participants 0.01% bFGF group= 0 of 45 participants Placebo group= 0 of 47 participants Increased in exudate within 8 weeks 0.001% bFGF group= 0 of 47 participants 0.01% bFGF group= 1 of 45 participants Placebo group= 0 of 47 participants

Bibliographic reference	**Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *European Journal of Dermatology*, *19*(5), 461-468.**
Source of funding	Kaken Pharmaceutical Co. Ltd
Comments	

Table 31: Hanft 2008

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Telbermin, recombinant human vascular endothelial growth factor Comparison: dressing, regular debridement, offloading Outcome: complete wound healing, wound area reduction, adverse events, time to complete healing 1) Has an appropriate method of randomisation been used? Unclear method of randomisation was used. Randomisation was stratified by study site and estimated ulcer surface area at screening. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups appear similar at baseline for all major confounding factors although P values were not provided. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients which included debridement, offloading and dressing changes 3 times a week. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**
	available? A slightly lower percentage of the telbermin subjects completed the entire study including the observational period. However numbers completing the treatment period were similar. 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up was appropriate (18 weeks) 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing. 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 55 Treatment group= 29 Placebo group= 26
Patient characteristics	Patients taken from: USA Inclusion: Aged 18–80 years Type 1 or type 2 diabetes HbA1c of ≤12% Grade 1A ulcer: University of Texas Diabetic Wound Classification- single full thickness wound below the malleolus, extending through the epidermis and dermis but not involving bones, ligaments, muscles or tendons Chronic ulcer of four weeks or more but less than six months Ulcer area following debridement of 1–4 cm^2 Ankle brachial pressure index of 0.6–1.2 on the study foot Use of effective contraception in females of child bearing potential Charcot foot not involving study ulcer

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**

Exclude:
Active ulcer infection or cellulitis of any ulcer
Ulcers with an aetiology unrelated to diabetes
Active osteomyelitis in the study foot
Ulcers related to an incompletely healed amputation site
Use of any investigational drug/therapy on the study foot within the past month
Previous use of growth factors on the study ulcer within the previous 3 months
Immunosuppressive treatment
History of neoplasia or current neoplasia
Proliferative diabetic retinopathy or wet age related macular degeneration
Connective tissue disease
Pregnancy or lactation
Multiple ulcers on the study foot
Renal failure
Poor nutritional status
Known hypersensitivity to any ingredients of telbermin, placebo or vehicle.
Known prior instability to complete required study visits.

Baseline characteristics: Unclear if significant differences. P values not provided in study.

Characteristics	Placebo group	Telbermin group
N	26	29
Age, y	59.3	59.5
Male/female	18/8	19/10
Mean weight	105.9	101.8
Ethnicity (white/black/Hispanic/native American or alaskan)	17/5/4/0	18/3/7/1
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	1.85	1.92

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**

Ulcer duration (months)	Not reported	Not reported
Ulcer location (plantar/dorsal/lateral/medial)	21/2/2/1	23/2/2/2
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.4	8.3
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	72 µg/cm² of topical telbermin in methylcellulose gel Wound care was standardised for all patients which included debridement, offloading and dressing changes 3 times a week.
Comparison	Placebo (formulated bulk solution without telbermin) in methylcellulose gel Wound care was standardised for all patients which included debridement, offloading and dressing changes 3 times a week.
Length of follow up	Length of follow up was maximum 19 weeks

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 84 days Unclear definition Treatment group : 15 of 29 participants placebo group: 9 of 26 participants On Kaplan Meier survival curves median time to complete healing was 58 days for telbermin treated participants and could not be calculated for placebo participants. The following complete wound healing scores are calculated by reading from a graph and from the percentages provided: Complete wound healing by 43 days Unclear definition Treatment group : 12 of 29 participants placebo group: 7 of 26 participants Complete wound healing by 29 days Unclear definition Treatment group : 7 of 29 participants placebo group: 3 of 26 participants Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided

Bibliographic reference	**Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.**
	Adverse events: At least 1 adverse event during the treatment period Treatment group : 14 of 29 participants placebo group: 13 of 26 participants At least 1 adverse event during the observation period Treatment group : 5 of 29 participants placebo group: 6 of 26 participants Infection of ulcer Treatment group : 4 of 29 participants placebo group: 5 of 26 participants One serious adverse event during the treatment period Unclear definition Treatment group : 2 of 29 participants placebo group: 2 of 26 participants One serious adverse event during the observational period Unclear definition Treatment group : 3 of 29 participants placebo group: 3 of 26 participants Adverse events occurring in two or more subjects during the treatment period: Nausea Treatment group : 2 of 29 participants Placebo group: 1 of 26 participants Vomiting Treatment group : 1 of 29 participants

Bibliographic reference	Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.
	Placebo group: 1 of 26 participants fatigue Treatment group : 2 of 29 participants Placebo group: 0 of 26 participants Pyrexia Treatment group : 1 of 29 participants Placebo group: 1 of 26 participants Infected skin ulcer Treatment group : 3 of 29 participants Placebo group: 0 of 26 participants Contusion Treatment group : 1 of 29 participants Placebo group: 1 of 26 participants Limb injury Treatment group : 0 of 29 participants Placebo group: 2 of 26 participants Pain in extremities Treatment group : 3 of 29 participants Placebo group: 0 of 26 participants Arthralgia Treatment group : 1 of 29 participants Placebo group: 1 of 26 participants Headache Treatment group : 2 of 29 participants

Bibliographic reference	Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. *J Wound Care*, *17*(1), 30-2.
	Placebo group: 1 of 26 participants cough Treatment group : 0 of 29 participants Placebo group: 2 of 26 participants Skin ulcer Treatment group : 2 of 29 participants Placebo group: 1 of 26 participants Erythema Treatment group : 1 of 29 participants Placebo group: 1 of 26 participants
Source of funding	Unclear source of funding
Comments	

Table 32: Steed 1995

Bibliographic reference	Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Arginine-Glycine-Aspartic Acide (RGD) Peptide Matrix Comparison: regular moist saline dressing changes twice a week, regular debridement, offloading Outcome: complete wound healing, wound area reduction, adverse events 1) Has an appropriate method of randomisation been used?

Bibliographic reference	**Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.**
	Patients were assigned a treatment group by a prearranged randomisation order designated in each centre. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for all major confounding factors although P values were not provided. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all patients which regular moist saline dressing changes twice a week, regular debridement, and offloading. Treatment took place in 6 different centres, however, with potential for differences in standard of care. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Eight in the RGD peptide matrix group and 6 in the placebo group were lost to follow up. Groups were similar for completion. 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up was appropriate (10 weeks) 9) Did the study use a precise definition of outcome? Unclear definitions for complete wound healing. 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 65 Treatment group= 40 Placebo group= 25
Patient characteristics	Patients taken from: USA

Bibliographic reference	**Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.**

Inclusion:

18 years or older

Foot ulcers for at least 1 month

Ulcer penetrates through the epidermis into the dermis without exposure of bone or tendon, measuring between 1 and 15 cm^2 in surface area

HbA1c levels <10%

Free of infection

No osteomyelitis on X-ray

Adequate arterial blood supply on Doppler and transcutaneous oxygen tension results

Exclude:

Receiving medications that may adversely effect healing e.g. systemic corticosteroids or antineoplastic agents

Medical conditions that may adversely effect healing e.g. immune system diseases, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, osteomyelitis, bleeding disorders, Raynaud's disease, chemotherapy for cancer.

Baseline characteristics: No reported significant differences. P values not provided in study.

Characteristics	RGD peptide matrix group	Placebo group
N	40	25
Age, y	61.8 ± 1.9	61.0 ± 2.2
Male/female	29:11	20:5
Mean weight	Not reported	Not reported
Ethnicity (white/black/Hispanic/native American or alaskan)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Non significant	Non significant
Type of diabetes type1/type2	Non significant	Non significant
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	3.5 ± 0.5	3.5 ± 0.6
Ulcer duration (months)	16.5 ± 2.7	19.0 ± 3.5
Ulcer location	62/18/20	68/16/16

Bibliographic reference	**Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.**
	(plantar/toes/lateral,medial,dorsal) % | | | Neuropathy | Not reported | Not reported Coronary artery disease | Not reported | Not reported Renal impairment | Not reported | Not reported Retinopathy | Not reported | Not reported Ankle Brachial Index Right Left | Non significant differences between groups | Non significant TCPO2, mmHg | Non significant | Non significant Previous amputation Minor Major | Not reported | Not reported Previous ulcers | Not reported | Not reported HbA1c, mean | Not reported | Not reported Mobility Walking with support Walking without support | Not reported | Not reported Wagner Classification Grade I Grade II Grade III Grade IV | Not reported | Not reported Total hospital stay | Not reported | Not reported
Intervention	Arginine-Glycine-Aspartic Acide (RGD) Peptide Matrix applied topically to wound Wound care was standardised for all patients which regular moist saline dressing changes twice a week, regular debridement, and offloading.
Comparison	Saline moistened gauze Wound care was standardised for all patients which regular moist saline dressing changes twice a week, regular debridement, and offloading.
Length of follow up	Length of follow up was 10 weeks
Location	USA

Bibliographic reference	**Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.**
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 10 weeks Unclear definition Treatment group : 14 of 40 participants placebo group: 2 of 25 participants P value 0.02 Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: All adverse events Unclear definition Treatment group : 26 of 40 participants placebo group: 29 of 25 participants Adverse events possibly related to the study treatment Unclear definition Treatment group : 3 of 40 participants placebo group: 4 of 25 participants Cellulitis

Bibliographic reference	**Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.**
	Unclear definition Treatment group : 3 of 40 participants placebo group: 1 of 25 participants Malodorous exudate Unclear definition Treatment group : 0 of 40 participants placebo group: 1 of 25 participants Ulcer inflammation Unclear definition Treatment group : 0 of 40 participants placebo group: 1 of 25 participants Increased erythema and pain Unclear definition Treatment group : 0 of 40 participants placebo group: 1 of 25 participants fever (with cellulitis) Unclear definition Treatment group : 0 of 40 participants placebo group: 1 of 25 participants
Source of funding	Telios Pharmaceuticals
Comments	

Table 33: Brigido 2004

Bibliographic reference	**Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: acellular regenerative tissue matrix. Change dressings at day 5, 10 and 15. Comparison: conventional therapy with curasol wound gel, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks Outcome: complete wound healing, wound area reduction, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for some characteristics however many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Unclear if wound care was standardised for all participants. Unclear regularity of dressing changes. Otherwise participants were kept offloaded and debrided as per standard of care. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation although unclear how this is possible when one set of participants have an obvious graft applied to the wound. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No loss to follow up reported 8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias. Follow up should have been longer to give better data for complete healing of wound (4 weeks) 9) Did the study use a precise definition of outcome? Clear definitions for complete wound healing given, full epithelialization without drainage was required. 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size

<table>
<tr><th>Bibliographic reference</th><th>Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.</th></tr>
<tr><td></td><td>11) Were investigators kept blind to participant’s exposure to the intervention?
Investigators were not kept blind to participant’s exposure to the intervention.
12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)</td></tr>
<tr><td>Number of patients</td><td>Randomised= 40
Treatment group= 20
Placebo group= 20</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Full thickness wound to lower extremity secondary to type 1 or type 2 diabetes
Chronic non-healing wounds present for at least 6 weeks without epidermal coverage
Wounds >1cm² in size

Baseline characteristics: No reported significant differences between groups. P values not provided in study.

<table>
<tr><th>Characteristics</th><th>GraftJacket tissue matrix group</th><th>Control group</th></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>Age, y</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Male/female</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mean weight</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (white/black/Hispanic/native American or alaskan)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Smokers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ulcer size at baseline (cm²)</td><td>Non-significant</td><td>Non-significant</td></tr>
<tr><td>Ulcer duration (weeks)</td><td>25 weeks</td><td>27 weeks</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.**

Ulcer location (plantar/toes/lateral,medial,dorsal) %	Not reported	Not reported
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Acellular regenerative tissue matrix (GraftJacket tissue matrix). Change dressings at day 5, 10 and 15. Participants were kept offloaded and debrided as per standard of care.
Comparison	Conventional therapy with curasol wound gel, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks
Length of follow up	Length of follow up was 4 weeks
Location	USA

Bibliographic reference	**Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.**
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 4 weeks Full epithelialization with no drainage No data provided, possibly no completely healed ulcers but unsure. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Serious adverse events Unclear definition Treatment group : 0 of 20 participants placebo group: 0 of 20 participants Drying of superficial portion of graft Unclear definition Treatment group : 4 of 20 participants placebo group: 0 of 20 participants Seroma Unclear definition Treatment group : 1 of 20 participants placebo group: 0 of 20 participants

Bibliographic reference	Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.
Source of funding	Unclear source of funding
Comments	

Table 34: Brigido 2006

Bibliographic reference	Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: acellular regenerative tissue matrix: Graftjacket. Change dressings at day 5, 10 and 15. With offloading. Comparison: conventional therapy with moist dressings (using Curasol cream), sharp debridement and offloading. Participants were evaluated weekly for 4 weeks Outcome: complete wound healing, wound area reduction, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline for some characteristics however many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Unclear if wound care was standardised for all participants. Unclear regularity of dressing changes. Otherwise participants were kept offloaded and debrided as per standard of care. Participants in the control group were debrided weekly. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation.

<table>
<tr><th>Bibliographic reference</th><th>Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.</th></tr>
<tr><td></td><td>7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available?
No loss to follow up reported
8) Did the study have an appropriate length of follow up? Unclear at what stage participants dropped out. Possible attrition bias.
Follow up was appropriate (16 weeks)
9) Did the study use a precise definition of outcome?
Clear definitions for complete wound healing given, full epithelialization without drainage was required.
10) Was a valid and reliable method used to determine that outcome?
Valid and reliable methods were used for measuring wound size
11) Were investigators kept blind to participant’s exposure to the intervention?
Investigators were not kept blind to participant’s exposure to the intervention.
12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)</td></tr>
<tr><td>Number of patients</td><td>Randomised= 28
Treatment group= 14
Control group= 14</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Full thickness chronic wound for at least 6 weeks without epidermal coverage
No evidence of active infection
Palpable/audible pulse to the affected lower extremity

Baseline characteristics: No reported significant differences between groups. P values provided

<table>
<tr><th>Characteristics</th><th>GraftJacket tissue matrix group</th><th>Control group</th></tr>
<tr><td>N</td><td>14</td><td>14</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.		
	Age, y	61.43 ± 7.18	66.21 ± 4.37
	Male/female	Not reported	Not reported
	Mean weight	Not reported	Not reported
	Ethnicity (white/black/Hispanic/native American or alaskan)	Not reported	Not reported
	Insulin therapy	Not reported	Not reported
	Duration of diabetes, y	Not reported	Not reported
	Type of diabetes type1/type2	Not reported	Not reported
	Smokers	Not reported	Not reported
	Ulcer size at baseline (cm^2)	Not reported	Not reported
	Ulcer duration (weeks)	Not reported	Not reported
	Ulcer location (plantar/toes/lateral,medial,dorsal) %	Not reported	Not reported
	Neuropathy	Not reported	Not reported
	Coronary artery disease	Not reported	Not reported
	Renal impairment	Not reported	Not reported
	Retinopathy	Not reported	Not reported
	Ankle Brachial Index Right Left	Not reported	Not reported
	TCPO2, mmHg	Not reported	Not reported
	Previous amputation Minor Major	Not reported	Not reported
	Previous ulcers	Not reported	Not reported
	HbA1c, mean	8.09 ± 0.98	7.89 ± 0.60
	Mobility Walking with support Walking without support	Not reported	Not reported
	Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
	Total hospital stay	Not reported	Not reported

Bibliographic reference	Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.
Intervention	Acellular regenerative tissue matrix (GraftJacket tissue matrix). Change dressings at day 5, 10 and 15. Participants were kept offloaded and debrided as per standard of care.
Comparison	Conventional therapy with curasol wound gel, sharp debridement and offloading. Participants were evaluated weekly by a surgeon
Length of follow up	Length of follow up was 16 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 16 weeks Full epithelialization with no drainage Treatment group : 12 of 14 participants Control group: 4 of 14 participants P value= 0.006 i.e. significant The mean time for participants in the Graftjacket treatment group to completely heal was 11.92 ± 2.87 weeks and 13.50 ± 3.42 weeks for the control group. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events:

Bibliographic reference	Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.
	Infection at the wound site Such as peri-wound erythema or local cellulitis Treatment group : 3 of 14 participants Control group: 5 of 14 participants Seroma Unclear definition Treatment group : 1 of 14 participants Control group: 0 of 14 participants
Source of funding	Unclear source of funding
Comments	

Table 35: Reyzelman 2009

Bibliographic reference	Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: acellular regenerative tissue matrix: Graftjacket. With offloading and debridement Comparison: conventional therapy with moist wound therapy, daily dressing changes, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks Outcome: complete wound healing, time to healing, wound area reduction, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation.

Bibliographic reference	**Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.**
	2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were reported similar at baseline. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all participants. All participants were kept offloaded and debrided at similar intervals as per standard of care. Rate of dressing changes may vary between groups however. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There were 8 participants lost to follow up following randomisation. 2 from the control group and 6 from the treatment group. Two participants in the treatment group were withdrawn for reasons other than adverse events. One participant's Graftjacket was completely dislodged and was deemed to be non-compliant for using an offloading device, despite offloading being apparent standard of care for both groups. This seems unclear. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Clear definitions for complete wound healing given, 100% epithelialization without drainage was required. 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods were used for measuring wound size and determining healing 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 86 Treatment group= 47 Standard of care group= 39

Bibliographic reference	**Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.**
Patient characteristics	Patients taken from: USA Inclusion: 18 years of age or older Type 1 or type 2 diabetes University of Texas Grade 1 or Grade 2 diabetic ulcer Ranging in size from 1–25 cm^2 Absence of infection Adequate circulation based on transcutaneous oxygen measurement at the dorsum of the foot ≥30 mmHg, Ankle brachial pressure index from 0.7 to 1.2 or at least Doppler arterial waveforms at the posterior tibialis or dorsalis pedis arteries. Excluded: HbA1c greater than 12% within the past 90 days Serum creatinine levels ≥ 3.0 mg/dl Sensitivity to gentamycin, linocmycin, polymyxin B or vancomycin Non revascularable surgical sites Ulcers probing to the bone Biomedical or topical growth factors within the previous 30 days Baseline characteristics: No reported significant differences between groups. P values provided

Characteristics	GraftJacket tissue matrix group	Control group
N	46	39
Age, y	55.4 ± 9.6	58.9 ±11.6
Male/female	Not reported	Not reported
Body Mass Index	33.1 ± 6.7	34.6 ± 8.5
Ethnicity (white/black/Hispanic/native American or alaskan)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported

Bibliographic reference	**Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.**

Type of diabetes type1/type2	5/41	2/37
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	3.6 ± 4.3	5.1 ± 4.8
Ulcer duration (weeks)	23.3 ± 22.4	22.9 ± 29.8
Ulcer location (toe/foot/heel/other)	15/15/4/5	15/15/4/5
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.2 ± 2.0	7.6 ± 1.6
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Acellular regenerative tissue matrix (GraftJacket tissue matrix). Wound care was standardised for all participants. All participants were kept offloaded and debrided at similar intervals as per standard of care. Rate of dressing changes in study group may be variable however.
Comparison	conventional therapy with moist wound therapy, daily dressing changes, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks Wound care was standardised for all participants. All participants were kept offloaded and debrided at similar intervals as per

Bibliographic reference	Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.
	standard of care. Rate of dressing changes was daily.
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing by 12 weeks Full epithelialization with no drainage Treatment group : 32 of 46 participants Control group: 18 of 39 participants P value= 0.0289 i.e. significant Odds ratio = 2.7 The mean time for participants in the Graftjacket treatment group to completely heal was 5.7 ± 3.5 weeks and 6.8 ± 3.3 weeks for the control group. This was non-significant. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events by 12 weeks Unclear definition Treatment group : 4 of 46 participants

Bibliographic reference	**Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). 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, 6(3), 196-208.**
	Control group: 2 of 39 participants Altered mental status and hypotension Unclear definition Treatment group : 0 of 46 participants Control group: 1 of 39 participants Infection and hallux amputation Unclear definition Treatment group : 1 of 46 participants Control group: 0 of 39 participants Graftjacket fell off Unclear definition Treatment group : 2 of 46 participants Control group: 0 of 39 participants Abscess Unclear definition Treatment group : 0 of 46 participants Control group: 1 of 39 participants Artery blockage requiring vascular surgery Unclear definition Treatment group : 1 of 46 participants Control group: 0 of 39 participants
Source of funding	Wright Medical Technology, Inc.
Comments	

Table 36: Akbari 2007

Bibliographic reference	**Akbari, A., Moodi, H., Ghiasi, F., Sagheb, H. M., & Rashidi, H. (2007). Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of Rehabilitation Research & Development, 44(5).**
Study type	Randomised control trial
Study quality	Summary Population: USA, excluding those with loss of protective sensation would exclude a large proportion of participants with diabetic foot ulcer Intervention: Vacuum compression therapy (1 hour a day, 4 times a week, for 10 sessions) Comparison: Wound care was standardised for all participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings. Outcome: Adverse events, mean ulcer surface area 1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used using computer generated numbers 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups were similar at baseline for all factors. Many important variables were not reported. Groups were reported statistically similar for mean foot ulcer surface area at baseline. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Outcome data was available for all participants, unclear if any were lost to follow up. 8) Did the study have an appropriate length of follow up? Length of follow up was not long enough for the important outcome of complete ulcer healing (3 weeks) 9) Did the study use a precise definition of outcome?

<table>
<tr><th>Bibliographic reference</th><th>Akbari, A., Moodi, H., Ghiasi, F., Sagheb, H. M., & Rashidi, H. (2007). Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of Rehabilitation Research & Development, 44(5).</th></tr>
<tr><td></td><td>Clear definitions for wound area given, none for complete ulcer healing given
10) Was a valid and reliable method used to determine that outcome?
Valid and reliable methods were used for measuring wound size
11) Were investigators kept blind to participant’s exposure to the intervention?
Investigators were kept blind to participant’s exposure to the intervention. A third party technician was responsible for collecting data on the area size of diabetic foot ulcers
12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors.</td></tr>
<tr><td>Number of patients</td><td>Randomised= 18
Treatment group= 9
Standard of care group= 9</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Diabetic foot ulcer corresponding to grade 2 of the University of Texas Diabetic Foot Wound Classification system

Excluded:
History of DVT
Haemorrhage in Ulcer
Significant loss of protective sensation
Vertigo

Baseline characteristics: No reported significant differences between groups. P values provided

<table>
<tr><td>Characteristics</td><td>Vacuum therapy</td><td>Control group</td></tr>
<tr><td>N</td><td>9</td><td>9</td></tr>
<tr><td>Age, y</td><td>58.2 ± 8.07</td><td>57.6 ± 8.02</td></tr>
<tr><td>Male/female</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Akbari, A., Moodi, H., Ghiasi, F., Sagheb, H. M., & Rashidi, H. (2007). Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of Rehabilitation Research & Development, 44(5).

Body Mass Index	23.44 ± 3.7	23.44 ± 3.7
Ethnicity (white/black/Hispanic/native American or alaskan)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (mm^2)	46.88 ± 9.28	46.62 ± 10.03
Ulcer duration (days)	45 ± 6.7	45 ± 6.7
Ulcer location (toe/foot/heel/other)	15/15/4/5	15/15/4/5
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Vacuum compression therapy (1 hour a day, 4 times a week, for 10 sessions) Wound care was standardised for all participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings.

Bibliographic reference	**Akbari, A., Moodi, H., Ghiasi, F., Sagheb, H. M., & Rashidi, H. (2007). Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of Rehabilitation Research & Development, 44(5).**
Comparison	Wound care was standardised for all participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings.
Length of follow up	Length of follow up was 3 weeks
Location	Iran
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: No data provided Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events by 3 weeks Unclear definition Treatment group : 0 of 9 participants Control group: 0 of 9 participants
Source of funding	Unfunded
Comments	

Table 37: Blume 2011

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Formulated collagen gel with growth factor GAM501, Formulated collagen gel alone Comparison: Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes. Outcome: Wound size, wound closure, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation. Groups were randomised into 5 groups. 2) Was there adequate concealment of allocation? Unclear if patient allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were statistically similar at baseline. Wound area by photograph on day 1 was less than 1.35 cm^2 in 33 out of 133 participants. 10 participants had wound sizes that decreased by greater than 33% during the run in. Eight participants met but exclusion criteria meaning 35 (31%) participants should have been excluded from enrolment on day one. Unclear how these participants were distributed between the groups. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes. Care took place over 22 different sites however with potential for differences in care. Data available was not separated by dosing regimen but was presented in 3 separate groups instead of 5: GAM501 growth factor gel, gel without growth factor and standard of care. This does not seem to adjust for the variance in the frequency of applications of treatments within the gel groups. 5) Were participants receiving care kept blind to treatment allocation? Participants were only blinded to treatment allocation of Growth factor gel vs. gel alone, not treatment vs. standard care. 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were only blinded to treatment allocation of growth factor gel vs. gel, not treatment vs. standard care. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**
	available? Of the 124 patients treated, 116 completed the study. Five withdrew from the growth factor gel and 2 withdrew from the gel alone group, 1 participant withdrew from the standard of care group. No outcome data was available for these participants. Intention to treat analysis was used for 124 participants who received treatment. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Clear definition for complete wound closure were given (complete epithelialization with no drainage) 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were not used. There were striking differences found between the acetate tracings and the corresponding wound photographs. For this reason blinded wound photograph analysis was used as the primary data source. 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were kept completely blinded 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 129 After exclusions and removing those who did not complete the study for the per protocol population= 116 Treatment with GAM501=72 FCG group= 33 Standard of care group= 19
Patient characteristics	Patients taken from: USA Inclusion: Type 1 and Type 2 diabetes Aged 18 or older Wagner Classification Grade 1 present for at least 6 weeks Peripheral neuropathy (Sammmes-weinstein monofilament test) Adequate blood flow (TcpO2 >40 mmHg or toe pressure ≥40 mmHg)

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**

Excluded:
HbA1c >12%
Ulcers on the heel
Cellulitis
Biopsy positive for beta haemolytic streptococci
Total bacterial load >1x10^6 CFU/g tissue
Decrease in ulcer size of >30% from screening to Treatment day 1

Baseline characteristics: No reported significant differences between groups. P values provided

Characteristics	GAM501	FCG group	Standard of care
N	72	33	54.8
Age, y	57.9 ± 10.9	56.2 ± 12.0	54.8 ± 12.3
Male/female	50/22	25/8	15/4
Body Mass Index	33.70 ± 7.54	33.08 ± 7.13	34.15 ± 7.18
Ethnicity (Caucasian/black or african American/Hispanic/American indian or Alaskan Native)	46/10/16/0	21/4/8/0	12/2/4/1
Insulin therapy	Not reported	Not reported	Not reported
Duration of diabetes, y	15	14	13
Type of diabetes type1/type2	6/63	2/29	16/1
Smokers	Not reported	Not reported	Not reported
Ulcer size at baseline (mm^2)	3.1 ± 1.7	2.9 ± 1.1	2.8 ± 1.3
Ulcer duration (months)	18.4 ± 28.6	17.1 ± 26.8	11.6 ± 12.0
Ulcer location (toe/foot/heel/other)	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported
Coronary artery disease	Not reported	Not reported	Not reported
Renal impairment	Not reported	Not reported	Not reported
Retinopathy	Not reported	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**

TCPO2, mmHg	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported
Previous ulcers	Not reported	Not reported	Not reported
HbA1c, mean	8.06 ± 1.82	8.07 ± 1.45	7.85 ± 1.34
Mobility Walking with support Walking without support	Not reported	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported	Not reported
Total hospital stay	Not reported	Not reported	Not reported

Intervention	GAM501 in formulated collagen gel, one application on day 1 OR GAM501 in formulated collagen gel, two application on day 1 and day 29 Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes
Comparison	Formulated collagen gel, one application on day 1 Formulated collagen gel, two application on day 1 and day 29 Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes
	Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and	Cure rates of foot ulcer resulting from diabetes:

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**
effect size	Ulcer closure by week 12 Full epithelialization without drainage GAM501 in formulated collagen gel group=27/66 Formulated collagen gel group= 14/31 Standard of care group= 5/16 Non-significant Using photographs as primary evidence source Ulcer closure by week 12 Full epithelialization without drainage GAM501 in formulated collagen gel group=21/51 Formulated collagen gel group= 6/17 Standard of care group= 4/13 Non-significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events likely or definitely related to treatment GAM501 in formulated collagen gel group=0/66 Formulated collagen gel group= 0/31

Bibliographic reference	**Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. *Wound Repair and Regeneration*, *19*(3), 302-308.**
	Standard of care group= 0/16 Non-significant
Source of funding	GAM501 and FCG are products in development by Cardium Therapeutics Inc. Two authors were employees of or owned stock options in the same company. One author is an employee of Pfizer. Sources of funding unclear.
Comments	

Table 38: Kaviani 2011

Bibliographic reference	**Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.*Photomedicine and laser surgery*, *29*(2), 109-114.**
Study type	Randomised control trial
Study quality	Summary Population: Iran Intervention: Low level laser therapy Comparison: Placebo treatment. Debridement of dead and infected tissue and offloading was done when required, oral antibiotics were used in case of clinical signs of infection, individualised topical dressings and treatments were used. Outcome: Complete healing, adverse events 1) Has an appropriate method of randomisation been used? Appropriate method of randomisation was used, a randomisation list was prepared by an independent statistician using the method of computerised random numbers. 2) Was there adequate concealment of allocation? Patient allocation was likely to be concealed by the independent statistician however this was not stated outright. 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were statistically similar at baseline for all factors reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care may not have been standardised for all participants. During treatment participants were assigned individualised

Bibliographic reference	**Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.*Photomedicine and laser surgery*, *29*(2), 109-114.**
	wound dressings and topical treatments. Wound care should have been standardised across all participants. It is unclear how dressing care varied exactly. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? 5 participants could not complete follow up till 20 weeks. Outcome data was available for all except one patient in the placebo group. There were a low number of participants in either group (13 and 10) 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (20 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of complete wound healing 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were used 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 23 Treatment group= 13 Placebo group= 10
Patient characteristics	Patients taken from: USA Inclusion: Diabetic foot ulcer for a minimum of 12 weeks Wagner classification I or II

Bibliographic reference	**Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.*Photomedicine and laser surgery*, *29*(2), 109-114.**

Excluded:
Presence of an active infection requiring hospitalisation
Gangrene
Systemic diseases such as collagen-vascular diseases
Renal failure
Evidence of ischaemia
Pregnancy
History of photosensitivity

Baseline characteristics: No reported significant differences between groups. P values provided

Characteristics	Low level laser	Placebo
N	13	10
Age, y	60.2 ± 9	59.4 ± 3.7
Male/female	8/3	4/3
Body Mass Index	Not reported	Not reported
Ethnicity (Caucasian/black or african American/Hispanic/American indian or Alaskan Native)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	19.5 ± 6.2	19 ± 4.1
Type of diabetes type1/type2	5/8	5/5
Smokers	1	0
Ulcer size at baseline (mm^2)	10.7 ± 25.7	7.8 ± 11
Ulcer duration (months)	11.4 ± 8.5	8.8 ± 3.6
Ulcer location (forefoot/midfoot/heel)	6/5/2	5/3/2
Neuropathy symptoms score	7.6 ± 2.2	7 ± 2.4
Coronary artery disease	Not reported	Not reported
Renal impairment	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.Photomedicine and laser surgery, 29(2), 109-114.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>TCPO2, mmHg</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c, mean</td><td>6.1 ± 2</td><td>7.2 ± 1.4</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="3">The low level laser therapy group received laser therapy 6 times a week for 2 weeks, then every other day until complete healing at a power density of 50 mW/cm²

Wound care may not have been standardised for all participants. During treatment participants were assigned individualised wound dressings and topical treatments. It is unclear how dressing care varied exactly.</td></tr>
<tr><td>Comparison</td><td colspan="3">Sham laser therapy 6 times a week for 2 weeks, then every other day until complete healing

Wound care may not have been standardised for all participants. During treatment participants were assigned individualised wound dressings and topical treatments. It is unclear how dressing care varied exactly.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">Length of follow up was 20 weeks</td></tr>
<tr><td>Location</td><td colspan="3">Iran</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Cure rates of foot ulcer resulting from diabetes:

Complete closure of the wound at 20 weeks
Unclear definition
Laser therapy group= 8 of 13 ulcers</td></tr>
</table>

Bibliographic reference	**Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.*Photomedicine and laser surgery*, *29*(2), 109-114.**
	Placebo group= 3 of 9 ulcers No significant difference (P=0.470) Mean time of complete healing (Kaplan meier) Laser therapy group= 11 weeks Confidence interval 7.3-14.7 Placebo group= 14 weeks, confidence interval 8.76-19.2 No significant difference Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events Unclear definition Laser therapy group= 2 of 13 participants Placebo group= 3 of 10 participants Myocardial infarction Unclear definition Laser therapy group= 1 of 13 participants Placebo group= 1 of 10 participants Amputation due to gangrene

Bibliographic reference	**Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.*Photomedicine and laser surgery*, *29*(2), 109-114.**
	Unclear definition Laser therapy group= 0 of 13 participants Placebo group= 2 of 10 participants Hospitalisation due to infection Unclear definition Laser therapy group= 1 of 13 participants Placebo group= 0 of 10 participants
Source of funding	Tehran University of Medical Sciences, no conflicts reported
Comments	

Table 39: Yingsakmongkol 2011

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**
Study type	Randomised control trial
Study quality	Summary Population: Thailand Intervention: WF10 (immunokine) Comparison: Placebo treatment. Wound debridement, wound dressing, offloading and appropriate antibiotic drugs depending on infection severity. Outcome: Wound severity score, inflammation severity score, necrotic tissue score, wound depth and wound area, adverse events and amputations

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**
	1) Has an appropriate method of randomisation been used? External statistician generated a 1:1 randomisation schedule using a randomised list 2) Was there adequate concealment of allocation? Patient allocation was likely to be concealed by the independent statistician however this was not stated outright. 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were statistically similar at baseline for all factors reported. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all participants. Wound debridement, wound dressing, offloading and appropriate antibiotic drugs depending on infection severity. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? One person from each group was lost to follow up. Outcome data was available for all participants. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (9 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of complete wound healing 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were used 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 40

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**
	Treatment group= 20 Placebo group= 20
Patient characteristics	Patients taken from: Thailand Inclusion: Aged 12-80 years Karnofsky Performance status greater than or equal to 60 Wound severity score greater than or equal to 8 HbA1c of 6-13% Excluded: Using other experimental therapies Extensive gangrene with unavoidable below knee amputation Poor nutritional status (albumin <2.5 g/dL) History of organ transplantation Using immunosuppressive, steroid or chemotherapeutic drugs Pregnant or breast feeding HIV positive End stage renal disease requiring dialysis Severe arterial occlusion that was in need of a surgical vascular procedure Baseline characteristics: No reported significant differences between groups. P values provided

Characteristics	WF10	Placebo
N	20	20
Age, y	59.4 ± 11.5	55.7 ± 13.1
Male/female	13/7	8/12

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**

Body Mass Index	25.2 ± 4.8	24.4 ± 3.9
Ethnicity (Caucasian/black or african American/Hispanic/American indian or Alaskan Native)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	10.7 ± 7.6	9.0 ± 7.3
Type of diabetes type1/type2	Not reported	Not reported
Smokers	3	0
Ulcer size at baseline (cm^2)	7.6 ± 9.8	8.0 ± 9.4
Ulcer duration (months)	17.6 ± 17.3	19.4 ± 21.2
Ulcer location (toe/dorsal/plantar/marginal/heel)	7/1/5/5/2	10/0/2/6/2
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Nephropathy	6	2
Retinopathy	12	13
Ankle Brachial Index Right Left	1.1 ± 0.2	1.2 ± 0.4
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	3	6
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.5 ± 1.9	8.8 ± 2.6
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**
	Total hospital stay | Not reported | Not reported
Intervention	Infusions of the study treatment in randomised sequence at dosage of 0.5 mL/kg body weight diluted in 500 mL of 0.9% normal saline. Administered over 6 hours once daily for 5 consecutive days. This cycle was repeated every 3 weeks for a total number of cycles of 3. Wound care was standardised for all participants. Wound debridement, wound dressing, offloading and appropriate antibiotic drugs depending on infection severity.
Comparison	Placebo was given in the same manner as the treatment (0.9% saline) Wound care was standardised for all participants. Wound debridement, wound dressing, offloading and appropriate antibiotic drugs depending on infection severity.
Length of follow up	Length of follow up was 9 weeks
Location	Thailand
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: No data provided Rates and extent of amputation: Amputation Unclear definition WF10 treatment group= 0 of 20 participants Placebo group= 0 of 20 participants Length of stay: No data provided

Bibliographic reference	**Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. *The Journal of Foot and Ankle Surgery*, *50*(6), 635-640.** **Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.**
	Health related quality of life: No data provided Adverse events: Reduced haemoglobin level <9 g/dL requiring red blood cell replacement WF10 treatment group= 7 of 20 participants Placebo group= 5 of 20 participants Thrombophlebitis Unclear definition WF10 treatment group= 1 of 20 participants Placebo group= 0 of 20 participants
Source of funding	OXO Chemie Co. Ltd
Comments	

Table 40: Han 2010

Bibliographic reference	**Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair and Regeneration*, *18*(4), 342-348.**
Study type	Randomised control trial
Study quality	Summary Population: South Korea

Bibliographic reference	**Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair and Regeneration*, *18*(4), 342-348.**
	Intervention: Uncultured, processed lipoaspirate cells Comparison: Placebo/control treatment with only fibrinogen and thrombin without cells applied topically over the wounds. Wound care was standardised for all participants and involved moist dressing, pressure offloading and ongoing debridements. Wound dressing was changed every 3-7 days. Outcome: Complete wound healing and adverse events 1) Has an appropriate method of randomisation been used? External statistician generated a 1:1 randomisation schedule using a randomisation code and a standardised permuted block approach. 2) Was there adequate concealment of allocation? Unclear if allocation was concealed, (likely) 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups were similar at baseline for all factors, no P values were provided. 4) Did the comparison groups receive the same care apart from interventions studied? Wound care was standardised for all participants and involved moist dressing, pressure offloading and ongoing debridements. Dressing changes every 3-7 days. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Two people from the treatment group were lost to follow up. Outcome data was available for all other participants who were entered into the intention to treat analysis (n=26) 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (8 weeks) 9) Did the study use a precise definition of outcome? A precise definition of outcome was used (completely epithelialized state in the absence of drainage that enabled participants to shower) 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were used 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were kept blinded to treatment allocation

<table>
<tr><th>Bibliographic reference</th><th>Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. Wound Repair and Regeneration, 18(4), 342-348.</th></tr>
<tr><td></td><td>12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors.</td></tr>
<tr><td>Number of patients</td><td>Randomised= 54
Treatment group= 26
Placebo group= 26</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: South Korea

Inclusion:
Tupe 1 or Type 2 diabetes
Foot ulcer size >1.0 cm² that has not displayed signs of healing for 6 weeks
Wagner grade 1 or 2
Transcutaneous oxygen pressure >30 mmHg
Ankle brachial pressure index >0.5

Excluded:
Infection, cellulitis,
Osteomyelitis diagnosed by MRI
Microbiologic culture results
Chronic renal insufficiency
Uncontrolled hyperglycaemia (HbA1c >9%)
Inability to tolerate offloading
Poor prognosis diseases including malignant tumours

Baseline characteristics: No reported significant differences between groups. P values provided

<table>
<tr><td>Characteristics</td><td>Lipoaspirate cells</td><td>Control group</td></tr>
<tr><td>N</td><td>26</td><td>26</td></tr>
<tr><td>Age, y</td><td>66.5 ± 7.5</td><td>68.4 ± 8.7</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair and Regeneration*, *18*(4), 342-348.		
	Male/female	15:11	14:12
	Body Mass Index	Not reported	Not reported
	Ethnicity (Caucasian/black or african American/Hispanic/American indian or Alaskan Native)	Not reported	Not reported
	Insulin therapy	Not reported	Not reported
	Duration of diabetes, y	Not reported	Not reported
	Type of diabetes type1/type2	2/24	1/25
	Smokers	Not reported	Not reported
	Ulcer size at baseline (cm^2)	4.3 ± 2.1	4.0 ± 2.1
	Ulcer duration (weeks)	12.5 ± 5.6	12.5 ± 5.5
	Ulcer location (dorsal/plantar)	14/12	13/13
	Neuropathy	Not reported	Not reported
	Coronary artery disease	Not reported	Not reported
	Nephropathy	Not reported	Not reported
	Retinopathy	Not reported	Not reported
	Ankle Brachial Index Right Left	Not reported	Not reported
	TCPO2, mmHg	52.7 ± 10.5	50.3 ± 11.2
	Previous amputation Minor Major	Not reported	Not reported
	Previous ulcers	Not reported	Not reported
	HbA1c, mean	7.2 ± 0.8	7.0 ± 1.0
	Mobility Walking with support Walking without support	Not reported	Not reported
	Wagner Classification Grade I Grade II Grade III Grade IV	 10 16	 14 12
	Total hospital stay	Not reported	Not reported

Bibliographic reference	**Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair and Regeneration*, *18*(4), 342-348.**
Intervention	Processed Lipoaspirate cells suspended in 0.3-0.7 mL of fibrinogen and dispersed on the wound. The PLA cell autograft was then sealed using 0.2-1.0 mL of thrombin. Wound care was standardised for all participants and involved moist dressing, pressure offloading and ongoing debridements. Wound dressing was changed every 3-7 days.
Comparison	Placebo/control treatment with only fibrinogen and thrombin without cells applied topically over the wounds. Wound care was standardised for all participants and involved moist dressing, pressure offloading and ongoing debridements. Wound dressing was changed every 3-7 days.
Length of follow up	Length of follow up was 8 weeks
Location	South Korea
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing completely epithelialized state in the absence of drainage that enabled participants to shower Lipoaspirate cell treatment group= 26 of 26 participants Control group= 16 of 26 participants P value <0.05 i.e. significant difference Time to complete healing (mean) Lipoaspirate cell treatment group= 33.8 ± 11.6 days Control group= 42.1 ± 9.5 days P<0.05 i.e. significant difference Rates and extent of amputation: No data provided Length of stay: No data provided

Bibliographic reference	**Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair and Regeneration*, *18*(4), 342-348.**
	Health related quality of life: No data provided Adverse events: Adverse events related to treatment Unclear definition Lipoaspirate cell treatment group= 0 of 26 participants Control group= 0 of 26 participants
Source of funding	Korean Ministry of Knowledge Economy
Comments	

Table 41: Tallis 2013

Bibliographic reference	**Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. *Clinical therapeutics*, *35*(11), 1805-1820.**
Study type	Randomised control trial
Study quality	Summary Population:USA Intervention: Clostridial collagenase ointment for debridement Comparison: Selective sharp debridement and saline moistened gauze. After surgical sharp debridement participants were treated with daily dressing change and application of treatment daily and with weekly assessment for further debridement. All participants were offloaded. Outcome: Wound assessment tool, % reduction of wound, adverse events 1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used using a computer generated randomisation sequence 2) Was there adequate concealment of allocation? Randomisation was centralised thereby making allocation concealment likely

Bibliographic reference	**Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. *Clinical therapeutics*, *35*(11), 1805-1820.**
	3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were comparable at baseline for all factors reported. Some important factors were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? After surgical sharp debridement participants were treated with daily dressing change and weekly assessment for further debridement. All participants were offloaded. All participants were instructed in the application of their own therapy and the daily dressing changes.This was a multicentre study with potential for differences in care across different sites 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Eight participants discontinued therapy before study completion, 5 from the treatment group and 3 from the control group. 2 in the treatment group and 1 in the control group were removed due to investigator decision, it is unclear what this means. Due to intention to treat analysis however, data was available for all participants. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? A precise definition of outcome was used for wound assessment scoring and percentage wound reduction. 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were used 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 48 Treatment group= 24 Placebo group= 24
Patient characteristics	Patients taken from: USA

Bibliographic reference	**Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. *Clinical therapeutics*, *35*(11), 1805-1820.**

Inclusion:
Full thickness neuropathic foot ulcer, 0.5-10 cm^2
Ulcer duration of at least 1 month
Willing and able to perform dressing changes daily
Willing and able to use appropriate offloading device
Adequate perfusion to target ulcer foot: transcutaneous oxygen pressure of >40 mm Hg or toe pressure >40 mm Hg
Adequate nutrition (albumin greater or equal than 2.0 g/dL

Excluded:
Active infection
Target wound tunnelling
Target wound over heel or Charcot deformity

Baseline characteristics: No reported significant differences between groups. P values provided

Characteristics	Clostridial collagenase debridement	Sharp debridement with saline gauze
N	24	24
Age, y	58.5 ± 13.3	63.5 ± 9.8
Male/female	16/8	16/8
Body Mass Index	Not reported	Not reported
Ethnicity (African American/white.hispanic/non-hispanic)	2/22/5/19	1/23/4/20
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	3.0 ± 2.1	2.4 ± 2.1
Ulcer duration (weeks)	Not reported	Not reported
Ulcer location	2/1/2/2/15/2/0	1/3/2/0/14/3/1

Bibliographic reference	**Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. *Clinical therapeutics*, *35*(11), 1805-1820.**

(distal/dorsal/lateral/medial/plantar/plantar distal/plantar lateral)		
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Nephropathy	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Clostridial collagenase ointment for debridement, applied once daily to the thickness of a nickel. After surgical sharp debridement participants were treated with daily dressing change and application of treatment daily for four week treatment period with weekly assessment. All participants were offloaded.
Comparison	Selective sharp debridement and saline moistened gauze. After surgical sharp debridement participants were treated with daily dressing change and application of treatment daily and with weekly assessment for further debridement. All participants were offloaded.
Length of follow up	Length of follow up was 12 weeks

Bibliographic reference	**Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. *Clinical therapeutics*, *35*(11), 1805-1820.**
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: No data provided Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Adverse events related to treatment Unclear definition Collagenase debridement group= 0 of 24 participants Saline moistened gauze group= 0 of 24 participants Adverse events not related to treatment Unclear definition Collagenase debridement group= 28 events Saline moistened gauze group= 33 events No significant difference between groups
Source of funding	Smith and Nephew Biotherapeutics
Comments	

Table 42: Moretti 2009

Bibliographic reference	**Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC musculoskeletal disorders*, *10*(1), 54.**
Study type	Randomised control trial
Study quality	Summary Population: Italy Intervention: External shock wave therapy, three applications for 1-2 minutes every 72 hours up to 3 applications. Comparison: Standard therapy: All patients were fitted with pressure relieving footwear, participants received debridement and silver cell dressing which was changed every 2-3 days, any infections were treated with antibiotics as required. Outcome: Rate of reepithelialisation, complete healing by 20 weeks, adverse events 1) Has an appropriate method of randomisation been used? Unclear method of randomisation used 2) Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were comparable at baseline for all factors reported. Many important factors were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy: All patients were fitted with pressure relieving footwear, participants received debridement and silver cell dressing which was changed every 2-3 days, any infections were treated with antibiotics as required. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no loss to follow up reported 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (20 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of complete healing

Bibliographic reference	**Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC musculoskeletal disorders*, *10*(1), 54.**
	10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were used, wound sizes were recorded digitally with a camera 11) Were investigators kept blind to participant's exposure to the intervention? Principle investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 30 Treatment group= 15 Placebo group= 15
Patient characteristics	Patients taken from: Italy Inclusion: Neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months Area >1 cm^2 Age 30-70 years Diameter of the lesion between 0.5 and 5cm Type 1 diabetes mellitus with insulin therapy for at least 5 years prior Peripheral neuropathy Ankle brachial pressure index > 0.7 Excluded: Non-palpable dorsalis pedis and posterior tibial arteries Peripheral vascular disease Coronary bypass Pregnancy Coagulation diseases History of neoplasia "other conditions" based on investigators clinical judgement

Bibliographic reference	**Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC musculoskeletal disorders*, *10*(1), 54.**

Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	External shock wave therapy	Standard therapy
N	15	15
Age, y	56.2 ± 4.9	56.8 ± 7.5
Male/female	9/6	7/8
Body Mass Index	Not reported	Not reported
Ethnicity (African American/white.hispanic/non-hispanic)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (mm^2)	297.8 ± 129.4	245 ± 100.9
Ulcer duration (weeks)	Not reported	Not reported
Ulcer location (distal/dorsal/lateral/medial/plantar/plantar distal/plantar lateral)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Nephropathy	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported

Bibliographic reference	**Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC musculoskeletal disorders*, *10*(1), 54.**
	Wagner Classification / Grade I / Grade II / Grade III / Grade IV: Not reported; Not reported Total hospital stay: Not reported; Not reported
Intervention	External shock wave therapy, three applications for 1-2 minutes every 72 hours up to 3 applications Standard therapy: All patients were fitted with pressure relieving footwear, participants received debridement and silver cell dressing which was changed every 2-3 days, any infections were treated with antibiotics as required.
Comparison	Standard therapy: All patients were fitted with pressure relieving footwear, participants received debridement and silver cell dressing which was changed every 2-3 days, any infections were treated with antibiotics as required.
Length of follow up	Length of follow up was 20 weeks
Location	Italy
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete healing by 20 weeks Unclear definition Treatment group= 8 of 15 participants Standard care group= 5 of 15 participants No P value provided Time to complete healing Treatment group= 60.8 ± 4.7 days Standard care group= 82.2 ± 4.7 days P value= <0.001 i.e. significant difference Rates and extent of amputation: No data provided

Bibliographic reference	**Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC musculoskeletal disorders*, *10*(1), 54.**
	Length of stay: No data provided Health related quality of life: No data provided Adverse events: Infection Unclear definition Treatment group= 1 of 15 participants Standard care group= 5 of 15 participants No P value provided
Source of funding	No competing interests declared
Comments	

Table 43: Lyons 2007

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: talactoferrin alfa, an immunomodulatory protein plus standard care Comparison: Placebo gel and standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices. Outcome: ≥75% wound closure, complete wound closure, adverse events

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
	1) Has an appropriate method of randomisation been used? Randomisation seems appropriate using a randomisation code. However patients who discontinued before 12 weeks of treatment could be replaced using a new randomisation code. This seems unusual. 2) Was there adequate concealment of allocation? Randomisation was done centrally thus concealing allocation 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups are comparable at baseline since this is not stated and no P values are reported. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices was provided for all participants. As treatment took place in 7 different centres care may have varied. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Loss to follow up seemed large, 18 participants withdrew prematurely. 7 discontinued due to target ulcer worsening, of 8 participants withdrawing early but with improving ulcers, 7 were from the treatment groups and 1 was from the placebo. Unclear overall how many were lost to each group and why. Data is available for all participants through intention to treat analysis. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of complete healing 10) Was a valid and reliable method used to determine that outcome? Valid and reliable methods for measuring wound size were not used, acetate tracings were used however these were apparently quality controlled with photograph achiving of the stages of ulcer healing. 11) Were investigators kept blind to participant's exposure to the intervention? Unclear if principle investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
Number of patients	Randomised= 46 2.5% treatment group= 15 8.5% treatment group= 15 Placebo gel= 16
Patient characteristics	Patients taken from: USA Inclusion: 18 years of age or older Diabetes mellitus HbA1c between 6% and 13% 1 or more diabetic neuropathic ulcers at or below the ankle that had not healed or decreased in size >30% within the 4 weeks prior study despite standard therapy Full thickness but not extending to the tendon, bone or joint capsule Post debridement size of 0.5 to 10 cm^2 Transcutaneous oxygen tension of ≥30 mm Hg Ankle brachial pressure index of ≥ 7 Excluded: Ulcer from another cause other than diabetes Signs of clinical infection Active Charcot foot ulcer Prior treatment with prior experimental therapy within the past 2 weeks (Regranex) or 4 weeks (graft therapy) Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Talactoferrin alpha 2.5% gel	Talactoferrin alpha 8.5% gel	Placebo gel

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**

N	15	15	16
Age, y	58 ± 10	53 ± 15	56 ± 14
Male/female	14/1	12/3	9/6
Body Mass Index	37.8 ± 9.0	33.0 ± 7.6	30.1 ± 4.5
Ethnicity (Caucasian/African-american/hispanic)	14/1/0	10/4/1	13/1/2
Insulin therapy	Not reported	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported	Not reported
Type of diabetes type1/type2	4/11	3/12	4/12
Smokers	Not reported	Not reported	Not reported
Ulcer size at baseline (mm^2)	2.6 ± 1.8	3.0 ± 2.0	1.9 ± 1.1
Ulcer duration (weeks)	9.7 ± 8.4	9.6 ± 11	8.9 ± 7.7
Ulcer location (distal/dorsal/lateral/medial/plantar/plantar distal/plantar lateral)	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported
Coronary artery disease	Not reported	Not reported	Not reported
Nephropathy	Not reported	Not reported	Not reported
Retinopathy	Not reported	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported
Previous ulcers	Not reported	Not reported	Not reported
HbA1c, mean	8.2 ± 1.9	8.7 ± 1.6	8.6 ± 1.9
Mobility Walking with support Walking without support	Not reported	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported	Not reported

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
	Total hospital stay | Not reported | Not reported | Not reported
Intervention	After sharp debridement of the target ulcer, talactoferrin alpha 2.5% was applied topically twice a day for 12 weeks with standard care. Standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices was provided for all participants. As treatment took place in 7 different centres care may have varied.
	After sharp debridement of the target ulcer, talactoferrin alpha 8.5% was applied topically twice a day for 12 weeks with standard care. Standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices was provided for all participants. As treatment took place in 7 different centres care may have varied.
Comparison	After sharp debridement of the target ulcer, placebo gel was applied topically twice a day for 12 weeks with standard care. Standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices was provided for all participants. As treatment took place in 7 different centres care may have varied.
Length of follow up	Length of follow up was 12 weeks, 4 months and 6 months
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete healing by 12 weeks Unclear definition Treatment 2.5% group= 3 of 15 participants Treatment 8.5% group= 3 of 15 participants placebo group= 3 of 16 participants No P value provided Complete healing by 4 months

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
	Unclear definition Treatment 2.5% group= 5 of 15 participants Treatment 8.5% group= 5 of 15 participants placebo group= 3 of 16 participants No P value provided Complete healing by 6 months Unclear definition Treatment 2.5% group= 4 of 15 participants Treatment 8.5% group= 5 of 15 participants placebo group= 3 of 16 participants No P value provided. Non-significant. Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: All adverse events Unclear definition Treatment 2.5% group= 31 events Treatment 8.5% group= 25 events placebo group= 26 events No P value provided

Bibliographic reference	**Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *The American journal of surgery*, *193*(1), 49-54.**
Source of funding	Agennix Inc. and the National Institute of Arthritis and Musculoskeletal and Skin Diseases
Comments	

Table 44: Veves 2002

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Promogran, collagen/oxidised regenerated cellulose dressing Comparison: Standard care: Moistened gauze and secondary dressing, dressings were changed when clinically required. Debridement was performed on the wound initially and then on any follow up visits as required. Patients performed their own dressing changes as required, there were strict criteria to how often a wound should be changed depending upon its clinical state. All participants were offloaded and instructed to avoid weight bearing. Outcome: complete wound closure, percentage wound healing, adverse events, time to complete ulcer healing. 1) Has an appropriate method of randomisation been used? Unclear method of randomisation. Groups were stratified for baseline ulcer size. 2) Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups are comparable at baseline since this is not stated and no P values are reported. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy as stated above may have varied between centres as the number of dressing changes between centres was found to be significantly different, however the average number of dressing changes was found to be similar between treatment groups overall. The outcomes of complete wound healing were also found to be significantly different between centers.

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**
	5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Loss to follow up seemed large, 34 participants in the promogran group and 54 in the control group did not complete the study. It is unclear at what stage these participants dropped out. Outcomes are given for all randomised participants at 12 weeks. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Clear definition of complete wound closure was provided: 100% reepithelialisation of the wound surface with the absence of drainage 10) Was a valid and reliable method used to determine that outcome? Crude measurements were used for total ulcer size but a valid and reliable method was used for the outcome of complete wound healing. 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 276 Promogran dressing group= 138 Standard wound care= 138
Patient characteristics	Patients taken from: USA Inclusion: 18 years or older A diabetic foot ulcer of at least 30 days duration

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**

Wagner grade I or II ulcer and area of at least 1 cm²
Adequate circulation
Debrided of necrotic/nonviable tissue at enrollment

Excluded:
Clinical signs of infection
Target wound with exposed bone
Concurrent illness that may interfere with healing
Known current abuse of alcohol or other drugs
Treatment with dialysis, radiotherapy, chemotherapy or systemic steroids at a dose that may have interfered with healing within the past 30 days
Known hypersensitivity to any of the dressing components
Inability or unwillingness of participant to be fitted with offloading device
Multiple diabetic ulcers on the same foot

Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Promogran dressing	Control group
N	138	138
Age, y (mean)	58	59
Male/female	95/43	108/30
Body Mass Index	Not reported	Not reported
Ethnicity (African-american/Native American/White/Hispanic)	15/16/85/22	12/16/88/22
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm²)	2.5	3.1
Ulcer duration (months)	3	3
Ulcer location (distal/dorsal/lateral/medial/plantar/plan	Not reported	Not reported

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**

tar distal/plantar lateral)		
Neuropathy	Not reported	Not reported
Coronary artery disease	Not reported	Not reported
Nephropathy	Not reported	Not reported
Retinopathy	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.6	8.5
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Promogran, collagen/oxidised regenerated cellulose dressing and standard care. Standard care: dressings were changed when clinically required. Debridement was performed on the wound initially and then on any follow up visits as required. Patients performed their own dressing changes as required, there were strict criteria to how often a wound should be changed depending upon its clinical state. All participants were offloaded and instructed to avoid weight bearing.
Comparison	Standard care: Moistened gauze and secondary dressing, dressings were changed when clinically required. Debridement was performed on the wound initially and then on any follow up visits as required. Patients performed their own dressing changes as required, there were strict criteria to how often a wound should be changed depending upon its clinical state. All participants were offloaded and instructed to avoid weight bearing..

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete healing by 12 weeks 100% reepithelialisation of the wound surface with the absence of drainage Promogran group= 51 of 138 participants Standard dressing group= 39 of 138 participants P value= 0.12 i.e. non-significant Complete healing by 12 weeks Mean time to healing (life tables) Promogran group= 7.0 ± 0.4 weeks Standard dressing group= 5.8 ± 0.4 weeks Complete healing by 12 weeks for those with ulcers of <6 months of duration 100% reepithelialisation of the wound surface with the absence of drainage Promogran group= 43 of 95 participants Standard dressing group= 29 of 89 participants P value= 0.056 i.e. non-significant Complete healing by 12 weeks for those with ulcers of <6 months of duration Mean time to healing (life tables) Promogran group= 6.9 ± 0.4 weeks Standard dressing group= 6.3 ± 0.4 weeks Complete healing by 12 weeks for those with ulcers of >6 months of duration 100% reepithelialisation of the wound surface with the absence of drainage Promogran group= 8 of 43 participants

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**
	Standard dressing group= 10 of 49 participants P value= 0.83 i.e. non-significant Complete healing by 12 weeks for those with ulcers of Wagner grade I 100% reepithelialisation of the wound surface with the absence of drainage Promogran group= 25 of 56 participants Standard dressing group= 20 of 63 participants P value= 0.15 i.e. non-significant Complete healing by 12 weeks for those with ulcers of Wagner grade II 100% reepithelialisation of the wound surface with the absence of drainage Promogran group= 27 of 82 participants Standard dressing group= 19 of 75 participants P value= 0.30 i.e. non-significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Non-serious events Unclear definition Promogran group= 37 of 138 participants Standard dressing group= 34 of 138 participants

Bibliographic reference	**Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery*,*137*(7), 822-827.**
	Serious events Unclear definition Promogran group= 25 of 138 participants Standard dressing group= 35 of 138 participants Death Promogran group= 2 of 138 participants Standard dressing group= 6 of 138 participants No differences between these groups found for either of these outcomes, No events were described as related to the study dressings.
Source of funding	Johnson and Johnson Wound Management
Comments	

Table 45: You 2012

Bibliographic reference	**You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.**
Study type	Randomised control trial
Study quality	Summary Population: South Korea Intervention: weekly cultured allogenic keratinocyte sheets Comparison: Standard care: dressing changes weekly, secondary dressing changes up to as many as three times a week if required. Treatment group received the keratinocyte sheet as the primary dressing, control group received Vaseline gauze. Sharp debridement and offloading were performed. Outcome: complete wound closure, percentage wound healing, adverse events, time to complete ulcer healing.

Bibliographic reference	**You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.**
	1) Has an appropriate method of randomisation been used? Block randomisation using a statistical analysis system were used 2) Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups are comparable at baseline since this is not stated and no P values are reported for baseline characteristics. Baseline characteristics are only provided for the per protocol population. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy as stated above may have varied between multiple centres in this study. A standardised approach was used however 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Loss to follow up in the per protocol analysis was 7 in the treatment group and 6 in the control group. An intention to treat analysis was also provided. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Clear definition of complete wound closure was provided: A completely epithelialized state in the absence of discharge and which enables the participant to shower 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 59 treatment group= 27

Bibliographic reference	**You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.**
	Standard wound care= 32 For per protocol analysis treatment group= 20 Standard wound care= 26
Patient characteristics	Patients taken from: USA Inclusion: Type 1 or type 2 diabetes Foot ulcer >1.0 cm^2 with no signs of healing for 6 weeks Wagner grade I or II Transcutaneous oxygen pressure ≥ 40 mmHg Excluded: Infection, cellulitis, Osteomyelitis diagnosed by MRI Pregnant or lactating Ulcers with deep vein thrombosis Venous insufficiency Concurrent illness or a condition that may interfere with wound healing Charcot deformity Sickle cell disease Conditions with poor prognosis Corticosteroids of immunosuppressive agents Malnutrition albumin <3.0 g/dL Baseline characteristics: No reported significant differences between groups. P values not provided.

Bibliographic reference	You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.

Characteristics	Promogran dressing	Control group
N	20	26
Age, y (mean)	63.5 ± 9.0	62.4 ± 9.4
Male/female	13/7	19/7
Body Mass Index	23.5 ± 2.7	22.8 ± 2.3
Ethnicity (African-american/Native American/White/Hispanic)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported
Smokers	2	3
Ulcer size at baseline (cm^2)	4.0 ± 3.5	5.2 ± 6.4
Ulcer duration (years)	0.33 ± 0.24	0.40 ± 0.68
Ulcer location (dorsal/plantar)	11/9	16/10
Neuropathy	13	16
Hypertension	15	19
Renal disorder	7	10
Ophthalmic disorder	5	5
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	50.2 ± 10.9	54.5 ± 11.0
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	7.3 ± 1.2	7.5 ± 1.3
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	 7 13	 9 17
Total hospital stay	Not reported	Not reported

Bibliographic reference	**You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.**
Intervention	Weekly cultured allogenic keratinocyte sheets Standard care: dressing changes weekly, secondary dressing changes up to as many as three times a week if required. Treatment group received the keratinocyte sheet as the primary dressing, control group received Vaseline gauze. Sharp debridement and offloading were performed.
Comparison	Standard care: dressing changes weekly, secondary dressing changes up to as many as three times a week if required. Treatment group received the keratinocyte sheet as the primary dressing, control group received Vaseline gauze. Sharp debridement and offloading were performed.
Length of follow up	Length of follow up was 12 weeks
Location	South Korea
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing (per protocol analysis) completely epithelialized state in the absence of drainage that enabled participants to shower Treatment group= 20 of 20 participants Control group= 18 of 26 participants P value <0.05 i.e. significant difference Time to complete healing (Kaplan Meier median) Treatment group= 35 days Control group= 57 days Complete wound healing (Intention to treat) completely epithelialized state in the absence of drainage that enabled participants to shower Treatment group= 23 of 27 participants Control group= 19 of 32 participants P value <0.05 i.e. significant difference Time to complete healing (unpaired t test) Treatment group= 41.6 ± 26.1 days

Bibliographic reference	You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.
	Control group= 43.6 ± 19.4 days P= 0.78 i.e. non-significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: All adverse events Unclear definition Treatment group= 6 of 20 participants Control group= 5 of 26 participants P value 0.67 i.e. non-significant difference Wound infections Unclear definition Treatment group= 2 of 20 participants Control group= 3 of 26 participants Pruritis Unclear definition Treatment group= 1 of 20 participants Control group= 0 of 26 participants Vomiting

Bibliographic reference	You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. *Wound Repair and Regeneration*, *20*(4), 491-499.
	Unclear definition Treatment group= 1 of 20 participants Control group= 0 of 26 participants Tremor Unclear definition Treatment group= 1 of 20 participants Control group= 0 of 26 participants Insomnia Unclear definition Treatment group= 1 of 20 participants Control group= 0 of 26 participants Ileus Unclear definition Treatment group= 0 of 20 participants Control group= 1 of 26 participants Upper respiratory tract infection Unclear definition Treatment group= 0 of 20 participants Control group= 1 of 26 participants
Source of funding	Tego Science
Comments	

Table 46: Jeffcoate 2009

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
Study type	Randomised control trial
Study quality	Summary Population: United Kingdom Intervention: Aquacel, a modern dressing product Comparison: Two types of traditional dressing: 1) N-A, a non-adherent, knitted, viscose filament gauze 2) Inadine, an iodine-impregnated dressing. Ulcer management involved regular debridement and offloading. Outcome: Number of ulcers healed at 24 weeks, time to healing, new ulcerations, major/minor amputations, secondary infections, quality of life, adverse events 1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used using blinded dressing codes. These were stratified by wound size and centre 2) Was there adequate concealment of allocation? Allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Baseline characteristics were well documented and reported similar between groups, no P values were provided however. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy as stated above may have varied between multiple centres in this study. This was compensated for by stratifying randomisation for treatment centre. Dressings could be changed by a district nurse or by an informed and willing participant. Dressings were changed daily, every other day or every third day depending upon need and clinical judgement. Frequency of dressing changes was documented as was frequency of visits. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Withdrawal was large and significantly different between groups. Eighty-eight participants with drew in total, that was 19.4% in the Inadine group, 29.1% withdrawal in the Aquacel group and 34.9% withdrawal for N-A. Intention to treat analysis was used along side per protocol analysis. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (24 weeks) 9) Did the study use a precise definition of outcome?

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	Healing was defined as complete epithelialisation maintained with no drainage for 4 weeks as confirmed by a blinded assessor 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blinded to treatment allocation. Dressings were removed before blinded inspection of the wound took place. 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 317 Inadine group= 108 Aquacel group= 103 N-A group= 106
Patient characteristics	Patients taken from: United Kindom Inclusion: Aged 18 or older Type 1 or type 2 diabetes Full thickness ulcer present for at least 6 weeks, not penetrating to the tendon, periosteum or bone, with a cross sectional area of 25-2500 mm^2 Excluded: Known allergy to any of the dressing preparations Infection of the bone Soft tissue infection requiring systemic antibiotics Ulcer on a limb being considered for revascularisation Non-removable cast without a dressing window Gangrene Non-removable eschar on debridement

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**

Sinus or deep track
Hallux amputated on affected side
Ankle brachial pressure index of less than 0.7
Toe systolic pressure of less than 30 mmHg
Ulceration judged to be caused primarily by disease other than diabetes
Any other serious illness likely to compromise the outcome of the trial
Critical renal disease
Immunosuppressants and systemic corticosteroids

Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Inadine	Aquacel	N-A
N	108	103	106
Age, y (mean)	58.8 ± 13.2	59.5 ± 11.5	61.9 ± 12.8
Male/female	81/27	81/22	78/27
Body Mass Index	Not reported	Not reported	Not reported
Ethnicity (African-american/Native American/White/Hispanic)	Not reported	Not reported	Not reported
Insulin therapy	44	43	35
Duration of diabetes, y	15.3 ± 9.8	16.0 ± 11.4	15.8 ± 11.4
Type of diabetes type1/type2	25/83	22/81	21/85
Smokers	17	15	22
Ulcer size at baseline (cm^2)	Not reported	Not reported	Not reported
Ulcer duration (years)	Not reported	Not reported	Not reported
Ulcer location (right foot/left foot/toe/forefoot/hindfoot/malleolus)	57/51/45/38/23/2	53/50/38/44/18/3	50/56/37/44/22/3
Neuropathy	Not reported	Not reported	Not reported
Cardiovascular disease	40	37	46
Nephropathy	19	22	26
Retinopathy	62	62	58
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported	Not reported

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	<table><tr><td>Previous amputation Minor Major</td><td>21</td><td>27</td><td>15</td></tr><tr><td>Previous ulcers</td><td>73</td><td>68</td><td>62</td></tr><tr><td>HbA1c, mean</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Mobility Walking with support Walking without support</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Wagner Classification Grade I Grade II Grade III Grade IV</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td><td>Not reported</td></tr></table>
Intervention	Aquacel, a modern dressing product Dressings could be changed by a district nurse or by an informed and willing participant. Dressings were changed daily, every other day or every third day depending upon need and clinical judgement. Frequency of dressing changes was documented as was frequency of visits.
Comparison	N-A, a non-adherent, knitted, viscose filament gauze Dressings could be changed by a district nurse or by an informed and willing participant. Dressings were changed daily, every other day or every third day depending upon need and clinical judgement. Frequency of dressing changes was documented as was frequency of visits.
	Inadine, an iodine-impregnated dressing. Dressings could be changed by a district nurse or by an informed and willing participant. Dressings were changed daily, every other day or every third day depending upon need and clinical judgement. Frequency of dressing changes was documented as was frequency of visits.
Length of follow up	Length of follow up was 24 weeks
Location	United Kingdom

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing at 12 weeks (intention to treat analysis) Complete epithelialisation maintained with no drainage for 4 weeks as confirmed by a blinded assessor Inadine group= 32 of 108 participants Aquacel group= 29 of 103 participants N-A group= 27 of 106 participants Inadine vs N-A, P value = 0.46 i.e. no significant difference Aquacel vs N-A, P value = 0.66 i.e. no significant difference Complete wound healing at 24 weeks (intention to treat analysis) Complete epithelialisation maintained with no drainage for 4 weeks as confirmed by a blinded assessor Inadine group= 48 of 108 participants Aquacel group= 46 of 103 participants N-A group= 41 of 106 participants Inadine vs N-A, P value = 0.39 i.e. no significant difference Aquacel vs N-A, P value = 0.38 i.e. no significant difference Complete wound healing at 12 weeks (per protocol analysis) Complete epithelialisation maintained with no drainage for 4 weeks as confirmed by a blinded assessor Inadine group= 32 of 96 participants Aquacel group= 29 of 81 participants N-A group= 27 of 80 participants Inadine vs N-A, P value = 0.95 i.e. no significant difference Aquacel vs N-A, P value = 0.78 i.e. no significant difference Complete wound healing at 24 weeks (per protocol analysis) Complete epithelialisation maintained with no drainage for 4 weeks as confirmed by a blinded assessor Inadine group= 48 of 87 participants Aquacel group= 46 of 73 participants N-A group= 41 of 69 participants

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	Inadine vs N-A, P value = 0.59 i.e. no significant difference Aquacel vs N-A, P value = 0.66 i.e. no significant difference Mean time to complete healing for those ulcers healed at 12 weeks (intention to treat) Inadine group= 74.1 ± 20.6 days (95% confidence interval 70.2-78.1) Aquacel group= 72.4 ± 20.6 days (95% confidence interval 68.4-76.5) N-A group= 75.1 ± 18.1 days (95% confidence interval 71.6-78.6) P value= 0.61 i.e. no significant difference Mean time to complete healing for those ulcers healed at 12 weeks (per protocol) Inadine group= 72.9 ± 21.6 days (95% confidence interval 68.5-77.3) Aquacel group= 69.3 ± 22.3 days (95% confidence interval 64.4-74.3) N-A group= 72.3 ± 20.1 days (95% confidence interval 67.8-76.8) P value= 0.5 i.e. no significant difference Mean time to complete healing for those ulcers healed at 24 weeks (intention to treat) Inadine group= 127.8 ± 54.2 days (95% confidence interval 117.5-138.2) Aquacel group= 125.8 ± 55.9 days (95% confidence interval 114.9-136.7) N-A group= 130.7 ± 52.4 days (95% confidence interval 120.6-140.8) P value= 0.80 i.e. no significant difference Mean time to complete healing for those ulcers healed at 24 weeks (per protocol) Inadine group= 118.1 ± 56.3 days (95% confidence interval 106.1-130.1) Aquacel group= 108.5 ± 58.2 days (95% confidence interval 94.9-122.1) N-A group= 110.7 ± 55.6 days (95% confidence interval 97.4-124.1) P value= 0.53 i.e. no significant difference Rates and extent of amputation:

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	Minor amputations Below the ankle Inadine group= 1 of 108 participants Aquacel group= 3 of 103 participants N-A group= 1 of 106 participants Major amputations Below the knee Inadine group= 0 of 108 participants Aquacel group= 1 of 103 participants N-A group= 1 of 106 participants Length of stay: No data provided Health related quality of life: Pain There were no apparent differences in the number of participants reporting pain by dressing allocation at any of the 12 visits (see study for elaboration on data here) Pain in the region of the wound at 12 weeks Intensity of pain graded on 100mm visual analogue scale Inadine group= 8 of 65 participants Aquacel group= 10 of 53 participants N-A group= 11 of 51 participants Pain in the region of the wound at 24 weeks Intensity of pain graded on 100mm visual analogue scale Inadine group= 5 of 41 participants Aquacel group= 4 of 27 participants

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	N-A group= 6 of 28 participants Health reported quality of life Self-reported Quality of life at baseline, 12 weeks or 24 weeks SF-36 Data tables provided in paper There was no differences observed between any of the groups across any of the domains at any of the time points Self-reported Quality of life at baseline, 12 weeks or 24 weeks SF-6D Data tables provided in paper There was no differences observed between any of the groups across any of the domains at any of the time points Self-reported Quality of life at baseline, 12 weeks or 24 weeks CWIS- Cardiff Wound impact Schedule Data tables provided in paper for Physical Functioning, Social Functioning, Well being There was no differences observed between any of the groups across any of the domains at any of the time points Adverse events: Secondary infection Number of cases of infection reported as serious adverse events by dressing allocation Inadine group= 10 of 108 participants Aquacel group= 7 of 103 participants N-A group= 7 of 106 participants P value = 0.43 i.e. no significant difference Secondary infection Number of cases of infection reported as adverse events by dressing allocation

Bibliographic reference	**Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Prepress Projects Limited.**
	Inadine group= 71 of 108 participants Aquacel group= 54 of 103 participants N-A group= 48 of 106 participants P value = <0.001 i.e. significant difference Episodes of reported non-serious adverse events by week 24 Unclear definition Inadine group= 239 of 108 participants Aquacel group= 227 of 103 participants N-A group= 244 of 106 participants P value= 0.72 Episodes of reported serious adverse events by week 24 Unclear definition Inadine group= 37 of 108 participants Aquacel group= 28 of 103 participants N-A group= 35 of 106 participants P value= 0.512 Death Inadine group= 1 of 108 participants Aquacel group= 2 of 103 participants N-A group= 2 of 106 participants
Source of funding	Health Technology Assessment, NIHR HTA programme
Comments	

Table 47: Driver 2006

Bibliographic reference	**Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management*, *52*(6), 68.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Autologous Platelet-rich Plasma Comparison: Standard care: Control wounds were treated with a saline gel. Sharp debridement guidelines were provided as part of the protocol. Patients were required to use fixed-ankle-foot orthoses for offloading. Dressing changes were twice weekly. Outcome: complete wound closure, percentage wound healing, adverse events, 1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used. Study employed an electronically generated randomisation schedule blocked per investigational centre. 2) Was there adequate concealment of allocation? Allocation appears to be adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? The mean and standard deviations of wound volume were significantly different between population groups in the intention to treat analysis. Groups were not statistically different for any other variables. In the per protocol analysis groups were different for proportions of Caucasians which was higher in the treatment group. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Standard therapy as stated above may have varied between multiple centres in this study. A standardised approach was used however and randomisation attempted to compensate for any differences in care between centres. 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation, each centre had one diagnosed “unblinded” member of staff to treat the participants. 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Groups were not equal for loss to follow up. 21 participants were lost to follow up in the treatment group compared to 11 lost to follow up in the control group. Intention to treat analysis was employed however this was found to be faulty due to the recruitment of 44% of participants breaking protocol or not completing therapy. Per protocol analysis was used as primary

Bibliographic reference	**Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management*, *52*(6), 68.**
	outcome. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (24 weeks) 9) Did the study use a precise definition of outcome? Clear definition of complete wound closure was provided: 100% epithelialized wound was required. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 72 treatment group= 40 Standard wound care= 32 For per protocol analysis treatment group= 19 Standard wound care= 21
Patient characteristics	Patients taken from: USA Inclusion: Type 1 or type 2 diabetes Between the ages of 18 and 95 years An ulcer of at least 4 weeks duration HbA1c less than 12 Index foot ulcer located on the plantar, medial or lateral aspect of the foot Wound area between 0.5-20 cm^2

Bibliographic reference	**Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management*, *52*(6), 68.**

Clinically non-infected
Full thickness without exposure of bone, tendon, muscle or ligament
Charcot deformity free of acute changes

Excluded:
Free of necrotic tissue, foreign bodies, sinus tract, tunnelling and undermining
Less than 4cm from any additional wound
None adequate perfusion
Pregnant or lactating
Ulcer decreasing by ≥50cm² in the seven days prior to treatment
Using another investigational device or treatment
Non-diabetic origin
Gangrene
Radiotherapy/chemotherapy
Acute Charcot foot
Antibiotics used within the previous 2 days
Osteomyelitis
Surgical correction required for ulcer to heal
History of alcohol or drug abuse
History of peripheral vascular repair within 30 days of therapy

Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Platelet rich gel	Control group
N	40	32
Age, y (mean) (per protocol)	56.4 ± 10.2	57.5 ± 9.1
Male/female	32/8	27/5
Body Mass Index	Not reported	Not reported
Ethnicity (Caucasian/Hispanic/black/other)	26/8/5/1	18/9/3/2
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Management, 52(6), 68.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Smokers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ulcer size at baseline (cm²) (per protocol)</td><td>4.0 ± 5.3</td><td>3.2 ± 3.5</td></tr>
<tr><td>Ulcer duration (years)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ulcer location (right foot/left foot/toe/heel)</td><td>23/17/13/18</td><td>18/14/14/10</td></tr>
<tr><td>Neuropathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Hypertension</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Renal disorder</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ophthalmic disorder</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ankle Brachial Index
Right
Left</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>TCPO2, mmHg</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c, mean</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="3">Platelet-rich Plasma gel applied topically and secured, changed twice weekly

Sharp debridement guidelines were provided as part of the protocol. Patients were required to use fixed-ankle-foot orthoses for offloading. Dressing changes were twice weekly.</td></tr>
<tr><td>Comparison</td><td colspan="3">Standard care: Control wounds were treated with a saline gel. Sharp debridement guidelines were provided as part of the protocol. Patients were required to use fixed-ankle-foot orthoses for offloading. Dressing changes were twice weekly.</td></tr>
</table>

Bibliographic reference	**Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management*, *52*(6), 68.**
Length of follow up	Length of follow up was 24 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure (per protocol analysis) by 12 weeks 100% epithelialized state Treatment group= 13 of 19 participants Control group= 9 of 21 participants P value 0.125 i.e. no significant difference Time to complete closure (Kaplan Meier median) Treatment group= 45 days Control group= 85 days P=0.126 i.e. no significant difference Complete wound closure (Intention to treat) by 12 weeks 100% epithelialized state Treatment group= 13 of 40 participants Control group= 9 of 32 participants P value 0.79 i.e. no significant difference Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided

Bibliographic reference	**Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management*, *52*(6), 68.**
	Adverse events: All adverse events Unclear definition Treatment group= 60 events Control group= 62 events All serious adverse events Fatal, life threatening, requires hospitalisation, results in significant disability, is an important medical event Treatment group= 6 events Control group= 17 events
Source of funding	AutoloGel Diabetic Foot Ulcer Group, unclear if funded whole study
Comments	

Table 48: Tom 2005

Bibliographic reference	**Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.*Archives of dermatology*, *141*(11), 1373-1377.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Topical tretinoin, applied daily for 10 minutes, for 4 weeks Comparison: Saline placebo, coloured to look the same. Applied topically for 10 minutes daily, for 4 weeks. Standard care included debridement when necessary and offloading of the wound. Cadexomer iodine gel was also applied to both groups and left on overnight, this was continued daily after treatment had finished. Outcome: complete wound healing, proportion wound healing, adverse events,

Bibliographic reference	**Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.*Archives of dermatology*, *141*(11), 1373-1377.**
	1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used. An independent third party produced a computer-generated randomisation list. 2) Was there adequate concealment of allocation? Allocation appears to be adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were comparable for all factors reported, some important factors were not reported 4) Did the comparison groups receive the same care apart from interventions studied? Participants received the same standard of care aside from intervention studied 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Groups were equal for loss to follow up. One participant was lost to either group in follow up. Number of participants was low overall however. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (16 weeks) 9) Did the study use a precise definition of outcome? Complete healing was not clearly defined 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Randomised= 24 treatment group= 13 Standard wound care= 11

Bibliographic reference	**Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.*Archives of dermatology*, *141*(11), 1373-1377.**
	Analysed treatment group= 12 Standard wound care= 10
Patient characteristics	Patients taken from: USA Excluded: Unable to give informed consent Had a known bleeding disorder Pregnant Infected ulcers or nearby tissues Lower extremity ulcers due to large artery disease Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Control group	Tretinoin group
N	11	13
Age, y (mean)	61.2 ± 3.9	58.3 ± 1.5
Male/female	Not reported	Not reported
Body Mass Index	Not reported	Not reported
Ethnicity (Caucasian/Hispanic/black/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	12.5 ± 2.9	14.8 ± 2.3
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	1.17 ± 0.69	0.87 ± 0.26
Ulcer duration (months)	11.9 ± 5.1	6.3 ± 2.0
Ulcer location (plantar/lateral/dorsum)	9/2/0	12/0/1
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported

<table>
<tr><th>Bibliographic reference</th><td colspan="2">Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.Archives of dermatology, 141(11), 1373-1377.</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><td>Renal disorder</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ophthalmic disorder</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ankle Brachial Index
Right
Left</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>TCPO2, mmHg</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous amputation
Minor
Major</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Previous ulcers</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>HbA1c, mean</td><td>8.3 ± 0.5</td><td>7.7 ± 0.4</td></tr>
<tr><td>Mobility
Walking with support
Walking without support</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Wagner Classification
Grade I
Grade II
Grade III
Grade IV</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Total hospital stay</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="2">Topical tretinoin, applied daily for 10 minutes, for 4 weeks

Standard care included debridement when necessary and offloading of the wound. Cadexomer iodine gel was also applied to both groups and left on overnight, this was continued daily after treatment had finished.</td></tr>
<tr><td>Comparison</td><td colspan="2">Saline placebo, coloured to look the same. Applied topically for 10 minutes daily, for 4 weeks.

Standard care included debridement when necessary and offloading of the wound. Cadexomer iodine gel was also applied to both groups and left on overnight, this was continued daily after treatment had finished.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">Length of follow up was 16 weeks</td></tr>
<tr><td>Location</td><td colspan="2">USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">Cure rates of foot ulcer resulting from diabetes:</td></tr>
</table>

Bibliographic reference	**Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.*Archives of dermatology*, *141*(11), 1373-1377.**
	Complete wound closure by 16 weeks Unclear definition Treatment group= 6 of 13 participants Control group= 2 of 11 participants Time to complete closure (Kaplan Meier median) Tretinoin therapy increased the proportion of ulcers that healed completely over 16 week period P=0.03 i.e. significant difference Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Pain/burning at site Unclear definition Treatment group= 3 of 13 participants Control group= 1 of 11 participants Erythema/oedema Unclear definition Treatment group= 0 of 13 participants Control group= 1 of 11 participants
Source of funding	Unclear source of funding

Bibliographic reference	**Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.*Archives of dermatology*, *141*(11), 1373-1377.**
Comments	

Table 49: Fife 2007

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: 1 µg or 10 µg Chrysalin, amino acid peptide representing the natural sequence of Thrombin. Applied topically in a volume of 0.1 cm^3 saline solution then after 1 minute covered with Cutinova foam and bandaged. Comparison: Saline placebo applied topically in a volume of 0.1 cm^3 saline solution then after 1 minute covered with Cutinova foam and bandaged. Standard therapy involved twice weekly visits for application of study treatment and dressing changes, debridement as needed to remove necrotic tissue and offloading of ulcer site. Outcome: complete wound closure by 20 weeks, adverse events, pain, overall condition, erythema, oedema 1) Has an appropriate method of randomisation been used? Unclear method of randomisation 2) Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were comparable for all factors reported, some important factors were not reported 4) Did the comparison groups receive the same care apart from interventions studied? Participants received the same standard of care aside from intervention studied 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available?

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	Intention to treat analysis was performed. In the per protocol analysis 6 were lost to follow up in the placebo group, 9 of the 1 µg Chrysalin group were lost to follow up and 4 of the 10 µg Chrysalin group, This is a significant proportion of the total populations. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (20 weeks) 9) Did the study use a precise definition of outcome? Complete healing was clearly defined 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors.
Number of patients	Intention to treat Randomised= 59 Placebo group= 21 1 µg Chrysalin group= 20 10 µg Chrysalin group= 18 Per-protocol Placebo group= 15 1 µg Chrysalin group= 11 10 µg Chrysalin group= 14
Patient characteristics	Patients taken from: USA Inclusion: Below the knee ulcers ranging from 0.9-38.5 cm^2, present for more than 8 weeks Wagner grade I, II and III

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**

Excluded:
Clinical infection of the ulcer
Uncontrolled systemic infection
Osteomyelitis
Poor diabetes control
Renal failure
Abnormal liver function
Treatment with steroids, chemotherapeutics or radiation within the past6 months
Cancer
History of drug or alcohol abuse
Wound oxygen tension of <20 mmHg
Women who are pregnant, nursing or of child bearing potential not using effective birth control

Baseline characteristics: No reported significant differences between groups. P values not provided.

Characteristics	Placebo group	1 µg Chrysalin	10 µg Chrysalin
N	21	20	18
Age, y (mean)	55.7 ± 12.8	59.3 ± 6.4	53.4 ± 10.5
Male/female	15/6	14/6	14/4
Weight (lbs)	196.3 ± 77.3	206.5 ± 41.8	229.5 ± 58.8
Ethnicity (Caucasian/black/hispanic/other)	11/6/3/1	12/4/4/0	11/2/5/0
Insulin therapy	Not reported	Not reported	Not reported
Duration of diabetes, y	Not reported	Not reported	Not reported
Type of diabetes type1/type2	Not reported	Not reported	Not reported
Smokers	Not reported	Not reported	Not reported
Ulcer size at baseline (cm^2)	4.11 ± 5.99	3.59 ± 5.31	3.15 ± 3.20
Ulcer duration (months)	Not reported	Not reported	Not reported
Ulcer location (plantar/lateral/dorsum)	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported
Hypertension	Not reported	Not reported	Not reported

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	Renal disorder: Not reported / Not reported / Not reported Ophthalmic disorder: Not reported / Not reported / Not reported Ankle Brachial Index Right Left: Not reported / Not reported / Not reported TCPO2, mmHg: Not reported / Not reported / Not reported Previous amputation Minor Major: Not reported / Not reported / Not reported Previous ulcers: Not reported / Not reported / Not reported HbA1c, mean: Not reported / Not reported / Not reported Mobility Walking with support Walking without support: Not reported / Not reported / Not reported Wagner Classification Grade I Grade II Grade III Grade IV: Not reported / Not reported / Not reported Total hospital stay: Not reported / Not reported /
Intervention	1 µg Chrysalin, amino acid peptide representing the natural sequence of Thrombin. Applied topically in a volume of 0.1 cm^3 saline solution then after 1 minute covered with Cutinova foam and bandaged. Standard therapy involved twice weekly visits for application of study treatment and dressing changes, debridement as needed to remove necrotic tissue and offloading of ulcer site.
	10 µg Chrysalin, amino acid peptide representing the natural sequence of Thrombin. Applied topically in a volume of 0.1 cm^3 saline solution then after 1 minute covered with Cutinova foam and bandaged. Standard therapy involved twice weekly visits for application of study treatment and dressing changes, debridement as needed to remove necrotic tissue and offloading of ulcer site.
Comparison	Saline placebo applied topically in a volume of 0.1 cm^3 saline solution then after 1 minute covered with Cutinova foam and bandaged. Standard therapy involved twice weekly visits for application of study treatment and dressing changes, debridement as

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	needed to remove necrotic tissue and offloading of ulcer site.
Length of follow up	Length of follow up was 20 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure by 20 weeks (intention to treat) Complete re-epithelialization Placebo group= 10 of 21 ulcers 1 µg Chrysalin group= 11 of 20 ulcers 10 µg Chrysalin group= 11 of 18 ulcers Complete wound closure by 20 weeks (per protocol) Complete re-epithelialization Placebo group= 3 of 15 ulcers 1 µg Chrysalin group= 5 of 11 ulcers 10 µg Chrysalin group= 8 of 14 ulcers No significant difference between groups in either analysis Time to complete closure (Kaplan Meier, median, per protocol) Placebo group= not reached (>140 days) 1 µg Chrysalin group= 122 days 10 µg Chrysalin group= 87 days No significant difference Complete wound closure by 20 weeks (foot ulcers) Complete re-epithelialization Placebo group= 4 of 13 ulcers

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	1 µg Chrysalin group= 9 of 12 ulcers 10 µg Chrysalin group= 7 of 10 ulcers 1 µg Chrysalin vs placebo, P value= <0.05 i.e. significant 10 µg Chrysalin vs placebo, P value= <0.05 i.e. significant Time to complete closure (Kaplan Meier, median, foot ulcers) Placebo group= not reached (>140 days) 1 µg Chrysalin group= 94 days 10 µg Chrysalin group= 71.5 days P value = <0.05 i.e. significant difference Complete wound closure by 20 weeks (heel ulcers) Complete re-epithelialization Placebo group= 0 of 5 ulcers 1 µg Chrysalin group= 6 of 7 ulcers 10 µg Chrysalin group= 6 of 7 ulcers 1 µg Chrysalin vs placebo, P value= <0.03 i.e. significant 10 µg Chrysalin vs placebo, P value= <0.03 i.e. significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Well-defined to severe erythema

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	Placebo group= 2 of 21 ulcers 1 µg Chrysalin group= 3 of 20 ulcers 10 µg Chrysalin group= 2 of 18 ulcers Well-defined to severe oedema Placebo group= 3 of 21 ulcers 1 µg Chrysalin group= 3 of 20 ulcers 10 µg Chrysalin group= 4 of 18 ulcers Worsened pain Placebo group= 2 of 21 ulcers 1 µg Chrysalin group= 2 of 20 ulcers 10 µg Chrysalin group= 2 of 18 ulcers Infection Placebo group= 1 of 21 ulcers 1 µg Chrysalin group= 1 of 20 ulcers 10 µg Chrysalin group= 1 of 18 ulcers Fever Placebo group= 1 of 21 ulcers 1 µg Chrysalin group= 0 of 20 ulcers 10 µg Chrysalin group= 0 of 18 ulcers Pain Placebo group= 1 of 21 ulcers 1 µg Chrysalin group= 1 of 20 ulcers 10 µg Chrysalin group= 0 of 18 ulcers Sepsis Placebo group= 0 of 21 ulcers

Bibliographic reference	**Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. *Wound repair and regeneration*, *15*(1), 23-34.**
	1 µg Chrysalin group= 0 of 20 ulcers 10 µg Chrysalin group= 1 of 18 ulcers Myocardial infarction Placebo group= 1 of 21 ulcers 1 µg Chrysalin group= 0 of 20 ulcers 10 µg Chrysalin group= 1 of 18 ulcers Gangrene Placebo group= 0 of 21 ulcers 1 µg Chrysalin group= 0 of 20 ulcers 10 µg Chrysalin group= 1 of 18 ulcers Urinary tract infection Placebo group= 0 of 21 ulcers 1 µg Chrysalin group= 0 of 20 ulcers 10 µg Chrysalin group= 1 of 18 ulcers Acute kidney failure Placebo group= 0 of 21 ulcers 1 µg Chrysalin group= 1 of 20 ulcers 10 µg Chrysalin group= 0 of 18 ulcers Osteomyelitis Placebo group= 0 of 21 ulcers 1 µg Chrysalin group= 1 of 20 ulcers 10 µg Chrysalin group= 0 of 18 ulcers
Source of funding	Chrysalis BioTechnology Inc.
Comments	

Table 50: Peters 2001

Bibliographic reference	**Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.*Archives of physical medicine and rehabilitation*, *82*(6), 721-725.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Micro-Z, a small electric stimulation device. Gives a treatment dose of 50V with 80 twin peak monophasic pulses per second, delivered for 10 minutes. Followed by 10 minutes of 8 pulses per second of current. Comparison: Placebo group used electric stimulation units that looked and acted identically to the treatment device but did not deliver current. Both groups received traditional wound care involving debridement, NU-GEL collagen wound gel and pressure reduction at the site of the ulceration. Dressings were changed twice a day by the patient, their family members and, or home health care providers. Patients were seen every week to evaluate healing progress. Outcome: complete wound closure by 12 weeks, rate of wound healing, adverse events, amputations 1) Has an appropriate method of randomisation been used? An appropriate method of randomisation was used 2) Was there adequate concealment of allocation? Allocation was adequately concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. No P values were provided. Post hoc analysis was performed to separate those who complied to therapy from those that did not. 4) Did the comparison groups receive the same care apart from interventions studied? Participants received the same standard of care aside from intervention studied 5) Were participants receiving care kept blind to treatment allocation? Participants were blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There appears to be no loss to follow up in either group 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome?

<table>
<tr><th>Bibliographic reference</th><th>Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.Archives of physical medicine and rehabilitation, 82(6), 721-725.</th></tr>
<tr><td></td><td>Complete healing was clearly defined as complete epithelialization
10) Was a valid and reliable method used to determine that outcome?
A valid and reliable method was used
11) Were investigators kept blind to participant’s exposure to the intervention?
Investigators were kept blinded to treatment allocation
12) Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors.</td></tr>
<tr><td>Number of patients</td><td>Randomised= 40
Placebo group= 20
Electrical stimulation group= 20</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
University of Texas Diabetic Wound Classification grades 1A-2A
Transcutaneous oxygen tension >30 mmHg

Excluded:
Soft tissue or bone infection
Malignancy
Cardiac conductivity disorder

Baseline characteristics: No reported significant differences between groups. P values not provided.

<table>
<tr><th>Characteristics</th><th>Placebo group</th><th>Electrical stimulation</th></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>Age, y</td><td>59.9 ± 7.0</td><td>54.4 ± 12.4</td></tr>
<tr><td>Male/female</td><td>16/4</td><td>19/2</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.*Archives of physical medicine and rehabilitation*, *82*(6), 721-725.**

Weight (lbs)	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	17.0 ± 7.5	16.4 ± 11.6
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm^2)	3.54 ± 5.56	1.63 ± 1.51
Ulcer duration (months)	5.5 ± 13.0	5.0 ± 6.4
Ulcer location (plantar/lateral/dorsum)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	43.4 ± 10.6	47.1 ± 13.0
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Micro-Z, a small electric stimulation device. Gives a treatment dose of 50V with 80 twin peak monophasic pulses per second, delivered for 10 minutes. Followed by 10 minutes of 8 pulses per second of current. Both groups received traditional wound care involving debridement, NU-GEL collagen wound gel and pressure reduction at

Bibliographic reference	**Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.*Archives of physical medicine and rehabilitation*, *82*(6), 721-725.**
	the site of the ulceration. Dressings were changed twice a day by the patient, their family members and, or home health care providers. Patients were seen every week to evaluate healing progress.
Comparison	Placebo group used electric stimulation units that looked and acted identically to the treatment device but did not deliver current. Both groups received traditional wound care involving debridement, NU-GEL collagen wound gel and pressure reduction at the site of the ulceration. Dressings were changed twice a day by the patient, their family members and, or home health care providers. Patients were seen every week to evaluate healing progress.
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure by 12 weeks Complete re-epithelialization Placebo group= 7 of 20 ulcers Electrical stimulation group= 13 of 20 ulcers P value= 0.058 Average time till wound healing Complete re-epithelialization Placebo group= 6.8 ± 3.4 weeks Electrical stimulation group= 6.9 ± 2.8 weeks Rates and extent of amputation: Amputations Placebo group= 1 of 20 participants

Bibliographic reference	**Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.*Archives of physical medicine and rehabilitation*, *82*(6), 721-725.**
	Electrical stimulation group= 0 of 20 participants Length of stay: No data provided Health related quality of life: No data provided Adverse events: Soft tissue infection Unclear definition Placebo group= 2 of 20 participants Electrical stimulation group= 2 of 20 participants
Source of funding	South Texas Health Research Centre, No conflict of interest declared
Comments	

Table 51: Marfella 2012

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**
Study type	Randomised control trial
Study quality	Summary Population: Italy, only type 2 diabetics Intervention: Vildagliptin, a dipeptidyl peptidase 4 inhibitor. 50 mg, twice a day Comparison: Standard care: before randomisation and at each study visit study ulcers received sharp debridement and saline-moistened gauze dressings. The ulcers were debrided when considered necessary. Individualised topical treatment

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**
	and dressings were used depending on the site and character of the ulcer. Off-loading protective shoe wear with individually fitted in-soles were used. Outcome: complete wound closure by 12 weeks, rate of wound healing, adverse events, amputations 1) Has an appropriate method of randomisation been used? Unclear method of randomisation 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. P values were provided. 4) Did the comparison groups receive the same care apart from interventions studied? Participants did not necessarily receive the same standard of care apart from interventions studied as individualised topical treatments and dressings were used depending on the site and character of the ulcer. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There appears to be no loss to follow up in either group or participants for which there is no outcome data available. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Complete healing was clearly defined as complete epithelialization with absence of drainage 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**
Number of patients	Randomised= 106 Placebo group= 53 Electrical stimulation group= 53
Patient characteristics	Patients taken from: Italy Inclusion: Type 2 diabetic participants Chronic non-healing diabetic foot ulcers for more than 3 month duration Adequate distal perfusion (transcutaneous oxygen pressure >30 mmHg, ankle brachial pressure index >0.7 and <1.2) Excluded: Active Charcot disease Ulcers resulting from electrical, chemical, or radiation burns and those with collagen vascular disease, ulcer malignancy, untreated osteomyelitis, or cellulitis Ulcer treatment with normothermic or hyperbaric oxygen therapy Corticosteroid use, immunosuppressive medications, or chemotherapy Recombinant or autologous growth factor products, skin or dermal substitute treatment within 30 days of study Or use of any enzymatic debridement treatments Pregnant or nursing Baseline characteristics: No reported significant differences between groups. P values provided.

Characteristics	Vildagliptin	Control group
N	53	53
Age, y	63 ± 15	64 ± 17
Male/female	34/19	35/18
BMI (kg/m²)	29 ± 2.8	30 ± 2.1
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	14	14

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**

Duration of diabetes, y	16 ± 6	17 ± 5
Type of diabetes type1/type2	All type 2	All type 2
Smokers	5	6
Ulcer size at baseline (cm^2)	4.1 ± 1.2	4.3 ± 1.5
Ulcer duration (days)	122 ± 22	126 ± 26
Ulcer location (plantar/ dorsum/lateral)	32/11/10	33/10/10
Neuropathy	Not reported	Not reported
Hypertension	32	33
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	1.0 ± 0.1	1.0 ± 0.2
TCPO2, mmHg	44.9 ± 12.1	44.2 ± 11.8
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.0 ± 1.2	8.1 ± 1.3
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Vildagliptin, a dipeptidyl peptidase 4 inhibitor. 50 mg, twice a day and standard care Standard care: before randomisation and at each study visit study ulcers received sharp debridement and saline-moistened gauze dressings. The ulcers were debrided when considered necessary. Individualised topical treatment and dressings were used depending on the site and character of the ulcer. Off-loading protective shoe wear with individually fitted in-soles were used.

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**
Comparison	Standard care: before randomisation and at each study visit study ulcers received sharp debridement and saline-moistened gauze dressings. The ulcers were debrided when considered necessary. Individualised topical treatment and dressings were used depending on the site and character of the ulcer. Off-loading protective shoe wear with individually fitted in-soles were used.
Length of follow up	Length of follow up was 12 weeks
Location	Italy
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure by 12 weeks Complete re-epithelialization with no drainage Vildagliptin group= 16 of 53 participants Control group= 8 of 53 participants P value= <0.05 Rates and extent of amputation: Amputations Minor amputation Vildagliptin group= 1 of 53 participants Control group= 2 of 53 participants Length of stay: No data provided Health related quality of life: No data provided Adverse events:

Bibliographic reference	**Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental diabetes research*, *2012*.**
	Ulcer related adverse events Local wound infection, cellulitis, osteomyelitis Vildagliptin group= 6 of 53 participants Control group= 16 of 53 participants P value= <0.05 Myocardial infarction Vildagliptin group= 0 of 53 participants Control group= 0 of 53 participants Stroke Vildagliptin group= 0 of 53 participants Control group= 0 of 53 participants
Source of funding	No conflicts of interest declared or funding
Comments	

Table 52: Gottrup 2013

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**
Study type	Randomised control trial
Study quality	Summary Population: Denmark Intervention: Collagen/ORC/silver therapy Comparison: Standard care: The same type of dressing was used in the test and control group and consisted of a foam dressing for moderately exuding wounds. The dressings were changed at least twice a week according to the condition of the

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**
	wound. Patients in both groups were treated with standard wound treatment protocol including debridement and offloading. Outcome: 50% reduction in wound area, wound healing, adverse events, infection 1) Has an appropriate method of randomisation been used? A clear and appropriate method of randomisation was used 2) Was there adequate concealment of allocation? Allocation was concealed using sealed envelopes 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. P values were provided. 4) Did the comparison groups receive the same care apart from interventions studied? Treatment took place in two separate centres however paper reported that they were structured specialized and comparable centres. All participants received the same standard care. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Loss to follow up was comparable between groups, there were no outcome data available for 2 control participants and 1 treatment participant. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (14 weeks) 9) Did the study use a precise definition of outcome? Complete healing was clearly defined as complete epithelialization, infection was defined as being based clinically upon signs of infection. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**
Number of patients	Randomised= 39 Control group= 15 Electrical stimulation group= 24
Patient characteristics	Patients taken from: Denmark Inclusion: Diabetic foot ulcer of at least 30 days duration Excluded: Local or systemic signs of infection Known allergies to contents of Promogran Collagen/ORC/silver Peripheral arterial disease Toe pressure of greater or equal to 45 mm Concomitant medications or conditions that may interfere with wound healing Baseline characteristics: No reported significant differences between groups. P values provided.

Characteristics	Collagen/ORC/Silver	Control group
N	24	15
Age, y	62.9 ± 13.5	57.3 ± 14.6
Male/female	22/2	13/2
BMI (kg/m²)	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	17.3 ± 11.9	14.4 ± 10.7
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (cm²)	2.1 ± 3.1	4.4 ± 6.3

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**

Ulcer duration (months)	12.9 ± 13.0	16.9 ± 36.6
Ulcer location (plantar/ dorsum/lateral)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	0.94 ± 0.11	0.97 ± 0.15
TCPO2, mmHg	95.62 ± 31.11	83 ± 30.8
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	6.54 ± 3.73	5.19 ± 4.17
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Collagen/ORC/silver therapy applied directly onto the wound bed and standard care Standard care: The same type of dressing was used in the test and control group and consisted of a foam dressing for moderately exuding wounds. The dressings were changed at least twice a week according to the condition of the wound. Patients in both groups were treated with standard wound treatment protocol including debridement and offloading.
Comparison	Standard care: The same type of dressing was used in the test and control group and consisted of a foam dressing for moderately exuding wounds. The dressings were changed at least twice a week according to the condition of the wound. Patients in both groups were treated with standard wound treatment protocol including debridement and offloading.
Length of follow up	Length of follow up was 14 weeks

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**
Location	Denmark
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Healed by week 14 Complete re-epithelialization Collagen/ORC/silver group= 12 of 23 participants Control group= 4 of 13 participants P value= >0.05 i.e. not significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: Withdrew due to infection Collagen/ORC/silver group= 0 of 23 participants Control group= 4 of 13 participants P value= 0.012 i.e. significant All adverse events in relation to treatment Collagen/ORC/silver group= 0 of 23 participants Control group= 5 of 13 participants

Bibliographic reference	**Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Repair and Regeneration*, *21*(2), 216-225.**
Source of funding	Systagenix
Comments	

Table 53: Alvarez 2003

Bibliographic reference	**Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *The Journal of foot and ankle surgery*, *42*(1), 30-35.**
Study type	Randomised control trial
Study quality	Summary Population: USA, only plantar ulcers were included Intervention: Non-contact normothermic wound therapy, maintains wound and surrounding skin surface temperature at 37 °C the wound cover was appled over the ulcer and served as the primary dressing. Warming treatments were performed 3 times daily for 1 hour. Wound cover was changed once daily. Otherwise standard care. Comparison: Standard care: Weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). Wound dressings were changed once daily. All patients were fitted with a therapeutic healing sandal and instructed to avoid wound bearing. Outcome: Wound area reduction, wound closure, adverse events 1) Has an appropriate method of randomisation been used? An appropriate computer generated method of randomisation was used 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. P values were not provided. Some important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Groups received the same care apart from intervention studied 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation?

Bibliographic reference	**Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *The Journal of foot and ankle surgery*, *42*(1), 30-35.**
	Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no apparent loss to follow up. Treatment numbers were low however. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate (12 weeks) 9) Did the study use a precise definition of outcome? Complete healing was clearly defined as full epithelialization of the wound with absence of drainage and no need for further dressing. 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 20 Control group= 10 Non-contact normothermic wound therapy group= 10
Patient characteristics	Patients taken from: USA Inclusion: Diabetic neuropathic foot ulcers Plantar surface of the foot Type 1 or type 2 diabetes Secondary to peripheral neuropathy Adequate circulation (ankle brachial pressure index >0.7 and palpable pulses) Ulcer extends through the dermis and into subcutaneous tissue without involvement fo the bone, tendons, muscle or joint capsule

Bibliographic reference	**Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *The Journal of foot and ankle surgery*, *42*(1), 30-35.**

Excluded:
Clinical signs of infection
Osteomyelitis
Cellulitis
Uncontrolled diabetes
Medical conditions that may impair healing
Corticosteroids, immunosuppressive agents, chemotherapy, radiotherapy within 1 month before entry

Baseline characteristics: No reported significant differences between groups. P not values provided.

Characteristics	Non-contact normothermic wound therapy	Control group
N	10	10
Age, y	61	53
Male/female	6/4	4/6
BMI (kg/m²)	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	5	4
Duration of diabetes, y	Not reported	Not reported
Type of diabetes type1/type2	1/8	0/9
Smokers	Not reported	Not reported
Ulcer size at baseline (cm²)	346	216
Ulcer duration (months)	Not reported	Not reported
Ulcer location (forefoot/other)	7/3	8/2
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported

Bibliographic reference	**Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *The Journal of foot and ankle surgery*, *42*(1), 30-35.**

Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Non-contact normothermic wound therapy, maintains wound and surrounding skin surface temperature at 37 °C the wound cover was appled over the ulcer and served as the primary dressing. Warming treatments were performed 3 times daily for 1 hour. Wound cover was changed once daily. Otherwise standard care.
Comparison	Standard care: Weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). Wound dressings were changed once daily. All patients were fitted with a therapeutic healing sandal and instructed to avoid wound bearing.
Length of follow up	Length of follow up was 12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Healed by week 6 Complete re-epithelialization with no drainage or requirement for further dressing Non-contact normothermic wound therapy group= 3 of 10 participants Control group= 1 of 10 participants P value= 0.11 i.e. not significant Healed by week 12

Bibliographic reference	**Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *The Journal of foot and ankle surgery*, *42*(1), 30-35.**
	Complete re-epithelialization with no drainage or requirement for further dressing Non-contact normothermic wound therapy group= 7 of 10 participants Control group= 4 of 10 participants P value= 0.069 i.e. not significant Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: All adverse events Unclear definition Non-contact normothermic wound therapy group= 0 of 10 participants Control group= 0 of 10 participants
Source of funding	Augustine Medical Inc.
Comments	

Table 54: Larijani 2008

Bibliographic reference	**Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.*DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**

Bibliographic reference	**Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.*DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
Study type	Randomised control trial
Study quality	Summary Population: Iran Intervention: ANGIPARS, Semelil, a naïve herbal extract, intravenous administration 4cc daily for 28 days. Drug diluted in 50-100 cc normal saline and infused during 30-60 minutes Comparison: Placebo: with standard care the comprised of wound debridement, irrigation with normal saline solution, systemic antibiotic therapy, pressure decompression, betadine bath and daily wound dressing. Outcomes: mean foot ulcer size, adverse events 1) Has an appropriate method of randomisation been used? Permuted block randomisation- unclear method of randomisation 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. P values were provided. Many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Groups received comparable care 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no apparent loss to follow up. Treatment numbers were low however. 8) Did the study have an appropriate length of follow up? Length of follow up was not appropriate for our primary outcome of interest (4 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of outcomes 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was not used, longest and widest width were recorded using a simple ruler which seems a crude estimate of wound area 11) Were investigators kept blind to participant’s exposure to the intervention?

Bibliographic reference	**Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.*DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
	Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 25 Control group= 9 Non-contact normothermic wound therapy group= 16
Patient characteristics	Patients taken from: Iran Inclusion: Chronic non-healing diabetic foot ulcer for several weeks-months Type 1 or type 2 On medication, either oral hypoglycaemic or insulin Ulcers which remained open without healing and had not shown improvement for more than 2 weeks Excluded: Severe heart failure under treatment with class III or higher functional classes of antiarrythmics and showing signs and symptoms of chronic and severe ischaemia Pulseless lower limbs Other diseases and situations that impair ulcer involvement Alcohol and drug abuse Chronic renal failure Progressive liver failure Corticosteroid treatment, immunosuppressives, radiotherapy, chemotherapy Any known drug hypersensitivity Baseline characteristics: No reported significant differences between groups. P not values provided. Characteristics | ANGIPARS | Control group

Bibliographic reference	Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.*DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).

N	16	9
Age, y	50.6 ± 12.65	59 ± 10.95
Male/female	13/3	5/4
Weight, kg	73.07 ± 18.2	65.42 ± 9.44
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	10.64 ± 4.76	14.83 ± 9.64
Type of diabetes type1/type2	2/14	0/9
Smokers	Not reported	Not reported
Ulcer size at baseline (mm^2)	479.93 ± 379.75	766.22 ± 960.5
Ulcer duration (months)	Not reported	Not reported
Ulcer location (forefoot/other)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Bibliographic reference	**Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.*DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
Intervention	ANGIPARS, Semelil, a naïve herbal extract, intravenous administration 4cc daily for 28 days. Drug diluted in 50-100 cc normal saline and infused during 30-60 minutes and standard therapy
Comparison	Standard care and placebo: Weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). Wound dressings were changed once daily. All patients were fitted with a therapeutic healing sandal and instructed to avoid wound bearing.
Length of follow up	Length of follow up was 4 weeks
Location	Iran
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: No data provided Rates and extent of amputation: No data provided Length of stay: No data provided Health related quality of life: No data provided Adverse events: All adverse events Unclear definition ANGIPARS= 0 of 16 participants Control group= 0 of 9 participants
Source of funding	ParsRoos Co.
Comments	

Table 55: Bahrami 2008

Bibliographic reference	**Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
Study type	Randomised control trial
Study quality	Summary Population: Iran Intervention: ANGIPARS, Semelil, a naïve herbal extract, oral therapy with 100 mg twice a day for 6 weeks in addition to conventional therapies OR ANGIPARS gel 3% added to the oral form of the same product besides conventional therapies for the same period of time Comparison: standard care the comprised of wound debridement, irrigation with normal saline solution, antibiotic therapy, pressure offloading, wound dressing. Study visits scheduled for every 2 weeks. Unclear how often dressings were changed. Outcomes: granulation tissue formation, adverse events, skin epithelialization, and wound surface areas changes 1) Has an appropriate method of randomisation been used? Permuted block randomisation- unclear method of randomisation 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? No differences in groups at baseline were reported. P values were provided. Many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Unclear if groups received comparable care in regards to standard care, for which no specifics were provided about regularity of treatment. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no apparent loss to follow up. Participant numbers were low however. 8) Did the study have an appropriate length of follow up?

Bibliographic reference	**Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
	Length of follow up was not appropriate for our primary outcome of interest (6 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of outcomes 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was not used, tracings of photographs seems a crude method of assessment 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 21 ANGIPARS oral= 6 ANGIPARS oral and gel= 6 Control group= 9
Patient characteristics	Patients taken from: Iran Inclusion: Adult 18-75 years Type 1 or type 2 diabetes One or more diabetic foot ulcers Open without healing and/or improvement for at least 2 weeks Excluded: Greater than or equal to Grade III Wagner classification diabetic foot ulcer Systemic or local infection Exposed bone at the wound site Life threatening or serious cardiac failure Severe and chronic ischaemia of lower limb without presence of pulsation Diseases with impact on healing

Bibliographic reference	**Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**

Chronic alcohol or drug abuse
Immunosuppressive drugs, cytotoxic agents, radiation therapy, chemotherapy

Baseline characteristics: No reported significant differences between groups. P not values provided.

Characteristics	ANGIPARS oral	ANGIPARS oral and 3% gel	Control group
N	6	6	9
Age, y	60.67 ± 2.951	51.00 ± 3.742	59.00 ± 3.651
Male/female	4/2	4/2	5/4
Weight, kg	78.750 ± 3.9407	79.417 ± 12.0751	65.429 ± 3.5714
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported	Not reported
Insulin therapy	Not reported	Not reported	Not reported
Duration of diabetes, y	10.64 ± 4.76	14.83 ± 9.64	Not reported
Type of diabetes type1/type2	0/6	0/6	0/9
Smokers	Not reported	Not reported	Not reported
Ulcer size at baseline (mm^2)	375.000 ± 118.145	916.666 ± 228.643	766.222 ± 320.169
Ulcer duration (months)	Not reported	Not reported	Not reported
Ulcer location (forefoot/other)	Not reported	Not reported	Not reported
Neuropathy	Not reported	Not reported	Not reported
Hypertension	Not reported	Not reported	Not reported
Renal disorder	Not reported	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported	Not reported
Previous ulcers	Not reported	Not reported	Not reported
HbA1c, mean	Not reported	Not reported	Not reported
Mobility Walking with support	Not reported	Not reported	Not reported

Bibliographic reference	**Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
	Walking without support Wagner Classification Grade I Grade II Grade III Grade IV: Not reported / Not reported / Not reported Total hospital stay: Not reported / Not reported / Not reported
Intervention	ANGIPARS, Semelil, a naïve herbal extract, oral therapy with 100 mg twice a day for 6 weeks in addition to conventional therapies
	ANGIPARS gel 3% added to the oral form of the same product besides conventional therapies for the same period of time
Comparison	Standard care the comprised of wound debridement, irrigation with normal saline solution, antibiotic therapy, pressure offloading, wound dressing. Study visits scheduled for every 2 weeks. Unclear how often dressings were changed.
Length of follow up	Length of follow up was 6 weeks
Location	Iran
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound healing Unclear definition ANGIPARS oral= 5 of 6 participants ANGIPARS oral and 3% gel = 6 of 6 participants Control group= 2 of 9 participants Rates and extent of amputation: No data provided Length of stay: No data provided

Bibliographic reference	**Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*, *16*(Suppl. 1).**
	Health related quality of life: No data provided Adverse events: All adverse events Unclear definition ANGIPARS oral= 0 of 6 participants ANGIPARS oral and 3% gel = 0 of 6 participants Control group= 0 of 9 participants
Source of funding	Unclear source of funding
Comments	

Table 56: Mulder 1994

Bibliographic reference	**Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair and Regeneration*, *2*(4), 259-269.**
Study type	Randomised control trial
Study quality	Summary Population: USA, Intervention: Iamin-2% gel, or glycyl-l-histidyl-l-lysine: copper complex, applied once a day for up to 8 weeks along with standard care. Comparison: A vehicle gel, applied once a day for up to 8 weeks along with standard care. Standard care involved: extensive sharp debridement at study entry; routine superficial debridement; daily dressing changes, standardised pressure-relieving foot wear; metered dosing of the gel; patient education; treatment of infection with systemica antibiotics and supportive care for limb oedema. Outcomes: adverse events, complete wound closure (≥98%), percentage wound closure

Bibliographic reference	**Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair and Regeneration*, *2*(4), 259-269.**
	1) Has an appropriate method of randomisation been used? Unclear method of randomisation 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? Only location of ulcer had data provided. The study stated that there were no differences between groups in regard to ulcer area and ulcer duration at baseline. Many important variables were not reported. 4) Did the comparison groups receive the same care apart from interventions studied? Unclear if groups received comparable care in regards to standard care. Gel administration was self-administered and may have varied between patients. 5) Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? There was no reported loss to follow up in regards to availability of outcome data, intention to treat analysis was used. 8) Did the study have an appropriate length of follow up? Length of follow up was appropriate for our primary outcome of interest (14 weeks) 9) Did the study use a precise definition of outcome? Unclear definition of outcomes in regard to what constitutes 100% wound closure 10) Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to measure wound area 11) Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blinded to treatment allocation 12) Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. (unlikely)
Number of patients	Randomised= 181 (99 participants were included in a further trial testing delayed Iamin gel treatment for which no data of interest were reported) Iamin-2% gel group=40

<table>
<tr><th>Bibliographic reference</th><td>Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. Wound Repair and Regeneration, 2(4), 259-269.</td></tr>
<tr><td></td><td>Vehicle gel= 42</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: Iran

Inclusion:
20-90 years of age
Adequately controlled diabetes as defined by a physician
Minimum ulcer size 25 mm², maximum 2700 mm²
General health confirmed by physical and laboratory examination

Excluded:
Infection of bone, or gangrene of target limb
Disease associated with hypercupremia (wilsons disease)
No palpable pedal pulse or other conditions known to cause cutaneous ulceration such as venous stasis or vasculitis
Experimental study involvement within 30 days
Systemic immunosuppressive or cytotoxic therapy within 30 days before study entry
No palpable dorsalis pedis or posterior tibial pulse
Doppler blood pressure greater than or equal to 40 mm Hg

Baseline characteristics: No reported significant differences between groups. Many important variables missing. No P values reported.

<table>
<tr><td>Characteristics</td><td>Vehicle gel</td><td>Iamin-2% gel</td></tr>
<tr><td>N</td><td>42</td><td>40</td></tr>
<tr><td>Age, y</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Male/female</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Weight, kg</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (Caucasian/black/hispanic/other)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair and Regeneration*, *2*(4), 259-269.**

Smokers	Not reported	Not reported
Ulcer size at baseline (mm²)	NS	NS
Ulcer duration (months)	NS	NS
Ulcer location (plantar/other)	32/10	28/12
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	Iamin-2% gel, or glycyl-l-histidyl-l-lysine: copper complex, applied once a day for up to 8 weeks along with standard care. Standard care involved: extensive sharp debridement at study entry; routine superficial debridement; daily dressing changes, standardised pressure-relieving foot wear; metered dosing of the gel; patient education; treatment of infection with systemica antibiotics and supportive care for limb oedema.
Comparison	A vehicle gel, applied once a day for up to 8 weeks along with standard care. Standard care involved: extensive sharp debridement at study entry; routine superficial debridement; daily dressing changes, standardised pressure-relieving foot wear; metered dosing of the gel; patient education; treatment of infection with systemica

Bibliographic reference	**Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair and Regeneration*, *2*(4), 259-269.**
	antibiotics and supportive care for limb oedema.
Length of follow up	Length of follow up was 14 weeks
Location	Iran
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Complete wound closure (for plantar ulcers) ≥98% wound closure, unclear definition Vehicle gel group=10 of 32 participants Iamin-2% gel group= 15 of 28 participants Non-significant No data provided for all ulcer types Complete wound closure (for small plantar ulcers) ≥98% wound closure, unclear definition Vehicle gel group=9 of 16 participants Iamin-2% gel group= 9 of 14 participants Non-significant Complete wound closure (for large plantar ulcers) ≥98% wound closure, unclear definition Vehicle gel group=1 of 16 participants Iamin-2% gel group= 6 of 14 participants P value= <0.05 i.e. significant difference Rates and extent of amputation: No data provided

Bibliographic reference	**Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair and Regeneration*, *2*(4), 259-269.**
	Length of stay: No data provided Health related quality of life: No data provided Adverse events: Infections Unclear definition Vehicle gel group=14 of 42 participants Iamin-2% gel group= 3 of 40 participants P value= <0.05 i.e. significant difference No significant difference reported between groups for all adverse events (no data provided however)
Source of funding	Links to Procyte, unclear source of funding
Comments	

Table 57: Bashmakov 2014

Bibliographic reference	**Bashmakov, Y. K., Assaad-Khalil, S. H., Abou Seif, M., Udumyan, R., Megallaa, M., Rohoma, K. H., ... & Petyaev, I. M. (2014). Resveratrol Promotes Foot Ulcer Size Reduction in Type 2 Diabetes Patients. International Scholarly Research Notices, 2014.**
Study type	Randomized controlled trial
Study quality	Summary Population: Egypt

Bibliographic reference	**Bashmakov, Y. K., Assaad-Khalil, S. H., Abou Seif, M., Udumyan, R., Megallaa, M., Rohoma, K. H., ... & Petyaev, I. M. (2014). Resveratrol Promotes Foot Ulcer Size Reduction in Type 2 Diabetes Patients. International Scholarly Research Notices, 2014.**
	Intervention:.Resveratrol Comparison:.Placebo Outcomes: Foot ulcer size, foot pressure test, fasting plasma glucose, C-reactive protein, fibrinogen 1) Has an appropriate method of randomisation been used? - Unclear method of randomisation was not reported 2) Was there adequate concealment of allocation? Unclear if allocation was concealed 3) Were the groups comparable at baseline for all major confounding/prognostic factors? – Yes 4) Did the comparison groups receive the same care apart from interventions studied? - Yes 5) Were participants receiving care kept blind to treatment allocation? – No - Participants were not blinded to treatment allocation 6) Were the individuals administering care kept blind to treatment allocation? - Yes 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? – No – 7 people withdrew but no report on which groups they we in 8) Did the study have an appropriate length of follow up? - Length of follow up was appropriate for our primary outcome of interest (60 days) 9) Did the study use a precise definition of outcome? – Yes 10) Was a valid and reliable method used to determine that outcome? - Yes 11) Were investigators kept blind to participant's exposure to the intervention? - Yes 12) Were investigators kept blind to other important confounding and prognostic factors? - No
Number of patients	Randomised=24 (31 randomised but 7 dropped out for reason not related to study protocol) Resveratrol 14 Placebo 10
Patient characteristics	Inclusion: Documented history of type 2 diabetes Foot ulcer for over 4 weeks Exclusion Not reported Baseline characteristics: No reported significant differences between groups. Many important variables missing. No P values reported. Characteristics | Resveratrol | Placebo

Bibliographic reference	Bashmakov, Y. K., Assaad-Khalil, S. H., Abou Seif, M., Udumyan, R., Megallaa, M., Rohoma, K. H., ... & Petyaev, I. M. (2014). Resveratrol Promotes Foot Ulcer Size Reduction in Type 2 Diabetes Patients. International Scholarly Research Notices, 2014.

N	14	10
Age, y	50.4 ± 10.1	59.8 ± 6.6
Male/female	8/6	7/3
Weight, kg	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	15.9 ± 6.9	15.2 ± 9.5
Type of diabetes type1/type2	0/14	0/10
Smokers	3	1
Ulcer size at baseline (cm^2)	6.9 ± 8.6	10.4 ± 12.9
Ulcer duration (months)	18.2 ± 17.1	15.0 ± 11.5
Ulcer location (plantar/other)	1/13	1/9
Neuropathy	Not reported	Not reported
Hypertension	8	8
Renal disorder	Not reported	Not reported
Ophthalmic disorder (retinopathy)	4	2
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	0	0
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	 9 5	 4 6
Total hospital stay	Not reported	Not reported

Bibliographic reference	**Bashmakov, Y. K., Assaad-Khalil, S. H., Abou Seif, M., Udumyan, R., Megallaa, M., Rohoma, K. H., ... & Petyaev, I. M. (2014). Resveratrol Promotes Foot Ulcer Size Reduction in Type 2 Diabetes Patients. International Scholarly Research Notices, 2014.**
Intervention	Resveratrol - one capsule containing 50mg of active substance (t-RSV-L, Lycotec Ltd, UK) twice a day with noncarbonated water after a meal standard care comprising infection control, debridement and offloading
Comparison	Placebo – capsule with inert substance and standard care comprising infection control, debridement and offloading
Length of follow up	Length of follow up 60 days
Location	Egypt
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: defined as complete wound closure Resveratrol: 5/14 Placebo 1/10 Rates and extent of amputation: Not reported Length of stay: Not reported Health related quality of life: Not reported Adverse events: Not reported
Source of funding	No funding reported and authors state ‘no conflicts f interest’
Comments	Uncertainty about results as 7/31 (22.7% withdrew but no details on group allocation or reason for withdrawal given)

Table 58: Siavash 2013

Bibliographic reference	**Siavash, M., Shokri, S., Haghighi, S., Shahtalebi, M. A., & Farajzadehgan, Z. (2013). The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal.**
Study type	Randomised controlled trial

Bibliographic reference	**Siavash, M., Shokri, S., Haghighi, S., Shahtalebi, M. A., & Farajzadehgan, Z. (2013). The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal.**
Study quality	Summary Population: Iran Intervention: .Royal Jelly 5% sterile Comparison:. Placebo Outcomes: duration of healing, Ulcr length reduction rate, Ulcer depth reduction rate, ulcer width reduction rate, complete healing 1) Has an appropriate method of randomisation been used? - Yes 2) Was there adequate concealment of allocation? Yes 3) Were the groups comparable at baseline for all major confounding/prognostic factors? - Yes 4) Did the comparison groups receive the same care apart from interventions studied? - Yes 5) Were participants receiving care kept blind to treatment allocation? - Yes 6) Were the individuals administering care kept blind to treatment allocation? - Yes 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? – Unclear - not reported 8) Did the study have an appropriate length of follow up? - Yes 9) Did the study use a precise definition of outcome? - Yes 10) Was a valid and reliable method used to determine that outcome? - Yes 11) Were investigators kept blind to participant's exposure to the intervention? - Yes 12) Were investigators kept blind to other important confounding and prognostic factors? - Unclear - not reported
Number of patients	Randomised by ulcer = 64 Royal Jelly = 32 Placebo = 32
Patient characteristics	Inclusion: People with type 2 diabetes with one or more foot ulcers Excluded: Patients with gangrene, osteomyelitis, severe sepsis, history of alcohol or drug abuse, cancer, congestive heart failure, end-stage renal disease, liver failure, use fo drugs that may interact with wound healing (glucocorticoids, immunosuppressive drugs and cyotoxic drugs) and those who preferred to received treatment outside the study Baseline characteristics: No reported significant differences between groups. Many important variables missing. No P values reported.

Bibliographic reference	**Siavash, M., Shokri, S., Haghighi, S., Shahtalebi, M. A., & Farajzadehgan, Z. (2013). The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal.**

Characteristics	Royal Jelly	Placebo
N (Ulcers)	32	32
Age, y	60.0 ± 7	60.6 ± 7
Male/female	NA	NA
Weight, kg	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	Not reported	Not reported
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	17 (No SD)	16 (No SD)
Type of diabetes type1/type2	Type 2	Type 2
Smokers	Not reported	Not reported
Ulcer size at baseline (mm^2)	Not reported	Not reported
Ulcer duration (months)	Not reported	Not reported
Ulcer location (plantar/other)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	22/32	21/32
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported

Bibliographic reference	**Siavash, M., Shokri, S., Haghighi, S., Shahtalebi, M. A., & Farajzadehgan, Z. (2013). The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal.**
	Total hospital stay | Not reported | Not reported
Intervention	Royal Jelly 5% sterile gel was administered to the ulcer three times a week alongside standard care consisting of offloading, infection control, vascular improvement and debridement [if necessary])
Comparison	Placebo gel was administer to the ulcer three times a week alongside standard care consisting of offloading, infection control, vascular improvement and debridement (if necessary))
Length of follow up	Length of follow up 3 months or complete healing
Location	Iran
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes:(defined as complete healing) Royal Jelly = 30/32 Placebo = 29/32 Complete wound closure (for plantar ulcers) Not reported Rates and extent of amputation: Not reported Length of stay: Not reported Health related quality of life: Not reported Adverse events: Not reported
Source of funding	None reported
Comments	

Table 59: Lavery 2014

Bibliographic reference	**Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... & Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal, 11(5), 554-560.**
Study type	Randomised controlled trial
Study quality	Summary Population: USA Intervention:.Grafix (human viable wound matrix - hNWM) Comparison: Standard care Outcomes: Complete wound closure, time to wound closure, adverse events 1) Has an appropriate method of randomisation been used? – Unclear – Method not reported 2) Was there adequate concealment of allocation? Unclear – Method not reported 3) Were the groups comparable at baseline for all major confounding/prognostic factors? - Yes 4) Did the comparison groups receive the same care apart from interventions studied? - Yes 5) Were participants receiving care kept blind to treatment allocation? - No 6) Were the individuals administering care kept blind to treatment allocation? - Yes 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? - Yes 8) Did the study have an appropriate length of follow up? - Yes 9) Did the study use a precise definition of outcome? - Yes 10) Was a valid and reliable method used to determine that outcome? - Yes 11) Were investigators kept blind to participant's exposure to the intervention? - No 12) Were investigators kept blind to other important confounding and prognostic factors? - Unclear – Not reported
Number of patients	Randomised= 97 hVWM = 50 Standard care = 47
Patient characteristics	Inclusion: Adults between 18 and 80 with type 1 or type 2 diabetes with index wound present for between 4 and 52 weeks and wound located below the malleoli on plantar or dorsal surface of the foot and between 1cm^2 and 15 cm^2 Excluded: HbA1c above 12%, evidence of active infection including osteomyelitis or cellulitis, inadequate circulation in the affected foot

Bibliographic reference	**Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... & Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal, 11(5), 554-560.**

defined by ankle brachial index <0.70or >1.30 , or tow brachial index ≤ 0.50 or Doppler study with inadequate arterial pulsation, exposed muscle, tendon, bone or joint capsule and reduction of wound area by ≥ 30% during the screening period.

Baseline characteristics: No reported significant differences between groups. Many important variables missing. No P values reported.

Characteristics	hVWM + Standard care	Standard care
N	50	47
Age, y	55.5 ± 11.5	55.1 ±12.0
Male/female	33/17	13/34
Weight, kg	Not reported	Not reported
Ethnicity (Caucasian/black/hispanic/other)	35/13/0/2	32/12/0/3
Insulin therapy	Not reported	Not reported
Duration of diabetes, y	15.4 ± 11.1	14.0 ±11.0
Type of diabetes type1/type2	Not reported	Not reported
Smokers	Not reported	Not reported
Ulcer size at baseline (mm^2)	3.41 ± 3.23	3.93 ± 3.22
Ulcer duration (months)	Not reported	Not reported
Ulcer location (plantar/other)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	8.0 ± 1.6	7.8 ± 1.5
Mobility Walking with support	Not reported	Not reported

Bibliographic reference	**Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... & Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal, 11(5), 554-560.**
	Walking without support Wagner Classification Grade I Grade II Grade III Grade IV Total hospital stay
Intervention	hVWM alongside standard care of debridement (using scalpel, tissue nippers and/or curette), wound dressing (non-adherent dressing (Adaptic, Systagenix, UK) or saline-moistened gauze or Allevyn (Smith & Nephew, UK) followed by an outer dressing and off-loading (custom built or walking boots for wounds on the sole of the foot or post-op shoe if the wound was on the dorsum of the foot or the ankle)
Comparison	Standard care of debridement (using scalpel, tissue nippers and/or curette), wound dressing (non-adherent dressing (Adaptic, Systagenix, UK) or saline-moistened gauze or Allevyn (Smith & Nephew, UK) followed by an outer dressing and off-loading (custom built or walking boots for wounds on the sole of the foot or post-op shoe if the wound was on the dorsum of the foot or the ankle)
Length of follow up	12 weeks
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: hVWM = 31/50 Standard care = 10/47 Complete wound closure Not reported Rates and extent of amputation:(extent not reported) hVWM = 0/50 Standard care = 1/47 Length of stay: Not reported Health related quality of life:

Walking without support		
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Bibliographic reference	**Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... & Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal, 11(5), 554-560.**
	Not reported Adverse events: (reported as any adverse event) hVWM = 22/50 Standard care = 31/47
Source of funding	The study was funded by Osiris Therapeutics, Inc (manufacturers of Grafix)
Comments	

Table 60: Gomez-Villa 2014

Bibliographic reference	**Gomez-Villa, R., Aguilar-Rebolledo, F., Lozano-Platonoff, A., Teran-Soto, J. M., Fabian-Victoriano, M. R., Kresch-Tronik, N. S., ... & Contreras-Ruiz, J. (2014). Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. Wound Repair and Regeneration, 22(4), 497-503.**
Study type	Randomised controlled trial
Study quality	Summary Population: Mexico Intervention:.Standard care + Intralesional recombinant human epidermal growth factor (rhEGF) Comparison:.Standard care + placebo Outcomes: completely healed, improvement in wound bed characteristics 1) Has an appropriate method of randomisation been used? - YES 2) Was there adequate concealment of allocation? YES 3) Were the groups comparable at baseline for all major confounding/prognostic factors? - YES. 4) Did the comparison groups receive the same care apart from interventions studied? - YES 5) Were participants receiving care kept blind to treatment allocation? - YES 6) Were the individuals administering care kept blind to treatment allocation? - YES 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data

<table>
<tr><th>Bibliographic reference</th><th>Gomez-Villa, R., Aguilar-Rebolledo, F., Lozano-Platonoff, A., Teran-Soto, J. M., Fabian-Victoriano, M. R., Kresch-Tronik, N. S., ... & Contreras-Ruiz, J. (2014). Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. Wound Repair and Regeneration, 22(4), 497-503.</th></tr>
<tr><td></td><td>available? - YES
8) Did the study have an appropriate length of follow up? - YES
9) Did the study use a precise definition of outcome? - YES
10) Was a valid and reliable method used to determine that outcome? - YES
11) Were investigators kept blind to participant’s exposure to the intervention? - YES
12) Were investigators kept blind to other important confounding and prognostic factors? - Unclear – Not reported</td></tr>
<tr><td>Number of patients</td><td>Randomised=34
Standard care + rhEGF = 17
Standard care = 17</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Patients over the age of 18, with a Grade A or B diabetic foot ulcer larger than 2cm^2

Excluded:
Patients were excluded due to untreated osteomyelitis and if radiographic signs, elevated erythrocyte sedimentation rate above 60mm/hour or clearly visible infected bone were observed. Patients were also excluded if they were pregnant, breastfeeding, has known sensitivity to rhEGF, inability to provide proper consent, renal failure (creatinine ≥ 20µg/dl), heart failure, ischemic heart disease, malignancies, use of immunosuppressive agents or corticosteroids, hepatic disease, acute systemic disease, uncontrolled diabetes, severe peripheral arterial disease.

Baseline characteristics: No reported significant differences between groups. Many important variables missing. No P values reported.

<table>
<tr><th>Characteristics</th><th>Standard care + rhEGF</th><th>Standard care</th></tr>
<tr><td>N</td><td>17</td><td>17</td></tr>
<tr><td>Age, y</td><td>62.1 ± 12,8</td><td>55.1 ± 10.6</td></tr>
<tr><td>Male/female</td><td>9/8</td><td>12/5</td></tr>
<tr><td>Weight, kg</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Ethnicity (Caucasian/black/hispanic/other)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Insulin therapy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>17.3 ± 10.0</td><td>15.3 ± 8.4</td></tr>
<tr><td>Type of diabetes type1/type2</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Gomez-Villa, R., Aguilar-Rebolledo, F., Lozano-Platonoff, A., Teran-Soto, J. M., Fabian-Victoriano, M. R., Kresch-Tronik, N. S., ... & Contreras-Ruiz, J. (2014). Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. Wound Repair and Regeneration, 22(4), 497-503.**

Smokers	Not reported	Not reported
Ulcer size at baseline (cm²)	19.2 ± 15.7	11.9 ± 11.8
Ulcer duration (weeks)	25.8 ± 44.0	36.5 ± 75.8
Ulcer location (plantar/other)	Not reported	Not reported
Neuropathy	Not reported	Not reported
Hypertension	Not reported	Not reported
Renal disorder	Not reported	Not reported
Ophthalmic disorder	Not reported	Not reported
Ankle Brachial Index Right Left	Not reported	Not reported
TCPO2, mmHg	Not reported	Not reported
Previous amputation Minor Major	Not reported	Not reported
Previous ulcers	Not reported	Not reported
HbA1c, mean	Not reported	Not reported
Mobility Walking with support Walking without support	Not reported	Not reported
Wagner Classification Grade I Grade II Grade III Grade IV	Not reported	Not reported
Total hospital stay	Not reported	Not reported

Intervention	rhEGF (75µg) was applied to the edge of the wound and to the wound bed by fine-needle injection thrice per week. Patients received a total fo 5mL in injections that were equally divided throughout the edges and wound bed evern Monday, Wednesday and Friday. Standard care consisted of debridement of necrotic or infected tissue and an antimicrobial dressing with ionic silver. Dressing could be applied moist in wounds with low exudate and dry in wounds with high exudate. Patients were asked to stay of their feet using crutches.

Bibliographic reference	**Gomez-Villa, R., Aguilar-Rebolledo, F., Lozano-Platonoff, A., Teran-Soto, J. M., Fabian-Victoriano, M. R., Kresch-Tronik, N. S., ... & Contreras-Ruiz, J. (2014). Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. Wound Repair and Regeneration, 22(4), 497-503.**
Comparison	Placebo applied as rhEGF Standard care consisted of debridement of necrotic or infected tissue and an antimicrobial dressing with ionic silver. Dressing could be applied moist in wounds with low exudate and dry in wounds with high exudate. Patients were asked to stay of their feet using crutches.
Length of follow up	Length of follow up 8 weeks
Location	Mexico
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: rhEGF = 4/17 Placebo = 0/17 Complete wound closure (for plantar ulcers) Not reported Rates and extent of amputation: Not reported Length of stay: Not reported Health related quality of life: Not reported Adverse events: reported as withdrawals rhEGF = 2/17 Placebo = 1/17
Source of funding	National Foundation for Education and Research in Dermnatology
Comments	

Table 61: Mueller 2003

Bibliographic reference	**Mueller, M. J., Sinacore, D. R., Hastings, M. K., Strube, M. J., & Johnson, J. E. (2003). Effect of Achilles Tendon Lengthening on Neuropathic Plantar Ulcers* A Randomized Clinical Trial. The Journal of Bone & Joint Surgery, 85(8), 1436-1445.**
Study type	Randomised controlled trial
Study quality	Summary Population: USA Intervention:.TOTAL CONTACT CAST WITH ACHILLES TENDON LENGTHENING Comparison:.TOTAL CONTACT CAST Outcomes: ULCER HEALING, QUALITY OF LIFE 1) Has an appropriate method of randomisation been used? - Yes 2) Was there adequate concealment of allocation? Yes 3) Were the groups comparable at baseline for all major confounding/prognostic factors? - YES 4) Did the comparison groups receive the same care apart from interventions studied? - YES 5) Were participants receiving care kept blind to treatment allocation? – No 6) Were the individuals administering care kept blind to treatment allocation? - No 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? - Yes 8) Did the study have an appropriate length of follow up? - No- outcomes were reported for 7 months when most ulcers should be healed anyway. 9) Did the study use a precise definition of outcome? - YES 10) Was a valid and reliable method used to determine that outcome? – Follow up by monthly phone call may not have been the most valid method. 11) Were investigators kept blind to participant's exposure to the intervention? - No 12) Were investigators kept blind to other important confounding and prognostic factors? - No
Number of patients	Total number of subjects=64 Achilles tendon lengthening= 31 Total Contact Casting= 33
Patient characteristics	Included: History of diabetes mellitus Loss of protective sensation Limitation of ankle dorsiflexion to ≤ 5 degrees

<table>
<tr><th>Bibliographic reference</th><th>Mueller, M. J., Sinacore, D. R., Hastings, M. K., Strube, M. J., & Johnson, J. E. (2003). Effect of Achilles Tendon Lengthening on Neuropathic Plantar Ulcers* A Randomized Clinical Trial. The Journal of Bone & Joint Surgery, 85(8), 1436-1445.</th></tr>
<tr><td></td><td>A palpable ankle pulse
A recurrent or non-healing ulcer on the forefoot

Exclusion criteria
Neurological problem complicating the rehabilitation
A history of Charcot fractures of the hindfoot
Unable to tolerate anesthesia required for Achilles tendon lengthening
Unable to walk

Baseline Characteristics
<table>
<tr><th></th><th>Group treated with Achilles Tendon Lengthening and total contact cast</th><th>Group treated with total contact cast alone</th></tr>
<tr><td>Age, years</td><td>56.6 ± 9.2</td><td>56.2 ±10.1</td></tr>
<tr><td>No of patients</td><td>31</td><td>33</td></tr>
<tr><td>Male/female</td><td>26/5</td><td>23/10</td></tr>
<tr><td>Type 1/Type 2 diabetes mellitus</td><td>5/26</td><td>11/22</td></tr>
<tr><td>Duration of diabetes mellitus, y</td><td>17.1 ±10.8</td><td>19.6 ± 12.6</td></tr>
<tr><td>Body-Mass index</td><td>33.3 ± 7.8</td><td>30.5 ± 6.8</td></tr>
<tr><td>HbA1c (%)</td><td>8.8 ± 1.9</td><td>8.8 ± 1.7</td></tr>
<tr><td>No of previous ulcers</td><td>3.7 ± 4.4</td><td>3.3 ± 4.0</td></tr>
<tr><td>Ulcer length</td><td>14.3 ± 9.2</td><td>15.1 ± 12.0</td></tr>
<tr><td>Ulcer width</td><td>11.3 ± 8.0</td><td>12.7 ± 11.9</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>The treatment group had Achilles tendon lengthening. Ulcers were dressed, debrided and offloaded using a total contact cast until ulcer healing.</td></tr>
<tr><td>Comparison</td><td>The control group had ulcers dressed, debrided and offloaded using a total contact cast until ulcer healing.</td></tr>
<tr><td>Length of follow up</td><td>7 months and 7 months following healing</td></tr>
</table>

Bibliographic reference	**Mueller, M. J., Sinacore, D. R., Hastings, M. K., Strube, M. J., & Johnson, J. E. (2003). Effect of Achilles Tendon Lengthening on Neuropathic Plantar Ulcers* A Randomized Clinical Trial. The Journal of Bone & Joint Surgery, 85(8), 1436-1445.**
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Cure rate at 7 months Achilles tendon lengthening group= 30 of 30 ulcers Control group= 29 of 33 ulcers P=0.12, i.e. non-significant Mean time to healing Achilles tendon lengthening group= 40.8 ± 28.1 days Control group= 57.5 ± 47.0 days P=0.14, i.e. non-significant Complete wound closure (for plantar ulcers) Not reported Rates and extent of amputation: Achilles tendon lengthening group= 0 of 30 persons Control group= 1 of 33 persons Length of stay: Not reported Health related quality of life: Not reported Adverse events: Not reported
Source of funding	Funding provided by the National Center for Medical Rehabilitation Research, The National Institutes of Health Grant
Comments	

Table 62: Blume 2008

Bibliographic reference	**Blume, P. A., Walters, J., Payne, W., Ayala, J., & Lantis, J. (2008). 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, 31(4), 631-636.**
Study type	Randomised controlled trial
Study quality	Summary Population: USA Intervention: Negative pressure wound therapy (vacuum assisted closure) Comparison: Advanced Moist Wound Therapy Outcomes: ULCER HEALING, amputation, infection 1) Has an appropriate method of randomisation been used? - Yes 2) Was there adequate concealment of allocation? Yes 3) Were the groups comparable at baseline for all major confounding/prognostic factors? - YES 4) Did the comparison groups receive the same care apart from interventions studied? - YES 5) Were participants receiving care kept blind to treatment allocation? – No 6) Were the individuals administering care kept blind to treatment allocation? - No 7) Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? - Yes 8) Did the study have an appropriate length of follow up? - Yes 9) Did the study use a precise definition of outcome? - YES 10) Was a valid and reliable method used to determine that outcome? – Yes 11) Were investigators kept blind to participant's exposure to the intervention? - No 12) Were investigators kept blind to other important confounding and prognostic factors? - No
Number of patients	Total= 342 Negative pressure wound therapy group= 169 Control group= 169
Patient characteristics	Included patients Diabetic adults ≥18 years with a stage 2 or 3 calcaneal, dorsal, or plantar foot ulcer ≥2 cm^2 in area after debridement Adequate blood circulation was assessed by a dorsum transcutaneous oxygen test ≥30 mm Hg Ankle brachial index values ≥0.7 and ≤1.2 with toe pressure ≥ 30 mmHg or Doppler arterial waveforms that were triphasic or

Bibliographic reference	**Blume, P. A., Walters, J., Payne, W., Ayala, J., & Lantis, J. (2008). 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, 31(4), 631-636.**
	biphasic at the ankle of the affected leg. Excluded 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 (HbA1c >12%) or inadequate lower extremity perfusion. Ulcer treatment with normothermic or hyperbaric oxygen therapy Concomitant medications such as corticosteroids, immunosuppressive medications, or chemotherapy; recombinant or autologous growth factor products, skin and dermal substitutes within 30 days of study start; or the use of any enzymatic debridement treatments. Pregnant or nursing mothers
Intervention	Vacuum assisted closure therapy
Comparison	Moist wound dressing, debridement and offloading
Length of follow up	112 day follow up
Location	USA
Outcomes measures and effect size	Cure rates of foot ulcer resulting from diabetes: Cure rate at 112 days Negative pressure wound therapy= 73 of 169 patients Control group= 48 of 166 patients P=0.007, i.e. significant Rates and extent of amputation: Amputation rate at 6 months Negative pressure wound therapy= 7 of 169 patients Control group= 17 of 166 patients P=0.035, i.e. significant Length of stay: Not reported

Bibliographic reference	**Blume, P. A., Walters, J., Payne, W., Ayala, J., & Lantis, J. (2008). 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, 31(4), 631-636.**
	Health related quality of life: Not reported Adverse events: Wound infection at 6 months Negative pressure wound therapy= 4 of 169 patients Control group= 1 of 166 patients P=0.371, i.e.non significant
Source of funding	KCI USA Incorporated
Comments	

G.13 Review question 13 full evidence tables

Table 63: Ross 2013

Bibliographic reference	**Ross, A. J., Mendicino, R. W., & Catanzariti, A. R. (2013). Role of Body Mass Index in Acute Charcot Neuroarthropathy. *The Journal of Foot and Ankle Surgery*, *52*(1), 6-8.**
Study type	Case Control
Study quality	The study addresses an appropriate and clearly focused question; attempting to elicit the relationship between increased BMI[1] and the development of acute Charcot neuropathy Cases and controls were taken from comparable populations however with some significant differences in demographic and clinical characteristics. Correction was employed to adjust for all significant variables. The same exclusion criteria are used for both cases and controls Since this was a retrospective study with data taken from clinical records, participation rates were similar between cases and controls. Five patients with Charcot foot were excluded due to lack of information about diagnosis of diabetes, age and chronic renal failure or peripheral vascular disease Since this was a retrospective study using data already collected participants and non-participants were not compared to establish their similarities and differences Cases are clearly defined and differentiated from controls. It is clearly established that controls are not cases Knowledge of primary exposure could not have influenced case ascertainment as all data was reviewed from patients with diabetic peripheral neuropathy seen over a pre-set period of time with defined inclusion/exclusion criteria. Measurement of exposure status could not have completely reliable as it was retrospectively extracted from clinical records. Patients also self-reported height and weight which calls into question the validity of the BMI[1] recordings. There was the possibility of misdiagnosis of acute vs chronic Charcot foot. The main confounders are identified and taken into account in the design and analysis using logistic regression techniques and correction analysis. Confidence intervals have been provided. Certain variables however could not be taken into account due to lack of data such as ethnicity and tobacco use. Certain other variables featured only in the Charcot group and as a result could not be included in logistic regression; these were presence of chronic kidney disease and osteoporosis.

<table>
<tr><th>Bibliographic reference</th><th>Ross, A. J., Mendicino, R. W., & Catanzariti, A. R. (2013). Role of Body Mass Index in Acute Charcot Neuroarthropathy. The Journal of Foot and Ankle Surgery, 52(1), 6-8.</th></tr>
<tr><td></td><td>This is a study conducted in an American population which may be generalizable to our UK population.

The paper studies the impact of being overweight or obese on the incidence of Charcot foot. BMI[1] is used as an outcome.

Comparisons are made between patients who have diabetic peripheral neuropathy and no Charcot foot and patients with diabetic peripheral neuropathy and Charcot foot.

Unclear how long the observation period was for the data collected on patients.

Effect size was expressed as an odds ratio

Unclear source of funding</td></tr>
<tr><td>Number of patients</td><td>Total number included= 49
Acute Charcot neuroarthropathy= 20
No acute Charcot neuroarthropathy= 29</td></tr>
<tr><td>Patient characteristics</td><td>Included
Available complete medical records for the variables of interest
Documented diabetic peripheral neuropathy with or without diagnosis of Charcot foot
Documented BMI or height and weight

Excluded
Documented history of non-diabetes related neuropathy
Recent infection within 6 months before the date of chart review
Recent trauma or surgery “that may have otherwise have incited an acute Charcot event”

Baseline characteristics

<table>
<tr><th></th><th>All patients n=49 (%)</th><th>ACN[2] n=20 (%)</th><th>No ACN[2] n=29 (%)</th><th>P value</th></tr>
<tr><td>Diabetes mellitus</td><td></td><td></td><td></td><td>0.225</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ross, A. J., Mendicino, R. W., & Catanzariti, A. R. (2013). Role of Body Mass Index in Acute Charcot Neuroarthropathy. *The Journal of Foot and Ankle Surgery*, *52*(1), 6-8.**

Insulin dependent Non-insulin dependent	28 (57) 21 (43)	15 (75) 5 (25)	13 (45) 16 (55)	
Peripheral Vascular disease	13 (27)	4 (31)	9 (69)	0.516
Gender Male Female	 19 (39) 30 (61)	 9 (47) 11 (37)	 10 (53) 19 (63)	0.555
Age (y)	63.16 ± 10.28	62.05 ± 9.44	63.93 ± 10.91	0.534
BMI[1] (kg/m²)	32.26 ± 6.76	32.84 ± 6.99	31.87 ± 6.69	0.625

Intervention	Patients were considered to have ACN[2] if 1 of the attending physicians made the diagnosis and provided subsequent documentation in the medical records. Diagnosis was determined from the radiographic, clinical and physical findings. Participants in the acute Charcot group were those with documented diabetic peripheral neuropathy with the diagnosis of Charcot foot. N= 20
Comparison	Participants in the control group were those with documented diabetic peripheral neuropathy without the diagnosis of Charcot foot. N= 29
Length of follow up	No follow up period as such. Unclear the length of retrospective observation
Location	USA
Outcomes measures and effect size	Independent risk factors for developing Charcot foot Results of logistic regression analysis with Charcot foot as dependent variable

Bibliographic reference	**Ross, A. J., Mendicino, R. W., & Catanzariti, A. R. (2013). Role of Body Mass Index in Acute Charcot Neuroarthropathy. *The Journal of Foot and Ankle Surgery*, *52*(1), 6-8.**

Variable	Omnibus Statistic	Wald Chi-square	P value	OR	95% Confidence interval
Block 1 Age Gender PVD[3] Type 1 diabetes	G2 (4, n=49)= 6.11	 0.003 0.509 0.80 4.29	 0.96 0.48 0.37 0.04	 0.99 1.57 0.50 3.90	 0.935-1.07 0.45-5.46 0.11-2.28 1.08-14.13
Block 2 BMI (≥25)	G2 (1, n=49)= 0.96	 0.95	 0.33	 1.05	 0.95-1.15

Source of funding	Unclear source of funding
Comments	SUMMARY: In the present investigation, no statistically significant association was found between an elevated BMI[1] and the development of acute Charcot neuropathy of the foot. Of the individual predictors, only diabetes classification was found to be statistically significant with the odds of a patient with type 1 diabetes having Charcot foot being 3.90 times greater than that for type 2 diabetes mellitus.

[1]BMI- body mass index
[2]ACN- acute Charcot neuroarthropathy
[3]PVD- peripheral vascular disease

Table 64: Foltz 2004

Bibliographic reference	**Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *The Journal of foot and ankle surgery*, *43*(2), 87-92.**
Study type	Case Control
Study quality	The study addresses an appropriate and clear question; attempting to determine which historical and physical findings would be accurate risk factors for the development of Charcot foot in people with diabetes.

Bibliographic reference	**Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *The Journal of foot and ankle surgery*, *43*(2), 87-92.**
	Other than the diagnosis of diabetes it is unclear if any attempt were made to match cases and controls for confounding factors. The Charcot disease group were found to be younger and have more type 1 diabetes. Unclear if the same exclusion criteria were applied for case and control subjects. It seems control subjects were only required to have diabetes and Charcot patients were required to have chronic, radiographically proven Charcot neuroarthropathy. Unclear if participation rates were similar between cases and controls. Participants and non-participants were not compared to establish their similarities and differences Cases are clearly defined and differentiated from controls. It is clearly established that controls are not cases Unclear if knowledge of any primary exposure could have influenced case ascertainment. Measurement of exposure status was reliable using valid standard medical examination methods to look for any vascular or neurological signs or symptoms. Investigators were unlikely to be blinded to the presence of Charcot however which could potentially introduce bias. The main confounders are identified and considered in the design and analysis although it seems that no attempts were made to match control and case groups. Major differences between the populations are described. Control patients were randomly selected from the diabetic population at a single clinic in Michigan. This is a study conducted in an American population which may be generalizable to our UK population. The paper studies the symptoms and signs of Charcot foot that could prove useful in predicting the development of Charcot foot, or for early suspicion and diagnosis. Comparisons are made between patients who have diabetic Charcot foot and control participants with diabetes. Unclear how long the observation period was for the data collected on patients. Data was collected during a routine clinic visit. Effect size was expressed as means with standard deviation for demographics, monofilament examination and health history.

<table>
<tr><td>Bibliographic reference</td><td>Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. The Journal of foot and ankle surgery, 43(2), 87-92.</td></tr>
<tr><td></td><td>Only significant differences were reported for tuning fork and deep-tendon reflex examination.

Unclear source of funding</td></tr>
<tr><td>Number of patients</td><td>Participants= 59
Charcot group= 18
Control group= 41</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Diabetes
Chronic, radiographically proven Charcot neuroarthropathy
Radiographic evidence of bone and joint destruction, fragmentation and remodelling
Control group: must have diabetes but no clinical or radiographic evidence of Charcot disease.

Baseline characteristics:

<table>
<tr><td></td><td>Charcot Group n=18 (average)</td><td>Control group n=41 (average)</td><td>P value</td></tr>
<tr><td>Gender (m/f)</td><td>14/4</td><td>23/18</td><td>0.1130</td></tr>
<tr><td>Age (y)</td><td>58.7 ± 10.8</td><td>65.2 ± 13.2</td><td>0.0700</td></tr>
<tr><td>Weight (kg)</td><td>102.1 ± 21.5</td><td>98.0 ± 25.2</td><td>0.5480</td></tr>
<tr><td>Height (cm)</td><td>69.0 ± 4.2</td><td>67.5 ± 4.0</td><td>0.4920</td></tr>
<tr><td>Body mass index (kg/m²)</td><td>32.8 ± 7.1</td><td>33.4 ± 7.8</td><td>0.9980</td></tr>
<tr><td>Diabetes duration (y)</td><td>18.17 ± 8.7</td><td>14.74 ± 10.6</td><td>0.1170</td></tr>
<tr><td>Diabetes type 1</td><td>3</td><td>1</td><td>0.0450</td></tr>
<tr><td>Diabetes type 2</td><td>15</td><td>40</td><td>0.7310</td></tr>
<tr><td>Oral agent use</td><td>6</td><td>20</td><td>0.2710</td></tr>
<tr><td>Insulin use</td><td>15</td><td>20</td><td>0.0100</td></tr>
<tr><td>Retinopathy</td><td>9</td><td>8</td><td>0.0200</td></tr>
<tr><td>Nephropathy</td><td>6</td><td>2</td><td>0.0030</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. The Journal of foot and ankle surgery, 43(2), 87-92.</td></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>History of ulcer</td><td>13</td><td>15</td><td>0.0100</td></tr>
<tr><td>History of foot trauma</td><td>10</td><td>–</td><td>–</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="4">Participants= 18
Diabetes and Charcot neuroarthropathy</td></tr>
<tr><td>Comparison</td><td colspan="4">Participants= 41
Diabetes mellitus without Charcot neuroarthropathy</td></tr>
<tr><td>Length of follow up</td><td colspan="4">No follow up as such, data was collected during a routine clinical visit</td></tr>
<tr><td>Location</td><td colspan="4">USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">Vascular examination findings:

No group differences on the presence of dorsalis pedis and posterior tibial pulse
Significant difference between groups regarding the presence of pedal oedema:
• The Charcot group showed trends of having moderate pedal oedema (scores of 2) (P<0.01)
• The control group had a greater number with severe pedal oedema (scores of 3) (P<0.01)
72% of the control group showed no signs of oedema compared with 44% of the Charcot group
Skin temperature measures in 5 foot locations were analysed and showed no significant differences.</td></tr>
<tr><td></td><td colspan="4">Neurological examination findings

Superficial pain sensation examination

<table>
<tr><th></th><th>Charcot Group (18)</th><th>Control group (41)</th><th>P value</th></tr>
<tr><td>Superficial pain sensation present, L</td><td>4</td><td>32</td><td><0.001</td></tr>
<tr><td>Superficial pain sensation present, R</td><td>4</td><td>30</td><td><0.001</td></tr>
</table>
Tuning fork examination
Responses missed out of 8</td></tr>
</table>

Bibliographic reference	**Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *The Journal of foot and ankle surgery*, *43*(2), 87-92.**

128-Hz Tuning fork	Charcot group	Control group	P value
L missed (0/8)	2	32	<0.001
R missed (0/8)	2	30	<0.001
L missed (2/8)	3	0	<0.001
R missed (2/8)	0	1	<0.001
L missed (4/8)	0	2	<0.001
R missed (4/8)	0	4	<0.001
L missed (6/8)	5	3	<0.001
R missed (6/8)	4	2	<0.001
L missed (8/8)	7	3	<0.001
R missed (8/8)	12	2	<0.001

Deep-tendon reflex examination

Reflex Graded (0/4)	Charcot group	Control group	P value
Quadriceps reflex L (0)	8	6	0.008
Quadriceps reflex R (0)	8	6	0.027
Quadriceps reflex L (1)	8	12	0.008
Quadriceps reflex R (1)	7	11	0.027
Quadriceps reflex L (2)	1	18	0.008
Quadriceps reflex R (2)	2	17	0.027
Quadriceps reflex L (3)	1	5	0.008
Quadriceps reflex R (3)	1	5	0.027
Gastrosoleus reflex L (0)	15	12	0.002
Gastrosoleus reflex R (0)	15	11	0.001
Gastrosoleus reflex L (1)	2	13	0.002
Gastrosoleus reflex R (1)	2	12	0.001
Gastrosoleus reflex L (2)	1	12	0.002

Bibliographic reference	**Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *The Journal of foot and ankle surgery*, *43*(2), 87-92.**

Gastrosoleus reflex R (2)	1	12	0.001
Gastrosoleus reflex L (3)	0	4	0.002
Gastrosoleus reflex R (3)	0	4	0.001

Semmes-Weinstein monofilament examination

Filament size	Force (g)	Charcot group	Control group	Standard deviation	P value
2.83, L	0.07	0	1.38	2.10	0.008
2.83, R	0.07	0.06	1.26	2.00	0.013
3.61, L	0.40	0.56	4.44	3.50	<0.001
3.61, R	0.40	0.5	4.62	3.50	<0.001
4.31, L	2.00	1.39	6.49	3.60	<0.001
4.31, R	2.00	1.39	6.44	3.70	<0.001
4.56, L	4.00	1.44	7.36	3.40	<0.001
4.56, R	4.00	1.33	7.56	3.50	<0.001
5.07, L	10.00	2.17	8.31	3.90	<0.001
5.07, R	10.00	2.33	8.21	3.00	<0.001
6.65, L	300.00	3.11	9.05	2.30	<0.001
6.65, R	300.00	3.56	9.08	2.30	<0.001

Source of funding	Unclear source of funding
Comments	SUMMARY: The results indicate that simple neurologic testing combined with a thorough patient history were the most beneficial tools to determine diabetics with a higher probability of developing Charcot neuroarthropathy. Specifically, history of retinopathy (P<0.02), nephropathy (P<0.003), and previous foot ulcer (P<0.01) were found to be predictive. The neurologic findings of vibratory sensation (<0.001), deep tendon reflexes (p<0.05), and the 5.07 (10g) Semmes-Weinstein monofilament test (P<0.001) were also highly correlative for the development of Charcot foot deformity. Vascular examination was found to differentiate poorly between groups. The application of this data may provide for earlier detection of Charcot arthropathy based on the predictive capabilities.

Bibliographic reference	**Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. *The Journal of foot and ankle surgery*, *43*(2), 87-92.**

Table 65: Stuck 2008

Bibliographic reference	**Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. *The American journal of medicine*, *121*(11), 1008-1014.**
Study type	Case control
Study quality	Population matches population of interest: a veteran population with diabetes in the United States Outcome matches outcome of interest: The study compared how various risk factors affected the chance of developing Charcot arthropathy as a complication of diabetes Individuals were all users of Veterans Affairs and were as a result likely to have received the same standard of care under Veterans Affairs hospitals and clinics. No further information is provided regarding the general care of patients. Follow up: This is a case control study therefore there is no follow up period as such, data was gathered from patients identified in the Department of Veterans Affairs inpatient and outpatient datasets between October 2002 and September 2003. Data gathered does not provide information on the adherence of patients to treatment however HBA1c results are provided which give a good indication of diabetes control. Participants have had diabetes for varying amounts of time, however this is adjusted for in the multivariate analysis. Unclear if groups were comparable with respect to availability of all outcome data. Supplementary database files from different years were used for the variables of race and marital status in the cases where data on these outcomes were missing. Patients with missing BMI[1] values were found to be younger and less likely to be Hispanic or African American than those not excluded in the sample because of missing BMI[1]. The study used precise and clear definitions of outcome. The method used to determine outcome however is unlikely to be reliable since data was drawn retrospectively from a database. The definition of a patient with diabetes is possibly not reliable and depends on a patient having used a diabetic drug, or have been hospitalised/seen in an outpatient clinic which may

<table>
<tr><th>Bibliographic reference</th><td>Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. The American journal of medicine, 121(11), 1008-1014.</td></tr>
<tr><td></td><td>exclude many diabetics who are on diet control. Diabetes severity was measured by number of years a patient has had diabetes and the HBA1c levels, this may not be the most accurate measurement of severity. Patient conditions used in the study were detected from diagnostic codes in the Veteran Affairs administrative files, these may not accurately represent a patient’s clinical status.

Approximately 98% of all diabetic patients among Veteran Affairs users could be found using this database, however some patients with Charcot arthropathy who use Medicare may have been missed.

The statistical analysis is appropriate for the design of this study using multivariate logistic regression. Data was also corrected for clustering using Huber-White sandwich estimators. All covariates were adjusted for.</td></tr>
<tr><td>Number of patients</td><td>Participants= 561,597
Number with Charcot foot= 652</td></tr>
<tr><td>Patient characteristics</td><td>Included
All veterans with diabetes mellitus using Veterans Affairs services in 2003
Patients with a BMI[1] value available

Baseline characteristics

<table>
<tr><th>Patient characteristics</th><th>All veterans with diabetes mellitus (%) n=561,597</th><th>Charcot foot incidence (%) n=652</th><th>P value</th></tr>
<tr><td>All</td><td>100.00</td><td>0.12</td><td></td></tr>
<tr><td>Age, y
<55
55-64
65-74
75-84
85+</td><td>
15.15
25.07
33.79
24.15
1.85</td><td>
0.13
0.19
0.10
0.06
0.07</td><td><0.001</td></tr>
<tr><td>Sex
Male
Female</td><td>
97.85
2.15</td><td>
0.12
0.15</td><td>0.286</td></tr>
<tr><td>Race</td><td></td><td></td><td>0.108</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. *The American journal of medicine*, *121*(11), 1008-1014.**			
	White	69.74	0.12	
	African American	11.51	0.10	
	Hispanic	3.04	0.13	
	Other	1.23	0.19	
	Unknown	14.48	0.10	
	Marital status			0.001
	Married	67.32	0.11	
	Not married	32.68	0.14	
	BMI[1]			<0.001
	<25	13.75	0.07	
	25-29	36.06	0.09	
	≥30	50.20	0.15	
	Diabetes duration			<0.001
	6+ y	19.73	0.19	
	≤5 y	80.27	0.10	
	Mean HbA1c			<0.001
	<7%	39.80	0.09	
	7–9%	31.97	0.15	
	>9%	8.50	0.19	
	Not measured	19.73	0.08	
	Disease groups			<0.001
	None	44.09	0.03	
	Obesity only	43.68	0.05	
	Peripheral neuropathy	5.71	0.49	
	Obesity and peripheral neuropathy	6.52	0.81	
Intervention	Patients with diabetes who developed Charcot foot in the study period			
Comparison	Patients with diabetes who did not develop Charcot foot			
Length of follow up	Observation period was from October 2002 and September 2003. As this was a case control study there was no follow up			

<table>
<tr><th>Bibliographic reference</th><td>Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. The American journal of medicine, 121(11), 1008-1014.</td></tr>
<tr><td></td><td>period, as such.</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Adjusted odds ratios of Charcot arthropathy among Veterans Health Affairs users with diabetes.
The odds ratios were adjusted for all covariates shown

<table>
<tr><th>Patient characteristics</th><th>Odds Ratio</th><th>95% Confidence Interval</th><th>P value</th></tr>
<tr><td>Age, y
<55
55–64
65–74
75–84
85+</td><td>
1.000
1.365
0.731
0.483
0.567</td><td>
–
1.126–1.656
0.572–0.934
0.371–0.629
0.293–1.097</td><td>
–
0.002
0.012
<0.001
0.092</td></tr>
<tr><td>Sex
Female
Male</td><td>
1.000
0.831</td><td>
–
0.460–1.500</td><td>
–
0.460</td></tr>
<tr><td>Race
White
African American
Hispanic
Other
Unknown</td><td>
1.000
0.614
0.855
1.485
0.699</td><td>
–
0.501–0.752
0.465–1.572
0.868–2.543
0.545–0.898</td><td>
–
<0.001
0.614
0.149
0.005</td></tr>
<tr><td>Marital Status
Not married
Married</td><td>
1.000
1.26</td><td>
–
1.033–1.537</td><td>
–
0.071</td></tr>
<tr><td>Diabetes ≥6 years
No
Yes</td><td>
1.000
1.26</td><td>
–
1.033–1.537</td><td>
–
0.023</td></tr>
<tr><td>Mean HbA1c
<7%
7–9%
>9%</td><td>
1.000
1.334
1.354</td><td>
–
1.060–1.680
1.055–1.737</td><td>
–
0.014
0.017</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. *The American journal of medicine*, *121*(11), 1008-1014.**

Not measured	1.014	0.796–1.292	0.909
Disease groups			
None	1.000	–	–
Obese only	1.589	1.152–2.191	0.005
Peripheral neuropathy	13.970	9.500–20.545	<0.001
Obesity and peripheral neuropathy	21.172	14.407–31.114	<0.001
Other comorbidities			
Renal failure	2.092	1.663–2.632	<0.001
Rheumatoid arthritis	1.905	1.138–3.189	0.014
Deficiency anaemia	1.798	1.499–2.158	<0.001
N	561,597		
Log pseudolikelihood	-4351.2		
Area under the ROC curve	0.85		

Source of funding	Unclear source of funding
Comments	SUMMARY: Obesity is significantly associated with an increased incidence of Charcot arthropathy independently of other risk factors, as is peripheral neuropathy alone. When obesity is combined with neuropathy, the Charcot arthropathy incidence rate increases multiplicatively. Prevention of Charcot arthropathy should take the interaction between obesity and neuropathy into consideration. Also at higher risk of developing Charcot arthropathy were those with renal failure and deficiency anaemia while those aged between 75–84 years and those of African American race were found to be at a lower risk of developing Charcot.

[1]BMI- body mass index

G.14 Review question 14 full evidence tables

Table 66: Mills 1991

Bibliographic reference	MILLS, J. L., BECKETT, W. C., & TAYLOR, S. M. (1991). The diabetic foot: consequences of delayed treatment and referral. Southern Medical Journal, 84(8), 970-974.
Study type	Observational, case series
Study quality	Summary Population: USA, amongst a population of a single vascular surgical service. Patients with infected and limb threatening lesions. Intervention: referral for definitive vascular care Outcome: rate of amputation, extent of amputation 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? There was no allocation between groups. Those who were referred late had had either un recognised or grossly underestimated infection. In some patients significant ischemia was not appreciated. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors 4. The comparison groups received the same care and support apart from the interventions studied? Comparison groups received the same care as patients were seen under a single vascular surgical service. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was taken retrospectively over a 2 year period at a mean follow up of 12.4 years. Follow up varied between patients. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion 9. The groups were comparable with respect to the availability of outcome data? There was no apparent loss to follow up. Results were taken from a retrospective review of records. 10. The study had an appropriate length of follow up?

Bibliographic reference	MILLS, J. L., BECKETT, W. C., & TAYLOR, S. M. (1991). The diabetic foot: consequences of delayed treatment and referral. Southern Medical Journal, 84(8), 970-974.
	Observation period was appropriate 2 years 11. The study used a precise definition of outcome? The study did use a clear definition of proposed outcomes 12. A valid and reliable method was used to determine the outcome? A valid and reliable method may not have been used as data was provided from retrospective review of records 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total n= 55 diabetic patients Number of infected forefeet= 62
Patient characteristics	Patients taken from: USA Inclusion: Patients with limb-threatening infection, wet gangrene, or ulceration confined to the forefoot Infection of sufficient severity to necessitate debridement with or without amputation in the operating room Exclusion: Minor lesions or infections that resolved with antibiotic therapy or minimal debridement alone Baseline characteristics: No baseline characteristics provided between treatment groups Overall: Mean age= 63.2 years Requiring insulin= 31 participants Oral hypoglycaemics alone= 24 Male: 35 participants Cause of foot lesion: Ischaemic: 19 cases Infectious: 29 cases

Bibliographic reference	MILLS, J. L., BECKETT, W. C., & TAYLOR, S. M. (1991). The diabetic foot: consequences of delayed treatment and referral. Southern Medical Journal, 84(8), 970-974.
	Mixed: 14 cases
Intervention	Delayed referral for surgical care Usual care after referral: All infected lesions were debrided promptly by resident vascular surgeons. Broad spectrum antibiotics were administered intravenously then tailored based on tissue cultures obtained at debridement. Patients with clearly palpable pedal pulses and normal Doppler ankle brachial pressure index had aggressive debridement/amputation without further vascular evaluation. If the ankle brachial pressure index was <0.6, the, the absolute Doppler-derived ankle-systolic pressure was <90 mm Hg, and/or if photoplethysmographic wave forms at multiple digital or transmetatarsal levels were obstructive revascularization procedures were done if indicated by arteriographic findings. This would be performed after initial control of the foot infection by nonanatomic debridement/amputation.
Comparison	Appropriate referral
Length of follow up	2 year observational period, mean follow up 12.4 years
Location	USA
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes No data provided Rates of hospital admission for foot problems resulting from diabetes No data provided Rates and extent of amputation 33 bypasses were required because of severe atherosclerotic occlusive disease, only one patient had unreconstructable arterial disease. A significant delay in referral for surgical care or inappropriate initial treatment was identified in 16 of the 55 participants. The

Bibliographic reference	MILLS, J. L., BECKETT, W. C., & TAYLOR, S. M. (1991). The diabetic foot: consequences of delayed treatment and referral. Southern Medical Journal, 84(8), 970-974.
	delays in referral ranged from 2 weeks to 12 months after the patient initially saw a physician for evaluation. In 10 patients, infection was either unrecognised or grossly under estimated In 6 patients, significant ischemia was not appreciated (all 6 of these patients had digital or forefoot gangrene and absent pedal pulses) These delays led to more proximal amputation levels in 6 patients (seven limbs) including three below-knee amputations in patients with limbs that were initially salvageable. Health related quality of life No data provided
Source of funding	Unclear source of funding
Comments	

Table 67: Alexandrescu 2008

Bibliographic reference	Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.
Study type	Observational, case series
Study quality	Summary Location: Two departmental hospitals, constituting an institutional diabetic programme Population: A consecutive series of 163 patients with 183 limbs with diabetic ischaemic wounds. Intervention: The implementation of multidisciplinary diabetic foot clinic employing 2 diabetologists, vascular surgeons, 3 orthopaedic surgeons, 2 podiatrists 2 radiologists, 1 plastic surgeon, 2 psychologists and 1 infectionist. These were joined to specialised nurse and orthotist staff. Before 2005 pre and post operative care for these patients was optionally multidisciplinary. Outcome: limb salvage rates. 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant

Bibliographic reference	**Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.**
	allocation to intervention is not expected to affect the outcome under study)? There was no allocation between groups. Groups were split by those who were admitted before and after the year 2005 when the multidisciplinary diabetic foot clinic was established. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if comparison groups received comparable care other than due to the changes implemented at the health care centre. It appears that similar criteria for revascularisation procedures were employed. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was taken consecutively over a 7 year period. Follow up varied between participants and this was adjusted for in the results. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion. All patients however were admitted for revascularisation procedures. 9. The groups were comparable with respect to the availability of outcome data? There was no loss to follow up reported. Limb salvage involved no request for major amputation and was confirmed if functional anatomy of the patient was recovered. 10. The study had an appropriate length of follow up? Observation period was appropriate 7 years. Post operative haemodynamic status was assessed by ankle brachial pressure and duplex scan one month after discharge and every 6 months thereafter. Mean total vascular follow up was 23.3 months (range 1-68 months). 11. The study used a precise definition of outcome? The study did use a clear definition of limb salvage: Limb salvage involved no request for major amputation and was confirmed if functional anatomy of the patient was recovered. Technical success was defined as correct revascularisation without residual stenosis > 20% resulting in direct flow from the iliac level into the pedal arch. 12. A valid and reliable method was used to determine the outcome? A valid and reliable method was used.

Bibliographic reference	**Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.**
	13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total n= 163 diabetic patients Number of limbs with ischaemic wounds= 183 Multidisciplinary clinic period= 97 limbs Pre multidisciplinary clinic period= 86 limbs
Patient characteristics	Patients taken from: Belgium Inclusion: Patients with diabetic neuro-ischaemic wounds Exclusion: Acute ischaemic presentation Presence of Wagner grade 5 lesions with extended limb loss and unavoidable major amputation Aneurismal disease and documented iodine media intolerence Baseline characteristics: No baseline characteristics provided between treatment groups Overall: age (>70 years)= 42% Requiring insulin= 34% Oral hypoglycaemics alone= not reported Male: 102 men Cause of foot lesion: neuro-ischaemic Peripheral neuropathy: 64% Wagner grade 3-4: 46% Hypertension: 72%

Bibliographic reference	**Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.**
	Smoking: 52% Coronary disease: 73% Chronic renal insufficiency: 47% End stage renal failure: 18% Extent of ulcers >2.5 cm: 37% Depth of tissue loss >2 mm: 29%
Intervention	The implementation of multidisciplinary diabetic foot clinic Employing 2 diabetologists, vascular surgeons, 3 orthopaedic surgeons, 2 podiatrists 2 radiologists, 1 plastic surgeon, 2 psychologists and 1 infectionist. These were joined to specialised nurse and orthotist staff. For each given case a therapeutic algorithm was applied: 1) debridement and removal of devitalised tissues, drainage of collections and bacteriological samples 2) assessment of the ischaemic and neuropathic participation, expeditious revascularisation and infection culture base eradication 3) Orthopaedic, podiatric and/or plastic surgical treatment 4) customised shoes, cast and rehabilitation of ambulation with psychological support 5) in a subset of patients owing to specific indications adjunctive therapies were employed (e.g. vacuum assisted closure, maggot therapy..)
Comparison	Before 2005 pre and post operative care for these patients was optionally multidisciplinary.
Length of follow up	7 year observational period, mean follow up 23.3 months (range 1-68 months)
Location	Belgium
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes No data provided Rates of hospital admission for foot problems resulting from diabetes

Bibliographic reference	Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.
	No data provided Rates and extent of amputation Cumulative patency rates (SEM): pre and post operative care for these patients was optionally multidisciplinary 6 months= 76% (± 5.5) 12 months= 72% (± 6.1) 24 months= 66% (± 7.1) Cumulative patency rates: The implementation of multidisciplinary diabetic foot clinic and treatment algorithm 6 months= 80% (± 5,1) 12 months= 77% (±5.6) 24 months= 73% (±6.6) A significant difference was found between the two intervals for limb salvage rates (P=0.040) No significant statistical deviation was found in the results of the angioplasty alone (p=0.381) Health related quality of life No data provided
Source of funding	Unclear source of funding
Comments	A comparison between the limb salvage rates before and after initiating the multidisciplinary clinic and associated treatment algorithm showed a significant difference. No statistical deviation was found regarding the technique itself for revascularisation in the same intervals.

Table 68: Edmonds 1986

Bibliographic reference	Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.
Study type	Observational, retrospective cohort study
Study quality	Summary

Bibliographic reference	Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.
	Location: a specialised foot clinic for diabetic patients employing a chiropodist, shoe-fitter, nurse, physician and surgeon Intervention: the establishment of the above foot clinic Population: patients with neuropathic diabetic foot and ischaemic diabetic foot Outcome: number of major amputations per year 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? There was no allocation between groups. Groups were split by those who were treated in the years prior to the clinic and those who were not. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? Unclear if groups were comparable at baseline including all major confounding factors over the period before and after the setting up of the clinic 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if comparison groups received comparable care other than due to the changes implemented by the foot protection team. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was taken prospectively for three years in the clinic. No one mean length of follow up was specified and follow up varied between participants depending on clinical condition 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion or for general adherence to treatment. 9. The groups were comparable with respect to the availability of outcome data? There was no loss to follow up reported. 10. The study had an appropriate length of follow up? Observation period was appropriate 3 years, unclear if length of follow up was appropriate 11. The study used a precise definition of outcome? The study did not use a clear definition of amputation or ulceration. 12. A valid and reliable method was used to determine the outcome?

Bibliographic reference	Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.
	Unclear if a valid and reliable method was used to determine outcome. Retrospective data were used to compare rates of amputation before and after the establishment of the clinic. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total n= 239 diabetic patients with foot ulcers
Patient characteristics	Patients taken from: England Inclusion: Diabetes mellitus with ulceration Neuropathic feet Ischaemic feet Exclusion: Not stated Baseline characteristics: No baseline characteristics provided between treatment groups Overall: Age mean= 59.3 ± 13.7 neuropathic group, 68.9 ± 10.5 ischaemic group Requiring insulin= 86 neuropathic, 42 ischaemic Type 2 diabetes= 62 neuropathic, 49 ischaemic Male: 69 neuropathic, 46 ischaemic White: not reported History of amputation not reported History of ulceration: not reported Peripheral neuropathy: not reported Wagner grade 3-4: not reported Hypertension: not reported

Bibliographic reference	Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.
	Smoking: not reported Coronary disease: not reported Chronic renal insufficiency: not reported End stage renal failure: not reported Extent of ulcers >2.5 cm: not reported Depth of tissue loss >2 mm: not reported Ischaemic ulcers= 80 Neuropathic ulcers= 101
Intervention	Treatment under a specialised foot clinic employing a chiropodist, shoe-fitter, nurse, physician and surgeon: These patients received intensive chiropody, control of sepsis, provision of footwear, treatment of oedema, pain relief for ischaemic lesions, education, vascular investigation, asking for smoking to be stopped.
Comparison	Pre specialised foot clinic (undefined care)
Length of follow up	mean follow up undefined
Location	England
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes No data provided Rates of hospital admission for foot problems resulting from diabetes No data provided Rates and extent of amputation The effect of the foot clinic on the number of major and minor operations was assessed by comparing the number of such procedures in both neuropathic and ischaemic patients from the diabetic clinic for two years before its establishment to those performed three years after.

Bibliographic reference	Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.
	Major amputations: Two years before clinic was established: 11 and 12 major amputations yearly Three years following: 7, 7, and 5 amputations yearly The number of minor operations (drainage operations and “Ray” amputations) Two years before clinic was established: 27 and 29 major amputations yearly Three years following establishment of clinic: 16, 21, and 15 amputations yearly Health related quality of life No data provided
Source of funding	Unclear source of funding
Comments	Reduced rate of amputation compared to the two years before establishment of clinic in both diabetic patients with neuropathic ulcers and ischaemic ulcers.

Table 69: Weck 2009

Bibliographic reference	Weck, F., Bleichhardt, G., & Hiller, W. (2009). The factor structure of the Illness Attitude Scales in a German population. International journal of behavioral medicine, 16(2), 164-171.
Study type	Observational, prospective study
Study quality	Summary Location: a structured healthcare system in the southeast of Germany Intervention: Organisation of structured healthcare system based on integrated outpatient treatment, acute inpatient care and rehabilitative treatment set up and signed by the local branch of Germanys largest Health Insurance Company, a hospital specialised in the acute care of diabetic foot, and a specialised rehabilitation clinic. All participating medical institutions shared a common set of diagnostic and therapeutic algorithms Population: 684 patients hospitalized because of diabetic foot ulceration Outcome: amputations, course of lesions, mortality 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Controls were taken from another regional hospital without interdisciplinary care of diabetic foot. Unclear method of allocation.

Bibliographic reference	Weck, F., Bleichhardt, G., & Hiller, W. (2009). The factor structure of the Illness Attitude Scales in a German population. International journal of behavioral medicine, 16(2), 164-171.
	2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? Groups were not comparable at baseline including all major confounding factors 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if comparison groups received comparable care other than due to the changes implemented by the foot protection team. There were most likely differences in care in the other regional hospital. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was taken prospectively for 7 years. Each participant had a follow up of 2 years in the intervention group however there was no follow up examinations in the control group. This means for comparison purposes follow up length would not have been appropriate. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion or for general adherence to treatment. 9. The groups were comparable with respect to the availability of outcome data? There was no loss to follow up reported. 10. The study had an appropriate length of follow up? Observation period was appropriate 7 years, length of follow up was not appropriate (2 years) in the intervention group and no follow up examinations available for the control group. 11. The study used a precise definition of outcome? The study used a clear definition of amputation and ulceration. 12. A valid and reliable method was used to determine the outcome? Unclear if a valid and reliable method was used to determine outcome. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total n= 1192

<table>
<tr><th>Bibliographic reference</th><th>Weck, F., Bleichhardt, G., & Hiller, W. (2009). The factor structure of the Illness Attitude Scales in a German population. International journal of behavioral medicine, 16(2), 164-171.</th></tr>
<tr><td></td><td>684 diabetic patients with diabetic foot ulceration
508 controls</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: England

Inclusion:
Covered by AOK insurance
Presenting with a recently manifested foot ulcer

Exclusion:
Acute myocardial infarction or stroke within the past 6 months
Terminal renal failure
Any kind of cancer

Baseline characteristics:

Classification Of ulcers and infection status was reported to be comparable between groups. P values not provided.

<table>
<tr><td></td><td>Structured health care</td><td>Controls</td></tr>
<tr><td>Reduced vibration perception</td><td>654</td><td>457</td></tr>
<tr><td>Creatinine >130 µmol/L</td><td>104</td><td>71</td></tr>
<tr><td>Prior amputation</td><td>249</td><td>Not disclosed</td></tr>
<tr><td>Below the knee</td><td>40</td><td>73</td></tr>
<tr><td>Above the knee</td><td>23</td><td>53</td></tr>
<tr><td>Coronary artery disease</td><td>567</td><td>396</td></tr>
<tr><td>Prior myocardial infarction</td><td>47</td><td>41</td></tr>
<tr><td>Prior stroke</td><td>51</td><td>48</td></tr>
<tr><td>Hypertension</td><td>621</td><td>441</td></tr>
<tr><td>Smoking</td><td>231</td><td>158</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Treatment under organisation of structured healthcare system based on integrated outpatient treatment, acute inpatient care and rehabilitative treatment set up and signed by the local branch of Germanys largest Health Insurance Company, a hospital</td></tr>
</table>

Bibliographic reference	Weck, F., Bleichhardt, G., & Hiller, W. (2009). The factor structure of the Illness Attitude Scales in a German population. International journal of behavioral medicine, 16(2), 164-171.
	specialised in the acute care of diabetic foot, and a specialised rehabilitation clinic. All participating medical institutions shared a common set of diagnostic and therapeutic algorithms
Comparison	Care at another regional hospital without interdisciplinary care of diabetic foot (undefined care)
Length of follow up	2 years for intervention group however the control group had no follow up examinations.
Location	Germany
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes The structured health care group had a significantly lower level of ulcer severity at discharge compared to controls after adjustment for age, ulcer severity, peripheral arterial disease, coronary heart disease, hypertension, smoking and MA. P=0.001 i.e. significant difference Rates of hospital admission for foot problems resulting from diabetes No data provided Rates and extent of amputation Major amputation Defined as amputation above the ankle Group treated by structured health care programme= 32 (4.7%) Control group= 110 cases (21.7%) P=<0.0001 (age adjusted) i.e. significant difference Minor amputations Group treated by structured health care programme= 215 of 684 participants Control group= 179 of 508 participants Health related quality of life Age adjusted mortality during initial hospitalisation (no follow up available for control group)

Bibliographic reference	**Weck, F., Bleichhardt, G., & Hiller, W. (2009). The factor structure of the Illness Attitude Scales in a German population. International journal of behavioral medicine, 16(2), 164-171.**
	Group treated by structured health care programme= 17 (2.5%) Control group= 48 (9.4%) P=<0.001 i.e. significant difference
Source of funding	Unclear source of funding
Comments	With structured health care programme involving interdisciplinary care and a shared treatment algorithm a significant reduction of major amputation rates was achieved (more than 75%) as compared to standard care.

Table 70: Rerkasem 2008

Bibliographic reference	**Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.** **Rerkasem, K., Kosachunhanun, N., Tongprasert, S., & Guntawongwan, K. (2009). A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. The international journal of lower extremity wounds, 8(3), 153-156.**
Study type	Observational, prospective study
Study quality	Summary Location: Chiang Mai University Hospital in Thailand Intervention: a foot care team consisting of endocrinologists, a rehabilitation physician, a family doctor, nurses, and plastic and vascular surgeons. Flow sheets based on diabetic foot protection algorithms were developed. Preventive services were provided routinely according to the flow chart including self-care education, a routine palliative foot service, and the provision of protective footwear. The consultation between specialists was carried out in flow sheets directly without any formal consultation form. Comparison: Standard care prior to the development of the protocol was undertaken using the interdepartmental consultation form for cases with ischaemia and neuropathy. Preventive measures were taken at the discretion of the physician and there were no detailed guidelines or flow sheets for these specific services. Population: 183 patients with diabetic foot ulcer Outcome: amputations, hospitalisation, length of hospitalisation 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Controls were taken from before the period that the service was established. Unclear if any other confounding factors may

Bibliographic reference	**Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.** **Rerkasem, K., Kosachunhanun, N., Tongprasert, S., & Guntawongwan, K. (2009). A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. The international journal of lower extremity wounds, 8(3), 153-156.**
	have affected the results during this time. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? Groups were comparable at baseline including major confounding factors reported 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if comparison groups received comparable care other than due to the changes implemented by the protocol. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Observational period was over 4 years. Unclear if participants were observed for an equal length of follow up. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion or for general adherence to treatment. 9. The groups were comparable with respect to the availability of outcome data? There was no loss to follow up reported. 10. The study had an appropriate length of follow up? Observation period was appropriate 4 years, length of follow up was most likely variable and may not have been appropriate in all cases. 11. The study used a precise definition of outcome? The study used a clear definition of amputation 12. A valid and reliable method was used to determine the outcome? Unclear if a valid and reliable method was used to determine outcome. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .

<table>
<tr><td>Bibliographic reference</td><td>Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.

Rerkasem, K., Kosachunhanun, N., Tongprasert, S., & Guntawongwan, K. (2009). A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. The international journal of lower extremity wounds, 8(3), 153-156.</td></tr>
<tr><td></td><td>Authors state that technology and facilities in the past may not have been as good as they are now. Also some data in the historical cohort group was sometimes unavailable.</td></tr>
<tr><td>Number of patients</td><td>Total n= 183 patients with diabetic foot ulcer

73 received diabetic foot protection
110 received standard care</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: Thailand

Inclusion:
Patients with diabetic foot ulcer

Exclusion:
Not defined

Baseline characteristics:

No significant differences for the confounding factors below (p values provided)
<table>
<tr><td></td><td>Diabetic foot protection (n=73)</td><td>Standard care (n=110)</td></tr>
<tr><td>Males</td><td>25</td><td>37</td></tr>
<tr><td>Age, mean (SD)</td><td>58.8 (11.9)</td><td>60.6 (10.5)</td></tr>
<tr><td>Hypertension</td><td>50</td><td>49</td></tr>
<tr><td>History of smoking</td><td>31</td><td>55</td></tr>
<tr><td>Hyperlipidemia</td><td>33</td><td>73</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Care provided by a foot care team consisting of endocrinologists, a rehabilitation physician, a family doctor, nurses, and plastic and vascular surgeons. Flow sheets based on diabetic foot protection algorithms were developed. Preventive services were provided routinely according to the flow chart including self-care education, a routine palliative foot service, and the provision of</td></tr>
</table>

Bibliographic reference	**Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.** **Rerkasem, K., Kosachunhanun, N., Tongprasert, S., & Guntawongwan, K. (2009). A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. The international journal of lower extremity wounds, 8(3), 153-156.**
	protective footwear. The consultation between specialists was carried out in flow sheets directly without any formal consultation form.
Comparison	Standard care prior to the development of the protocol was undertaken using the interdepartmental consultation form for cases with ischaemia and neuropathy. Preventive measures were taken at the discretion of the physician and there were no detailed guidelines or flow sheets for these specific services.
Length of follow up	4 years observation period, unclear individual length of follow up
Location	Thailand
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Rates of hospital admission for foot problems resulting from diabetes Not reported Rates and extent of amputation Number of major amputations Defined as either a below knee or above knee amputation Under diabetic foot protection period= 0 above knee amputations Control period= 3 above knee amputations P=0.28 i.e. not significant Under diabetic foot protection period= 3 below knee amputations Control period= 12 below knee amputations P=0.1 i.e. not significant Minor amputations

Bibliographic reference	**Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.** **Rerkasem, K., Kosachunhanun, N., Tongprasert, S., & Guntawongwan, K. (2009). A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. The international journal of lower extremity wounds, 8(3), 153-156.**
	The loss of any part of a lower limb (not including major amputations) Under diabetic foot protection period Toe- 4 amputations Transmetatarsal- 0 amputations Syme- 0 amputations Control period Toe- 10 amputations Transmetatarsal- 4 amputations Syme- 1 amputations The incidence of major amputations in the protocol and standard care groups was 4.1% and 13.6% respectively (P=0.03) Health related quality of life In the second study 56 participants who received diabetic foot protection and 40 patients who received standard care respectively were recruited to provide information about quality of life using the short-form 36 questionnaire. Patients who had been seen under the diabetic foot protection service had significantly higher scores on the SF-36 questionnaire for both physical and mental health dimensions than standard care patients. Total SF-26 score Under diabetic foot protection period= 54.7 ± 21.6 Control period= 46.0 ± 16.5 P=0.03 i.e. significant
Source of funding	Unclear source of funding
Comments	Protocol and facilitated interdisciplinary care amongst patients with diabetic foot ulcer was associated with significantly fewer major amputations and improving quality of life.

Table 71: Larsson 1995

Bibliographic reference	**Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.**
Study type	Observational, prospective study
Study quality	Summary Location: Department of orthopaedics, University Hospital Lund Intervention: a comprehensive medical and orthopaedic programme for the prevention and treatment of diabetic foot ulcers. Team consisting of a dialectologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist, and an orthotist and working in close cooperation with the department of vascular surgery and the department of infectious diseases. Comparison: Prior to 1983 diabetic patients with foot lesions were treated where they first attended, most commonly in Primary Health Care or Departments of Infectious Diseases, Dermatology, General Surgery, or Orthopaedics. When required, interdisciplinary consultations were performed, usually by means of referral letters, not seldom resulting in considerable delay. Population: 294 patients with known diabetes mellitus (144 men and 150 women) had 387 primary amputations. 71% of the amputations were precipitated by foot ulcer. Outcome: amputations, extent of amputation 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Controls were taken from before the period that the service was established. Unclear if any other confounding factors may have affected the results during this time. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no attempts to balance groups for confounders 3. The groups were comparable at baseline, including all major confounding factors? Groups were comparable at baseline including major confounding factors reported 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if comparison groups received comparable care other than due to the changes implemented by the programme. See intervention section for other changes of care that may have occurred over this time period. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Observational period was over 11 years. Unclear if participants were observed for an equal length of follow up. 8. Groups were comparable for intervention completion?

Bibliographic reference	Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.
	Unclear if groups were comparable for compliance or intervention completion or for general adherence to treatment. 9. The groups were comparable with respect to the availability of outcome data? There was no loss to follow up reported. 10. The study had an appropriate length of follow up? Observation period was appropriate 11 years, data was taken retrospectively from participants who had undergone amputations. 11. The study used a precise definition of outcome? The study used a clear definition of amputation and ulceration 12. A valid and reliable method was used to determine the outcome? Unclear if a valid and reliable method was used to determine outcome. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total n= 294 patients with known diabetes, who had 387 amputations The study reports general amputation incidence rates in the years following the setting up of the clinic
Patient characteristics	Patients taken from: Sweden Inclusion: Known diabetes mellitus with amputation Exclusion: Not defined Baseline characteristics: The proportion of men varied from 40 to 67% between different years The overall median age was 77 (range 32-94) years Median age being 74 for men and 79 for women

Bibliographic reference	**Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.**
	57% of patients were treated with insulin, 26% with oral agents and 17% with diet only.
Intervention	Care provided by a comprehensive medical and orthopaedic programme for the prevention and treatment of diabetic foot ulcers. Team consisting of a diabetologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist, and an orthotist and working in close cooperation with the department of vascular surgery and the department of infectious diseases. Other highlighted aspects of care that may have varied over the observation period included: • Increased availability of preventive foot care and protective shoewear and increasing focus on protective risks for diabetic foot ulcer. • An early co-ordinated evaluation of possible limiting factors for healing, and the implementation, with a minimum of delay of optimal strategies to achieve healing • Increased use of non-invasive vascular testing, extended indications for percutaneous transluminal angioplasty, and more distal PTA and bypass procedures. • Maintenance of strict amputation criteria and criteria for primary level selection • A long-term follow-up after healing either primarily or after amputation.
Comparison	Prior to 1983 diabetic patients with foot lesions were treated where they first attended, most commonly in Primary Health Care or Departments of Infectious Diseases, Dermatology, General Surgery, or Orthopaedics. When required, interdisciplinary consultations were performed, usually by means of referral letters, not seldom resulting in considerable delay.
Length of follow up	11 years observation period, unclear individual length of follow up
Location	Sweden
Outcomes measures and effect size	The proportion of patients who had been treated by the foot care team increased from 35 to 76% between the first and last 3 year period ($p<0.001$). The proportion undergoing angiography or invasive vascular intervention within 1 year prior to amputation increased from 33 to 54% ($p<0.01$) and from 14 to 29% ($p<0.05$) respectively. Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes In 195 patients (50% of total), a minor or major gangrene was present at the time of amputation and this proportion decreased

Bibliographic reference	**Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.**

from 53 to 36% (p<0.05) between the first and last 3 year period (data not provided)

The proportion of patients with a deep infection as an indication for amputation increased from 24 to 60% (p<0.001; data not provided)

Rates of hospital admission for foot problems resulting from diabetes
Not reported

Rates and extent of amputation

	Through and above the knee	Below knee	Below ankle	Total
1982	12	20	6	38
1983	8	19	12	39
1984	4	18	13	35
1985	10	35	7	52
1986	9	17	10	36
1987	9	21	6	36
1988	9	10	15	34
1989	10	3	8	21
1990	8	7	9	24
1991	9	9	13	31
1992	4	4	12	20
1993	2	6	13	21
Total	94	169	124	387

Incidence of amputation in diabetic patients with or without vascular disease per 100000 inhabitants and year, according to age group.

Bibliographic reference	**Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.**

	Amputation at all levels. Any age	Major amputations at any age	Major amputations <60 years	Major amputations 60-79 years	Major amputations ≥80 years
1982	19.1	16.1	0	50.6	272.0
1983	19.5	13.3	0	43.3	219.2
1984	17.4	10.9	0	43.1	137.5
1985	25.8	22.3	1.8	72.3	294.6
1986	17.6	12.7	1.2	49.0	128.0
1987	17.5	14.6	2.4	45.4	167.3
1988	16.3	9.1	1.2	38.8	67.1
1989	9.9	6.2	0	16.1	104.5
1990	11.2	7.0	0	19.3	115.1
1991	14.3	8.3	1.7	28.8	74.3
1992	9.1	3.6	0	19.1	24.2
1993	9.4	3.6	1.1	18.9	0

The total annual incidence of primary amputations decreased by 49%. The incidence of major amputations decreased by 78% From 16.1 to 3.6/100000 inhabitants ($p<0.001$)

Calculated per 1000 diabetic subjects the total incidence of amputation decreased from 7.9 to 4.1 and the incidence of major amputations from 6.7 to 1.5.

The total reamputation rate decreased from 36 to 22% between the first and last 3 year period ($P<0.05$; data not provided)

Health related quality of life

The mortality within 30 days after primary amputation was 9% in the first and 15% in the last 3 year period.(non significant)

Source of funding	Supported by the Swedish Medical Research Council
Comments	Multidisciplinary care amongst other changes to practice resulted in a substantial long-term decrease in the total incidence of major amputations as well as a decrease in the total in the total incidence of amputations in diabetic patients.

Table 72: Armstrong 2012

Bibliographic reference	**Armstrong, D. G., Bharara, M., White, M., Lepow, B., Bhatnagar, S., Fisher, T., ... & Mills, J. L. (2012). The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. Diabetes/metabolism research and reviews, 28(6), 514-518.**
Study type	Observational, prospective study
Study quality	Summary Location: USA, a single institution evaluating all patients with diabetic foot complications requiring foot surgery or vascular intervention Intervention: An interdisciplinary team established: composed of podiatric physicians caring for the structural and surgical aspects of the foot (toe) and vascular surgeons caring for the vascular supply into the foot (flow). Consultation from other services such as the hospitalist service for metabolic control ; the infectious disease service; the prosthetic service and case management/social work. Referrals could be made from various outpatient clinics/medical specialties and emergency room at the tertiary care centre. Depending on vascular status either the “flow team” or “toe team” too prime care over the patient. On the basis of vascular supply to the foot patients were provided surgical intervention and referred to other specialties for supplementary care. This approach triggered prompt referrals and streamlined care delivery. (more detailed elements of team care found in paper) Comparison: Limb-salvage service only consisting of vascular surgery with medicine and allied patient care services being called in on an ad hoc basis. Population: 790 operations related to the treatment of diabetic foot complications requiring surgery or vascular intervention in 374 patients. Data taken from 24 months before and after integrating podiatric surgery with a vascular surgical limb-salvage service. Outcome: amputation.
Number of patients	Total n= 374
Patient characteristics	Inclusion: Diabetic foot complications requiring foot surgery or vascular intervention Exclusion: Patients with diabetes and intact protective sensation undergoing elective foot surgery

Bibliographic reference	**Armstrong, D. G., Bharara, M., White, M., Lepow, B., Bhatnagar, S., Fisher, T., ... & Mills, J. L. (2012). The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. Diabetes/metabolism research and reviews, 28(6), 514-518.**
	Baseline characteristics: No baseline characteristics reported
Intervention	An interdisciplinary team established: composed of podiatric physicians caring for the structural and surgical aspects of the foot (toe) and vascular surgeons caring for the vascular supply into the foot (flow). Consultation from other services such as the hospitalist service for metabolic control ; the infectious disease service; the prosthetic service and case management/social work. Referrals could be made from various outpatient clinics/medical specialties and emergency room at the tertiary care centre. Depending on vascular status either the “flow team” or “toe team” too prime care over the patient. On the basis of vascular supply to the foot patients were provided surgical intervention and referred to other specialties for supplementary care. This approach triggered prompt referrals and streamlined care delivery. (more detailed elements of team care found in paper)
Comparison	Limb-salvage service only consisting of vascular surgery with medicine and allied patient care services being called in on an ad hoc basis.
Length of follow up	Outcomes compared 24 months before and after integrating podiatric surgery with a vascular surgical limb salvage service.
Location	USA
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Resource use and costs (including referral rates) Not reported Rates of hospital admission for foot problems resulting from diabetes Not reported Length of hospital stay Not reported Rates and extent of amputation 790 operations were performed related to treatment of diabetic foot complications in 374 patients.

Bibliographic reference	**Armstrong, D. G., Bharara, M., White, M., Lepow, B., Bhatnagar, S., Fisher, T., ... & Mills, J. L. (2012). The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. Diabetes/metabolism research and reviews, 28(6), 514-518.**
	502 were classified as non-vascular diabetic foot surgery and 288 were vascular interventions. Surgery classified as urgent foot surgery Before team implementation= 77.7% After team implementation= 48.5% Odds ratio= 3.7 (95% CI 2.4-5.5) P<0.0001 i.e. significant difference. High/low amputation ratio Before team implementation= 0.35 After team implementation= 0.27 Mid foot amputations Before team implementation= 8.2% After team implementation= 26.1% Odds ratio= 4.0 (95% CI 2.0-83.3) P<0.0001 i.e. significant difference. A 37.5% reduction in below knee amputations was realised. Health related quality of life Not reported
Source of funding	Non reported
Comments	This study showed a reduction in urgent surgery and a decrease in high/low amputation ratio (as a result of an increase in mid foot amputation) following the implementation of an interdisciplinary team service.

Table 73: Yesil 2009

Bibliographic reference	**Yesil, S., Akinci, B., Bayraktar, F., Havitcioglu, H., Karabay, O., Yapar, N., ... & Eraslan, S. (2009). Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey. Experimental and clinical endocrinology & diabetes, 117(7), 345.**
Study type	Observational, prospective study

<table>
<tr><th>Bibliographic reference</th><th>Yesil, S., Akinci, B., Bayraktar, F., Havitcioglu, H., Karabay, O., Yapar, N., ... & Eraslan, S. (2009). Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey. Experimental and clinical endocrinology & diabetes, 117(7), 345.</th></tr>
<tr><td>Study quality</td><td>Summary
Location: Turkey, a single university hospital.
Intervention: A diabetic foot care team was established consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician. This team met on a weekly basis. Patients were followed up as outpatients by the same diabetic foot care team for at least 6 months.
Patients received Wagner risk assessment, standard ulcer care (bed rest, proper offloading, parenteral antibiotics and debridement or amputation when indicated.)
Comparison: Before establishment of the clinic, consultations for the management of the diabetic foot ulcer were conducted by the physician whom the patient applied to.
Population: The management of 437 patients with diabetic foot ulceration. Data taken from between January 1999 and January 2008 with the clinic established in 2002.
Outcome: amputation, ulceration</td></tr>
<tr><td>Number of patients</td><td>Total n= 437</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Foot ulcer episodes who were admitted to this hospital between 1999-2008
Of which data were collected prospectively for a follow up of 6 months

Exclusion:
Patients who could not attend clinic regularly

Baseline characteristics:

<table>
<tr><td></td><td>Before diabetic foot team (n=137)</td><td>After diabetic foot team (n=437)</td></tr>
<tr><td>Age, y</td><td>63.80 ± 11.41</td><td>62.29 ± 10.32</td></tr>
<tr><td>Male</td><td>62%</td><td>70%</td></tr>
<tr><td>Type 2 diabetes</td><td>97.8%</td><td>96.1%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Yesil, S., Akinci, B., Bayraktar, F., Havitcioglu, H., Karabay, O., Yapar, N., ... & Eraslan, S. (2009). Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey. Experimental and clinical endocrinology & diabetes, 117(7), 345.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Diabetes duration, y</td><td>14.57 ± 7.84</td><td>16.30 ± 9.64</td></tr>
<tr><td>Previous insulin use</td><td>59.1%</td><td>67.5%</td></tr>
<tr><td>Smoking</td><td>50.4%</td><td>38%</td></tr>
<tr><td>Neuropathy</td><td>89.8%</td><td>82.4%</td></tr>
<tr><td>nephropathy</td><td>48.2%</td><td>54%</td></tr>
<tr><td>Wagner score %
1
2
3
4
5</td><td>
8.8
38
28.5
21.9
2.9</td><td>
10.5
35.5
28.6
23.6
1.8</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>A diabetic foot care team was established consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician. This team met on a weekly basis. Patients were followed up as outpatients by the same diabetic foot care team for at least 6 months.</td></tr>
<tr><td>Comparison</td><td>Before establishment of the clinic, consultations for the management of the diabetic foot ulcer were conducted by the physician whom the patient applied to.</td></tr>
<tr><td>Length of follow up</td><td>6 month follow up (at least)</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
<table>
<tr><td></td><td>Before Diabetic foot team (n=137)</td><td>After Diabetic foot team (n=437)</td><td>P value</td></tr>
<tr><td>Unhealed ulcers (n, %)</td><td>22 (16.1%)</td><td>59 (13.5%)</td><td>0.293</td></tr>
<tr><td>Healed ulcers (n,%) (without amputation)</td><td>60 (43.8%)</td><td>220 (50.3%)</td><td>0.203</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Yesil, S., Akinci, B., Bayraktar, F., Havitcioglu, H., Karabay, O., Yapar, N., ... & Eraslan, S. (2009). Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey. Experimental and clinical endocrinology & diabetes, 117(7), 345.</th></tr>
<tr><td></td><td>Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes
Not reported

Length of hospital stay

<table>
<tr><td></td><td>Before Diabetic foot team</td><td>After Diabetic foot team</td><td>P value</td></tr>
<tr><td>Inpatient treatment (days)</td><td>39.47 ± 28.29</td><td>26.99 ± 21.27</td><td><0.001</td></tr>
</table>

Rates and extent of amputation

<table>
<tr><td></td><td>Before Diabetic foot team</td><td>After Diabetic foot team</td><td>P value</td></tr>
<tr><td>Overall amputations (n,%)</td><td>55 (40.1%)</td><td>158 (36.2%)</td><td>0.418</td></tr>
<tr><td>Minor amputations (n,%)</td><td>27 (19.7%)</td><td>103 (23.6%)</td><td>0.413</td></tr>
<tr><td>Major amputations (n,%)</td><td>28 (20.4%)</td><td>55 (12.6%)</td><td>0.026</td></tr>
</table>

Health related quality of life
Not reported</td></tr>
<tr><td>Source of funding</td><td>None stated</td></tr>
<tr><td>Comments</td><td>This study showed a reduction in rates of major amputation and length of hospital stay following implementation of a diabetic foot multidisciplinary team.</td></tr>
</table>

Table 74: Faglia 1998

Bibliographic reference	**Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Barbano, P., ... & Morabito, A. (1998). Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications, 12(2), 96-102.**
Study type	Observational, prospective study
Study quality	Summary Location: Italy, a diabetological unit for foot ulcer, single centre. Intervention: Patients were admitted to hospital if they had a full thickness gangrene or abscess. Subjects with superficial ulcer were also admitted if the ulcer was large, infected and showed a defective healing in 30 days of outpatient treatment. Comprehensive protocol combined with a multidisciplinary approach in a dedicated centre. Patients were referred from outpatient centre, casualty department and from other hospitals. Protocol involved aggressive and radical debridement, abcesses were drained and toe amputation and ray resection carried out when required, antibiotic therapy, optimized metabolic control sought, vascular status checked and arteriography performed as required to evaluate the opportunity for vascular intervention. During hospitalisation all patients received orthopaedic devices for offloading. Patients also received hyperbaric oxygen therapy. (see paper for more details) Comparison: Rates of amputation were compared with the previous two periods before criteria for admission to hospital and therapeutic-diagnostic protocol were established. Population: 115 diabetic patients consecutively hospitalised for foot ulcer. Outcome: amputation, For study quality please see GRADE tables
Number of patients	Total n= 115 diabetic patients Division of General Surgery period= 42 Diabetology centre, processing stage of the multidisciplinary protocol period= 78 Standardised application of the multidisciplinary protocol= 115
Patient characteristics	Patients taken from: Inclusion: Diabetic patients consecutively hospitalised for foot ulcer Admitted if either full-thickness gangrene or abscess Subjects with superficial ulcer were admitted if the ulcer was large, infected and showed a defective healing in 30 days of outpatient treatment

<table>
<tr><td>Bibliographic reference</td><td>Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Barbano, P., ... & Morabito, A. (1998). Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications, 12(2), 96-102.</td></tr>
<tr><td></td><td>Exclusion: Non mentioned

Baseline characteristics:

<table>
<tr><td></td><td>1986-1989 (n=78)</td><td>1990-1993 (n=115)</td><td>P</td></tr>
<tr><td>Wagner grade 2</td><td>18</td><td>13</td><td></td></tr>
<tr><td>Wagner grade 3</td><td>8</td><td>32</td><td></td></tr>
<tr><td>Wagner grade 4</td><td>52</td><td>70</td><td>0.03</td></tr>
<tr><td>Ankle brachial pressure index</td><td>0.80 ± 0.27</td><td>0.64 ± 0.25</td><td>0.01</td></tr>
<tr><td>Angiography</td><td>44</td><td>98</td><td>0.00</td></tr>
<tr><td>Vascular Procedures</td><td>10</td><td>29</td><td>0.05</td></tr>
<tr><td>Infection</td><td>57</td><td>105</td><td>0.01</td></tr>
</table>

Overall:
age = 63.4 ± 9.9
Requiring insulin= 60.9%
Oral hypoglycaemics alone= 39.1%
Male: 73%
Cause of foot lesion: not reported
Peripheral neuropathy: not reported
Wagner grade
2= 11.3%
3= 27.8%
4= 60.9%
Hypertension: 51.3%
Smoking: 35.5%
Coronary disease: 47.8%
Chronic renal insufficiency: 20%
End stage renal failure:not reported
Prior wound= 28.7%</td></tr>
<tr><td>Intervention</td><td>Patients were admitted to hospital if they had a full thickness gangrene or abscess. Subjects with superficial ulcer were also</td></tr>
</table>

Bibliographic reference	Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Barbano, P., ... & Morabito, A. (1998). Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications, 12(2), 96-102.
	admitted if the ulcer was large, infected and showed a defective healing in 30 days of outpatient treatment. Comprehensive protocol combined with a multidisciplinary approach in a dedicated centre. Patients were referred from outpatient centre, casualty department and from other hospitals. Protocol involved aggressive and radical debridement, abcesses were drained and toe amputation and ray resection carried out when required, antibiotic therapy, optimized metabolic control sought, vascular status checked and arteriography performed as required to evaluate the opportunity for vascular intervention. During hospitalisation all patients received orthopaedic devices for offloading. Patients also received hyperbaric oxygen therapy. (see paper for more details)
Comparison	Rates of amputation were compared with the previous two periods before criteria for admission to hospital and therapeutic-diagnostic protocol were established.
Length of follow up	Observation period 8 years total
Location	Italy
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Resource use and costs (including referral rates) Not reported Rates of hospital admission for foot problems resulting from diabetes Not reported (cohort taken from hospitalised patients) Length of hospital stay Not reported Rates and extent of amputation Major amputations (above or below the knee) Period from 1979 to 1981, patients admitted to general surgical department (n=42)= 17 major amputations 40.5% Period from 1986 to 1989, patients admitted to diabetology centre, processing stage of multidisciplinary protocol (n=78)= 26 major amputations 33.3% Period from 1990 to 1993, standardised application of multidisciplinary protocol (n=115)= 27 major amputations 23.5% Odds ratio (95% CI)= 0.66 (0.46-0.96) i.e. significant difference

Bibliographic reference	Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Barbano, P., ... & Morabito, A. (1998). Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications, 12(2), 96-102.
	Health related quality of life Not reported
Source of funding	
Comments	This study showed significantly fewer major amputations in the period in which a comprehensive diagnostic and treatment protocol as well as a multidisciplinary approach in a dedicated centre was employed.

Table 75: Trautner 2007

Bibliographic reference	Trautner, C., Haastert, B., Mauckner, P., Gätcke, L. M., & Giani, G. (2007). Reduced Incidence of Lower-Limb Amputations in the Diabetic Population of a German City, 1990–2005 Results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care, 30(10), 2633-2637.
Study type	Observational, prospective study
Study quality	Summary Location: Germany, three hospitals in Leverkusen. Intervention: An interdisciplinary ward for inpatient treatment including preoperative and post-operative care opened in 2001. As a rule surgery is only performed after common indication rounds with diabetologists and surgeons. Rigorous debridement and, if possible, revascularisation is an integral part of treatment. Antiseptics, antibiotics, moist dressings, maggots and vacuum assisted closure are also parts of this treatment scheme. When patients are discharged they are treated by the now-established outpatient network with 80 physicians having received a training programme to help reduce the problem of delayed diagnosis and referral of patients with diabetic foot problems Following implementation of changes nearly all diabetic patients with the need for specialist care (at diagnosis or in the case of complications) are seen by a diabetologist and return to their general practicioners afterwards. Comparison: Until 1999, mainly patient education on an inpatient basis, even for relatively healthy patients without serious complications or comorbidity was carried out in the department of internal medicine. Internists were only consulted at all with respect to metabolic control. Population: 501 diabetic patients were identified who were residents of Leverkusen and had a first non-traumatic lower-limb amputations in the three local hospitals during the defined period. Outcome: amputation rates

Bibliographic reference	**Trautner, C., Haastert, B., Mauckner, P., Gätcke, L. M., & Giani, G. (2007). Reduced Incidence of Lower-Limb Amputations in the Diabetic Population of a German City, 1990–2005 Results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care, 30(10), 2633-2637.**
Number of patients	Total n= 501
Patient characteristics	Inclusion: Lower limb amputations performed in 1990-1991, 1994-2005 Diagnosis of diabetes (subgroup) Exclusion: Not city residents Previous amputees Baseline characteristics: Type 2 diabetes: 411 of 501 Diabetes duration, y: 15.1 ± 10.7
Intervention	An interdisciplinary ward for inpatient treatment including preoperative and post-operative care opened in 2001. As a rule surgery is only performed after common indication rounds with diabetologists and surgeons. Rigorous debridement and, if possible, revascularisation is an integral part of treatment. Antiseptics, antibiotics, moist dressings, maggots and vacuum assisted closure are also parts of this treatment scheme. When patients are discharged they are treated by the now-established outpatient network with 80 physicians having received a training programme to help reduce the problem of delayed diagnosis and referral of patients with diabetic foot problems Following implementation of changes nearly all diabetic patients with the need for specialist care (at diagnosis or in the case of complications) are seen by a diabetologist and return to their general practicioners afterwards.
Comparison	Until 1999, mainly patient education on an inpatient basis, even for relatively healthy patients without serious complications or comorbidity was carried out in the department of internal medicine. Internists were only consulted at all with respect to metabolic control.
Length of follow up	Data retrospectively observed over 5 years
Location	Germany
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes

Bibliographic reference	**Trautner, C., Haastert, B., Mauckner, P., Gätcke, L. M., & Giani, G. (2007). Reduced Incidence of Lower-Limb Amputations in the Diabetic Population of a German City, 1990–2005 Results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care, 30(10), 2633-2637.**

Not reported

Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes
Not reported (cohort taken from hospitalised patients)

Length of hospital stay
Not reported

Rates and extent of amputation

Year	Incidence rate (95% CI) in diabetic population: Standard=total population (per 100,000 person years)	Incidence rate (95% CI) in diabetic population: Standard=diabetic population (per 100,000 person years)
1990	224 (136-311)	549 (382-715)
1991	143 (75-210)	356 (221-491)
1994	226 (141-312)	544 (383-705)
1995	175 (96-255)	386 (252-521)
1996	180 (101-259)	426 (286-566)
1997	455 (0-989)	433 (290-576)
1998	195 (113-278)	463 (316-611)
1999	191 (113-269)	474 (330-618)
2000	165 (93-237)	415 (282-549)
2001	78 (48-107)	304 (187-421)
2002	131 (67-195)	335 (218-451)
2003	119 (67-171)	360 (237-482)
2004	113 (52-174)	281 (173-389)
2005	235 (136-335)	428 (295-560)

Bibliographic reference	**Trautner, C., Haastert, B., Mauckner, P., Gätcke, L. M., & Giani, G. (2007). Reduced Incidence of Lower-Limb Amputations in the Diabetic Population of a German City, 1990–2005 Results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care, 30(10), 2633-2637.**
	Over 15 years an estimated reduction in amputations above the toe level by 37.1% (95% CI 12.3-54.8) results. Estimated relative risk per calendar year was 0.976 (95% CI 0.958-0.996) P<0.0164 in the diabetic population i.e. significant effect Estimated relative risk per calendar year was 0.970 (95% CI 0.948-0.991) P<0.006 in the diabetic population when only all first amputations above the toe were included. (n=527) i.e. significant effect Estimated relative risk per calendar year was 0.970 (95% CI 0.943-0.997) P<0.0318 in the diabetic population when only all first amputations above the ankle were included. (n=352) i.e. significant effect Health related quality of life Not reported
Source of funding	Kinetic Concepts Inc., Smith and Nephew
Comments	This study showed that since the late 1990s after a network of specialised physicians and defined clinical pathways for wound treatment and metabolic control were introduced the rate of amputations fell amongst the diabetic population.

Table 76: Nather 2010

Bibliographic reference	**Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.**
Study type	Observational, prospective study
Study quality	Summary Location: Singapore, National University Hospital. Intervention: Multidisciplinary Diabetic Foot Team combined with a clinical pathway. The team was composed of an orthopaedic surgeon an endocrinologist, an infectious disease specialist, a vascular surgeon, podiatrists, nurses specialised in

Bibliographic reference	Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.
	wound care, foot care, foot screening and a case manager. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (not requiring above/below knee amputation) while those diagnosed with stage 6 were put on part 2 of the pathway (requiring below knee or above knee amputation). The clinical pathway ensured that patients would be seen by all members of the diabetic foot team during hospitalisation and would be treated in an efficient multidisciplinary setting A weekly team ward round is carried out to ensure the patients have optimal glycaemic control, appropriate antibiotic coverage, follow up on surgery, podiatric care, education, foot care and foot wear with an appropriate discharge plan. Comparison: Year before team formation. Population: 939 patients with diabetic foot problems. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (n=777) while those diagnosed with stage 6 were put on part 2 of the pathway (n=162) Outcome: average length of stay, readmission rates, hospitalisation cost per patient, major reamputation rate and complication rate compared to the year before establishment of the team (team established in 2003)
Number of patients	Total n= 939 2002= 61 (year before team foundation) 2003= 70 2004= 148 2005= 180 2006= 262 2007= 218
Patient characteristics	Inclusion: Classified as diabetic foot Exclusion: Not reported Baseline characteristics: No baseline characteristic were provided comparing groups of interest

<table>
<tr><th>Bibliographic reference</th><th>Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.</th></tr>
<tr><td></td><td>Mean age: 60.0 years
Ratio males to females 1:1</td></tr>
<tr><td>Intervention</td><td>Multidisciplinary Diabetic Foot Team combined with a clinical pathway. The team was composed of an orthopaedic surgeon an endocrinologist, an infectious disease specialist, a vascular surgeon, podiatrists, nurses specialised in wound care, foot care, foot screening and a case manager. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (not requiring above/below knee amputation) while those diagnosed with stage 6 were put on part 2 of the pathway (requiring below knee or above knee amputation). The clinical pathway ensured that patients would be seen by all members of the diabetic foot team during hospitalisation and would be treated in an efficient multidisciplinary setting
A weekly team ward round is carried out to ensure the patients have optimal glycaemic control, appropriate antibiotic coverage, follow up on surgery, podiatric care, education, foot care and foot wear with an appropriate discharge plan.</td></tr>
<tr><td>Comparison</td><td>Year before team formation.</td></tr>
<tr><td>Length of follow up</td><td>6 year observation period</td></tr>
<tr><td>Location</td><td>Singapore</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
Not reported

Resource use and costs (including referral rates)

Mean hospitalisation cost per patient

<table>
<tr><th></th><th>Mean hospitalisation cost per patient</th><th>P value</th></tr>
<tr><td>2002</td><td>$8,847.17</td><td>-</td></tr>
<tr><td>2003</td><td>$9,935.59</td><td>NS</td></tr>
<tr><td>2004</td><td>$7,659.55</td><td>NS</td></tr>
<tr><td>2005</td><td>$6,195.77</td><td>NS</td></tr>
<tr><td>2006</td><td>$6,320.19</td><td>NS</td></tr>
<tr><td>2007</td><td>$6,383.79</td><td>NS</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.**

Rates of hospital admission for foot problems resulting from diabetes

Readmission rate

	Readmission rate	P value
2002	13.11%	-
2003	7.14%	NS
2004	6.76%	NS
2005	7.22%	NS
2006	5.34%	NS
2007	8.26%	NS

Length of hospital stay

	Average length of stay (days)	P value
2002	20.36	-
2003	19.03	NS
2004	13.74	0.0005
2005	10.81	<0.0005
2006	11.67	0.0009
2007	12.2	0.0005

Rates and extent of amputation

Major amputation rate (above or below knee)

	Rate of major amputation	P value
2002	31.13%	_

Bibliographic reference	**Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.**

2003	25.71%	NS
2004	19.59%	NS
2005	14.44%	0.004
2006	14.12%	0.002
2007	11.01%	<0.0005

Health related quality of life
Not reported

Source of funding	No funding recieved
Comments	This study showed that since 2003 and the introduction of the multidisciplinary team with well defined clinical pathways the rate of major amputation and length of hospital stay was significantly reduced.

Table 77: Hedetoft 2009

Bibliographic reference	**Hedetoft, C., Rasmussen, A., Fabrin, J., & Kølendorf, K. (2009). Four-fold increase in foot ulcers in type 2 diabetic subjects without an increase in major amputations by a multidisciplinary setting. Diabetes research and clinical practice, 83(3), 353-357.**
Study type	Observational, retrospective study
Study quality	Summary Location: Denmark Intervention: Establishment of a multidisciplinary team in the clinic employing diabetes specialist, orthopaedic surgeon, podiatrist and nurse reviewing the patients simultaneously. Comparison: The amputees were divided into two groups dependent of a regular review in in the clinic before and after the amputation (for more than 4 visits)= Group A. a regular review after the amputation or only briefly seen after the amputation= Group B. Population: All the clinical records of type 2 diabetic patients who had undergone leg amputation seen in the diabetic foot clinic in the observation period of 6 years were examined. 88 subjects underwent 142 amputations, 42 major amputations and 100 minor amputations. Outcome: amputation.

<table>
<tr><th>Bibliographic reference</th><th>Hedetoft, C., Rasmussen, A., Fabrin, J., & Kølendorf, K. (2009). Four-fold increase in foot ulcers in type 2 diabetic subjects without an increase in major amputations by a multidisciplinary setting. Diabetes research and clinical practice, 83(3), 353-357.</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Number of patients</td><td>Total n= 88</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Type 2 diabetic
Underwent a leg amputation seen in the outpatient diabetic foot clinic from 1998 to 2003
Orthopaedic surgery of patients who underwent amputations from 1995 to 2003, all patients with type 2 diabetes

Exclusion:
Not stated

Baseline characteristics:
<table>
<tr><td></td><td>Group A</td><td>Group B</td></tr>
<tr><td>Amputees</td><td>28</td><td>60</td></tr>
<tr><td>Age</td><td>67.3 ± 8.4</td><td>68.4 ± 9.2</td></tr>
<tr><td>Diabetes duration</td><td>19.3 ± 9.2</td><td>12.7 ± 7.8</td></tr>
<tr><td>Women</td><td>4</td><td>12</td></tr>
<tr><td>Men</td><td>24</td><td>48</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Establishment of a multidisciplinary team in the clinic employing diabetes specialist, orthopaedic surgeon, podiatrist and nurse reviewing the patients simultaneously.</td></tr>
<tr><td>Comparison</td><td>The amputees were divided into two groups dependent of a regular review in in the clinic before and after the amputation (for more than 4 visits)= Group A. a regular review after the amputation or only briefly seen after the amputation= Group B.</td></tr>
<tr><td>Length of follow up</td><td>Observation period of 6 years</td></tr>
<tr><td>Location</td><td>Denmark</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
Not reported</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Hedetoft, C., Rasmussen, A., Fabrin, J., & Kølendorf, K. (2009). Four-fold increase in foot ulcers in type 2 diabetic subjects without an increase in major amputations by a multidisciplinary setting. Diabetes research and clinical practice, 83(3), 353-357.</td></tr>
<tr><td></td><td>
Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes
Not reported

Length of hospital stay
Not reported

Rates and extent of amputation

In the observation period of 6 years: 88 subjects underwent 142 amputations, 42 major amputations and 100 minor amputations. In the same period the number of type 2 diabetic patients with foot ulcers attending the clinic increased from 50 to nearly 200 and the number of patients with type 2 diabetes increased from 250 to 1217. There was no increase in the number of major amputations in this period
<table>
<tr><td></td><td colspan="2">Group A (n=28)</td><td colspan="2">Group B (n=60)</td><td colspan="2">P value</td></tr>
<tr><td></td><td>Major</td><td>Minor</td><td>Major</td><td>Minor</td><td>Major</td><td>Minor</td></tr>
<tr><td>Amputees</td><td>10</td><td>18</td><td>19</td><td>41</td><td>0.036</td><td>0.01</td></tr>
<tr><td>Amputations</td><td>14</td><td>44</td><td>28</td><td>56</td><td>0.046</td><td>NS</td></tr>
<tr><td>Reamputations</td><td colspan="2">21</td><td colspan="2">32</td><td colspan="2">NS</td></tr>
<tr><td>Foot ulcers (%)</td><td>100</td><td>100</td><td>100</td><td>100</td><td>NS</td><td>NS</td></tr>
</table>

Health related quality of life
Not reported
</td></tr>
<tr><td>Source of funding</td><td>Danish Diabetes Foundation</td></tr>
<tr><td>Comments</td><td>This study showed a significant reduction in the rate of major amputations in the group that were followed in multidisciplinary clinic before amputation (P<0.05) although this group had a shorter duration of diabetes and less retinopathy, nephropathy</td></tr>
</table>

Bibliographic reference	Hedetoft, C., Rasmussen, A., Fabrin, J., & Kølendorf, K. (2009). Four-fold increase in foot ulcers in type 2 diabetic subjects without an increase in major amputations by a multidisciplinary setting. Diabetes research and clinical practice, 83(3), 353-357.
	and AMI/stroke.

Table 78: Chiu 2011

Bibliographic reference	Chiu, C. C., Huang, C. L., Weng, S. F., Sun, L. M., Chang, Y. L., & Tsai, F. C. (2011). A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. Journal of Plastic, Reconstructive & Aesthetic Surgery, 64(7), 867-872.
Study type	Observational, case control study
Study quality	Summary Location: Taiwan, Taipei Medical university hospital ran treatment programme Intervention: Surveillance and care by experienced specialists (endocrinologists, vascular surgeons and plastic surgeons) When infection was superimposed, purulent discharges were drained and the devitalised tissues debrided within 12 hours. Flap reconstruction was used for wound coverage and nourishing the vascularised tissue. Angioplasty or bypass was performed when required. (see decision algorithm in paper) Comparison: Doctors were given no specific guidelines for deciding on the timing of debridement and selection of conventional wound treatments. Patients were chosen to match the intervention group in terms of demographic profiles, medical history, laboratory and examination data. Population: Patients with infected diabetic foot ulcers. 350 patients in the diabetic foot ulcer treatment programme and 386 patients as controls Outcome: amputation
Number of patients	Total n= 736
Patient characteristics	Inclusion: Non-ischaemic infected wounds or ischaemic infected wounds Wound depth penetrating the tendon or capsule Wound area larger than 3 x 3cm Exclusion: None stated

<table>
<tr><th>Bibliographic reference</th><td>Chiu, C. C., Huang, C. L., Weng, S. F., Sun, L. M., Chang, Y. L., & Tsai, F. C. (2011). A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. Journal of Plastic, Reconstructive & Aesthetic Surgery, 64(7), 867-872.</td></tr>
<tr><td></td><td>Baseline characteristics:

<table>
<tr><td></td><td>Programme group</td><td>Control group</td></tr>
<tr><td>Age</td><td>62.3 ± 7.6</td><td>64.1 ± 7.7</td></tr>
<tr><td>Gender (male/female)</td><td>189/161</td><td>210/176</td></tr>
<tr><td>Diabetes duration, y</td><td>14 ± 12.2</td><td>20 ± 9.3</td></tr>
<tr><td>University of Texas classification
B
D</td><td>
188
162</td><td>
201
185</td></tr>
<tr><td>Congestive heart failure %</td><td>5.1</td><td>4.8</td></tr>
<tr><td>Renal dysfunction %</td><td>1.7</td><td>1.3</td></tr>
<tr><td>Smoking %</td><td>57.2</td><td>63.2</td></tr>
</table>
</td></tr>
<tr><th>Intervention</th><td>Surveillance and care by experienced specialists (endocrinologists, vascular surgeons and plastic surgeons) When infection was superimposed, purulent discharges were drained and the devitalised tissues debrided within 12 hours. Flap reconstruction was used for wound coverage and nourishing the vascularised tissue. Angioplasty or bypass was performed when required. (see decision algorithm in paper)</td></tr>
<tr><th>Comparison</th><td>Doctors were given no specific guidelines for deciding on the timing of debridement and selection of conventional wound treatments. Patients were chosen to match the intervention group in terms of demographic profiles, medical history, laboratory and examination data.</td></tr>
<tr><th>Length of follow up</th><td>Follow up continued until the wound healed or until amputation</td></tr>
<tr><th>Location</th><td>Taiwan</td></tr>
<tr><th>Outcomes measures and effect size</th><td>
Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
Not reported

Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes</td></tr>
</table>

Bibliographic reference	Chiu, C. C., Huang, C. L., Weng, S. F., Sun, L. M., Chang, Y. L., & Tsai, F. C. (2011). A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. Journal of Plastic, Reconstructive & Aesthetic Surgery, 64(7), 867-872.
	Not reported Length of hospital stay Length of hospital stay Treatment programme group= 23.5 ± 5.8 days Non-treatment programme group= 29.3 ± 17.9 days P =0.188 i.e. not significant difference Length of hospital stay in Stage D patients (ischaemic infected wounds) Treatment programme group (n=162)= 24.5 ± 6.4 days Non-treatment programme group (n=185)= 33.8 ± 19.9 days P =0.014 i.e. significant difference Rates and extent of amputation The odds ratio for amputation when the diabetic foot ulcer treatment programme group was compared to the non treatment programme group was 2.89 (95% CI 1.28-6.53) i.e. significant difference. After stratification for stage D patients (ischaemic infected wounds): The odds ratio for amputation when the diabetic foot ulcer treatment programme group was compared to the non treatment programme group was 2.91 (95% CI 1.03-8.22) i.e. significant difference. A greater proportion of patients in the non-treatment programme group experienced amputation: Treatment programme group= 34 (9.7%) Non-treatment programme group= 91 (23.6%) P<0.001 i.e. significant difference Reamputation rate after 5 year follow up Treatment programme group= 11 of 350 patients (3.1%)

Bibliographic reference	**Chiu, C. C., Huang, C. L., Weng, S. F., Sun, L. M., Chang, Y. L., & Tsai, F. C. (2011). A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. Journal of Plastic, Reconstructive & Aesthetic Surgery, 64(7), 867-872.**
	Non-treatment programme group= 28 (7.3%) Odds ratio of likelihood of reamputation= 0.425 95% CI 0.11-1.65) P= 0.204 i.e. no significant difference Level of amputation Treatment programme group= toe 92%, below knee 7%, above knee 1% Non-treatment programme group= toe 63%, below knee 25%, above knee 12% Health related quality of life Not reported
Source of funding	Chi Mei Foundation Hospital Grant
Comments	This study showed a significant reduction in the rate of amputations. For patients at stage D, the hospital stay in the non intervention group was longer than in those treated under a multidisciplinary team with treatment algorithm and care pathway.

Table 79: Cahn 2014

Bibliographic reference	**Cahn, A., Elishuv, O., & Olshtain-Pops, K. (2014). Establishing a multidisciplinary diabetic foot team in a large tertiary hospital: a Workshop. Diabetes/metabolism research and reviews.**
Study type	Observational, retrospective study
Study quality	Summary Location: Israel, a large tertiary care hospital Intervention: A diabetic foot unit within the orthopaedics department was gradually established allowing multidisciplinary team members lead by an endocrinologist and orthopaedic foot surgeon to target appropriate patients. An ambulatory day care unit was opened up to enable better follow up post discharge. Comparison: Pre establishment of the multidisciplinary diabetic foot team. Patients were typically hospitalised in the orthopaedics department and then were treated by physicians expert in foot surgery, vascular surgery and interventional radiology departments or skin grafts and surgical flaps in the plastic surgery department. Occasionally they were admitted to the medical or dermatological departments. Different departments provided consultations as needed however were not working together and no protocol was adhered to. Consultations were often not requested or not performed in a timely manner. Population: Patient records with the diagnosis of diabetic foot or amputation who were hospitalised 2010-2011. 93 patients were treated in 2010 and 101 in 2011.

<table>
<tr><th>Bibliographic reference</th><th>Cahn, A., Elishuv, O., & Olshtain-Pops, K. (2014). Establishing a multidisciplinary diabetic foot team in a large tertiary hospital: a Workshop. Diabetes/metabolism research and reviews.</th></tr>
<tr><td></td><td>Outcome: amputation</td></tr>
<tr><td>Number of patients</td><td>Total n= 194

2010= 93
2011= 101</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Patient records with the diagnosis of diabetic foot or amputation who were hospitalised 2010-2011

Exclusion:
Not stated

Baseline characteristics:

<table>
<tr><td></td><td>2010</td><td>2011</td></tr>
<tr><td>n</td><td>93</td><td>101</td></tr>
<tr><td>Male %</td><td>74</td><td>75</td></tr>
<tr><td>Age (average)</td><td>67.95</td><td>65.01</td></tr>
<tr><td>Chronic renal failure %</td><td>45</td><td>54</td></tr>
<tr><td>Dialysis %</td><td>20</td><td>17</td></tr>
<tr><td>Ischaemic heart disease %</td><td>58</td><td>49</td></tr>
<tr><td>Wagner %
1-2
3
4-5</td><td>
15
34
51</td><td>
14
32
54</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>A diabetic foot unit within the orthopaedics department was gradually established allowing multidisciplinary team members lead by an endocrinologist and orthopaedic foot surgeon to target appropriate patients. An ambulatory day care unit was opened up to enable better follow up post discharge.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Cahn, A., Elishuv, O., & Olshtain-Pops, K. (2014). Establishing a multidisciplinary diabetic foot team in a large tertiary hospital: a Workshop. Diabetes/metabolism research and reviews.</th></tr>
<tr><td>Comparison</td><td>Pre establishment of the multidisciplinary diabetic foot team. Patients were typically hospitalised in the orthopaedics department and then were treated by physicians expert in foot surgery, vascular surgery and interventional radiology departments or skin grafts and surgical flaps in the plastic surgery department. Occasionally they were admitted to the medical or dermatological departments. Different departments provided consultations as needed however were not working together and no protocol was adhered to. Consultations were often not requested or not performed in a timely manner.</td></tr>
<tr><td>Length of follow up</td><td>2 year observation period</td></tr>
<tr><td>Location</td><td>Israel</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
Not reported

Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes
Not reported

Length of hospital stay
Not reported

Rates and extent of amputation

<table>
<tr><td></td><td>2010 (n=93)</td><td>2011 (n=101)</td><td>P value</td></tr>
<tr><td>Major amputations</td><td>34</td><td>19</td><td>0.03</td></tr>
<tr><td>Minor amputations</td><td>26</td><td>29</td><td>NS</td></tr>
<tr><td>Percentage amputations major (major/total)</td><td>56.7%</td><td>39.6%</td><td>0.0748</td></tr>
</table>

Health related quality of life</td></tr>
</table>

Bibliographic reference	Cahn, A., Elishuv, O., & Olshtain-Pops, K. (2014). Establishing a multidisciplinary diabetic foot team in a large tertiary hospital: a Workshop. Diabetes/metabolism research and reviews.
	Not reported
Source of funding	None stated
Comments	This study showed a significant reduction in the rate of major amputations in those treated under a multidisciplinary team with protocol.

Table 80: Williams 2012

Bibliographic reference	Williams, D. T., Majeed, M. U., Shingler, G., Akbar, M. J., Adamson, D. G., & Whitaker, C. J. (2012). A diabetic foot service established by a department of vascular surgery: an observational study. Annals of vascular surgery, 26(5), 700-706.
Study type	Observational, prospective study
Study quality	Summary Location: UK, a department of vascular surgery Intervention: 1) The provision of rapid access referral pathways for severe diabetic foot disease, facilitating early assessment by a vascular team with an interest in wound healing (see paper for details) 2) weekly podiatry, orthotic and vascular clinics running concurrently, optimising multidisciplinary communication and management 3) Co-ordinated fortnightly vascular or podiatry clinical reviews for patients requiring intensive outpatient management 4) all patients with diabetic foot disease requiring inpatient management admitted where possible to the vascular ward Comparison: Before 2006 there were no clear guidelines for diabetic foot disease referrals to secondary care in the region. Patients with worsening or severe tissue loss/necrosis, evidence of local abscess or ulceration with cellulitis, or tissue loss with possible vascular insufficiency (Wagner stages 3-5) were commonly referred to hospital physicians with some referrals to other surgical specialties including vascular surgery. For the majority of patients subsequent referral to vascular surgery occurred if and when it seemed appropriate and patients would remain under the care of the physicians. Procedural intervals inherent to referrals and patients remaining on medical wards create potential pitfalls in appreciating disease severity and deterioration with increased delays before surgical assessment is made. Population: diabetic patients in whom critical peripheral arterial disease is suspected. Outcome: Major amputation, operating room minor amputation and wound procedures, ward admission and length of stay, vascular surgical intervention, endovascular intervention.
Number of patients	Total not given (prevalence study and results given per 10,000 of the diabetic population)

Bibliographic reference	**Williams, D. T., Majeed, M. U., Shingler, G., Akbar, M. J., Adamson, D. G., & Whitaker, C. J. (2012). A diabetic foot service established by a department of vascular surgery: an observational study. Annals of vascular surgery, 26(5), 700-706.**
Patient characteristics	Inclusion: Data collected on major and minor lower limb amputations, surgical debridements, vascular interventions, admission rates, length of stay and the proportion of patients admitted by the diabetic foot team. Exclusion: Not stated Baseline characteristics: Not provided
Intervention	1) The provision of rapid access referral pathways for severe diabetic foot disease, facilitating early assessment by a vascular team with an interest in wound healing (see paper for details) 2) weekly podiatry, orthotic and vascular clinics running concurrently, optimising multidisciplinary communication and management 3) Co-ordinated fortnightly vascular or podiatry clinical reviews for patients requiring intensive outpatient management 4) all patients with diabetic foot disease requiring inpatient management admitted where possible to the vascular ward
Comparison	Before 2006 there were no clear guidelines for diabetic foot disease referrals to secondary care in the region. Patients with worsening or severe tissue loss/necrosis, evidence of local abscess or ulceration with cellulitis, or tissue loss with possible vascular insufficiency (Wagner stages 3-5) were commonly referred to hospital physicians with some referrals to other surgical specialties including vascular surgery. For the majority of patients subsequent referral to vascular surgery occurred if and when it seemed appropriate and patients would remain under the care of the physicians. Procedural intervals inherent to referrals and patients remaining on medical wards create potential pitfalls in appreciating disease severity and deterioration with increased delays before surgical assessment is made.
Length of follow up	6 year observational period
Location	United Kingdom
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Resource use and costs (including referral rates) Not reported

Bibliographic reference	**Williams, D. T., Majeed, M. U., Shingler, G., Akbar, M. J., Adamson, D. G., & Whitaker, C. J. (2012). A diabetic foot service established by a department of vascular surgery: an observational study. Annals of vascular surgery, 26(5), 700-706.**

Rates of hospital admission for foot problems resulting from diabetes

Admissions to vascular ward for patients with diabetes and lower limb disease

	2004/2005	2005/2006	**2006/2007**	2007/2008	2008/2009	2009/2010
Number	36	63	**59**	58	47	34

Length of hospital stay

Median length of stay for patients with diabetic foot disease. No significant difference in the median length of stay was seen before and after the introduction of the foot service. (P= 0.422)

	2004	2005	**2006**	2007	2008	2009
Length of stay (days)	16	18	**17**	13	14	15.5

Rates and extent of amputation

Major amputations rate (above and below knee amputations)

A yearly major amputation rate that peaked in 2005 at 23 (24.7/10000) decreased in 2009 to 1 (1.07/10000).
Relative risk= 0.043 (95% CI 0.006-0.322) i.e. significant difference

Amputations	2004	2005	**2006**	2007	2008	2009	2004-2005	2006-2009
Major								
Diabetic	18	23	**11**	8	7	1	41	27

Bibliographic reference	**Williams, D. T., Majeed, M. U., Shingler, G., Akbar, M. J., Adamson, D. G., & Whitaker, C. J. (2012). A diabetic foot service established by a department of vascular surgery: an observational study. Annals of vascular surgery, 26(5), 700-706.**

Non diabetic	7	12	**5**	7	8	3	19	23
Percent	72	66	**69**	53	47	25	68	54

Minor amputations rate (surgical debridements, partial foot amputations, toe amputations)

Amputations	2004	2005	**2006**	2007	2008	2009	2004-2005	2006-2009
Minor								
Diabetic	32	49	**50**	31	13	7	81	101
Non diabetic	2	3	**5**	6	10	6	5	27
Percent	94	94	**91**	84	57	54	91	79

Health related quality of life
Not reported

Source of funding	Not stated
Comments	This study showed that the integration of a vascular unit with community care has been associated with improved outcomes for patients with diabetic foot disease. Improvements were not related to increased number of vascular procedures or hospitalisations, but did coincide with a greater proportion of patients attending the foot unit. The referral of patients to the unit facilitates the rapid management of severe disease, reducing delays deleterious to outcomes.

Table 81: Setacci 2013

Bibliographic reference	**Setacci, C., Sirignano, P., Mazzitelli, G., Setacci, F., Messina, G., Galzerano, G., & de Donato, G. (2013). Diabetic foot: surgical approach in emergency. International journal of vascular medicine, 2013.**
Study type	Observational, prospective study
Study quality	Summary

<table>
<tr><th>Bibliographic reference</th><th>Setacci, C., Sirignano, P., Mazzitelli, G., Setacci, F., Messina, G., Galzerano, G., & de Donato, G. (2013). Diabetic foot: surgical approach in emergency. International journal of vascular medicine, 2013.</th></tr>
<tr><td></td><td>Location: Italy, centre of vascular and endovascular surgery
Intervention: application of new shared protocol
1) early diagnosis with a 24 hour on call diabetic foot team to perform a duplex scan and to identify an infective disease if present 2) urgent treatment of severe foot infection with aggressive surgical debridement 3) early revascularisation within 24 hours 4) definitive treatment, wound healing, reconstructive surgery, orthosis.
Comparison: 3 years prior to the application of the protocol.
Population: patients with diabetic foot infections and critical limb ischaemia
Outcome: Major amputation</td></tr>
<tr><td>Number of patients</td><td>Total n= 375</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Diabetic foot infections and critical limb ischaemia

Exclusion:
Non stated

Baseline characteristics:

<table>
<tr><td></td><td>Standard care</td><td>Intervention period</td></tr>
<tr><td>Mean age</td><td>75.6</td><td>76.7</td></tr>
<tr><td>Male</td><td>81.7%</td><td>78.6%</td></tr>
<tr><td>Coronary artery disease</td><td>63%</td><td>64.4%</td></tr>
<tr><td>COPD</td><td>35.9%</td><td>38.7%</td></tr>
<tr><td>Renal failure</td><td>57.8%</td><td>58.4%</td></tr>
<tr><td>Hypertension</td><td>88.5%</td><td>91.8%</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>All patients were revascularised within 24 hours of debridement under the protocol</td></tr>
<tr><td>Comparison</td><td>The mean time between debridement and revascularisation was 3 days (range 1-7 days)</td></tr>
<tr><td>Length of follow up</td><td>6 months of follow up</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and</td><td></td></tr>
</table>

Bibliographic reference	Setacci, C., Sirignano, P., Mazzitelli, G., Setacci, F., Messina, G., Galzerano, G., & de Donato, G. (2013). Diabetic foot: surgical approach in emergency. International journal of vascular medicine, 2013.
effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Resource use and costs (including referral rates) Not reported Rates of hospital admission for foot problems resulting from diabetes Not reported Rates and extent of amputation Major amputations rate (above and below knee amputations) Major amputation rate at 6 months Intervention group= 24.6% Comparison group= 39.6% Hazard ratio= 0.58, P value = 0.0024 Health related quality of life Number of deaths at 6 months (mortality) Intervention group= 9 (4.4%) Comparison group= 22 (11%) Hazard ratio= 0.41, P value = 0.0224
Source of funding	None declared
Comments	This study showed a reduction of major amputations associated with the implementation of an interdisciplinary protocol within a centre of vascular and endovascular surgery

Table 82: Elgzyri 2014

Bibliographic reference	**Elgzyri, T., Larsson, J., Nyberg, P., Thörne, J., Eriksson, K. F., & Apelqvist, J. (2014). Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. European Journal of Vascular and Endovascular Surgery, 48(4), 440-446.**
Study type	Observational, prospective study
Study quality	Summary Location: Sweden, a multidisciplinary foot centre Intervention: patients were treated with a standardised preset protocol in and out of hospital until healing. Team consisted of a diabetologist, an orthopaedic surgeon, an orthotist, a podiatrist and a registered nurse educated in diabetes. Comparison: Time to revascularisation was calculated from the first presentation to the diabetic foot clinic. Patients who were treated within 8 weeks were compared to those who had treatment delayed. Population: diabetic patients with ischaemic foot ulcer. Outcome: time to revascularisation as a factor affecting healing/amputation
Number of patients	Total n= 475
Patient characteristics	Inclusion: Diabetes mellitus Foot ulcer (Wagner grade 1-5, at or below the ankle) and a systolic toe pressure <45 mmHg and/or systolic ankle pressure <80 mmHg Patients with non-palpable foot pulses with an ulcer Wagner grade 4-5 or pain at rest Exclusion: Non stated Baseline characteristics: General characteristics Male: 60% Age, y: 74 (66-80) Diabetes duration, y: 15 (10-24) HbA1c (%) 7.8 (6.2-9.0) Nephropathy: 38%

Bibliographic reference	**Elgzyri, T., Larsson, J., Nyberg, P., Thörne, J., Eriksson, K. F., & Apelqvist, J. (2014). Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. European Journal of Vascular and Endovascular Surgery, 48(4), 440-446.**
	Wagner grade ≥ 3: 21%
Intervention	Patients were treated with a standardised preset protocol in and out of hospital until healing. Team consisted of a diabetologist, an orthopaedic surgeon, an orthotist, a podiatrist and a registered nurse educated in diabetes.
Comparison	Time to revascularisation was calculated from the first presentation to the diabetic foot clinic. Patients who were treated within 8 weeks were compared to those who had treatment delayed.
Length of follow up	Median follow up time was 10 months (5-16 months)
Location	Sweden
Outcomes measures and effect size	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Not reported Resource use and costs (including referral rates) Not reported Rates of hospital admission for foot problems resulting from diabetes Not reported Length of hospital stay Not reported Rates and extent of amputation Survival analysis for factors affecting healing without major amputation Univariate analysis Time to revascularisation ≤8 weeks 1.96 (1.52-2.52) P value <0.001 Health related quality of life Not reported

Bibliographic reference	**Elgzyri, T., Larsson, J., Nyberg, P., Thörne, J., Eriksson, K. F., & Apelqvist, J. (2014). Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. European Journal of Vascular and Endovascular Surgery, 48(4), 440-446.**
Source of funding	Research Funds Skane University Hospital, Malmo, the Skane Research Foundation, and Thelma Zoega's Foundation, Helsingborg Sweden.
Comments	This study showed that time to revascularisation ≤8 weeks (from the time of presentation to the centre to revascularisation) was a significant factor in predicting healing without major amputation

Table 83: Rubio 2014

Bibliographic reference	**Rubio, J. A., Aragón-Sánchez, J., Jiménez, S., Guadalix, G., Albarracín, A., Salido, C., ... & Álvarez, J. (2014). Reducing Major Lower Extremity Amputations After the Introduction of a Multidisciplinary Team for the Diabetic Foot. The international journal of lower extremity wounds, 13(1), 22-26.**
Study type	Observational, prospective study
Study quality	Summary Location: Spain, hospital based multidisciplinary team Intervention: A multidisciplinary diabetic foot unit, team for the diagnosis and treatment of diabetic foot disease. Coordinated by an endocrinologist and a podiatrist. Introduced in march 2008. Comparison: Comparing the incidence rates of amputation before and after establishing the multidisciplinary team over a 9 year period. Population: 374 amputations in people with diabetes were performed in the health care area during the period of study. Outcome: rate of lower extremity amputation
Number of patients	Total n= 374 amputations in patients with diabetes (data separable)
Patient characteristics	Inclusion: Lower extremity amputations performed at any Madrid hospital between 2001 and 2011. (data separable for diabetes) Exclusion: None stated Baseline characteristics: For the diabetic population Age, mean: 70.7 ± 13.2 Men: 68% Women: 32%
Intervention	A multidisciplinary diabetic foot unit, team for the diagnosis and treatment of diabetic foot disease. Coordinated by an endocrinologist and a podiatrist. Introduced in march 2008.

<table>
<tr><th>Bibliographic reference</th><td>Rubio, J. A., Aragón-Sánchez, J., Jiménez, S., Guadalix, G., Albarracín, A., Salido, C., ... & Álvarez, J. (2014). Reducing Major Lower Extremity Amputations After the Introduction of a Multidisciplinary Team for the Diabetic Foot. The international journal of lower extremity wounds, 13(1), 22-26.</td></tr>
<tr><td>Comparison</td><td>Comparing the incidence rates of amputation before and after establishing the multidisciplinary team over a 9 year period.</td></tr>
<tr><td>Length of follow up</td><td>10 year observation period, data reported in incidence per 100,000 inhabitants per year</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
Not reported

Resource use and costs (including referral rates)
Not reported

Rates of hospital admission for foot problems resulting from diabetes
Not reported

Length of hospital stay
Not reported

Rates and extent of amputation
Incidence of lower extremity amputations in diabetic population per 100000 inhabitants and per year (mean (95% confidence interval))

<table>
<tr><td>Study period</td><td>All</td><td>Minor</td><td>Major</td></tr>
<tr><td>2001-2011 (total)</td><td>10.8 (9.1-12.5)</td><td>5.5 (4.2-6.7)</td><td>5.3 (4.3-6.3)</td></tr>
<tr><td>2001-2007 (pre MDT)</td><td>11.8 (9.3-14.3)</td><td>5.7 (3.9-7.5)</td><td>6.1 (4.9-7.2)</td></tr>
<tr><td>2008-2011 (post MDT)</td><td>9.1 (7.6-10.6)</td><td>5.0 (2.3-7.8)</td><td>4.0 (2.6-5.5)</td></tr>
<tr><td>P value</td><td>0.090</td><td>0.732</td><td>0.020</td></tr>
</table>

Health related quality of life
Not reported</td></tr>
</table>

Bibliographic reference	**Rubio, J. A., Aragón-Sánchez, J., Jiménez, S., Guadalix, G., Albarracín, A., Salido, C., ... & Álvarez, J. (2014). Reducing Major Lower Extremity Amputations After the Introduction of a Multidisciplinary Team for the Diabetic Foot. The international journal of lower extremity wounds, 13(1), 22-26.**
Source of funding	No financial support received
Comments	This study showed a significantly reduced major amputation rate after implementation of the multidisciplinary team approach for managing diabetic foot disease

G.15 Review question 15 full evidence tables

Table 84: Chantelau 2013

Bibliographic reference	**Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.*Swiss Med Wkly*, *143*, w13831.**
Study type	Retrospective cohort
Study quality	Summary Population: Germany, those with possible osteomyelitis were not included however this could very well be an important subgroup of patients Intervention: Magnetic resonance imaging, MRI Comparison: diagnosis based on Xray cross-checked by MRI, diagnosis based on Xray not cross-checked by MRI Outcome: medical history, timing of diagnosis and treatment, regional distribution of skeletal damage, foot deformity, healing without skeletal deformity, duration of treatment, adverse effects, follow up morbidity. 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Patients were treated at the same clinic, data was taken retrospectively, some were checked by X-ray first then cross-checked by MRI, some were investigated by Xray first and were neglected to be cross-checked by MRI and others were only investigated by MRI. It is unclear if there were any fundamental differences between these groups of patients to account for the difference of diagnostic approach, participants formed a natural cohort based on the physicians decision on investigation for the suspected Charcot patient. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? Data was retrospective and there was no attempt to balance the comparison groups for potential confounders 3. The groups were comparable at baseline, including all major confounding factors?

Bibliographic reference	**Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.*Swiss Med Wkly*, *143*, w13831.**
	Unclear if groups were comparable at baseline, since characteristics were not compared between those who received X-ray instead of MRI as primary investigation 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if the comparison groups received the same care. As this was a retrospective cohort study it may have been difficult to prove exactly what care was given in each case. Although all participants were treated in the same diabetic clinic, this took place over a period of 12 years and care may have varied during this time. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Length of follow up is inseparable from the outcome of interest, time to remission. Participants were followed up until transition to shoes (remission). 8. Groups were comparable for intervention completion? Unclear if groups were comparable for intervention completion 9. The groups were comparable with respect to the availability of outcome data? Groups were comparable for availability of outcome data as no loss to follow up was reported. Unclear for how many participants there was no data available. 10. The study had an appropriate length of follow up? Length of follow up was until transition to shoes from total contact cast. This is appropriate for the outcome of interest. 11. The study used a precise definition of outcome? The study used precise definitions of treatment, disease, investigations and outcomes 12. A valid and reliable method was used to determine the outcome? A valid and reliable method was not necessarily used to determine the outcome as data was taken retrospectively with no quality assessment possible 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors .
Number of patients	Total= 71 cases, 59 participants

<table>
<tr><td>Bibliographic reference</td><td>Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.Swiss Med Wkly, 143, w13831.</td></tr>
<tr><td></td><td>Cases diagnosed as Charcot disease stage 0= 27
Cases diagnosed as Charcot disease stage 1= 44</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: Germany

Inclusion:
Cases treated and followed up by the diabetic foot clinic until complete healing of the acute Charcot foot

Exclusion:
Coexisting plantar ulceration
Possible skeletal septic pathology

Baseline characteristics:

<table>
<tr><td>Characteristics</td><td>Type 1 diabetes mellitus</td><td>Type 2 diabetes mellitus</td></tr>
<tr><td>N</td><td>24</td><td>35</td></tr>
<tr><td>Age, y (95% Confidence interval)</td><td>55</td><td>62</td></tr>
<tr><td>Male/female</td><td>8/16</td><td>22/13</td></tr>
<tr><td>BMI (kg/m²)</td><td>24.6</td><td>30.9</td></tr>
<tr><td>Neuropathy
Retinopathy
Nephropathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>32</td><td>10</td></tr>
<tr><td>Type of diabetes
Type 1
Type 2</td><td>As above</td><td>As above</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Cases of acute Charcot foot</td><td>33</td><td>38</td></tr>
<tr><td>Cases per patient</td><td>1.4</td><td>1.1</td></tr>
<tr><td>Cases stage 1/0</td><td>13/20</td><td>14/24</td></tr>
<tr><td>End stage renal disease</td><td>3</td><td>0</td></tr>
<tr><td>Distal pedal pulses present</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Magnetic resonance imaging, MRI</td></tr>
</table>

Bibliographic reference	**Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.*Swiss Med Wkly*, *143*, w13831.**
	Standard care involved complete offloading and immobilisation of the affected foot immediately (wheelchair or hospital bed), Patients were then provided with a bivalve removable total contact cast, although a small minority received a prefabricated polypropylene ankle-foot orthosis
Comparison	X-ray as primary method of investigation followed by magnetic resonance imaging Standard care involved complete offloading and immobilisation of the affected foot immediately (wheelchair or hospital bed), Patients were then provided with a bivalve removable total contact cast, although a small minority received a prefabricated polypropylene ankle-foot orthosis
	X-ray as primary method of investigation with no follow up by magnetic resonance imaging Standard care involved complete offloading and immobilisation of the affected foot immediately (wheelchair or hospital bed), Patients were then provided with a bivalve removable total contact cast, although a small minority received a prefabricated polypropylene ankle-foot orthosis
Length of follow up	Length of follow up was variable
Location	Germany
Outcomes measures and effect size	The time from onset of symptoms until institution of total contact casting was not found to be significantly affected by stage of disease process. However it was found to be significantly affected by choice of investigation: Median time from symptom onset to treatment Received MRI investigation first (n=50)= received casting after 1 month Received X-ray investigation first, cross-checked by MRI (n=21)= received casting after 2.5 months P value= <0.02 i.e. significant difference Received only X-ray investigation (n=13)= received casting after 4.5 months Detection of stage 0 Charcot foot Received MRI investigation first (n=19)= 19 cases detected Received X-ray investigation first, cross-checked by MRI (n=8)= 8 cases detected Received only X-ray investigation (n=8)= 0 cases detected Median time from symptom onset to treatment for stage 0 Charcot foot

Bibliographic reference	**Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.*Swiss Med Wkly*, *143*, w13831.**
	Received MRI investigation first (n=19)= received casting after 1 month Received X-ray investigation first, cross-checked by MRI (n=8)= received casting after 0.5 months Received only X-ray investigation (n=8)= received casting after 5 months
Source of funding	Study declares no source of support, no conflict of interest
Comments	

Table 85: Chantelau 2006

Reference	**Chantelau, E., & Poll, L. W. (2006). Evaluation of the diabetic Charcot foot by MR imaging or plain radiography-an observational study. *Experimental and clinical endocrinology & diabetes*, *114*(08), 428-431.**
Patient characteristics	**Population:** retrospective case series of the charts of participants with diabetic charcot neuroarthropathy **Number of patients included:** 20 participants, 26 Charcot feet **Number of patients excluded:** data was only reported for those with a final diagnosis of charcot foot **Mean age:** 59 years (median) **Males/females:** 11 men, 9 women (charcot group) **Country:** Germany **Other comments:** Results were obtained by having investigations examined by expert in radiology blinded to the clinical findings of the participants. It is unclear if the radiologists were blinded to the final diagnosis of the participants.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? A random selection of participants was not enrolled, patients were taken retrospectively from the medical records of a specialised diabetic foot clinic 2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? Unclear if any participants were inappropriately excluded. Exclusion criteria included participants with past or present foot ulcer,

	osteomyelitis, bone resections or amputations. This would exclude many participants who may be of interest. **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? It is unclear if investigators of the MRI were unaware of the findings of the plain radiograph 5) If a threshold was used, was it pre-specified? No threshold appears to have been pre-specified however there was some qualitative assessment involved in the interpretation of the radiographical results which could be user dependent. **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? The reference standard was based on clinical and radiological findings, data was taken retrospectively with the true diagnosis likely revealed over time. 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were not interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was likely an appropriate interval between index test and reference standard however this is unclear. 9) Did all patients receive the same reference standard? All participants received the same reference standard 10) Were all patients included in the analysis? Unclear if all participants with Charcot foot who fitted the inclusion criteria were included
Reference standard	**Reference standard:** The reference standard was based on clinical and radiological findings, undefined. **Details:** Unclear **Number unable to participate in the reference test :** Nil
Index test(s)	**(1) Plain Radiography** **Test:** a board qualified radiologist blinded to the clinical findings qualitatively and quantitvely analysed all the X-rays. **Number unable to participate in the index test and reasons given:** Not stated
	(2) Magnetic resonance imaging **Test:** a board qualified radiologist blinded to the clinical findings qualitatively and quantitvely analysed all the MRIs. **Number unable to participate on the index test and reasons given:** Not stated
Results	At stage 0, number of Charcot feet showing clinical signs of Charcot foot (n=7) Stress bone injuries, oedema of adjacent soft tissues and joint effusion MRI findings: 7 of 7 feet X-ray findings: 0 of 7 feet (normal bone anatomy) P value= 0.02

	At stage I and II, (n=14) MRI confirmed X-ray findings. MRI additionally diagnosed bone oedema, soft tissue oedema and joint effusion At stage III, MRI confirmed X-ray findings, additionally diagnosing residual bone oedema and joint effusion. At stage 0, median number of affected bones disclosed Number of affected bones and joints per foot MRI findings: 4 affected bones, 5 affected joints X-ray findings: 0 affected bones, 0 affected joints P value= 0.0001 At stage I and II, median number of affected bones disclosed Number of affected bones and joints per foot MRI findings: 5 affected bones, 5 affected joints X-ray findings: 5 affected bones, 5 affected joints Non significant At stage III, median number of affected bones disclosed Number of affected bones and joints per foot MRI findings: 8 affected bones, 5 affected joints X-ray findings: 8 affected bones, 5 affected joints Non significant

Table 86: Chantelau 2005

Reference	**Chantelau, E. (2005). The perils of procrastination: effects of early vs. delayed detection and treatment of incipient Charcot fracture. *Diabetic medicine*, *22*(12), 1707-1712.**
Patient characteristics	**Population:** retrospective case series of the charts of participants with diabetic charcot neuroarthropathy seen in one university hospital **Number of patients included:** 24 participants **Number of patients excluded:** Not stated

	Mean age: In the early treatment group= 61 years median, in delayed treatment group= 52 years median **Males/females:** In the early treatment group= 5/6, in delayed treatment group= 8/5 **Country:** Germany **Other comments:** Data was drawn retrospectively from database of participants who had undetectable fractures on X-ray after the onset of symptoms. Outcomes are drawn from those treated at a later stage of Charcot compared to those treated at an earlier stage, however it is hard to say how many participants with incidious Charcot foot would have necessarily progressed to overt Charcot foot. By their own nature more severe forms of Charcot will result in worse deformities and progression to fracture and will have been diagnosed later than incidious forms. A test and treat RCT approach would give more valuable information on the best use of investigations.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? A random selection of participants was not enrolled, patients were taken retrospectively from the medical records of a specialised diabetic foot clinic 2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? Unclear if any participants were inappropriately excluded. Inclusion criteria only included participants who had had undetectable fractures on X-ray after the onset of symptoms. Results therefore cannot give a true effect of the sensitivity of the X-ray test for early stage acute Charcot foot. **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? Investigators were not blinded to the results of other investigations or clinical findings 5) If a threshold was used, was it pre-specified? No threshold appears to have been pre-specified **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? The reference standard was based on clinical and radiological findings, data was taken retrospectively with the true diagnosis likely revealed over time. 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were not interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was likely an appropriate interval between index test and reference standard however this is unclear. 9) Did all patients receive the same reference standard? All participants received the same reference standard

	10) Were all patients included in the analysis? Unclear if all participants with Charcot foot who fitted the inclusion criteria were included
Reference standard	**Reference standard:** The reference standard was the outcomes of those with later diagnosis and treatment of Charcot foot after fractures appeared on plain radiograph (Overt Charcot foot) (n=13) **Details:** treatment with total contact cast and offloading **Number unable to participate in the reference test :** Not stated
Index test(s)	**(1) Plain Radiography:** The outcomes of those with earlier diagnosis and treatment of Charcot foot before fractures appeared on plain radiograph (established on the basis of clinical symptoms plus bone abnormalities on X-ray e.g. osteoarthritis, MRI (bone oedema), CT (hidden line fractures), or bone technetium scan (e.g. increased isotope uptake). Incipient Charcot foot (n=11) **Test:** further details unclear, treatment with total contact cast and offloading **Number unable to participate in the index test and reasons given:** Not stated
Results	Number misdiagnosed prior to treatment Overt Charcot foot group= 13 of 13 participants Incipient Charcot foot group= 6 of 11 participants P value= 0.013 i.e. significant difference (although this finding is hardly surprising it shows that misdiagnosis could be a significant reason for delayed treatment) Time from onset of symptoms until application of total contact casting Overt Charcot foot group= 3 months (median) Incipient Charcot foot group=1.0 months (median) P value= >0.05 i.e. not significant Time from application of total contact casting to healing Healing defined as absence of clinical signs of inflammation accompanied by bone remodelling on plain radiograph, or absence of inflammation in those without fracture together with absence of complete fracture on repeat X-ray, MRI or bone scan. Overt Charcot foot group= 5.5 months (median) Incipient Charcot foot group=3 months (median) P value= >0.05 i.e. not significant Progression to definite fractures of either the tarsometatarsal joints or of the talonavicular joint Overt Charcot foot group= 13 of 13 participants Incipient Charcot foot group=1 of 11 participants P value= <0.001 i.e. significant difference

	Progression to gross foot deformity Plano-valgus-abductus foot, rocker bottom foot, extremely flat foot Overt Charcot foot group= 12 of 13 participants Incipient Charcot foot group=1 of 11 participants P value= <0.001 i.e. significant difference Types of investigations performed Proportion of participants with MRI, technetium scan, or CT scan Overt Charcot foot group= 2 of 13 participants Incipient Charcot foot group=8 of 11 participants P value= <0.012 i.e. significant difference

Table 87: Basu 2007

Reference	**Basu, S., Chryssikos, T., Houseni, M., Malay, D. S., Shah, J., Zhuang, H., & Alavi, A. (2007). Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection?. *Nuclear medicine communications*, *28*(6), 465-472.**
Patient characteristics	**Population:** Retrospective review of the results from a prospective trial designed to investigate the usefulness of FDG PET imaging in the complicated diabetic foot. **Number of patients included:** 63 participants were included. These were split into 4 groups. Groups A) 17 participants with a clinical diagnosis of Charcot's neuroarthropathy B) 21 participants with uncomplicated diabetic foot C) 5 participants with a proven osteomyelitis secondary to complicated diabetic foot D) 20 non-diabetic participants with normal lower extremities. **Number of patients excluded:** data was only reported for those with a final diagnosis of osteomyelitis and charcot foot **Mean age:** 59.4 ± 8.6 years (charcot group) **Males/females:** 11 men, six women (charcot group) **Country:** USA **Other comments:** Results were obtained by having investigations examined by experts blinded to the participants final diagnosis and comparing their findings with the results of follow up.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? Unclear if a random selection of participants was enrolled, patients were taken from an ongoing prospective trial for which no further details were provided.

	2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? No there were many other participants for which the results were not provided, possibly due to investigations not having been performed. These could have given us more information on the rates of false positives between patient groups. **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? Investigators of both the MRI scan and the FDG PET scan were blinded to the final diagnosis of the participants 5) If a threshold was used, was it pre-specified? No threshold appears to have been pre-specified however there was some qualitative assessment involved in the interpretation of the radiographical results which could be user dependent. **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? The reference standard was either the surgical and histopathological findings or the results of long term follow up in those who did not undergo surgery. Both are likely to correctly reveal the true diagnosis. 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were not interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was likely an appropriate interval between index test and reference standard however this is unclear. 9) Did all patients receive the same reference standard? Not all participants received the same reference standard. The reference standard was either the surgical and histopathological findings or the results of long term follow up in those who did not undergo surgery 10) Were all patients included in the analysis? All participants with Charcot foot or osteomyelitis as final diagnosis were included in the final analysis.
Reference standard	**Reference standard:** Surgical and histological findings, or the results of long term follow up (undefined) **Details:** All specimens including debrided tissue and bone fragments from surgery were examined by standard staining techniques and microbiological examination results **Number unable to participate in the reference test :** Not stated
Index test(s)	**(1) FDG PET image acquisition and analysis** **Test:** experienced nuclear physicians blinded to the radiological data and final diagnosis qualitatively and quantitvely analysed all PET images A dedicated whole body full ring GSO crystal based PET instrument was used with 5.2 MBq of FDG per kg of bodyweight **Number unable to participate in the index test and reasons given:** Not stated
	(2) Magnetic resonance imaging

	Test: Interpreted by experienced radiologists of the institute for structural abnormalities of the feet blinded to final diagnosis and FDG PET results 1.5 T magnet **Number unable to participate on the index test and reasons given:** Not stated
Results	**FDG PET- for those diagnosed with Charcot disease (n=17)** results calculated from data provided

		Reference test		
		+	**-**	**Total**
Index test	**+**	16 (TP)	0 (FP)	16
	-	0 (FN)	6 (TN)	6
	Total	16	6	22

Sensitivity: 1.000 (95%CI: 0.969, 1.000); Specificity: 1.000 (95%CI: 0.917, 1.000)
LR+: 13.588 (95%CI: 0.955, 193.311); LR−: 0.032 (95%CI: 0.002, 0.482)

MRI- for those diagnosed with Charcot disease (n=17)

		Reference test		
		+	**-**	**Total**
Index test	**+**	11 (TP)	0 (FP)	11
	-	5 (FN)	6 (TN)	11
	Total	16	6	22

Sensitivity: 0.688 (95%CI: 0.429, 0.946); Specificity: 1.000 (95%CI: 0.917, 1.000)
LR+: 9.471 (95%CI: 0.653, 137.315); LR−: 0.313 (95%CI: 0.151, 0.646)

Table 88: Moura-Neto 2012

Reference	**Moura-Neto, A., Fernandes, T. D., Zantut-Wittmann, D. E., Trevisan, R. O., Sakaki, M. H., Santos, A. L. G., ... & Parisi, M. C. R. (2012). Charcot foot: skin temperature as a good clinical parameter for predicting disease outcome.*Diabetes research and clinical practice*, *96*(2), e11-e14.**
Patient characteristics	**Population:** Review of the results from a prospective case series designed to investigate the usefulness of infrared temperature monitoring in the assessment of remission and safe immobilization withdrawal amongst patients presenting with acute Charcot foot **Number of patients included:** 28 **Number of patients excluded:** Not stated

	Mean age: 58.8 years **Males/females:** 14 males, 14 females **Country:** Brazil **Other comments:** There is questionable theory behind testing temperature difference as a suitable parameter for predicting safe withdrawal of immobilisation whilst using temperature difference to diagnose the outcome of relapse. If the investigation is flawed this may affect both the variable tested and the outcome recorded.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? Selection of patients was not random, unclear if consecutive 2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? Unlcear if there were any inappropriate exclusions. Exclusion criteria not clearly stated. **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? Investigators could not have known the results of follow up 5) If a threshold was used, was it pre-specified? A threshold was defined as a temperature difference of less than 2°C between the same spot on the affected and non-affected limb **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? Results of long term follow up would be likely to correctly reveal a relapse. Using a temperature difference between affected and non-affected limb of greater than 2°C to diagnose relapse may not, on its own, be a suitable measure of Charcot relapse. 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were not interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was likely an appropriate interval between index test and reference standard however this is unclear. 9) Did all patients receive the same reference standard? All participants were followed up in the same manner with the same definition or relapse described. 10) Were all patients included in the analysis? No loss to follow up recorded
Reference standard	**Reference standard:** The results of long term follow up (1 year) **Details:** All participants had monthly follow up visits for a year in order to catch any feet presenting with relapse

	Number unable to participate in the reference test : Not stated
Index test(s)	**(1) Infrared skin thermometer (Minitemp, Raytec)** **Test:** skin temperature taken at the same spot on affected and non-affected feet. Temperature difference calculated. **Number unable to participate in the index test and reasons given:** Not stated
Results	Number who progressed to consolidation/remission by 1 year Defined as a temperature difference of less than 2°C, cross checked by radiology for consolidation Remission= 25 No remission= 3 Following withdrawal of immobilisation based on temperature difference, frequency of relapse after 1 year follow up Relapse defined as temperature difference greater than 2°C Number= 0 of 25 participants No other outcomes reported

Table 89: Hopfner 2004

Reference	**Höpfner, S., Krolak, C., Kessler, S., Tiling, R., Brinkbäumer, K., Hahn, K., & Dresel, S. (2004). Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. *Foot & ankle international*, *25*(12), 890-895.**
Patient characteristics	**Population:** Germany**.** Case series of participants with Charcot foot conditions requiring surgical intervention **Number of patients included:** 16 participants **Number of patients excluded:** not stated **Mean age:** 60.1 ± 10 years **Males/females:** 9 men, 7 women **Country:** Germany **Other comments:** Results were obtained by having investigations examined by experts blinded to the participants final diagnosis and other investigations. Results confirmed by surgery.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? Unclear if a random selection of participants was enrolled, or if patients were recruited consecutively

	2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? Unclear **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? Yes 5) If a threshold was used, was it pre-specified? No threshold appears to have been pre-specified **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? The reference standard was the surgical and histopathological findings, these are likely to be accurate 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was an appropriate interval between index test and reference standard and all investigations had to be performed within a week of each other. 9) Did all patients receive the same reference standard? All participants received the same reference standard. 10) Were all patients included in the analysis? Unclear if all participants who could fit the inclusion criteria were included, unclear inclusion criteria.
Reference standard	**Reference standard:** Surgical findings **Details:** Not provided **Number unable to participate in the reference test :** Not stated
Index test(s)	**(1) Ring PET** **Test:** two experienced examiners blinded to the results of the other tests Siemans ECAT EXACT HR **Number unable to participate in the index test and reasons given:** Not stated
	(2) Hybrid PET **Test:** two experienced examiners blinded to the results of the other tests Marconi AXIS y-PET² scanner **Number unable to participate in the index test and reasons given:** Not stated
	(3) Magnetic resonance imaging

Test: two experienced examiners blinded to the results of the other tests

Siemans Harmony scanner (1.0 Tesla field strength)

Number unable to participate on the index test and reasons given: Not stated

Results

Ring PET- number of lesions consistent with Charcot neuroarthropathy (n=39). results calculated from data provided

Lesions defined as 24 osseous lesions with bone detritus without evidence of osteomyelitis; 6 secondary, circumscribed foci of inflammation in adjacent soft tissue with no evidence of infection; 9 lesions with inflammatory tissue along typically affected articulations

		Reference test		
		+	**-**	**Total**
Index test	**+**	37 (TP)	0 (FP)	37
	-	2 (FN)	0 (TN)	2
	Total	39	0	39

Sensitivity: 0.949 (95%CI: 0.867, 1.000); Specificity: NA (95%CI: NA)

LR+: 1.875 (95%CI: 1.720, 2.043); LR−: 0.125 (95%CI: 0.042, 0.372)

Hybrid PET- number of lesions consistent with Charcot neuroarthropathy (n=39). results calculated from data provided

Lesions defined as 24 osseous lesions with bone detritus without evidence of osteomyelitis; 6 secondary, circumscribed foci of inflammation in adjacent soft tissue with no evidence of infection; 9 lesions with inflammatory tissue along typically affected articulations

		Reference test		
		+	**-**	**Total**
Index test	**+**	30 (TP)	0 (FP)	30
	-	9 (FN)	0 (TN)	9
	Total	39	0	39

Sensitivity: 0.769 (95%CI: 0.624, 0.914); Specificity: NA (95%CI: NA)

LR+: 1.525 (95%CI: 1.282, 1.815); LR−: 0.475 (95%CI: 0.277, 0.814)

Magnetic Resonance Imaging, MRI- number of lesions consistent with Charcot neuroarthropathy (n=39). results calculated from data provided (excluding 3 participants with extensive metal artifacts interfering with detection)

Lesions defined as 24 osseous lesions with bone detritus without evidence of osteomyelitis; 6 secondary, circumscribed foci of inflammation in adjacent soft tissue with no evidence of infection; 9 lesions with inflammatory tissue along typically affected articulations

		Reference test		
		+	**-**	**Total**
Index	**+**	31 (TP)	0 (FP)	31

	test	**-**	2 (FN)	0 (TN)	2
		Total	33	0	33
	Sensitivity: 0.939 (95%CI: 0.843, 1.000); Specificity: NA (95%CI: NA) LR+: 1.853 (95%CI: 1.674, 2.051); LR−: 0.147 (95%CI: 0.050, 0.434)				
Summary	Results indicate both ring PET and MRI are effective in the preoperative detection of small, inflammatory, non-infectious Charcot lesions. The most important limitation of MRI is its restricted efficacy in patients with metal implants.				

Table 90: Beltran 1990

Reference	**Beltran, J., Campanini, D. S., Knight, C., & McCalla, M. (1990). The diabetic foot: magnetic resonance imaging evaluation. *Skeletal radiology*, *19*(1), 37-41.**
Patient characteristics	**Population:** Retrospective case series of participants with suspected foot infection and/or neuropathic joint **Number of patients included:** 14 participants **Number of patients excluded:** not stated **Mean age:** not stated **Males/females:** not stated **Country:** USA **Other comments:** Results were obtained by having investigations examined by experts blinded to the participants clinical findings and other investigations. Results confirmed by follow up.
QUADAS 2 quality assessment	**Patient Selection: could the selection of patients have introduced bias?** 1) Was a consecutive or random selection of patients enrolled? Unclear if a random selection of participants was enrolled, or if patients were recruited consecutively 2) Was a case-control study design avoided? Yes 3) Did the study design avoid inappropriate exclusions? Unclear **Could the conduct or interpretation of the index test have introduced bias?** 4) Were the index test results interpreted without knowledge of the results of the reference standard? Yes 5) If a threshold was used, was it pre-specified? No threshold appears to have been pre-specified **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6) Is the reference standard likely to correctly classify the target condition? The reference standard was the subsequent follow up and development of symptoms of infection or Charcot features on plain radiograph, these are likely to be accurate 7) Were the reference standard results interpreted without knowledge of the results of the index test? The reference standard results were not interpreted without knowledge of the results of the index test **Could the patient flow have introduced bias?** 8) Was there an appropriate interval between index test and reference standard? There was an appropriate interval between index test and reference standard 9) Did all patients receive the same reference standard? All participants received the same reference standard. 10) Were all patients included in the analysis? Unclear if all participants who could fit the inclusion criteria were included, unclear inclusion criteria.

<table>
<tr><td>Reference standard</td><td>Reference standard: long term follow up and development of disease
Details: Not provided
Number unable to participate in the reference test : Not stated</td></tr>
<tr><td>Index test(s)</td><td>(1) Plain radiograph
Test: two experienced examiners blinded to the results of the other tests and clinical findings
No further details provided
Number unable to participate in the index test and reasons given: Not stated</td></tr>
<tr><td></td><td>(2) Magnetic resonance imaging
Test: two experienced examiners blinded to the results of the other tests and clinical findings
1.5 Tesla magnet
Number unable to participate on the index test and reasons given: Not stated</td></tr>
<tr><td>Results</td><td>Plain radiograph- number of participants with Charcot neuroarthropathy diagnosed (n=5). results calculated from data provided
Neuropathic joint was diagnosed with observation of joint collapse, subluxations and dislocations, bone sclerosis and bone fragmentation well manifested on plain film.
<table>
<tr><td colspan="2"></td><td>Reference test</td><td></td><td></td></tr>
<tr><td colspan="2"></td><td>+</td><td>-</td><td>Total</td></tr>
<tr><td rowspan="3">Index test</td><td>+</td><td>2 (TP)</td><td>0 (FP)</td><td>2</td></tr>
<tr><td>-</td><td>3 (FN)</td><td>9 (TN)</td><td>12</td></tr>
<tr><td>Total</td><td>5</td><td>9</td><td>14</td></tr>
</table>
Sensitivity: 0.400 (95%CI: 0.000, 0.929); Specificity: 1.000 (95%CI: 0.944, 1.000)
LR+: 8.333 (95%CI: 0.480, 144.823); LR−: 0.600 (95%CI: 0.293, 1.227)</td></tr>
</table>

	Magnetic Resonance Imaging, MRI- number of lesions consistent with Charcot neuroarthropathy (n=39). results calculated from data provided (excluding 3 participants with extensive metal artifacts interfering with detection) Neuropathic joint was diagnosed with observation of irregular destruction of the subchondral corticies of a joint accompanied by low signal intensity of the underlying trabecular bone.

		Reference test		
		+	**-**	**Total**
Index test	**+**	5 (TP)	0 (FP)	5
	-	0 (FN)	9 (TN)	9
	Total	5	9	14

Sensitivity: 1.000 (95%CI: 0.900, 1.000); Specificity: 1.000 (95%CI: 0.944, 1.000)
LR+: 18.333 (95%CI: 1.227, 274.024); LR−: 0.088 (95%CI: 0.006, 1.241)

Summary	MRI was found to be accurate in detecting and differentiating between neuroarthropathy and osteomyelitis and superior to plain radiography in the detection of Charcot foot.

G.16 Review question 16 full evidence tables

Table 91: Pakarinen 2011

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. *Diabetes care*, *34*(7), 1514-1516.**
Study type	Randomised control trial
Study quality	Summary Population: Finland. Participants were patients with diagnosis of acute midfoot Charcot neuropathy. Intervention: 4mg of IV zoledronic acid (bisphosphonate), 3 times with 1 month intervals. Standard care. Comparison: Placebo. Standard care included initial non-weight bearing below the knee contact cast. When the temperature

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. *Diabetes care*, *34*(7), 1514-1516.**
	difference between the feet was 1-2°C and no other clinical signs of active Charcot processes were present, partial weight bearing was allowed and a fixed ankle-foot orthosis was applied. Full weight bearing permitted when feet reached <1°C temperature difference with no evidence of erythema or oedema. Outcome: Clinical resolution of Charcot foot, Length of immobilisation, amputation, adverse events, Charcot relapse. 1. Has an appropriate method of randomisation been used? Unclear method of randomisation 2. Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline. 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received similar care apart from intervention given 5. Were participants receiving care kept blind to treatment allocation? Unclear if participants were blinded to treatment allocation 6. Were the individuals administering care kept blind to treatment allocation? Unclear if individuals administering care were blinded to treatment allocation 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? 4 participants were lost to follow up. Unclear if groups were similar for the number lost to follow up 8. Did the study have an appropriate length of follow up? Follow up was appropriate (1 year) 9. Did the study use a precise definition of outcome? A precise definition of outcome was used 10. Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11. Were investigators kept blind to participant's exposure to the intervention? Unclear if investigators were kept blind to participant's exposure to the intervention. 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. .
Number of patients	Randomised= 39 (4 subsequently excluded)

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. *Diabetes care*, *34*(7), 1514-1516.**
	Treatment group= 18 Placebo group = 17
Patient characteristics	Patients taken from: Finland Inclusion: Acute midfoot Charcot neuroarthropathy, based on clinical examination and radiological findings. Warm, swollen foot with erythema over the warmest area of the foot. Increase of ≥2°C on infrared thermometer compared with the same site on the contralateral foot. MRI: periarticular focal bone marrow oedema, absent sinus tracts or soft tissue fluid collections and preservation of periarticular subcutaneous fat. Exclusion: Renal insufficiency (serum creatinine >400 µmol/L) Previous bisphosphonate treatment Baseline characteristics:

Characteristics	Zoledronic acid group	Placebo group
N	18	17
Age, y	53.8 ± 9.1	56.0 ± 9.2
Male/female	5/13	1/16
BMI (kg/m²)	29.0 ± 6.4	28.4 ± 6.1
Neuropathy Retinopathy Nephropathy	17 9 15	15 9 9
Duration of diabetes, y	17.3 ± 14.0	16.9 ± 12.4
Type of diabetes Type 1 Type 2	 8 10	 5 12
HbA1c	8.2 ± 1.4	7.9 ± 1.6
Foot ulcer	2	1
Charcot foot involvement site Tarso-metatarsal and/or naviculocuneform Talo-navicular and/or calcaneo-cuboidal	 14 4	 15 2

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. *Diabetes care*, *34*(7), 1514-1516.**
	<table><tr><td>Abnormal foot architecture</td><td>11</td><td>7</td></tr><tr><td>Initial foot temperature difference</td><td>3.3 ± 1.6</td><td>3.2 ± 2.1</td></tr><tr><td>Distal pedal pulses present</td><td>17</td><td>17</td></tr></table>
Intervention	4mg of IV zoledronic acid (bisphosphonate), 3 times with 1 month intervals. Standard care.
Comparison	Placebo. Standard care included initial non-weight bearing below the knee contact cast. When the temperature difference between the feet was 1-2°C and no other clinical signs of active Charcot processes were present, partial weight bearing was allowed and a fixed ankle-foot orthosis was applied. Full weight bearing permitted when feet reached <1°C temperature difference with no evidence of erythema or oedema.
Length of follow up	Length of follow up was 1 year
Location	Finland
Outcomes measures and effect size	Amputation No data provided Mortality No data provided Ulceration No data provided Time to remission Median time for total immobilization Immobilisation in a cast plus time of immobilization in orthosis. Treatment group= 27 weeks (10-62 weeks) Placebo group= 20 weeks (20-52 weeks) P value= 0.02. i.e. statistically significant Relapse of Charcot neuropathy Treatment group= 1 of 18 participants

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. *Diabetes care*, *34*(7), 1514-1516.**
	Placebo group= 1 of 17 participants No side effects reported
Source of funding	Competitive Research Funding of Tampere University Hospital.
Comments	

Table 92: Chantelau 1997

Bibliographic reference	**Chantelau, E., & Schnabel, T. (1997). Palliative radiotherapy for acute osteoarthropathy of diabetic feet: a preliminary study. *Practical Diabetes International*, *14*(6), 154-156.**
Study type	Randomised control trial
Study quality	Summary Population: Germany. Participants with acute neurogenic osteoarthropathy. Intervention: Radiotherapy was performed three times weekly to a total dose of 2.45 Gy. Standard therapy. Comparison: Sham radiotherapy included 6 sessions with 0 Gy. Standard therapy included complete relief of pressure from affected foot by bed rest or wheel chair, systematic treatment with oral antibiotics to prevent infection, low dose heparin as an anti-thrombotic agent. Outcome: Patient compliance, healing time, adverse events 1. Has an appropriate method of randomisation been used? Unclear method of randomisation 2. Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Groups appear similar at baseline for all factors, no P values were provided. Groups were similar for number and distribution of bone lesions. 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received similar care apart from intervention given. For the outcome of healing time for compliant/non-compliant participants it was unclear if groups were similar at baseline. More participants in the compliant group received true radiotherapy than in the non-compliant group. 5. Were participants receiving care kept blind to treatment allocation?

<table>
<tr><th>Bibliographic reference</th><th>Chantelau, E., & Schnabel, T. (1997). Palliative radiotherapy for acute osteoarthropathy of diabetic feet: a preliminary study. Practical Diabetes International, 14(6), 154-156.</th></tr>
<tr><td></td><td>Participants were blinded to treatment allocation
6. Were the individuals administering care kept blind to treatment allocation?
Individuals administering care were blinded to treatment allocation
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available?
Groups were similar for availability of outcome data
8. Did the study have an appropriate length of follow up?
Follow up varied depending upon healing time, this was appropriate.
9. Did the study use a precise definition of outcome?
A precise definition of outcome was used
10. Was a valid and reliable method used to determine that outcome?
A valid and reliable method was used to determine outcome.
11. Were investigators kept blind to participant’s exposure to the intervention?
Investigators were kept blind to participant’s exposure to the intervention.
12. Were investigators kept blind to other important confounding and prognostic factors?
Unclear if investigators were kept blind to other important confounding and prognostic factors.
.</td></tr>
<tr><td>Number of patients</td><td>Randomised= 12
Treatment group= 6
Placebo group = 6</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: Germany

Inclusion:
Acute diabetic osteoarthropathy of known duration less than 2 months
Defined by clinical criteria: redness, swelling and hyperthermia
Xray findings: fracture, osteolysis

Baseline characteristics:

<table>
<tr><th>Characteristics</th><th>Radiotherapy group</th><th>Placebo group</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="3">Chantelau, E., & Schnabel, T. (1997). Palliative radiotherapy for acute osteoarthropathy of diabetic feet: a preliminary study. Practical Diabetes International, 14(6), 154-156.</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>N</td><td>6</td><td>6</td></tr>
<tr><td>Age, y (95% Confidence interval)</td><td>58 (24-64)</td><td>52 (43-62)</td></tr>
<tr><td>Male/female</td><td>2/4</td><td>4/2</td></tr>
<tr><td>BMI (>27 kg/m²)</td><td>3</td><td>4</td></tr>
<tr><td>Neuropathy
Retinopathy
Nephropathy</td><td>6</td><td>5</td></tr>
<tr><td>Duration of diabetes, y</td><td>21 (10-44)</td><td>19 (10-28)</td></tr>
<tr><td>Type of diabetes
Type 1
Type 2</td><td>
2
4</td><td>
1
5</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Foot ulcer</td><td>1</td><td>1</td></tr>
<tr><td>Charcot foot involvement site</td><td>Distributions similar</td><td>Distributions similar</td></tr>
<tr><td>Abnormal foot architecture</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Initial foot temperature difference</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Distal pedal pulses present</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><th>Intervention</th><td colspan="3">Radiotherapy was performed three times weekly to a total dose of 2.45 Gy. Standard therapy.</td></tr>
<tr><th>Comparison</th><td colspan="3">Sham radiotherapy included 6 sessions with 0 Gy. Standard therapy included complete relief of pressure from affected foot by bed rest or wheel chair, systematic treatment with oral antibiotics to prevent infection, low dose heparin as an anti-thrombotic agent.</td></tr>
<tr><th>Length of follow up</th><td colspan="3">Length of follow up was variable</td></tr>
<tr><th>Location</th><td colspan="3">Germany</td></tr>
<tr><th>Outcomes measures and effect size</th><td colspan="3">Amputation
No data provided

Mortality
No data provided

Ulceration
No data provided</td></tr>
</table>

Bibliographic reference	**Chantelau, E., & Schnabel, T. (1997). Palliative radiotherapy for acute osteoarthropathy of diabetic feet: a preliminary study. *Practical Diabetes International*, *14*(6), 154-156.**
	Time to remission Overall healing time Defined as clinical and roentenological healing time. Treatment group= 7 months (confidence interval of 8-20 months) Placebo group= 9.7 months (confidence interval of 4-15 months) i.e. not statistically significant Patient compliance Non-compliant defined as not regularly using the wheel chair and walking on affected foot at least once a day (6 participants) Compliant group (6 participants)= 5.5 months (confidence interval of 3-7 months) Non-compliant group (6 participants)= 9.7 months (confidence interval of 8-20 months) i.e. statistically significant Of the complaint participants 4 had received radiotherapy
Source of funding	Unclear source of funding
Comments	

Table 93: Hanft 1998

Bibliographic reference	**Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. *The Journal of foot and ankle surgery*, *37*(6), 510-515.**
Study type	Randomised control trial
Study quality	Summary Population: USA Intervention: Combined magnetic bone growth stimulator device used for ½ an hour every day. Standard care Comparison: Participant could be treated with total contact cast or fixed ankle walker depending on contraindications.

Bibliographic reference	**Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. *The Journal of foot and ankle surgery*, *37*(6), 510-515.**
	Outcome: Time to consolidation and end of treatment. 1. Has an appropriate method of randomisation been used? Unclear method of randomisation. 21 participants were randomly assigned treatment groups and the 10 further participants were added to the treatment group, this is not true randomisation. 2. Was there adequate concealment of allocation? Unclear if allocation was adequately concealed 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear if groups were similar at baseline 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received similar care apart from intervention given. Some participants received total contact cast walkers and others fixed ankle walkers, although this was not found to cause a significant difference on the outcome of interest. 5. Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6. Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Groups were similar for availability of outcome data 8. Did the study have an appropriate length of follow up? Follow up varied depending upon healing time, this was appropriate. 9. Did the study use a precise definition of outcome? A precise definition of outcome was used 10. Was a valid and reliable method used to determine that outcome? A valid and reliable method was used to determine outcome. 11. Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear if investigators were kept blind to other important confounding and prognostic factors. .
Number of patients	Randomised= 31

<table>
<tr><td>Bibliographic reference</td><td>Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. The Journal of foot and ankle surgery, 37(6), 510-515.</td></tr>
<tr><td></td><td>Treatment group= 21
Placebo group = 10</td></tr>
<tr><td>Patient characteristics</td><td>Patients taken from: USA

Inclusion:
Peripheral neuropathy secondary to diabetes mellitus
Clinical, thermographic, and radiographic evidence of acute Charcot joint

Exclusion:
Presence of open ulceration or wound on the limb being studied
Active skin or bone infection
Previous history of a Charcot episode on the limb being studied
Renal failure
Inability to comply with treatment
Treatment used for 75% of allotted time

Baseline characteristics:

<table>
<tr><td>Characteristics</td><td>CMF group</td><td>Control group</td></tr>
<tr><td>N</td><td>21</td><td>10</td></tr>
<tr><td>Age, y (95% Confidence interval)</td><td>57.5</td><td>55.9</td></tr>
<tr><td>Male/female</td><td>4/6</td><td>12/9</td></tr>
<tr><td>Obesity</td><td>10</td><td>5</td></tr>
<tr><td>Neuropathy
Retinopathy
Nephropathy</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Duration of diabetes, y</td><td>21 (10-44)</td><td>19 (10-28)</td></tr>
<tr><td>Type of diabetes
Type 1
Type 2</td><td>
11
10</td><td>7/3</td></tr>
<tr><td>HbA1c</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Foot ulcer</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. *The Journal of foot and ankle surgery*, *37*(6), 510-515.**
	Charcot foot involvement site: Not reported / Not reported Abnormal foot architecture: Not reported / Not reported Initial foot temperature difference: Not reported / Not reported Distal pedal pulses present: Not reported / Not reported
Intervention	Combined magnetic bone growth stimulator device used for ½ an hour every day. Standard care
Comparison	Participant could be treated with total contact cast or fixed ankle walker depending on contraindications.
Length of follow up	Length of follow up was variable
Location	USA
Outcomes measures and effect size	Amputation No data provided Mortality No data provided Ulceration No data provided Time to remission Mean time to consolidation Radiographic evidence of complete consolidation when temperature differences were within 2°C of each other and volumes were within 10% of each other. Treatment group= 11.1 weeks (±3.2) Control group= 23.2 weeks (±7.7) P value= <0.001 i.e. statistically significant. Duration of Charcot neuroarthropathy prior to treatment, gender, age, type of diabetes, obesity, type of offloading were all found to have no statistical effect in the time to consolidation in the same population.

Bibliographic reference	**Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. *The Journal of foot and ankle surgery*, *37*(6), 510-515.**
Source of funding	Unclear source of funding
Comments	

Table 94: Shah 2011

Bibliographic reference	**Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. *Indian journal of orthopaedics*, *45*(4), 359.**
Study type	Retrospective cohort
Study quality	Summary Population: India. Intervention: tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by external immobilisation Comparison: tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by retrograde intramedullary interlocked nailing Outcome: radiological union, development of complications, clinical follow up 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? The type of surgical procedure a patient underwent was the senior author's choice apparently irrespective of the stage or condition of the bone. It is unclear whether there are any other factors that could have affected this choice or if any were related to the outcomes recorded. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no apparent attempts to balance groups for confounding factors 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors especially since each groups seemed to have differing exclusion criteria. Many baseline characteristics were not reported. Exclusion criteria for the retrograde nail group seemed to rule out more participants with increasingly severe disease this would be highly confounding. 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if the comparison groups received the same care. As this was a retrospective cohort study it may have been difficult to

Bibliographic reference	**Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. *Indian journal of orthopaedics*, *45*(4), 359.**
	prove exactly what care was given in each case. Some participants were receiving treatment for ulceration beforehand. It is unclear if the same surgeon was used for all operations. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? No evidence of adjustment of analysis for length of follow up for certain outcomes such as achievement of bony fusion. 8. Groups were comparable for intervention completion? Groups were comparable for intervention completion 9. The groups were comparable with respect to the availability of outcome data? Groups were comparable for availability of outcome data as no loss to follow up was reported 10. The study had an appropriate length of follow up? Length of follow up was an average of 3.2 years for all participants, this is appropriate but could vary wildly between 1-10 years. Outcomes of interest were within 40 weeks however. 11. The study used a precise definition of outcome? The study did not use a clear definition of consolidation or union of joint. 12. A valid and reliable method was used to determine the outcome? A valid and reliable method was used to determine outcome although data was retrospective 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors Participation numbers in the study were low (n=11) .
Number of patients	Total= 11 Uniplanar external fixator group= 6 Retrograde intramedullary nailing group= 5

Bibliographic reference	**Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. *Indian journal of orthopaedics*, *45*(4), 359.**
Patient characteristics	Patients taken from: Singapore Inclusion: Patients with tibio-talar arthrodesis for Charcot's neuroarthropathy Exclusion: For participants treated with external fixator: Ulceration over potential external fixator pin sites For participants treated with retrograde nail: Normal subtalar joint Significant tibial deformity with malunion, greater than 10 degrees in any plane Marked loss of calcaneal body height Active infections of foot or ankle Baseline characteristics:

Characteristics	External fixation group	Internal fixation group
N	6	5
Age, y (95% Confidence interval)	Not reported	Not reported
Male/female	Not reported	Not reported
Obesity	Not reported	Not reported
Neuropathy Retinopathy Nephropathy	6	5
Duration of diabetes, y	Not reported	Not reported
Type of diabetes Type 1 Type 2	Not reported	Not reported
HbA1c	Not reported	Not reported
Foot ulcer	Not reported	Not reported
Charcot foot involvement site	Not reported	Not reported
Abnormal foot architecture	Not reported	Not reported
Initial foot temperature difference	Not reported	Not reported
Distal pedal pulses present	6	5

Bibliographic reference	**Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. *Indian journal of orthopaedics*, *45*(4), 359.**
Intervention	Tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by external immobilisation Standard care included open reduction, debridement, synovectomy, compression of cancellous tibio-talar bony surfaces
Comparison	Tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by retrograde intramedullary interlocked nailing Standard care included open reduction, debridement, synovectomy, compression of cancellous tibio-talar bony surfaces
Length of follow up	Length of follow up was variable. Average 3.2 years
Location	Singapore
Outcomes measures and effect size	Amputation Below the knee amputation due to fulminating infection Uniplanar external fixator group= 1 of 6 participants Retrograde intramedullary nailing group= 0 of 5 participants Mortality No data provided Ulceration No data provided Time to remission Number of participants achieving union Radiological union within 30 weeks Uniplanar external fixator group= 0 of 6 participants Retrograde intramedullary nailing group= 5 of 5 participants Radiological union within 40 weeks Uniplanar external fixator group= 1 of 6 participants Retrograde intramedullary nailing group= 5 of 5 participants

Bibliographic reference	**Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. *Indian journal of orthopaedics*, *45*(4), 359.**
	Non-Union No radiological union by 40 weeks Uniplanar external fixator group= 4 of 6 participants Retrograde intramedullary nailing group= 0 of 5 participants
Source of funding	Study declares no source of support, no conflict of interest
Comments	

Table 95: Bharath 2013

Bibliographic reference	**Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. *Indian journal of endocrinology and metabolism*, *17*(1), 110.**
Study type	Randomised control trial
Study quality	Summary Population: India. Participants with the presence of hot swollen foot with or without redness of the overlying skin after the exclusion of conditions resembling Charcot foot. Intervention: Zoledronic acid injection 5 mg, as an intravenous infusion (diluted in 100ml, normal saline infused over 30 minutes, after hospital admission with total contact casting Comparison: Alendronate 70 mg, once a week, till the complete resolution of acute Charcot foot along with total contact casting. Feet were strictly offloaded with the help of a walker. Outcome: skeletal scintigraphy, time taken for complete clinical resolution 1. Has an appropriate method of randomisation been used? Unclear method of randomisation 2. Was there adequate concealment of allocation? Unclear if allocation was adequately concealed

Bibliographic reference	**Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. *Indian journal of endocrinology and metabolism*, *17*(1), 110.**
	3. Were the groups comparable at baseline for all major confounding/prognostic factors? Groups were similar at baseline for all reported factors 4. Did the comparison groups receive the same care apart from interventions studied? Both groups received similar care apart from intervention given 5. Were participants receiving care kept blind to treatment allocation? Participants were not blinded to treatment allocation 6. Were the individuals administering care kept blind to treatment allocation? Individuals administering care were not blinded to treatment allocation 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? 5 participants were lost to follow up. Unclear if groups were similar for the number lost to follow up. Only 30 remained for the outcome of interest due to being the only participants who reached complete clinical resolution. Unclear how many were lost to follow up from each group as a result of this. 16 remained in the zoledronic acid group and 14 in the alendronate group. 8. Did the study have an appropriate length of follow up? Period of observation was appropriate (2 years), length of follow up was dependent on time taken to achieve complete clinical resolution. 9. Did the study use a precise definition of outcome? A precise definition of outcome was used 10. Was a valid and reliable method used to determine that outcome? A valid and reliable method was not used to determine outcome as it depended purely upon the temperature difference between two feet with no mention of other clinical signs or radiographic findings. 11. Were investigators kept blind to participant's exposure to the intervention? Investigators were not kept blind to participant's exposure to the intervention. 12. Were investigators kept blind to other important confounding and prognostic factors? Investigators were not kept blind to other important confounding and prognostic factors. .
Number of patients	Randomised= 45 (15 subsequently excluded) Zoledronic acid group= 16 Alendronate group = 14
Patient characteristics	Patients taken from: India

Bibliographic reference	**Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. *Indian journal of endocrinology and metabolism*, *17*(1), 110.**

Inclusion:
Participants with the presence of hot swollen foot with or without redness of the overlying skin after the exclusion of conditions resembling Charcot foot.

Exclusion:
Fever
Elevated leucocyte counts
Serum creatinine ≥3 mg/dL
Clinical or radiological features of Osteomyelitis of foot bone
Clinical or radiological features of peripheral vascular occlusive disease
Presence of foot ulcer
Hypocalcaemia
Planned dental procedure
Previously treated for Charcot foot
On bisphosphonate treatment for any other reason
Surgical procedure of affected foot in the past
Rheumatoid arthritis or gout in the past

Baseline characteristics:

Characteristics	Zoledronic acid group	Placebo group
N	23	22
Age, y	55.4 ± 10.2	57.9 ± 8.3
Male/female	Not reported	Not reported
BMI (kg/m²)	25.9 ± 2.2	24.2 ± 2.3
Neuropathy Retinopathy Nephropathy	Not reported	Not reported
Duration of diabetes, y	13.1 ± 5.6	15.5 ± 6.0
Type of diabetes Type 1	Not reported	Not reported

Bibliographic reference	**Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. *Indian journal of endocrinology and metabolism*, *17*(1), 110.**
	Type 2 / HbA1c: 9.2 ± 1.55 / 8.7 ± 1.8 Foot ulcer: Not reported / Not reported Charcot foot involvement site (Tarso-metatarsal and/or naviculocuneform; Talo-navicular and/or calcaneo-cuboidal): Not reported / Not reported Abnormal foot architecture: Not reported / Not reported Initial foot temperature difference: Not reported / Not reported Distal pedal pulses present: 23 / 22 Duration of Charcot symptoms in months: 2.3 ± 1.5 / 3.27 ± 1.5
Intervention	Zoledronic acid injection 5 mg, as an intravenous infusion (diluted in 100ml, normal saline infused over 30 minutes, after hospital admission with total contact casting
Comparison	Alendronate 70 mg, once a week, till the complete resolution of acute Charcot foot along with total contact casting. Feet were strictly offloaded with the help of a walker.
Length of follow up	Length of observation was 1 year
Location	India
Outcomes measures and effect size	Amputation No data provided Mortality No data provided Ulceration No data provided Time to remission Median time for complete clinical resolution of symptoms Defined as a temperature difference between normal and affected foot <1°F when checked on two different occasions.

Bibliographic reference	**Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. *Indian journal of endocrinology and metabolism*, *17*(1), 110.**
	Zoledronic acid group= 126 ± 44.8 days Alendronate group = 117 ± 29.1 days P value= 0.74 i.e. no statistical significant difference between groups
Source of funding	Study declared no funding and no competing interests
Comments	

Table 96: Game 2012

Bibliographic reference	**Game, F. L., Catlow, R., Jones, G. R., Edmonds, M. E., Jude, E. B., Rayman, G., & Jeffcoate, W. J. (2012). Audit of acute Charcot's disease in the UK: the CDUK study. *Diabetologia*, *55*(1), 32-35.**
Study type	Retrospective cohort
Study quality	Summary Population: UK and Ireland Intervention: Initial offloading with a non-removable off-loading device Comparison: Initial offloading with a removable offloading device Outcome: median time to resolution of acute Charcot foot 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Unclear if the reason for allocation was or was not related to any other confounding factors. Data was provided anonymously by various clinicians in 76 different centres. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no apparent attempts to balance groups for confounding factors 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Groups may have been subject to selection bias since we have no idea by what criteria patients were submitted to the study and if certain participants were not reported who should have been. 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if the comparison groups received the same care. As data was provided anonymously over the internet it would have

Bibliographic reference	Game, F. L., Catlow, R., Jones, G. R., Edmonds, M. E., Jude, E. B., Rayman, G., & Jeffcoate, W. J. (2012). Audit of acute Charcot's disease in the UK: the CDUK study. *Diabetologia*, *55*(1), 32-35.
	been difficult to prove exactly what care was given in each case. It is more likely that care varied significantly as some participants were found to have received bisphosphonates and others did not. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Length of follow up would be related to the outcome of interest i.e. median time to resolution of acute Charcot foot 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion 9. The groups were comparable with respect to the availability of outcome data? Unclear if groups were comparable for availability of outcome data, there was no data on resolution of acute Charcot foot available for 69 participants 10. The study had an appropriate length of follow up? Observation period was appropriate (2 years) 11. The study used a precise definition of outcome? The study did not use a clear definition of resolution of Charcot joint and this would be likely to vary between centres as would diagnosis of Charcot joint, which was based simply on clinician decision with no guidelines. 12. A valid and reliable method was used to determine the outcome? A valid and reliable method may not have been used as data was provided anonymously from various different centres 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors . It is also possible that a clinician's decision to treat with non-removable or removable device could be related to the severity of the disease, although there is nothing to suggest this it is unclear how confounding factors may be spread between the two treatment groups.
Number of patients	Total= 288 Initial non-removable offloading group= 88 Initial removable offloading group= 123

Bibliographic reference	**Game, F. L., Catlow, R., Jones, G. R., Edmonds, M. E., Jude, E. B., Rayman, G., & Jeffcoate, W. J. (2012). Audit of acute Charcot's disease in the UK: the CDUK study. *Diabetologia*, *55*(1), 32-35.**
Patient characteristics	Patients taken from: UK and Ireland Inclusion: New cases of acute Charcot foot at centres in the UK and Ireland over a period of 20 months Exclusion: None given Baseline characteristics: No baseline characteristics provided between treatment groups Overall: Mean age= 57.0 ± 11.3 years Male: 71.2% Type 2 diabetes: 70% Previous episodes of Charcot: 15%
Intervention	Initial therapy with non-removable offloading device Standard care may vary between centres
Comparison	Initial therapy with removable offloading device Standard care may vary
Intervention (2)	Therapy with bisphosphonates Standard care may vary between centres
Comparison (2)	No therapy with Bisphosphonates Standard care may vary
Length of follow up	Computerised prompts were used to request follow up information at intervals of 3 months up to 18 months after registration, therefore follow up may vary between participants.

Bibliographic reference	**Game, F. L., Catlow, R., Jones, G. R., Edmonds, M. E., Jude, E. B., Rayman, G., & Jeffcoate, W. J. (2012). Audit of acute Charcot's disease in the UK: the CDUK study. *Diabetologia*, *55*(1), 32-35.**
Location	UK and Ireland
Outcomes measures and effect size	Amputation No data provided Mortality No data provided Ulceration No data provided Time to remission Treatment with non-removable vs removable offloading device Median (range) time to resolution Definition unclear (clinicians assessment) Initial offloading with non-removable device (n=88)= 9 months (range 3-25 months) Never had a non-removable cast (n=123)= 12 months (range 3-36) P value= 0.001 i.e. significant difference Treatment with bisphosphonates vs no bisphosphonates Median (range) time to resolution Definition unclear (clinicians assessment) Treatment with intravenous/oral bisphosphonates (44.8%)= 12 months (range 3-39 months) No treatment with bisphosphonates (55.2%)= 10 months (range 2-29) P value= 0.005 i.e. significant difference There appeared to be no interaction between the type of offloading used and the use of bisphosphonates (P value= 0.194) no further details were provided however for other potential confounding factors.
Source of funding	Funded by Diabetes UK
Comments	

Table 97: Pakarinen 2002

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Honkonen, S. E., Peltonen, J., Oksala, H., & Lahtela, J. (2002). Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. *Scandinavian journal of surgery*, *91*(2), 195-201.**
Study type	Retrospective cohort
Study quality	Summary Population: Finland Intervention: Treated with cast and total non-weightbearing at initial presentation Comparison: Not treated with cast and total non-weightbearing at initial presentation Outcome: Number undergoing surgical treatment 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Unclear if the reason for allocation was or was not related to any other confounding factors. Some participants were misdiagnosed upon initial presentation. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no apparent attempts to balance groups for confounding factors 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Participants varied in stage of Charcot at presentation, type of surgery and immobilisation and location of Charcot disease. 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if the comparison groups received the same care. It is more likely that care varied significantly as some participants were found to have received bisphosphonates and others did not, different types of cast were also employed and length of casting. 5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was gathered retrospectively and follow up varied, presumably participants were followed up until treatment completion but this is unclear. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion 9. The groups were comparable with respect to the availability of outcome data?

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Honkonen, S. E., Peltonen, J., Oksala, H., & Lahtela, J. (2002). Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. *Scandinavian journal of surgery*, *91*(2), 195-201.**
	Unclear if groups were comparable for availability of outcome data 10. The study had an appropriate length of follow up? Observation period was appropriate (6 years) however follow up likely varied (average 21 months (range 1-81)) 11. The study used a precise definition of outcome? The study used a broad definition of outcome: Whether the participant had undergone surgical treatment for Charcot foot. 12. A valid and reliable method was used to determine the outcome? Retrospective checking of records was used which may not be reliable. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors . It is also possible that a clinician's decision to treat with surgery could be related to the severity of the disease at presentation, although there is nothing to suggest this it is unclear how confounding factors may be spread between the two treatment groups.
Number of patients	Total= 36 feet, 32 participants Treated with cast and total non-weightbearing at initial presentation= 18 Not treated with cast and total non-weightbearing at initial presentation= 18
Patient characteristics	Patients taken from: Finland, one university hospital Inclusion: All feet diagnosed as Charcot neuroarthropathy at Tampere University Hospital Exclusion: None given Baseline characteristics: No baseline characteristics provided between treatment groups Overall:

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Honkonen, S. E., Peltonen, J., Oksala, H., & Lahtela, J. (2002). Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. *Scandinavian journal of surgery*, *91*(2), 195-201.**
	Mean age= not reported 22 males, 10 females Type 2 diabetes n=19, Type 1 diabetes n=13
Intervention	Cast and total non-weightbearing at initial presentation Standard care may have varied
Comparison	No cast and total non-weightbearing at initial presentation Standard care may have varied
Length of follow up	Average 21 months (range 1-81 months)
Location	Finland
Outcomes measures and effect size	Amputation Number undergoing surgical treatment Including exostectomy, arthrodesis, below knee amputation Cast and total non-weightbearing at initial presentation (n=18)= 2 of 18 participants No cast and total non-weightbearing at initial presentation (n=18)= 8 of 18 participants P value= 0.03 i.e. significant difference There was no statistical difference in diagnostic delay between the operated (37 weeks) and non-operated (25 weeks) patients. No further details were provided however for other potential confounding factors. Mortality No data provided Ulceration No data provided

Bibliographic reference	**Pakarinen, T. K., Laine, H. J., Honkonen, S. E., Peltonen, J., Oksala, H., & Lahtela, J. (2002). Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. *Scandinavian journal of surgery*, *91*(2), 195-201.**
	Time to remission No data provided
Source of funding	Unclear source of funding
Comments	

Table 98: Clohisy 1988

Bibliographic reference	**Clohisy, D. R., & Thompson, R. C. (1988). Fractures associated with neuropathic arthropathy in adults who have juvenile-onset diabetes. *The Journal of Bone & Joint Surgery*, *70*(8), 1192-1200.**
Study type	Retrospective cohort
Study quality	Summary Population: USA, participants with juvenile-onset diabetes, neuropathic arthropathy and fractures Intervention: Treated with non-weight-bearing protective devices Comparison: allowed weight-bearing Outcome: Required orthosis, amputation, could not walk 1. The method of allocation to intervention groups was unrelated to potential confounding factors (the reason for participant allocation to intervention is not expected to affect the outcome under study)? Unclear if the reason for allocation was or was not related to any other confounding factors. Data was taken retrospectively from hospital databases over a period of 10 years during which time care may have changed, participants or their families were also interviewed which is susceptible to recall bias. 2. Attempts were made with the design or analysis to balance the comparison groups for potential confounders? There were no apparent attempts to balance groups for confounding factors 3. The groups were comparable at baseline, including all major confounding factors? It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. The paper states that groups were not statistically different for number with bilateral fractures however. Participants varied in stage of Charcot at presentation, severity of trauma, age, comorbidities, time from symptoms to diagnosis of fracture and location of Charcot disease and it is unclear how these were distributed between groups. 4. The comparison groups received the same care and support apart from the interventions studied? Unclear if the comparison groups received the same care. It is more likely that care varied significantly as some participants were taken from over 10 years during which time care may have varied not only due to the intervention of interest.

Bibliographic reference	**Clohisy, D. R., & Thompson, R. C. (1988). Fractures associated with neuropathic arthropathy in adults who have juvenile-onset diabetes. *The Journal of Bone & Joint Surgery*, *70*(8), 1192-1200.**
	5. Participants receiving care and support were kept blind to intervention allocation? Participants were not blinded to intervention allocation 6. Individuals administering care and support were kept blind to intervention allocation? Individuals administering care were not blinded to intervention allocation 7. All groups were followed for an equal length of time, or analysis was adjusted to allow for differences in length of follow up? Data was gathered retrospectively and follow up varied, all participants were followed up for a minimum of 9 months and median length of follow up was 5 years. 8. Groups were comparable for intervention completion? Unclear if groups were comparable for compliance or intervention completion 9. The groups were comparable with respect to the availability of outcome data? Unclear if groups were comparable for availability of outcome data 10. The study had an appropriate length of follow up? Observation period was appropriate (10 years) however follow up varied hugely (median 5 months (range 9months-9years)) 11. The study used a precise definition of outcome? The study used a precise definition of outcome: Group 1 was patients who were treated with non-weight-bearing protective devices within two months after the onset of symptoms. Patients who received weight bearing as tolerated or a short walking cast were placed in group 2. 12. A valid and reliable method was used to determine the outcome? Retrospective checking of records was used which may not be reliable. Even less reliable was the calling of participant's families or interviews with the participants themselves that would be susceptible to recall bias. 13. Investigators were kept blind to participant's exposure to the intervention? Investigators were not kept blinded to exposure to the intervention 14. Investigators were kept blind to other important confounding factors? Investigators were not kept blinded to other important confounding factors . Numbers were low with 7 participants in Group 1 and 11 participants in Group 2
Number of patients	Total= 18 participants Treated with non-weight-bearing protective devices within 2 months of treatment= 7 allowed weight-bearing within 2 months of treatment= 11
Patient characteristics	Patients taken from: USA, one university hospital

Bibliographic reference	**Clohisy, D. R., & Thompson, R. C. (1988). Fractures associated with neuropathic arthropathy in adults who have juvenile-onset diabetes. *The Journal of Bone & Joint Surgery*, *70*(8), 1192-1200.**
	Inclusion: Juvenile onset diabetes All diabetic patients who had a radiograph of the foot or ankle made at one university hospital between 1974 and 1984 Exclusion: Osteomyelitis Treated elsewhere (unreachable) Baseline characteristics: No baseline characteristics provided between treatment groups Overall: Median age at onset of diabetes= 15.5 years Median age at time of fracture= 33.5 years (25-52 years range) 10 males, 8 females Juvenile onset diabetes n=18, Insulin therapy= 18
Intervention	Treated with non-weight-bearing protective devices within 2 months of treatment Standard care may have varied
Comparison	allowed weight-bearing within 2 months of treatment Standard care may have varied
Length of follow up	Median 5 years (range 9 months-9 years)
Location	USA
Outcomes measures and effect size	Amputation Number undergoing amputation Unclear definition Treated with non-weight-bearing protective devices within 2 months of treatment (n=7)= 0 of 7 participants

Bibliographic reference	**Clohisy, D. R., & Thompson, R. C. (1988). Fractures associated with neuropathic arthropathy in adults who have juvenile-onset diabetes. *The Journal of Bone & Joint Surgery*, *70*(8), 1192-1200.**
	allowed weight-bearing within 2 months of treatment (n=11)= 3 of 11 participants No P value provided Mortality No data provided Ulceration No data provided Time to remission No data provided Number who could not walk Unclear definition Treated with non-weight-bearing protective devices within 2 months of treatment (n=7)= 0 of 7 participants allowed weight-bearing within 2 months of treatment (n=11)= 4 of 11 participants No P value provided
Source of funding	No funding received
Comments	