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Debridement of Diabetic Foot Ulcers: Public Health and Clinical Implications. A Systematic Review, Meta-Analysis, and Meta-Regression

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Debridement of Diabetic Foot Ulcers: Public Health and Clinical Implications. A Systematic Review, Meta-Analysis, and Meta-Regression

David Dayya, DO, MPH, PhD

University of Connecticut, [2016]

Abstract

Background

Diabetic Foot ulceration has devastating complications. These include amputations resulting in poor quality of life, and serious infections including osteomyelitis and life threatening sepsis. Diabetic wounds can be protracted, take significant time to heal, and they can recur after they have healed. They can be very costly and consume healthcare resources. These consequences have serious public health and clinical implications. Debridement is often used as a standard of care in efforts to help avert these consequences. It is used to remove nonviable or necrotic tissue such as nonviable tissue in order to facilitate the wound healing process and help prevent these disabling outcomes. What is/are the most effective method(s) of debridement remains unclear? This systematic review of the literature on debridement of diabetic foot ulcers synthesizes all experimental evidence in an effort to help answer this important question.

Foot ulceration affects 15% of diabetics at some point in their lives. The prevalence of diabetic foot ulcers is 4.6% in the UK, 8.3% in the US, and includes 7% of the world's population. The non-healing wound increases the risk of amputations, complicating infections, healthcare costs, and reduces quality of life. Debridement is regarded as an effective intervention to accelerate ulcer healing and to decrease the risk of serious complications.

Current published literature is unclear on which specific method of debridement interventions have the optimal effect on these important public health and clinical implications including: amputation rates, complicating infection rates, quality of life, cost of care) and clinical implications (wound healing rates, wound recurrence rates, and time to complete healing.

Analyzing moderators or prognostic risk factors can facilitate the development of population-specific guidelines or recommendations on the effects of debridement. This can promote better understanding of which groups may benefit from debridement based on prognostic factors. This understanding could increase adherence to the common practices used in diabetic wound care including debridement, provided the evidence supports its efficacy.

Objectives

The current systematic review and meta-analysis was conducted in order to obtain overall effect sizes of all debridement interventions on the following outcomes (Amputation frequency, Complicating wound infection rates such as Methicillin Resistant Staphylococcus Aureus (MRSA), Quality of life, Proportion of ulcers healing, Proportion of ulcer recurrence, Cost, and Time to complete healing). The goal was to evaluate the variability and consistency of these effects across the current literature on this topic. Any significant variability across the current literature was investigated using moderator analysis based on study-specific and sample-specific characteristics.

Does the use of any form of debridement in diabetic foot ulcers demonstrate benefit over any other form of debridement including standard gauze dressings with respect to amputation frequency, complicating infection rates, quality of life, cost, proportion of ulcers healed, recurrence rates, and time to healing? Are any prognostic or other moderating factors predictive of benefit in some populations or groups? This study summarizes and synthesizes the evidence in a comprehensive qualitative systematic review and quantitative systematic review/meta-analysis of all randomized control trials (RCT's) on this research question.

Methods

A comprehensive literature search was conducted to retrieve articles that met the following inclusion criteria.

Inclusion/Exclusion Criteria

The following inclusion/exclusion criteria were utilized:

- a) Individual studies, Systematic reviews (SR's) and/or meta-analyses (MA's) that included randomized controlled trials (RCT's) on debridement of diabetic foot ulcers. Comparison of any method of debridement (i.e. the removal of nonviable tissue from the wound, by either mechanical or non-mechanical debridement) with control or an alternative method of debridement were included. The search included any form of debridement but did not include studies on Negative Pressure Wound Therapy (NPWT). NPWT includes mechanical debridement but has other functions.
- b) Adult Type 1, or Type 2 diabetics with ischemic, neuropathic, or neuro-ischemic diabetic foot ulcers. The wounds were not limited in severity or in grading system utilized including Wagner Wound Grade, and the Texas Classification systems.
- c) There were no other limitations based on age, gender, country, healthcare setting, or language.
- d) RCT's, and Systematic reviews/Meta-analyses that included other wound types i.e. venous stasis ulcers, arterial insufficiency ulcers in non-diabetics, pressure ulcers, and atypical ulcers were excluded.

- e) Studies that were nonrandomized (observational studies) were excluded. Systematic Reviews/Meta-analyses that were limited to nonrandomized studies were excluded. All systematic reviews were retrieved along with RCT's for purposes of comparison and contrasting them with the results of this review.

Search methods

The search included: The Cochrane Wounds Group Specialized Register; The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); Ovid MEDLINE, PubMed, EMBASE, EBSCO, CINAHL, and Web of Science.

Selection criteria

Randomized controlled trials (RCTs) evaluating any method of debridement used in diabetic foot ulcers. There was no restriction on articles/trials based on language or publication status.

Data collection and analysis

Data extraction and assessment of study quality were undertaken by two independent reviewers and referred to a methods expert and content expert when there was disagreement. When necessary, if disagreements were not resolved they were referred to the Wounds Group to resolve any remaining discordance between reviewers.

The primary outcomes of interest included: 1) Amputation rates, 2) Complicating wound infection rates, and 3) Quality of life.

The secondary outcomes of interest included: 4) Proportion of participants with ulcers completely healed, 5) Time to complete healing, 6) Proportion of ulcers recurring after healing, and 7) Cost of treatment.

These outcomes have direct bearing on clinical and public health implications including morbidity and mortality. These consequences cause significant hardships for individuals with wounds. A major amputation (above or below knee) is considered by experts to be a predictor of increased 5-year mortality.

Results

Descriptive Statistics

Sample sizes

This review included an analysis of thirty studies with a total of 2654 participants. All 30 studies reported total sample size for each of the included studies. The mean sample size for the included studies was 152 (SD = 119) participants. The included studies ranged from sample sizes of 18 to 619 participants.

Range of follow-up and study period duration

The range of follow up was 10 days to 24 weeks for the included studies. The study period or duration ranged from 1992 – 2012 for the included studies.

Participant characteristics (age, gender, ethnicity)

The mean ages for the samples in the included studies ranged from 52.1 years through 69.3 years. A total of 23 studies reported mean age, 1 study reported a median age of 59.5 years (Roberts 2001), while 6 other studies did not report age. The mean age for the sample of studies was 59.01 (SD = 4.31) years.

Gender was reported in 21/30 (70%) of studies. The number of male participants ranged from 12 to 240, while the number of female participants ranged from 1 to 88 for the reported studies.

Ethnicity was reported in 5/30 (16.7%) studies.

Socioeconomic status was reported in 1/30 (3.3%) study.

Geographic location and healthcare setting

A majority of the studies were conducted in the US or Europe 21/30 (70%) and published in English 28/30 (93%). The study settings included outpatient or specialized clinics 17/30 (56.7%), hospital settings 8/30 (26.7%), and both inpatient-hospital and outpatient settings 2/30 (6.7%), and was unclear in 5/30 (16.7%) studies.

Wound severity

Thirteen studies reported on wound severity, which included wounds up to Wagner grade 4, and wounds up to Texas classification Grade 3. The size of the wound was reported in 20/30 (67%) studies. Depth of wound was specified in 5/30 (16.7%) studies. A total of 14/30 (70%) studies reported on wound duration which ranged from 0 – 60 weeks.

Clinical prognostic factors

8/30 (26.7%) studies reported on hemoglobin a1c which ranged from 7.25% – 9.25%. 14/30 (70%) studies reported on duration of diabetes which ranged from 13 to 21 years. The proportion of baseline peripheral arterial insufficiency was reported in 9/30 (30%) studies. BMI was reported in 5/30 (16.7%) studies.

Table 1 Descriptive summaries of the 30 included studies used in this systematic review and meta-analysis.

Table 1 of Descriptive Statistics	
Total number of studies	30
Total number of participants	2564
Sample size range	18 to 619
Average sample size per study	152
Total Range of follow up	10 days to 24 weeks
Total Study period or duration	1992 - 2012
Studies reporting age	24/30 (70%)
Mean age (range)	52.1 – 69.3 years
Total number of studies reporting gender	21/30 (70%)
Range of number of males	12 to 240
Range of number of females	1 to 88
Number of studies reporting ethnicity	5/30 (16.7%)
Number of studies reporting socioeconomic status	1/30 (3.3%)
Geographic setting	Europe and US (70%)
Publication Language	English 93%
Healthcare setting	Hospital 8/30 (26.7%) Outpatient 17/30 (56.7%) Both 2/30 (6.7%)
Studies reporting wound size (area)	20/30 (67%)
Studies reporting wound duration	14/30 (70%)
Studies reporting Hemoglobin a1c (Hgb a1c)	8/30 (26.7%)
Hgb a1c (range)	7.25% - 9.25%
Studies reporting on duration of diabetes	14/30 (70%)
Duration of diabetes (range)	13 to 21 years
Studies reporting baseline peripheral arterial insufficiency	9/30 (30%)
Studies reporting BMI	5/30 (16.7%)

Intervention comparisons

Nineteen combinations of debridements or debridement with the control condition were made. This included 12 forms of debridement: 1) sharp, 2) larva, 3) low frequency ultrasound, 4) jet/irrigation lavage, 5) wet to dry gauze, 6) hydrogel, 7) foam, 8) silver based foam dressing, 9) fibrous-hydrocolloid, 10) alginates, 11) honey/jam, and 12) collagenase. The debridements were either compared to each other, or to a gauze/control condition. The control condition included moistened gauze that usually was moistened with saline but could have included an antiseptic (e.g. iodine). The intervention arms were paired with a “standard therapy” (adjunctive wound care measures).

These comparisons included debridement interventions against standard gauze therapy (moistened/saline gauze which may be categorized as a form of autolytic debridement) which was frequently used as a control condition in the included studies OR one form of debridement compared to another form of debridement.

There were significant effects of debridement for some of the outcomes of interest reported in single studies that utilized distinct debridement combination. These combinations could not be pooled in the meta-analysis portion of this systematic review since each of the distinct debridement combinations was only available in one study. These findings are summarized below with respect to the outcomes of interest.

Comparison 1 ([Piaggese 1998](#)) – Sharp surgical debridement demonstrated a statistically significant reduction in quality of life score by 2.2 as compared with nonsurgical management - 2.20 (95% CI -3.16 to -1.24), (Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.11$, $I^2=0\%$). Sharp surgical debridement demonstrated a statistically significant increase in time to complete healing by 82 days as compared with nonsurgical management 81.68 (95% CI 41.07 to 122.29).

Comparison 2 ([Goretti 2008](#)) – Superoxide solution demonstrated a significant beneficial effect as compared with standard local treatment using povidone iodine dressing. There was a decrease in time to complete healing by 6 days compared with standard local treatment with povidone iodine -6.00 (95% CI -6.94 to -5.06).

Comparison 5 ([Whalley 2001](#)) – Hydrogel purilon as compared with hydrogel intrasite reported a difference of 35% versus 19% in proportion of ulcers healing. It was unclear whether this was significant beneficial effect as there was not enough information reported to make that determination (e.g. no reported counts of events/nonevents).

Comparison 8 ([Lalau 2002](#)) – Calcium alginate demonstrated a significant increase in time to complete healing by 2.8 days as compared with gauze 2.80 (95% CI 1.46 to 4.14).

Comparison 12 ([Jeffcoate 2009](#)) – Iodine impregnated fiber dressing demonstrated a 45% increase in the number of infections as compared with gauze dressing 1.45 (95% CI 1.13 to 1.86).

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Comparison 15 ([EhsanUrRehman 2013](#)) – Honey soaked gauze as compared with iodine saline dressing demonstrated a cost difference of 334 Jordanian Dinars in mean difference (MD - 334.00, 95% CI -373.99 to -294.01).

Comparison 16 ([Hammouri 2004](#)) – Honey/saline dressing demonstrated a statistically significant decrease in treatment cost as compared with iodine peroxide saline – 334.00 (95% CI – 373.99 to – 294.01).

Eight other distinct comparisons that were described in single studies could not be pooled, as there were no other similar intervention comparisons in at least one other study. These studies included: Comparison 3 ([Amini 2013](#)) Low frequency ultrasound compared with sharp debridement, Comparison 4 ([Markevich 2000](#)) Larvae compared with hydrogel, Comparison 7 ([Clever 1995](#)) Polyurethane gel as compared with polyurethane foam, Comparison 9 ([Apelqvist 1990](#)) Hydrocolloid as compared with adhesive Zinc, Comparison 11 ([Roberts 2001](#)) Foam dressing as compared with saline nonadherent gauze dressing, Comparison 14 ([Foster 1994](#)) Hydrocellular polyurethane as compared with Calcium alginate, Comparison 17 ([Rhaïem 1998](#)) Sugar Jam with Hydrogen peroxide and topical antibiotic as compared with hydrogen peroxide and topical antibiotic, and Comparison 18 ([Belcaro 2010](#)) Silver (standard cleaning and compression management methods) dressing group as compared with (standard cleaning and compression management methods without silver ointment). These comparisons either did not report or did not demonstrate any significant difference in treatment effects for this systematic review's prespecified outcomes of interest.

Four of the 19 distinct comparisons did include 2 or more studies. These 4/19 comparisons were pooled in meta-analyses for the pre-specified outcomes of interest if reported. This included comparisons 6, 10, 13, and 19.

Pooled data in four separate comparisons including: Comparison 6 Hydrogel compared with gauze (3 studies pooled including: ([D'Hemecourt 1998](#); [Jensen 1998](#); [Vandeputte 1997](#)), Comparison 10 Foam dressing compared with Wet to Dry (2 studies pooled including: ([Blackman 1994](#); [Mazzone 1993](#)), Comparison 13 Hydrofiber compared with gauze (2 studies pooled including: ([Jeffcoate 2009](#); [Piaggese 2001](#)), and Comparison 19 - Any debridement compared with gauze (10 studies pooled including: ([Jeffcoate 2009](#); [Jensen 1998](#); [Piaggese 2001](#); [Piaggese 1998](#); [Vandeputte 1997](#); [Lalau 2002](#); [D'Hemecourt 1998](#); [Donaghue 1998](#); [Goretti 2008](#); [Roberts 2001](#)) found no significant beneficial difference, except for the proportion of ulcers completely healed in Comparison 19 - Any debridement as compared with gauze, and Comparison 6 – Hydrogel as compared with gauze.

Comparison 6 - Hydrogel demonstrated a significant beneficial effect as compared with saline gauze. There was a 71% increase in the number of ulcers healed as compared with good wound care 1.71 (95% CI 1.16 to 2.52), (Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.95$, $I^2=0\%$).

Comparison 19 - Any debridement demonstrated a 17% increase in the number of ulcers healed as compared with saline gauze 1.17 (95% CI 1.00 to 1.36), (Heterogeneity: $\chi^2 = 13.89$, $I^2 = 28\%$). However, when the two studies available only as abstracts were removed in a subgroup analysis a weaker and nonsignificant beneficial difference was found. 1.12 (95% CI 0.95 to 1.32), (Heterogeneity: $\chi^2 = 2.23$, $I^2 = 55.1\%$).

There was no significant study heterogeneity that was explained with any of univariate models that were analyzed, except gender. The effects demonstrated low to moderate heterogeneity for the specified outcomes used in this systematic review. Moderators that were analyzed included age, peripheral arterial disease, duration of diabetes, gender, data collection year, and study follow-up duration. All moderators were scrutinized for the recommended number of studies per covariate for each of the prespecified outcomes of interest. There were 6 moderators that satisfied these requirements for the intervention comparison Any debridement as compared with gauze. This analysis was only possible for two of the outcomes of interest this included proportion of infections, and proportion of ulcers healed. There was no significant association or effect using the moderators for either of these two outcomes of interest. A Meta-regression was performed and none of the candidate moderators yielded results any different from the null hypothesis with the exception of the moderator “gender”. This coincides with data that support a gender differential favoring males in the development of wounds in diabetics and amputations having a higher sex predilection among male diabetics. However, the effect was nonsignificant prior to the use of gender as a moderating variable.

Publication bias was assessed and based on the combination of funnel plot and statistical tests (Beggs, Eggers). No significant publication bias was observed despite the fact that 13/30 studies were supported financially by industry.

The GRADE approach was utilized to construct summary of findings tables in order to summarize our conclusions using a structured standardized evidence grading format. This yielded very low to low evidence of efficacy.

Conclusion

Currently there exists weak research evidence to suggest that debridement in one form is more effective in diabetic foot ulcers than other competing forms of debridement or standard gauze for the outcomes of interest in this review. Many of the randomized studies included in this review used small sample sizes that may have been underpowered with too few events/nonevents to make meaningful conclusions. This is evidenced by studies of varying sizes yielding too few events in the intervention arms making it challenging to detect true effects. The included studies often demonstrated significant risk of bias that contributed to the low quality evidence. The studies were variable in the inclusion/exclusion criteria reported.

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The findings of researchers could be better supported by following standardized reporting guidelines such as the CONSORT statement. The existing body of literature complicates efforts to synthesize the evidence in systematic reviews. Stakeholders, including patients, physicians, public health professionals, and policy makers, may consider individualized decision making such as indications/contraindications, allergies, tolerability, response, and cost as alternatives pending more definitive standardized RCT's on this research question. The range of insufficient information in reporting and variation in methods used are summarized in this systematic review. Investigators interested in this research question may benefit from the findings reported in this systematic review as an aide in guiding the design of future randomized studies.

**Debridement of Diabetic Foot Ulcers: Public Health and Clinical Implications.
A Systematic Review, Meta-Analysis, and Meta-Regression**

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Doctor of Philosophy Dissertation

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A Systematic Review, Meta-Analysis, and Meta-Regression

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Chapter 1

Background

Diabetic Foot ulceration has devastating complications. These include amputations resulting in poor quality of life, and serious infections including osteomyelitis and life threatening sepsis. Diabetic wounds can be protracted, take significant time to heal and they can recur after they have healed. They can be very costly and consume healthcare resources. These consequences have serious public health and clinical implications. Debridement is often used as a standard of care in efforts to help avert these consequences. It is used to remove nonviable or necrotic tissue in order to facilitate the wound healing process and help prevent these disabling outcomes. What is/are the most effective method(s) of debridement remains unclear? This systematic review of the literature on debridement of diabetic foot ulcers synthesizes all experimental evidence in an effort to help answer this important question.

Global Data Reports

In 2009 the International Working Group on the Diabetic Foot (IWGDF) began its efforts to produce consensus guidelines on the diabetic foot. In 2011 the IWGDF estimated that worldwide approximately 366 million people have diabetes, which includes 7.0% of the world's population. 80% of these people live in developing countries. The IWGDF 2012 estimated that by the year 2030 there will be 552 million individuals globally who are afflicted with Diabetes (Type 1 and Type 2) or approximately 8% of the adult population. Younger people are developing DM at an alarming rate. Annually approximately 1 million people undergo a limb amputation, or 1 amputation occurs every 30 seconds. The majority of amputations are preceded by a foot ulcer.

The most important risk factors involved in the development of these ulcers include peripheral neuropathy, foot deformities, relatively minor foot trauma, and peripheral arterial disease (PAD). Once the ulcer appears, infection and peripheral arterial disease are considered major causes leading to amputation. The burden of amputations in the developing world is greater than it is in the developed world. The working group estimated that approximately one quarter of wounds will not heal, and 28% may progress to the point where they require amputation ([Bakker 2012](#); [IWGDF 2012](#); [Ragnarson 2000](#)).

There is a significant psychosocial impact in that people with foot ulcers and amputations often have comorbid depression and a reduced quality of life ([Cosgrove 2012](#); [Kumari 2004](#)). There is an increase in “social isolation”. Stress can have immunocompromising effects ([Nakata 2012](#)). Risk of amputation is increased in people living alone, and those who lack the social support of family and friends. Timely healing was found to be important in improving quality of life. The working group has stated that investing in diabetic foot care guidelines is one of the most cost-effective forms of health-care expenditure ([IWGDF 2012](#)).

These global data by the IWGDF is contrasted below with country-specific data using US and UK data. This is done in order to better compare global health data on this question with health data from two industrialized countries in Europe and North America. This contrast is to help the reader better appreciate the context of global health data from the developing world against country-specific health data from selected representative countries in the industrialized world.

US Data Reports

In the United States the diabetes epidemic includes 25.8 million children and adults, or 8.3% of the U.S. population, approximating 1 in 12 people. A total of 18.8 million people are diagnosed, 7.0 million people are undiagnosed. There are approximately 79 million people living with pre-diabetes. This includes over 104.8 million individuals with some stage of diabetes, or approximately 1/3 of the U.S population. These data correspond with the rising rates of obesity, hypertension, and the increasing age of the US population. There were 1.9 million incident cases of diabetes diagnosed in people aged 20 years and older in 2010. The disease burden varies among race and ethnicity including 7.1% of non-Hispanic whites, 8.4% of Asian Americans, 12.6% of non-Hispanic blacks, and 11.8% of Hispanics. The annual death toll includes 231,404 deaths exceeding HIV/AIDS, and Breast Cancer combined. The diabetes epidemic is the number 1 cause of blindness or 4.8% of 30 million people. It is the leading cause of kidney failure accounting for 44% of new cases or 202,290 people per year, and as in the UK is the leading cause of amputations in the United States ([ADA 2011](#); [USAHQR 2012](#); [USCDC 2012](#); [Ramsey 1999](#)).

Surgical amputations in the United States have reached staggering levels among diabetics including 65,700 (60% of nontraumatic amputations in 2006). The prevalence of diabetic foot ulcers is estimated to be up to 8% of the diabetic population. Approximately 15% of diabetics are expected to develop a wound in their lifetime.

Based on pathophysiology irrespective of diabetes status 82% of amputations are due to vascular disease (includes diabetics), 22% due to trauma, 4% due to congenital causes, and 4% due to tumors. Approximately 1.6 million people are living with amputations in the U.S. and approximately 113,000 lower limb amputations are performed each year from all causes in the US ([ADA 2011](#); [USAHQR 2012](#); [USCDC 2012](#)).

Among diabetics approximately 75 percent of all amputations occur in people over the age of 65. Amputation rates are higher in males than they are in females, 12% versus 10.8% respectively. African-Americans with diabetes have a 1.5 to 2.5 time's greater rate of amputation than their Caucasian counterparts with diabetes ([Ashry 1998](#)). Poor circulation including microarterial occlusive disease is the main cause of amputation and accounts for over half of all amputations that occur among diabetics ([ADA 2011](#); [USAHQR 2012](#); [USCDC 2012](#)). Major amputations (above knee, or below knee) are a marker for increased mortality. It is estimated that 5-year mortality may be increased as high as 61% - 74% after a major amputation ([Robbins 2008](#); [Tentolouris 2004](#)).

UK Data Reports

Approximately 4.6 % of the UK population or 2.9 million people are estimated to have diabetes, which is increased from 2% of the population almost a decade earlier. 10% of diabetics have Type 1 diabetes and 90% have Type 2 diabetes. Foot ulceration is thought to affect 15% of people with diabetes at some time in their lives. In the UK people with diabetes are 15 times more likely to undergo lower limb amputations than people without diabetes. In the UK 70 % of people die within 5 years of having an amputation due to diabetes. Diabetes accounts for one-half of all limb amputations in the UK ([DiabetesUKorg 2013](#)).

These data are not significantly changed from those previously reported in 1997 and 2009. ([SIGN 1997](#); [SIGN 2009](#); [Spencer 2000](#)).

The World Health organization reports that 9.2% of males and 7.6% of females have raised blood glucose in the UK based on 2008 data estimates. 67.7% of males and 60.8% of females are overweight or obese. 65.6% of males and 65.7% of females have raised cholesterol while 46.4% and 40.8% had raised blood pressure in 2008. These risk factors are collectively referred to as “metabolic syndrome” and are driving the rising trend in diabetes, diabetic foot ulcers and the associated complications including amputations ([WHO 2011](#); [Calman 1998](#)).

Estimated Costs

Global Cost Estimates

The International working group on the Diabetic Foot (IWGDF) has issued a report on the cost of Diabetic foot ulcers and amputations. Foot related problems may use 12-15% of healthcare resources for diabetes in the developed world, whereas in developing countries this may be as high as 40% ([Bakker 2012](#); [IWGDF 2012](#)) see [Table 2](#) below.

Table 2 IWGDF 2012 (Reproduced here with permission from the IWGDF)					
Table of Costs of Treating Foot Ulcers and Amputations					
Reference	Country	Number of Patients	Costs (year of costing)	USD 2005 equivalent	Comments
Ulcers not requiring amputation					
Apelqvist et al, 1994	Sweden	197	Sweden 197 SEK 51,000 (1990)	8,654	All ulcer types; total
Harrington, et al, 2000	USA	400,000	USA 400,000 USD 3,999-6 (1996)	4,982-7,821	Inpatient and outpatient costs
Holzer et al, 1998	USA	1846 c	USD 1,929 (1992)	2,695	Inpatient and outpatient costs, those >64 yr. excluded
Metha et al, 1999	USA	5149	USA 5149 USD 900-2,600 (1995)	1,150-3,322	Private insurance charges; mean age 51 yr.
Ragnarson Tennvall et al, 2000	Sweden	88	Sweden 88 SEK 136,600 (1997)	18,719	Deep foot infection; total direct costs
Ramsey et al, 1999	USA	514 d	USD 27,987 (1995)	35,758	Including 2 yr. after diagnosis
Van Acker et al 2000	Belgium	120	Belgium 120 USD 5,227 (1993)	7,039	Inpatient and outpatient costs
Costs of lower extremity amputations					

Apelqvist et al 1994	Sweden	27	Sweden 27 SEK 258,000 (1990)	43,778	All ulcer types; minor LEA; total direct costs
Apelqvist et al 1994	Sweden	50	Sweden 50 SEK 390,000 (1990)	66,176	All ulcer types; major LEA; total direct Costs
Ashry et al 1998	USA	5062	USA 5062 USD 27,930 (1991)	39,891	Hospital charges Only
Holzer et al, 1998	USA	504 c	USD 15,792 (1992)	22,062	Gangrene/amputation, those >64 yr. excluded
van Houtum et al, 1995	Netherlands	1575 e	NLG 28,433 (1992)	19,052	Hospital costs only
Panayiotopoulos et al, 1997	UK	20	UK 20 GBP 15,500 (1994-95)	33,587	Inpatient and prostheses costs (46% diabetics)
Ragnarson Tennvall et al, 2000	Sweden	77	Sweden 77 SEK 261,000 (1997)	35,767	Deep infection; minor LEA; total direct costs
Ragnarson Tennvall et al, 2000	Sweden	19	Sweden 19 SEK 234,500 (1997)	32,136	Deep infection; major LEA; total direct costs
Van Acker et al, 2000	Belgium	7	Belgium 7 USD 18,515 (1993)	24,933	Inpatient and outpatient costs; minor LEA

Van Acker et al, 2000	Belgium	9	Belgium 9 USD 41,984 (1993)	56,538	Inpatient and outpatient costs; major LEA
<p>Footnotes</p> <p>For comparison of the results, costs were first adjusted for inflation to 2005 prices with the consumer price index f and then converted to USD with the appropriate currency exchange rate for 2005.</p> <p>NA = not applicable.</p> <p>LEA = Lower Extremity Amputation.</p> <p>Minor = amputation below the ankle;</p> <p>Major = amputation above the ankle.</p> <p>a Based on data from observational studies</p> <p>b Based on data from databases and other secondary sources</p> <p>c Number of episodes</p> <p>d Includes 80 amputations</p> <p>e Number of hospitalizations</p>					

US Cost Estimates

The estimated total cost of diabetes in the United States in 2007 was \$218 billion, exceeding 1/5 of a trillion dollars. This includes direct and indirect costs. The peak age-range for amputations is between 41 and 70 years. This is a time period of prime working age and productivity for adults. This poses a significant health challenge to our workforce since amputations can result in permanent impairment often qualifying an individual for disability benefits resulting in lost wages, and productivity ([Holtzer 1998](#)). This poses a significant stress on the family unit.

It imposes an economic burden upon society at large in providing for impaired and disabled individuals. The rate of amputations is rising and these factors are directly contributing to this alarming trend ([ADA 2011](#); [USAHQR 2012](#); [USCDC 2012](#)).

US Government estimates for the 2007 GDP portion allocated for direct healthcare costs was \$2.2 trillion or 16% of the GDP ([NCHS 2010](#)). Chronic diseases, including heart disease, stroke, cancer, and diabetes, cause 7 out of 10 deaths and are responsible for 75% of the \$2 trillion spent on health care ([CDC 2009](#)). In comparison the direct and indirect costs for Diabetes in 2007 approximate 10% of 2.2 trillion dollars. Up to 15% of costs for DM in the developed world is estimated to be allocated for foot related problems, approximately 33 billion dollars in the US ([IWGDF 2012](#); [Harrington 2000](#)).

UK Cost Estimates

The UK National Health Service (NHS) spends an estimated £10 billion per year on diabetes or 10% of the National Health Service budget. Total direct and indirect costs for diabetes in the UK is £23.7 billion per year ([DiabetesUKorg 2013](#)). In the previous protocol from 2001 it was estimated that £12.4 million was spent on amputations per year. A report published in March of 2012 by the British National Health Service (NHS) - Diabetes estimates that £650 million (£1 in £150 in the NHS total expenditures) is spent on foot ulcers or amputations each year ([NHS 2012](#); [King's Fund 1996](#)).

Description of the condition

Etiology of Diabetic Foot Ulcers

The diabetic foot ulcer is considered multifactorial in its etiology.

Wound progression

Wound repair and closure helps re-establish hemostasis, preserving the barrier function of the skin in order to prevent infection, and maintaining the overall protective role of the skin. An ulcer is the result of a break in the dermal barrier, with subsequent erosion of underlying subcutaneous tissue. In severe cases, the breach may be extended to muscle and bone. The progression to ulceration may be attributed to an impaired arterial supply, neuropathy, musculo-skeletal deformities, or a combination of these factors ([Bauer 2000](#)). If the process of wound healing is impaired and the wound progresses then the risks of infection, amputation, morbidity and mortality increase ([Sheffield 2004](#)).

Wound development and progression are a major risk factor for amputation and follow what is considered a predictable course among experts in the field. Wounds healing progresses through the following phases: 1) Hemostasis/Coagulation phase, 2) Inflammatory phase 3) Proliferative phase, 4) Maturation/Remodeling phase ([Baronski 2008](#); [Myers 2008](#); [Sheffield 2004](#)).

Problems with wound healing may impede wound progression and are considered multifactorial in diabetics. These prognostic problems may include some or all of the following: vascular insufficiency/peripheral arterial disease, peripheral neuropathy (sensory, motor, and autonomic), immunosuppression, critical colonization/infection. These prognostic problems may be more common in the presence of nonviable tissue (contributing to an increased risk of infection and delayed wound healing), smoking (contributory to the risk of vascular insufficiency, and inflammatory burden), and poor nutritional status (inadequate protein and nutrients required for wound healing). It is believed that these combined problems contribute to the wound stagnating within the inflammatory phase of the healing process. Typically, the development of a wound involves a relatively minor soft-tissue injury or insult possibly compounded by these other factors. The trauma can be the result of friction, mechanical shearing forces, direct pressure, or penetrating tissue injury including sharp or blunt trauma ([Baronski 2008](#); [Myers 2008](#); [Sheffield 2004](#)).

These factors are believed to have a major role in the pathogenesis of diabetic foot ulcerations leading to wound progression and the associated complications including serious infection and amputation ([Davies 1989](#)).

Vascular Insufficiency

Disease of blood vessels are a major cause of complications in diabetes and affects all types of vessels ([Faris 1991a](#)). The Framingham study reported that more than 50% of men and women with diabetes had absent foot pulses ([Abbott 1990](#)).

Peripheral vascular disease (PVD) tends to occur at a younger age in people with diabetes and is believed to involve smaller blood vessels and capillaries further away from the heart. Reports from US, UK and Finland ([Pecoraro 1990](#); [Reiber 1999](#); [Siitonen 1993](#)) have concur that PVD is a major contributory factor in the pathogenesis of foot ulceration and subsequent major amputations ([Boulton 2000](#)).

Impaired blood flow can occur at both the microvascular and macrovascular arterial circulation levels in diabetics and can compound the problem of delayed wound healing by leading to inadequate tissue oxygenation. Microcirculation involvement includes the occlusion of small blood vessels and capillaries, whereas macrovascular insufficiency is defined as the occlusion of medium and large sized blood vessels. Hemodynamically significant macrovascular arterial insufficiency is considered an advanced stage of peripheral arterial disease (PAD). This may warrant surgical revascularization procedures ([Panayiotopoulos 1997](#)). These vascular occlusions and the resulting wound hypoxia poses a major risk factor in the development of non-healing problem wounds ([IWGDF 2012](#); [Neuman 2008](#); [Sheffield 2004](#)). A host of considerations are believed to compound vascular insufficiency which restricts the delivery of oxygen and nutrients required for adequate wound healing, immune function, and can increase susceptibility of co-infections. Considerations may include nutritional status, cardiovascular insufficiency, hydration status, psychosocial factors, smoking and alcohol history, patient compliance, socioeconomic status, availability of ancillary treatment modalities, proficiency and expertise of the healthcare provider involved in the wound care, the type of wound and the presence of wound occurrence from combined wound mechanisms, the age of the patient, and possibly the type of debridement method provided to the patient for removal of nonviable tissue from the wound bed and periwound ([Bakker 2012](#); [Edwards 2011](#); [IWGDF 2012](#); [Smith 2002](#); [Sheffield 2004](#)).

Neuropathy (Sensory, Motor, Autonomic)

Impairment of nerve function is an important and frequent complication of diabetes. All types of nerve fibers can be affected including motor, sensory and autonomic nerve fibers and their associated functions. Impaired nerve function in the foot is common in people with diabetes although the person themselves may be unaware of its presence. Neuropathy remains one of the major factors leading to the development of foot lesions in people with diabetes ([Le Quesne 1991](#)).

This is a frequent occurrence among diabetics. Approximately 60-70% of diabetics have neurologic disease, most often a peripheral neuropathy involving the lower extremities ([ADA 2011](#); [USAHQR 2012](#); [USCDC 2012](#)). This microvascular disease component is believed to cause occlusion within the vasonervorum which provides the blood supply to the nerves. This is may be due to the direct cytotoxic effect of the hyperglycemia. This form of microvascular occlusive disease contributes to the development of peripheral neuropathy. Since diabetic neuropathy involves motor, sensory and autonomic nerve fibers the pathologic deficits may include the deformed, insensate, and dry cracking foot.

a) Sensory neuropathy

Damage to the nerves carrying signals from the foot renders the foot insensitive to temperature, vibration, pressure, and pain. This is referred to as sensory neuropathy. The loss of sensation means that small injuries often go undetected.

b) Motor neuropathy

Denervation of muscles has direct effects on the function of the foot. The small muscles of the foot, the extensor digitorum brevis, lumbrical and interosseous muscles are commonly affected. Paralysis of these small muscles results in the metatarsophalangeal joints becoming hyper-extended and the interphalangeal joints becoming flexed. The joints initially remain mobile, but later degenerative changes occur and the joints become fixed ([Le Quesne 1991](#)). The consequence of such muscle wastage is a foot shape that increases foot pressures over bony prominences where wounds most commonly occur in diabetics.

c) Autonomic neuropathy

Autonomic neuropathy is thought to contribute to the pathogenesis of ulceration, neuropathic edema, and Charcot arthropathy ([Le Quesne 1991](#)). Impairment of sweating is suggested to contribute, through dehydration, to the formation of hyperkeratotic plaques and fissures in the skin. If this callus (increased glycation of keratin) becomes too thick, it presses on the soft tissues underneath contributing to ulceration ([Edmonds 2000a](#)). Callus is defined as a buildup of keratinized skin, in reaction to persistent pressure ([Cutting 1999](#)), and can itself exert pressure on the soft tissues of the foot.

The dry cracking foot is a function of the anhidrosis that can develop due to the autonomic neuropathic changes. Impaired temperature regulation from the autonomic neuropathy may contribute to these local effects ([IWGDF 2012](#)).

Immunosuppression/Critical Colonization/Infection

Diabetes is considered an immune-compromising condition. It has been observed that white blood cells may behave atypically in a hyperglycemic (high glucose) environment. They demonstrate dysfunctional behavior and do not marginate, migrate, or secrete the cytokines sufficiently that are required in order to combat infection. This can increase the risk of critical colonization and infection. Critical colonization is defined as a concentration of bacteria at least 100,000 organisms per gram of tissue. The immunosuppressive state that may occur in Diabetes in the presence of an open wound can lead to critical colonization and infection which are complicating factors that can increase the risk of non-healing chronic wound ([IWGDF 2012](#); [Sheffield 2004](#)).

The chronicity of this condition may increase the risk of Methicillin Resistant Staphylococcus Aureus (MRSA), which is among the cultured organisms found in chronic wounds and a major public health concern. Infections that have reached the deeper bony level of tissue involvement may become especially problematic making them refractory to treatment. The patient can be at risk for life threatening sepsis from a wound as an infectious source ([IWGDF 2012](#); [Sheffield 2004](#)). This may warrant urgent amputation to remove the source of life threatening sepsis.

Pathway to Ulceration

Despite the presence of the predisposing factors noted above, an uninjured foot may not develop serious problems. Physical trauma is an inciting event e.g. a puncture wound, localized pressure, repeated mechanical trauma, heat or chemical injury ([Faris 1991b](#)).

When there is sensory impairment, a small lesion may progress because it may go unrecognized and the source of injury not alleviated. Lack of sensation allows the damage to progress to ulceration. Impairment of the blood supply may result in delayed healing. Complicating infection may contribute as an additional risk factor by increasing the amount of damaged tissue ([Faris 1991b](#)).

Chronic wounds may continue to progress beyond full thickness (limited to the epidermis and dermis). This progression can extend further involving deeper tissues including the hypodermis, muscle, tendon, and bone. Progression of vascular compromise and infection may lead to tissue ischemia, non-viable tissue, and gangrene. This pathway ultimately may lead to limb amputation. Deep seated wound infections such as chronic osteomyelitis and significant bone destruction can become considerations in the decision to amputate limbs ([ADA 2011](#); [Bakker 2012](#); [Edwards 2011](#); [Smith 2002](#); [USAHQR 2012](#); [USCDC 2012](#)).

Common Grading systems used to classify the severity of diabetic wounds

The Wagner grading system and the Texas classifications are internationally utilized grading systems. These grading systems were compared and the results concluded that increasing stage, regardless of the grade, is associated with increased risk of amputation and a delay in ulcer healing time. The University of Texas system's inclusion of stage suggested it was a superior predictor of outcome ([Oyibo 2001](#)) See [Table 3](#); [Table 4](#) below.

Table 3 Wagner Wound Grade Classification System					
Grade					
0	1	2	3	4	5
No ulcer in a high risk foot	Wound involving full skin thickness	Wound extending to ligament and muscle	Wound with cellulitis or abscess	Localized gangrene	Extensive gangrene involving the whole foot

Table 4 University of Texas Wound Classification System				
	Grade			
Stage	0	1	2	3
	Pre or Post ulcerative lesion completely epithelialized	Superficial wound not involving tendon, muscle, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
A No Infection, or Ischemia	0A	1A	2A	3A
B Infection but no ischemia	0B	1B	2B	3B
C Ischemia but no infection	0C	1C	2C	3C
D Infection and ischemia are present	0D	1D	2D	3D

Description of the intervention

Debridement as the Wound Care Intervention of Interest

Currently debridement is considered a central component of conventional treatment in wound care (the removal of non-viable or necrotic “dead” tissue from the wound). This component of wound care is used to remove non-viable tissue which may pose a risk of colonization and infection. Nonviable tissue may impede wound healing by obstructing cellular migration across the wound. It is believed to impede the normal development of the wound bed and prevent granulation tissue formation ([Baronski 2008](#); [Sheffield 2004](#); [Strohal 2013](#)).

Debridement is considered to be a means of enabling the clinician to better gauge the size of the wound. Debridement may facilitate drainage from the wound. Removal of nonviable tissue may reduce the risk of infection and facilitate cellular migration of cells in the wound healing process. It is believed that an accurate wound culture should be obtained post-debridement and following saline irrigation of the wound itself ([Sheffield 2004](#); [Strohal 2013](#)).

Treatment is focused on closing the wounds within the first 4-6 weeks of their development.

Wounds that decrease their surface area by 20 – 40 % within the first 4 weeks are considered to have a higher likelihood of closing by experts ([Baronski 2008](#); [Sheffield 2004](#)). Desirable goals include reducing the time to complete healing, accelerate healing rates, and reducing the rates of recurrence of wounds. If the wound is closed in a timely manner the risks of complicating infections, and amputation may be prevented thus improving the patient’s overall quality of life.

The following are considered alternate methods of wound debridement:

Mechanical Debridement – This method uses mechanical energy such as surgical debridement, high pressure saline irrigation, whirlpool, wet to dry saline dressings, ultrasound, or jet lavage. The nonselective nature of these forms of debridement can remove granulation tissue that is produced during the proliferative phase of wound healing [Table 5](#).

- i) ***Sharp Surgical Debridement*** – This may be performed either in the inpatient or outpatient settings. It may be done in the operating room suite if an extensive debridement is required in lieu of an outpatient “office” surgical procedure when the debridement is less extensive and superficial. Ultimately the decision on what setting in which to perform the debridement is based both upon the patient’s comfort level and how extensive a debridement procedure is required. Expert opinion in sharp surgical debridement has generally dictated that all the nonviable and necrotic tissue should be removed and debrided down to bleeding tissue, in effect creating a new acute wound. This repeats the phases of wound healing from the beginning. This is often not possible without injuring healthy tissue in the process of attempting to remove nonviable (dead) tissue. This dissection process can be time-intensive and is considered semi or non-selective. The injury of healthy tissue results from the delicate task of separating viable from nonviable tissue using standard sharp dissection instruments i.e. scalpels and curettes.

Gross dissection using instruments classified as blunt are not capable of ultra-selective microdissection even in the hands of the most skilled health professionals. Microdissection may only be possible with the use of biosurgery or maggot debridement therapy described later. This may be problematic in that every “new” injury increases the risk for a complicating superinfection ([Bakker 2012](#); [Edwards 2011](#); [Smith 2002](#); [Strohal 2013](#)).

- ii) ***Wet to Dry Mechanical Debridement*** removes non-viable tissue by allowing gauze saturated with saline and applied to a wound to dry. The gauze then become adherent to the wound during the drying phase. The gauze is then removed, which can non-selectively pull away both non-viable tissues along with viable granulation tissue ([Sheffield 2004](#); [Strohal 2013](#)).
- iii) ***Aqueous high pressure lavage/irrigation*** involves a jet-stream of saline that mechanically removes nonviable tissue. This is considered a non-selective form of debridement and is capable of removing granulation tissue. This theoretically may pose a risk to the healthcare provider performing the debridement. The mist created by the high pressure irrigation may expose the provider to contamination ([Sheffield 2004](#); [Strohal 2013](#)). ***Whirlpool*** also involves a form of high pressure hydro-irrigation except the entire limb or patient is immersed in a whirlpool bath during irrigation. Cross contamination is possible using this method as other wounds and body surfaces may be immersed in the same water. This is also considered a non-selective form of debridement ([Sheffield 2004](#); [Strohal 2013](#)).

- iv) ***Ultrasound Debridement*** utilizes sound energy to mechanically debride wounds. This is usually carried out through contact or noncontact low frequency ultrasound energy.

- v) ***Biosurgery or Maggot Debridement Therapy (MDT)*** - This has been an area of interest for over 400 years and provides a complex system of wound care. Maggots are larva of flies such as *Lucilia Sericata* that consume nonviable tissue selectively. This is typically done in the U.S. with another form of larva, the blow fly maggot variety (*Phoenicia Sericata* larvae). Medicinal maggots are believed to carry out this biosurgical debridement of nonviable tissue selectively as compared with blunt dissection using sharp surgical instruments. This may reduce the risk of secondary or superinfection. The species of flies used are cultured for this purpose and provide a source of enzymatic debridement. The maggots are capable of consuming bacteria and are believed to produce antimicrobial secretions. This has been demonstrated in mechanistic in vitro studies ([Margolin 2010](#)). Maggot debridement therapy may have antimicrobial properties including those from hospital acquired resistant organisms such as MRSA. They may secrete substances that stimulate wound healing ([Margolin 2010](#)).

Non-Mechanical Debridement

- i) ***Enzymatic Debridement*** – This involves the use of exogenous enzyme products that digest the non-viable tissue as opposed to exclusively relying on endogenously produced wound enzymes such as matrix metalloproteinases that provide autolytic debridement.
- ii) ***Autolytic Debridement*** – This approach involves keeping the wound moist which may facilitate the endogenous enzymes produced by the wound itself in order to auto-digest or “self-digest” nonviable tissue. The use of agents such as hydrogel facilitates moist wound healing and allows endogenous locally produced enzymes to digest the non-viable tissues. Many topical agents that are applied directly to skin facilitate autolytic debridement such as topical antimicrobials even though they are also used to treat local wound infections. The ability of a variety of topical agents to maintain a moist wound environment permits concurrent autolytic debridement irrespective of the other functions of the topical agent used. Other dressings that facilitate autolytic debridement include: Alginates, Hydrocolloids, Foam, Film, and Honey. Moist saline gauze is commonly used and has served as a control or standard form of debridement in studies ([Sheffield 2004](#); [Strohal 2013](#)). See [Table 5](#) for a comparison of methods of debridement.

The evidence to support these various forms of debridement and their impact on such important indicators as amputation frequency, complicating wound infection frequency, cost, quality of life, and wound healing rates, recurrence, and time to complete healing will be scrutinized in this review.

Standard Wound Care Prevention and Treatment

The treatment of diabetic foot ulcer generally involves a multidisciplinary team approach and includes comprehensive advanced wound care. This team may be comprised of a primary care physician, wound care physician, a wound care nurse, a nutritionist, orthotics consultant, physical therapist, and a hyperbaracist. This comprehensive advanced wound care approach provided by a multi-disciplinary team may include the following interventions: ([Baronski 2008](#); [Sheffield 2004](#)).

i) Off-loading: Weight bearing redistribution is the considered the most important consideration for wound healing of the diabetic foot ulcer. This provides support by redistribution of weight bearing away from the wound and relocates it to the adjacent surfaces of the affected foot or leg through the use of orthotics. Alternatively, complete offloading can be achieved by using wheelchairs, walkers, crutches, or other wheeled mobile devices to remove all weight bearing entirely (non-weight bearing) from the affected wound ([Sheffield 2004](#)).

ii) Physical Therapy: The use of offloading equipment may require special instruction routinely provided by a physical therapy department. This may require instruction in the proper use of crutches, wheelchair, or other ancillary mobile non-weight bearing equipment.

The patient may require rehabilitation due to long periods of immobility in order to regain function and strength in order to maintain function and support the use of offloading devices.

iii) Medical Optimization of Comorbidities including Diabetes: The patient may require optimization of current treatment for diabetes and other conditions that if left untreated or poorly controlled may impede wound healing.

iv) Nutritional Consultation Services and Supplementation: These services have been utilized to address nutritional deficiency states that may impede wound healing. Laboratory markers such as Total Lymphocyte Count, pre-Albumin, Albumin, and Total Protein along with clinical parameters have been used to help direct the proper nutritional interventions.

v) Infection Eradication: If the wound is critically colonized or infected then this may impair wound healing and antimicrobial therapy is often prescribed. Treatment can be directed locally or systemically depending on the extent of the infection.

vi) Medical and Surgical Vascular interventions: Hemodynamically significant macrovascular insufficiency can compound microarterial insufficiency and may require vascular surgical evaluation. Therapy may involve more extensive medical treatment or it may require surgical revascularization. Surgical revascularization could include angioplasty, stenting, atherectomy, or surgical bypass grafting.

vii) Hyperbaric Oxygen Therapy: Periwound tissue hypoxia can be measured using transcutaneous oximetry. If tissue hypoxia is found to be reversible with normobaric or hyperbaric oxygen challenge; then adjuvant hyperbaric oxygen therapy has been considered adjuvant therapy in healing problem wounds in diabetics. This testing may suggest microvascular insufficiency. Hyperbaric oxygen therapy may increase tissue oxygen tensions up to fifteen times normal. Angiogenesis and vasculogenesis are believed to be stimulated by the use of hyperbaric oxygen therapy, which may enhance the blood supply around the wound. Pro-inflammatory intracellular adhesion molecules are down regulated providing an anti-inflammatory effect ([Thom 1989](#)). Edema may be decreased by the use of hyperbaric oxygen therapy through peripheral vasoconstriction without a negative effect on tissue oxygenation.

Oxygen diffusion is increased up to a factor of 4 in the affected tissues ([Fife 2007](#)).

Antimicrobial tissue penetration and leukocyte function is believed to be enhanced by the use of hyperbaric oxygen therapy. Susceptible organisms such as anaerobic or facultative anaerobic organisms that do not tolerate high oxygen environments may be inhibited by the use of hyperbaric oxygen therapy. An increase in stem cell production, differentiation, and presence in the wound bed has been demonstrated ([Thom 2005](#)). Hyperbaric oxygen therapy may be especially useful in those diabetics that have had wound care for greater than 4 weeks with poor or no response to treatment ([Sheffield 2004](#); [UHMS 2008](#)).

Mechanism of the Intervention

Debridement - Current practice

Debridement involves the removal of devitalized, contaminated or foreign material from within or adjacent to a wound, until surrounding viable tissue is exposed. It is widely practiced in diabetic foot care ([Dorland's 1998](#)). Debridement is regarded by many as an effective intervention to speed up ulcer healing. Sharp debridement of an ulcer, including the removal of callus (which may surround or “roof over” an ulceration) and all devitalized tissue may facilitate wound healing, though direct evidence of this is lacking.

Once an ulcer has developed the aim is to heal it in as short a time period as possible and prevent recurrence. Margolis conducted a meta-analysis of the control group healing of 10 treatment trials in people with diabetic neuropathic foot ulcers and estimated that 24% heal within 12 weeks and 31% by 20 weeks with good wound care ([Margolis 1999](#)).

High quality management of the diabetic foot often requires multidisciplinary input and good communication between primary and tertiary care providers ([Young 2000](#)).

Edmonds ([Edmonds 2000b](#)) suggests six aspects of "control" to be addressed when caring for people with diabetes, particularly in relation to foot health:

- mechanical control;
- wound control;
- microbiological control;
- vascular control;
- metabolic control;
- educational control.

Debridement (*see* [Table 5](#) Methods of debridement) is recommended by the SIGN diabetic foot guidelines ([SIGN 1997](#)) alongside antibiotic therapy for infection and pressure relief as a treatment for patients who have developed ulceration or gangrene with risk of amputation. The Royal College of General Practitioners' Guidelines ([RCGP 2000](#)) also recommend debridement as a treatment of the ulcerated foot alongside local wound management and appropriate dressings. Neither of the guidelines recommend a specific method of debridement.

Edmonds gave the following rationale for debridement of neuropathic ulcers which included [\(Edmonds 2000b\)](#):

- enables the true dimensions of the ulcer to be perceived
- allows drainage of exudate and removal of dead tissue, both render infection less likely
- enables a deep swab to be taken for culture
- encourages healing.



Figure 1 Serial images depicting measurements of wound progress over the course of sequential combined forms of debridement lasting 12 weeks including sharp, enzymatic, and autolytic.

The diabetic foot ulcer has serious consequences to the individual patient, their families, the healthcare system, and to society as a whole. The patients who undergo amputations, serious infections along with the associated impairment and disability results in financial hardship and lost productivity. The patient faces a reduced quality of life along and an increase in 5-year mortality.

These outcomes may be averted if efforts are made to accelerate successful wound healing.

Wound care is considered by many to be a multidisciplinary team approach. The standard of care in wound care includes debridement. There are numerous methods of debridement and it is unclear which method(s) is/are effective.

Chapter 2 Literature Search for Prior Systematic Reviews with a Similar Research Question

Introduction/Background

Systematic Reviews and Meta-analyses are important tools in Evidence Based Medicine and Healthcare. These tools provide researchers with an exhaustive, objective, and transparent scientific approach using duplicate efforts in synthesizing the evidence around a specific research question. They provide researchers with the means of determining what the best available evidence concludes. The systematic review itself is a scientific investigation that is comprehensive, transparent, promotes duplication of effort, and facilitates replication ([Cooper 2009](#); [Higgins 2008](#)).

This may include a qualitative systematic review, and when possible a quantitative systematic review. The qualitative systematic review exhaustively pools together and collectively summarizes all the available evidence retrieved and extracted on a specific research question. It does so by using objective search methods, a data extraction tool, and an objective risk of bias evaluation tool to assess and judge the quality of the evidence ([Cooper 2009](#); [Higgins 2008](#)).

The researchers can determine if a quantitative systematic review (meta-analysis) is warranted based on the results of the qualitative systematic review. The meta-analysis is a quantitative synthesis or combination of the evidence from the sample of studies that are included in the review. The quantitative systematic review may pool together these raw data originally used in the included studies. Alternatively, and more commonly the summary statistics from each of the included separate studies are pooled together. This will include the various effect estimates

which may have been measured on different scales. If the scales differ the researchers can transform the different effect estimates into a common scale effect estimate. The effect estimates could include mean differences, odds ratios, relative risk ratios, standardized mean differences, or correlation coefficients ([Cooper 2009](#); [Higgins 2008](#)).

Pre-requisite to any planned systematic review requires an exhaustive search of the literature systematically for other systematic reviews (SR's) that may have been conducted on a similar research question.

The retrieval of prior systematic reviews that evaluated competing debridement interventions to treat diabetic foot ulcers for comparative effectiveness is an essential component of this current review. The goal is to help determine what is/are the most effective form(s) of debridement in treating non-healing wounds in diabetics. The prior systematic reviews may have afforded researcher's new information on reducing the risk of amputations and associated mortality, reducing complicating wound infections, improving quality of life, accelerating healing rates, and reducing costs.

Contrasting our systematic review against other similar reviews is essential to determine if our systematic review is to add additional knowledge to the body of literature on this important research question.

Objectives

This review included the literature search and retrieval of all other systematic reviews on this research question using similar inclusion and exclusion criteria. These other systematic reviews could then be compared and contrasted with this review.

Methods

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria that were utilized to retrieve all prior systematic reviews on the same research question included the following:

- a) Systematic reviews (SR's) and/or meta-analyses (MA's) that included randomized controlled trials (RCT's) on debridement of diabetic foot ulcers. The search included any form of debridement but did not include SR's on Negative Pressure Wound Therapy (NPWT). NPWT includes debridement as one of its numerous functions but this form of therapy has been studied in a separate Cochrane review.
- b) Adult Type 1, or Type 2 diabetics with ischemic, neuropathic, or neuroischemic diabetic foot ulcers. The wounds were not limited in severity or in grading system utilized including Wagner Wound Grade, and Texas Classification.
- c) There were no other limitations based on age, gender, country, healthcare setting, or language.
- d) RCT's that included other wound types i.e. venous stasis ulcers, arterial insufficiency ulcers in non-diabetics, pressure ulcers, and atypical ulcers were excluded.
- e) Systematic reviews that were limited to nonrandomized trials or that focused exclusively on other wound types were excluded.

Database searched

Data sources were searched and collected accordingly per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement Reporting guidelines.

The searches utilized the following databases and dates: Ovid Medline (1996 – 2013 March Week 4), PubMed (1940's – Present), Ovid Embase (1996 – 2013 week 13), Embase via Scopus (1960 – Present), EBSCO CINAHL (1981 to Present), Web of Science (1974 – Present), The Cochrane Library, Cochrane Wounds Group Specialized Register (4/15/2015). The detailed search methods utilized are included under Search Strategies ([Appendix 1](#)).

Data Extraction

Two independent reviewers reviewed the search results and independently extracted all systematic reviews that met the pre-determined inclusion criteria. These data from the SR's were extracted from the SR's along with the respective authors conclusions for comparison with this review using the same data extraction tool ([Appendix 2](#)) used for our review of randomized controlled trials (RCT's) for our systematic review. However, the SR's were not pooled and no meta-analysis was conducted on the retrieved SR's. The data extraction was used to facilitate a qualitative review of the SR's for contrast purposes with this systematic review. The retrieved bibliographies were hand searched to locate additional RCT's for this SR.

These data extracted from systematic reviews included:

- a) Author/year which served as a study ID.
- b) Number of studies included in the systematic review.
- c) Study types including randomized, non-randomized and the number of studies for each designation.
- d) Total number of participants included.
- e) Follow up period

- f) Study period
- g) Wound severity or grade
- h) Debridement intervention type(s).
- i) Outcomes included in the systematic reviews.
- j) Identification as a Cochrane review or not.
- k) The SR's authors concluding statements regarding the outcome effects and their findings along with the strength of the evidence were extracted verbatim and are listed in quotations.

These are summarized in Table 3a below in the results section.

Results

The search retrieved 10 related systematic reviews. Four of the studies retrieved combined both randomized and nonrandomized studies. This practice is discouraged as randomized studies and nonrandomized studies should generally be combined with similarly designed studies in separate systematic reviews i.e. randomized studies alone and nonrandomized studies alone. The reasoning behind this approach is that non-randomized studies are generally considered to be at higher risk of demonstrating biased exaggerated effect estimates than randomized studies. Despite this concern the findings in the four systematic reviews that included non-randomized studies are came to comparable conclusions with other systematic reviews that were limited to randomized studies. See table 3a below.

The number of systematic reviews that used similar inclusion/exclusion criteria as this review (i.e. Type 1 or 2 Diabetic participants with foot ulcers, randomized studies, and any debridement method) are listed in the following table:

Table 6 Comparison of systematic reviews preceding this current systematic review												
#	[Review]	[# Studies included]	[Study Type(s)]	[Total sample size]	Follow up period	Study period	Type of wound	[Participant Type]	[Intervention Type]	Outcomes	Cochrane Review	[Conclusions]
1	Edwards 2011	6 (3/6 pooled)	6 Randomized	488	10 days to 24 weeks	1995 to 2001	DFU	Diabetics (1,2)	4 comparisons Hydrogel v gauze (pooled) Larva Surgical debridement	4 Ulcers healed Time to Complete Healing Recurrence Adverse Events	Yes	Low evidence
2	Mason 1999	10 total (4 on debridement not pooled)	8 Randomized 2 Nonrandomized	202	4 weeks to 2 months	Unclear	DFU	Diabetics (2)	Film Alginate	Ulcers healed Mean time to healing	No	Low evidence "evidence base for treating infections and dressing wounds is poor" Summarized studies
3	Game 2012	5	4 Randomized (not pooled), 30 ischemic	149			100 DFU	Diabetics (1,2), Ischemic, Venous	Sharp Debridement, Aquacel, Larva, Hydrotherapy	Ulcers healed, Time to Healing,	No	Low evidence "scientific evidence to confirm the benefit of sharp

			1 Nonrand omized		12 weeks – 6 months	1998 - 2007	30 Ischem ic 19 venous			Infection, Amputation		debridement was not strong", "weak evidence to support the use of hydrogels", "no benefit in larva and hydrotherap y"
4	Hinchliffe 2008	10	6 Randomi zed (not pooled) 4 Nonrand omized	575	5 weeks to 20 weeks	1989 to 1998	DFU	Diabetic s (1,2)	Hydrogel, Alginates, Carboxymet hylcellulose, Polymeric semipermea ble membranes	Ulcers healed, Healing time,	No	Low evidence "evidence to underpin the use of sharp debridement and debriding agents is not strong, evidence is, urgently needed to substantiate role of larvae, topical antiseptics and all dressing products. No data were available to support the current widespread use of silver-

												containing dressings
5	Dumville 2015	6 (2/6 studies pooled for alginate v BWCD, and 2 pooled for Alginate v foam)	6 Randomized	375	4 weeks to 8 weeks	1992 - 2004	DFU	Diabetics (1,2)	Alginate v. BWCD Alginate v. Foam Silver fibrous-hydrocolloid dressing v alginate	(3) Ulcers healed, HRQoL, Adverse Events	Yes	Low Evidence "no research evidence to suggest that alginate wound dressings are more effective in healing diabetic foot ulcers than other types of dressing"
6	Dumville 2011	6	6 Randomized 4 pooled	157	8 weeks – 24 weeks	1993 - 2001	DFU	Diabetics (1,2)	Foam(vs)BWCD Foam(vs)Alginate Foam(vs)Hydrocolloid	(4) Ulcers healed Adverse events	Yes	Low evidence "no research evidence to suggest that foam wound dressings are more effective in healing diabetic foot ulcers than other types of dressing".
7	Dumville 2013 Hydrocolloid	5 (2/5 studies pooled)	6 Randomized	535			DFU	Diabetics (1,2)	Fibrous-Hydrocolloid [Hydrofiber] (vs)Basic Wound Contact	Ulcers healed HRQoL Adverse Events	Yes	Moderate evidence "no research evidence that any type of hydrocolloid wound

					8 weeks to 24 weeks	1995 - 2007			Dressings (BWCD) Foam Alginate			dressings is more effective in healing diabetic foot ulcers than other dressings"
8	Dumville 2013 Hydrogel	5 studies (3/5 pooled)	5 Randomized	446	10 days - 20 weeks	1997 - 2001	DFU	Diabetics (1,2)	Hydrogel(vs)BWCD Larva PDGF Purilon/intra site hydrogel	Ulcers healed	Yes	"moderate evidence for efficacy hydrogel v. BWCD uncertain due to risk of bias. Other comparisons , low evidence'
9	Voight 2011	8 (5 studies pooled)	8 Randomized (2 pooled) 1 study discernable on DFU others mixed wound etiology	178	2 weeks	2006	Subgroups of Venous Ulcers and DFU outcomes	Diabetics	Low frequency Ultrasound(vs)Sharp	Complete healing, Wound size reduction	No	"no difference demonstrated in complete healing between LFHICU and sharps debridement in patients with diabetic foot ulcers, quality of the evidence as it relates to biases was poor"

							undisc erned					
1 0	Tian 2013	4	1 Randomi zed 3Nonran domized	356	10 days	1998	DFU	Diabetic s	MDT(vs) Hydrogel MDT(vs) Conventiona l MDT(vs) Sharp MDT(vs) SWC	*Complete healing, Time to Healing, Amputation, Incidence of Infection	No	"no evidence between healing rates for MDT vs standard treatment. MDT resulted in greater proportion of patients to achieve complete healing vs control group. MDT more effective than standard treatment decreasing time to healing, rate of amputation for DFUs; however, no evidence that MDT reduces infection vs standard care."

These systematic reviews included a range of 4 to 10 studies. Six of the systematic reviews were restricted to randomized studies, whereas 4 systematic reviews included randomized and non-randomized studies. The publication years ranged from 1999 – 2013. The number of participants ranged from 149 - 575 participants. The number of comparisons ranged from 1 - 4 methods of debridement in the studies retrieved for the 10 systematic reviews SR's listed in table 3a above. The types of debridement included sharp, autolytic (hydrogel, foam, alginates, hydrocolloids, semipermeable polymeric membranes, silver-containing), larva or maggot debridement, and hydrotherapy. Four of these systematic reviews were Cochrane reviews.

Two out of 10 studies included venous ulcers in addition to diabetic foot ulcers, and one of these two studies also included ischemic ulcers. The outcome measures of interest included the following: amputation frequency, infections rates, complete healing rates, time to complete healing, wound size reduction, health related quality of life (HRQoL), wound recurrence, and adverse events. The majority of systematic reviews ranged in their findings on the quality of the evidence from Low evidence to no evidence that forms of non-autolytic debridement studied were beneficial. Two studies suggested moderate evidence to low evidence that forms of autolytic debridement were beneficial.

Conclusion

The study's findings were relatively consistent in that they reported weak or poor evidence to conclude that one form of debridement was superior to either an alternate form of debridement; or the control condition or standard treatment. The form of debridement used as control was autolytic debridement specifically using moistened gauze with either saline or an antiseptic such as iodine.

Iodine is frequently used to clean wounds as part of adjunctive measures of wound preparation prior to and post-debridement. Many of the conclusions reported in these reviews regarding the direction of future trials included the need for larger sample sizes, and standardized reporting among authors. The findings in these systematic reviews were relatively consistent in that they found weak evidence that any debridement or debridement dressing type was more effective than other dressings in healing diabetic foot ulcers.

Patients, healthcare providers, policy makers, and all other stakeholders are strongly cautioned in altering clinical practice on the basis of findings derived from small trials of unclear or high risk of bias including nonrandomized studies.

Stakeholders are cautioned on extrapolation of findings to other wound types, though diabetic wounds are considered among the most recalcitrant of wounds. Therefore, findings related to these resistant wound types may be applicable to researchers studying more resistant wound types. The findings in reviewing the literature for systematic reviews that were conducted on a similar research question support the need to design and conduct a comprehensive exhaustive systematic review that strictly utilizes all of our best available evidence i.e. randomized controlled trials. The systematic review of experimental evidence should retrieve the maximum number of comparisons that were made between debridement types in order to help delineate how these interventions compare to each another. This will assist all stakeholders in making important clinical, public health and policy decisions regarding debridement interventions.

Chapter 3 Systematic Review Objectives

Study Aims

Study Aim 1. Perform a comprehensive and worldwide systematic review of the literature on all forms of debridement as a treatment for diabetic foot ulcers.

Study Aim 2. Assessment of the evidence of the effectiveness of all commonly used forms of debridement as a treatment for diabetic foot ulcers, and the quantitative evidence assessment of the possible variability or heterogeneity among the comparisons.

Study Aim 3. Meta-regression and subgroup analysis for possible characteristics that may be moderating the variability of the effectiveness of debridement as a treatment across populations, settings, and study characteristics.

Research Questions and Research Hypotheses

Study Aim 1. Perform a comprehensive and worldwide systematic review of the literature on all forms of debridement as a treatment for diabetic foot ulcers.

Research Question 1. How many experimental studies have been published on the topic of debridement of diabetic foot ulcers?

Research Hypothesis 1a (RH1a): There exists a sufficient number of experimental studies on the topic of debridement of diabetic foot ulcers to enable the researcher to conduct a meta-analysis.

Research Question 2. Has all the literature on this topic been published or is there a substantial body of literature that remains unpublished?

RH2a: There exists a substantial body of literature on the topic of debridement of diabetic foot ulcers that remains unpublished and is eligible for inclusion in the meta-analysis.

Research Question 3. For the studies that exist are they of sufficient quality with relatively low risk of bias that makes them eligible for inclusion in our analysis?

RH3a: There exist both published and unpublished experimental studies that meet the eligibility criteria for inclusion in a meta-analysis that are of sufficient quality and relatively low risk of bias.

Study Aim 2. Assessment of the evidence of the effectiveness of all commonly used forms of debridement as a treatment for diabetic foot ulcers, and the quantitative evidence assessment of the possible variability or heterogeneity among the comparisons.

Research Question 4. Does any form of debridement and standard wound care as compared to autolytic debridement and standard wound care:

i) Reduce the time to complete healing of diabetic foot ulcers?

RH4a: There will be a difference in time to complete healing of diabetic foot ulcers using debridement in any form as compared to standard wound care and autolytic debridement, with significant variability in the distribution of the effects.

ii) Improve healing rates of diabetic foot wounds?

RH4b: The healing rates of diabetic foot ulcers using debridement in any form will be different as compared to standard wound care and autolytic debridement with significant variability in the distribution of the effects.

iii) Decrease recurrence rates of diabetic foot wounds?

RH4c: There is a difference in the frequency of recurrent diabetic foot ulcers using debridement in any form with standard wound care as compared to autolytic debridement and standard wound care, with significant variability in the distribution of the effects.

iv) Decrease the frequency of amputations that may result from diabetic foot wounds?

RH4d: There is a difference in the frequency of amputations associated with diabetic foot ulcers using debridement in any form as compared to autolytic debridement with standard wound care, with significant variability in the distribution of the effects.

v) Decrease the frequency of Methicillin Resistant Staphylococcus Aureus (MRSA) or other wound infections that may complicate diabetic foot wounds?

RH4e: There is a difference in the frequency of MRSA or other wound infections in diabetic foot ulcers using debridement in any form against autolytic debridement with standard wound care.

vi) Reduce healthcare costs for diabetic foot wounds?

RH4f: There is a difference in the healthcare costs associated in treating diabetic foot ulcers using debridement in any form as compared to using autolytic debridement with standard wound care.

vii) Improve the quality of life for those with diabetic foot wounds?

RH4g: There is a difference in quality of life indicators in treating diabetic foot ulcers using debridement in any form as compared to autolytic debridement with standard wound care.

Research Question 5. Which specific method(s) of debridement is/are most effective at achieving the desirable outcomes listed? Do the specific method(s) of debridement:

i) Differ in the time to complete healing of diabetic foot ulcers?

RH5a: The time to complete healing of diabetic foot ulcers is dependent on the method of debridement used.

ii) Improve healing rates of diabetic foot wounds?

RH5b: The healing rates of diabetic foot ulcers are dependent on the method of debridement used.

iii) Decrease recurrence rates of diabetic foot wounds?

RH5c: The frequency of recurrent diabetic foot ulcers is dependent on the method of debridement used.

iv) Decrease the frequency of amputations that may result from diabetic foot wounds?

RH5d: The frequency of amputations associated with diabetic foot ulcers is dependent on the method of debridement used.

v) Decrease the frequency of Methicillin Resistant Staphylococcus Aureus (MRSA) or other wound infections that may complicate diabetic foot wounds?

RH5e: The frequency of MRSA or other wound infections is dependent on the method of debridement used.

vi) Reduce healthcare costs for diabetic foot wounds?

RH5f: The healthcare costs associated with treating diabetic foot ulcers is dependent on the method of debridement used.

vii) Improve the quality of life for those with diabetic foot wounds?

RH5g: The Quality of life indices among those with diabetic foot ulcers is dependent on the method of debridement used.

Study Aim 3. Meta-regression and subgroup analysis for possible characteristics that may be moderating the variability of the effectiveness of debridement as a treatment across populations, settings, and study characteristics.

Research Question 5. Do there exist any prognostic or other moderating factors that are population specific, disease specific, or study specific characteristics that explain the variability of the effect sizes for the various forms of debridement?

RH5a: There exist moderating factors responsible for the variability of the effect sizes among the debridement interventions compared.

Chapter 4

Methods

In accordance with our primary aim, Study Aim 1, this method sections describes in detail the methods used to perform a comprehensive and worldwide systematic review of the literature on all forms of debridement as a treatment for diabetic foot ulcers. The search was designed to capture all randomized controlled trials and all systematic reviews pertaining to our research question. Data sources were collected accordingly per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement Reporting guidelines [Moher 2009](#).

Inclusion/Exclusion Criteria

Types of studies

All Randomized controlled trials (RCTs), either published or unpublished were included, which compare the effectiveness of two or more methods of debridement in the treatment of diabetic foot ulcers. There will be no restriction in the search or in the studies included for analysis based on language, or country of origin.

Non-randomized studies were excluded. This exclusion includes prospective cohort studies, case controlled studies, cross sectional studies, data archival analysis, Case series/Case studies.

Mechanistic in vitro or animal studies were also rejected.

Types of participants

Studies with samples of participants that have Type 1 or 2 diabetes, with an active foot ulcer or wounds of neuropathic, neuro-ischemic, or ischemic etiology were included. The review was limited to participants ≥ 18 years of age. There were no other limitations based on age, gender, country, healthcare setting, or language. The wounds are not limited in severity or in grading system utilized including Wagner Wound Grade, and Texas Classification.

Studies that included non-diabetics were excluded. Studies that included venous stasis wounds, nondiabetic arterial insufficiency wounds, pressure ulcers, or atypical wounds were excluded.

Types of interventions

Comparison of any method of debridement (i.e. the removal of necrotic tissue from the wound, by either mechanical or non-mechanical debridement) with no debridement, control, or an alternative method of debridement were included [Table 5](#).

These debridement methods included: autolytic debridement (including moistened saline gauze, or antiseptic treated gauze as a control condition), sharp surgical debridement, enzymatic debridement, biosurgery (or Maggot Debridement Therapy, MDT), mechanical debridement (including wet to dry, and ultrasound debridement). The search included any form of debridement but did not include SR's on Negative Pressure Wound Therapy (NPWT). NPWT includes debridement as one of its functions but this form of therapy has other mechanisms and has been studied in a separate Cochrane review [Dumville 2013b](#).

The ancillary and adjunctive services that are provided as part of routine standard of care discussed were coded to control for them as possible modifying factors favoring the intervention or control effect. It was anticipated that both the control group and debridement intervention groups would have received these other adjunctive services. However, the researchers coded accordingly to ensure there was no evidence of differential standards of care in favor of treatment or control.

The term “autolytic debridement” is a process that occurs, naturally, in all wounds. Autolytic debridement is however enhanced with the application of certain “autolytic debridement agents”, hence using autolytic debridement as a control is based on the naturally occurring phenomenon in all wounds such as proteolytic enzymes e.g. Matrix - Metalloproteinases that are released from the wound for “self-digestion” or debridement of the wound. We have restricted the “control condition” specifically to using autolytic debridement with saline moist gauze, and or antiseptic agents such as betadine, or chlorhexidine. Autolytic debridement agents (e.g. hydrogel) that facilitate moist wound healing other than “saline moistened gauze and antiseptic agents” (control condition) were compared as experimental interventions against alternate forms of autolytic debridement, or other forms of debridement (mechanical). These alternate forms of autolytic debridement were often compared to the “control group” defined here as gauze, saline moistened gauze, or antiseptic dressings in the included studies. Wet to dry saline moistened gauze was designated as a form of mechanical debridement and not autolytic debridement. Using saline moistened gauze and antiseptic cleaning solutions has been widely used for an extensive period as a form of default wound dressing. This warranted the use of this type of autolytic debridement with gauze, saline moistened gauze, and/or antiseptic solutions as a control condition in this systematic review ([Strohal 2013](#)).

Types of outcome measures

Included studies were searched for any of the following outcome measures reported.

1. Amputation frequency – The frequency of amputations, and type major (above or below knee) or minor (digital, ray, transmetatarsal, forefoot)
2. MRSA or other complicating wound infection frequency – These may include the frequency of MRSA or other wound complicating infections such as osteomyelitis, cellulitis, or Clostridia infection and gas gangrene.
3. Quality of Life (QOL) – This may include subjective ordinal scales such as an SF-36 questionnaire or some other established alternative quality of life metric.
4. Healing rates -The rate of reduction in wound size expressed in either absolute or relative terms.
5. Time to complete healing or the proportion of people whose ulcers heal completely at a fixed point in time.
6. Recurrence rates - The proportion of ulcers recurring among participants in or near the same location as the previously healed ulcer.
7. Cost of care – This could have been presented as cost per wound treated or based on a reference cost of treatment and is conducted in cost effectiveness analysis (CEA). Cost was not standardized across included studies that reported on this outcome. Currency and cost of treatment was also anticipated to vary across countries.

Primary outcomes

The primary outcomes of interest that were considered to be most relevant included 1-3: These outcomes have direct bearing on clinical and public health implications.

Secondary outcomes

The secondary outcomes of interest were considered to have indirect but important bearing on the primary outcomes and included 4 – 7.

Search methods for identification of studies

Three separate searches were conducted between March of 2013 and March of 2015, see [Appendix 1](#). They included two separate searches by the trials search coordinator at the Cochrane Review Group - wounds in March of 2013 and in March of 2015. A separate institutional search in collaboration with the University of Connecticut medical research librarian was also conducted in April of 2014.

Six computer databases were searched, as were other relevant sources. The specialized trials register of the Cochrane Review Group - Wounds was searched for Randomized Controlled Trials (RCT) on debridement of diabetic foot ulcers without any country, language, or year restriction that are available to date. The register is compiled by searching bibliographic databases such as MEDLINE, CINAHL, EMBASE, Cochrane Controlled Trials Register, Web of Science, CINAHL, World Health Organization, Conference Proceedings and Abstracts relevant to wound care including International Working Group on the Diabetic Foot, the

European Wound Management Association, the American Professional Wound Care Association, and the European Tissue Repair Society ([Booth 2006](#); [Cooper 2009](#); [DeLuca 2008](#); [Warren 2011](#)). Searches were limited to humans and to experimental studies.

The search strategy incorporated the type of participants including adult (≥ 18 years of age) type 1 and type 2 diabetics with Diabetic or lower extremity non-healing ulcerations/wounds.

The intervention is any treatment classified as a form of debridement.

This systematic review was restricted to include all randomized controlled trials and all existing systematic reviews related to the research question ([Lefebvre 2011](#)).

Hand searching included conference proceedings and journals not indexed in electronic databases. Citations within systematic reviews and the bibliographies of included studies were scrutinized to identify additional studies.

Manufacturers and distributors of debridement products were contacted for details of unpublished and ongoing trials. Experts in the field of diabetic foot management were also contacted for details of unpublished and ongoing trials. The search was not limited by language or publication status.

Upon completion of our search the studies that were accepted and met the two independent reviewers' shared inclusion/exclusion criteria were retrieved along with studies for which the reviewers were not able to determine eligibility based solely on the title and abstracts alone. These studies were retrieved and the full text article was scrutinized further if not excluded earlier based on title and/or abstract.

Electronic searches

A comprehensive literature search was conducted. The literature searches were conducted separately with the assistance of the trials search coordinator at the Cochrane Review Group – Wounds, and with the assistance of the University of Connecticut Medical Health Sciences Librarian. The search terms included medical subject headings and other search terms that are directly related to the aims of this study. Detailed search strategies and search terms used for this review are illustrated in [Appendix 1](#).

For this review we searched the following electronic databases to find reports of relevant RCTs:

- The Cochrane Wounds Group Specialized Register (4/15/2015);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (1898 to present);
- Ovid MEDLINE (1996 to March Week 4 2013);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, (1946 to Present, 2013 to April 14 2015);
- Ovid EMBASE (1974 to 2015, June 16 1996 to 2013 Week 13, 2013 to April 14 2015);
- EBSCO CINAHL (1981 - present, 2013 to April 15 2015)
- EMBASE via Scopus (1960 to present)
- Web of Science (1974 to present)

Searching other resources

We searched the bibliographies of all included studies and all existing systematic reviews related to the research question.

Selection of studies

Studies were selected independently for inclusion based on the consensus of two independent reviewers. An independent subject/content area expert, and an independent methods expert were available for technical support and to resolve any discordance between the two primary reviewers.

Any disagreements were initially resolved through discussion between the two primary reviewers and then if unresolved referred to the respective independent experts. Any disagreements that still remained were referred for arbitration to the Cochrane Review Groups – Wounds. However, no disagreements were referred to the review group, as they were all resolved internally. Any studies that required full article retrieval and were subsequently rejected were included in the excluded studies section with the reason for rejection [See Characteristics of Excluded studies](#) section. These steps are in accordance with efforts to maximize the transparency and redundancy in the process ([Cooper 2009](#); [Higgins 2008](#)).

Data collection and analysis

A coding system using a data extraction form was developed and pilot tested for use with all the variables selected for coding. See [Appendix 2](#) for the full version of the data extraction form used in this analysis. The coding data extraction form created included study-specific characteristics, quality-specific characteristics, participant-specific characteristics, and intervention-specific characteristics. The breadth of the coding form comprises summary statistical fields, prognostic predictor variables, outcome variables, study design and quality indicators including risk of bias indicators, and demographic information.

The program Microsoft Access was used to create an electronic data entry form/program based on the data extraction form in [Appendix 2](#). This was to facilitate data entry, and reduce data entry errors that can occur by inputting data directly into a data grid by the two independent reviewers.

The variables were extracted and transferred onto an Excel spreadsheet independently by each reviewer using the (reliability pre-tested) data extraction tool ([Cooper 2009](#); [Higgins 2008](#)). The extraction of these characteristics were dependent upon reporting status in the respective studies selected. Many of the pre-specified variables were either not reported or were not uniformly reported in the studies.

Variables that represented study-specific characteristics were grouped together including for example publication year, and data collection year. The estimated year of data collection (earliest date for data collection or manuscript submission/publication) were used. If the study was unpublished and/or the date unknown, then the length of follow-up and/or year of manuscript was used as an estimate for data collection year. Other study-specific characteristics included language, and the source, or type of publication (abstract, conference proceeding, journal article, book, unpublished manuscript, thesis/dissertation) were extracted.

The variables included in the coding form represented sample characteristics, e.g. age (mean and standard deviation), gender (percentage of males and females in the sample), region (country or city where the study was conducted), hospital or outpatient settings (specialized center, or private office settings), and racial/ethnic composition (the proportion of minorities in each of the respective samples). Ethnicity was coded as a moderator for the higher risk of amputations that has been observed in minority groups, and for lower socioeconomic status. Socioeconomic status was included as a surrogate for healthcare literacy, and access to healthcare.

Covariates or modifiers that are suspected of influencing wound healing and represent clinically prognostic risk factors were extracted. Separate from the nonclinical sample characteristic moderators described above, clinically relevant modifiers were included such as peripheral vascular disease status (percentage of the sample), periwound tissue oxygen levels (mean and standard deviation), diabetes disease severity indicators such as hgb1c (mean and standard deviation), diabetes duration (percentage of the sample), Body Mass Index (BMI, mean and standard deviation), hypertension status (percentage of the sample), and immunosuppression status (percentage of the sample). Immunosuppression was coded and included percentage of the sample that were HIV positive or receiving Immunosuppressive medication, if reported in the study.

Study characteristics included quality-specific indicators (following the Cochrane Risk of Bias table format) was collected from the individual studies selected for the review, and were coded for analysis. Specific quality indicators included: random sequence generation, allocation concealment, blinding (specific to participants, personnel delivering interventions, and outcome assessors), incomplete outcome data, and selective reporting, and other bias (e.g. industry support).

Data extraction and management

Data extraction

A comprehensive data extraction tool or coding form was created to acquire relevant data based on the prevailing standards in wound care. The data extraction form had a total of 237 possible variables. These variables represented outcome variables of interest and moderators.

Efforts were made to help facilitate and minimize the risk of incorrect data entry between the two independent authors and an electronic data entry form was created using the Microsoft Access program.

After retrieval of the included studies data were extracted in duplicate by two separate independent reviewers.

The data extraction tool that was created was reliability tested between the 2 reviewers and utilized all of the included studies. The reliability testing of the data extraction coding form was conducted after data extraction and prior to the data analysis phase of this systematic review. All of the variable results were used except for the outcome variables. The data extraction was evaluated and expected to demonstrate a kappa statistic that reflected at minimum a 0.74 or greater agreement prior to its use on studies selected for inclusion ([Higgins 2008](#)). Any discrepancies between the two reviewers were reconciled until all entries were finalized and identical. The data extraction form served as the sole data extraction tool for each of the studies selected. Any disagreements in extracted content were fully resolved by discussion and if unresolved would be referred to the content and methods expert, and if still unresolved, to the Cochrane Review Group Wounds for arbitration ([Cooper 2009](#); [Higgins 2008](#)).

Collectively the 30 individual studies selected did contain every outcome effect of interest. The Meta-analysis portion of the analysis was conducted on similar studies based on shared outcome effects as all studies did not necessarily report on all of the outcomes of interest. The way that missing data were handled in the studies (i.e. Bayesian methods, imputation methods, last observation carried forward) was reported in the systematic review.

Intention-to-treat analysis was evaluated further by the reviewers in order to determine if the specific method used and classified by the authors as intention-to-treat was reported in the methods section of each study ([Harel 2012](#)).

Reliability testing

Reliability testing was conducted on all of the modifying factors for the 30 included studies as these represented the majority of the 235 variables in the data extraction coding form.

The dichotomous variables were compared between the two researchers using cross tabulations. Percent agreement and kappa statistics were calculated. The kappa statistics representing each of the categorical variables were averaged, and the mean kappa was 0.33, which is representative of poor agreement between coders for the data extraction coding form.

The continuous variables were compared between the two researchers using correlation matrices. Pearson's correlations were obtained for each of the respective continuous variables and then they were subsequently averaged. The mean Pearson's correlation was 0.75 which is representative of good agreement between the researchers. This contrasted significantly with the kappa for the categorical data.

This difference likely reflected the inherent subjectivity in many of the dichotomous variables that included quality assessment judgments, whereas the continuous variables represented more objective variables e.g. hemoglobin a1c. Another possibility may have been a differences in background knowledge between the two researchers.

The third source of discordant data extraction may have been that the data extraction tool included some questions with ambiguous meaning to the reviewers. The data extraction coding form was then edited for future updates of the present systematic review with the intent of reducing discordant responses between reviewers.

Regardless of the source of discordant data extraction all disagreements were reconciled in a series of meetings. A general reliability calculator was used for the reliability process ([Huedo-Medina 2013](#)). The general reliability calculator is a program that utilizes an excel spreadsheet with predesigned formula to permit data entry in either a Pearson correlation matrix for continuous variables or a cross tabulation for categorical variables. The program helps generate the Pearson correlations and chi square values for all variables compared. It then can be used to calculate reliability between two reviewers using a data extraction coding form.

Assessment of risk of bias in included studies

The assessment of the risk of bias for each of the studies included in the systematic review relied on the Cochrane Collaboration's Risk of Bias table format. The risk of bias tables included the following indicators the this systematic review ([Higgins 2008](#); [Hulley 2007](#)):

- i) Allocation sequence generation (randomization status and method of randomization reported)
- ii) Allocation of concealment (concealment of the order of random allocation from the investigators assigning individuals to treatment groups reported) ([EBN 2001](#))

- iii) Blinding (blinding status of participants, investigators, and outcome assessors reported) ([EBN 2001](#))
- iv) Incomplete outcome data addressed (reporting of missing data along with procedures used to address missing data)
- v) Free of selective reporting (selective reporting of outcomes pre-specified in the protocol or the methods)
- vi) Free of other bias (other potential threats to validity related to the specific study design used, early stopping of study, baseline imbalance between the comparison groups i.e. high suspicion of confounding/effect modification)

These risk of bias considerations were extracted accordingly into the data coding form ([Higgins 2008](#)).

Funnel plot assessment of reporting bias was conducted on the individual studies included in the review. A minimum of 10 studies is recommended for assessment of publication bias. The funnel plot graphs standard error against the effect size. The positive/negative study classification can then be graphically compared for smaller and larger studies. If the studies fall in a symmetric pattern around the null value than the likelihood of publication bias is lessened. If the funnel plot is asymmetric favoring positive effect sizes this suggests publication bias.

Beggs and Eggers statistical tests were also utilized to evaluate for reporting bias. These test are explained further below ([Cooper 2009](#); [Higgins 2008](#)).

Measures of treatment effect

The effect measures included dichotomous events/nonevents data which were used to generate Relative risks (RR) for proportion of sample with amputation, proportion of sample with infections, proportion of sample with wound recurrence, and proportion of sample with wound completely healed. Difference in means (MD) or standardized mean difference (SMD) were used for continuous data such as time to complete healing, cost, quality of life index. Mean difference was favored for purposes of reporting in this systematic review provided the scale and measurement were comparable. This was used because mean difference is inherently better understood by the reader than is standardized mean difference.

Dichotomous events/nonevents data used to calculate the effect estimate risk ratio (RR):

- 1) Proportion with amputations
- 2) Proportion with complicating infections
- 3) Proportion with ulcers completely healed
- 4) Proportion with ulcer recurrence

Continuous data (MD), (SMD)

- 5) Quality of Life Index

6) Time to complete healing

7) Treatment cost

Statistical Analysis

Effect size (ES) estimates for the association of each independent variable with each of the outcomes were extracted accordingly using an effect size extraction program ([Huedo-Medina 2013](#)). The trials varied in the effect measures reported. The Effect size calculator utilizes an excel spreadsheet with included formulas that converts effect sizes into different forms interchangeably.

Proportion of participants with amputations, infections, complete ulcer healing, and ulcer recurrence were reported for each of the included studies from events and nonevents for both the intervention and control groups. The results were extracted from dichotomous events/nonevents data into the respective proportions and these effects were transformed into Relative Risk ratios (RR). Risk difference (RD). Numbers Needed to Treat for an additional Beneficial outcome (NNTB), and Numbers Needed to Treat for an additional Harmful outcome (NNTH) were then subsequently calculated ([Morris 2002](#)).

Time to complete healing, and cost of care were reported as continuous effect sizes measures using mean differences (MD) along their respective standard deviations (SD) for both the intervention and control groups.

Quality of life was reported using subjective questionnaire scales on a continuous or ordinal scale. These scales were not necessarily standardized across studies using similar or identical

debridement interventions. Therefore, the effect sizes were converted to mean differences if a similar scale was used, or to a standardized mean differences (d) if the scales differed.

These procedures were used in order to make it possible to compare the effects of the intervention regardless of the outcome metric used. These conversions or transformations were contingent upon the same intervention being used in at least two studies.

The standardized mean difference is defined as the difference between the treatment and control groups divided by the pooled standard deviation for two-groups design, or the difference between two d for pre-post group design, one for the experimental and another for the control group. The pre-post design d (Cohen's d) is defined as the posttest and baseline difference of sample means divided by the baseline standard deviation ([Becker 1988](#); [Hedges 1981](#); [McGrath 2006](#)).

In the absence of means and standard deviations, other statistical information (e.g., F -values, p -values) could be used as surrogates for effect estimates, these statistics were also extracted. Although using test statistics and p -values is less ideal than using the direct effect size estimates ([Huedo-Medina 2006](#); [Huedo-Medina 2013](#); [Sanchez 2003](#); [Hedges 1985](#)). Effect sizes for the same outcomes may be reported differently in different studies. Therefore, transformation of the outcome effect sizes into the same effect estimate in order to standardize them for comparison purposes was required. This was utilized in the meta-analysis by transforming the statistical information reported into a uniform effect size estimate for analysis, e.g. RR, OR, MD, standardized mean difference, d , using HLSM-Meta software version 0.9 ([Huedo-Medina 2006](#); [Huedo-Medina 2013](#)).

Unit of analysis issues

The unit of analysis reported was based on a single outcome response per individual. There were studies that reported simultaneous treatment of wounds on multiple sites for each individual; the authors of the studies generally based the outcome assessments on the most severe of these wounds.

Few studies reported multiple time points or observations for the same outcome (e.g. repeated measurements, recurring events). The studies all reported post design (final observations). The limited studies that did report multiple time points, were reported in this study as post design (e.g. final observations number with amputations by the end of the study) for both the intervention and control groups. In the studies where initial measurements or observations were reported these were summarized for the reader in tabular format along with wound severity based on classification and/or wound duration at baseline.

The follow up periods and the length of the study are reported, and summarized between studies for the reader. This review prioritized sustained or long term outcome or last reported outcome responses for debridement interventions, as these were considered the optimal long-term indicators of outcome success or failure.

Study treatment of missing data

The individual included studies were not expected to contain every outcome effect of interest for this review. The pooled data for the meta-analyses utilized similar studies based on shared outcome effects and interventions. The respective included studies sharing similar intervention comparisons and outcomes were then grouped and analyzed together.

When these data were extracted the method used to address missing data was scrutinized and reported accordingly, e.g. Intention to treat analysis, last observation carried forward, Bayesian methods, or imputation. The method of missing data treatment was scrutinized for each of the respective included studies and if reported the method was subsequently reported in this systematic review ([Harel 2012](#)).

If studies with continuous outcome measures reported effect sizes but did not report the associated standard deviations; then the respective continuous study outcome was not analyzed in the meta-analysis phase of this review. In studies reporting dichotomous outcomes, if the actual number of events/nonevents were not reported or could not be extracted or calculated from a respective study; then the outcome was not included in the meta-analysis phase of this review.

Assessment of reporting biases

Publication bias and other reporting biases were addressed using funnel plots, statistical tests and through the use of Cochrane risk of bias tables. The authors acknowledge that asymmetric funnel plots are not necessarily caused by publication bias (and that publication bias does not necessarily cause asymmetry in a funnel plot). For example, the other reasons that may bias the results toward exaggerated positive findings in smaller studies might include differences in methodological quality, heterogeneity in the intervention effects in certain higher risk groups, and random error.

Cochrane risk of bias tables were used to assess each study for sequence generation, allocation concealment, blinding (including 3 categories participant, personnel delivering interventions, outcome assessor), reporting biases, and other biases including funding sources, unpublished abstracts.

Funnel plot assessment of publication bias was conducted on the studies included in the review. This was based on standard assessment that includes sample size and positive/negative effect size magnitude and direction. Asymmetries of effect sizes suggest reporting biases as they may be found associated with a propensity to report positive studies disproportionately as compared to negative studies ([Cooper 2009](#); [Higgins 2008](#)).

Alternatively, tests were used for publication bias including Beggs technique uses a nonparametric rank correlation test to detect publication bias in meta-analyses ([Begg 1994](#)). The test is an adjusted rank correlation test which is considered a statistical analogue of the funnel plot. The test generates a Kendall's tau between the standardized effect size and the variances (or standard errors) of these effects. Tau is interpreted analogous to a correlation. A value of zero indicating no relationship between effect size and precision (variance or standard error). Values in either direction away from "0" indicates an association.

The test is considered powerful and useful for large meta-analyses that include at least 75 studies or greater, but moderate power for meta-analyses with at least 25 - 75 included studies. The test is not ideal for small studies. Bias cannot be ruled out if the test result is non-significant. The test is considered complementary to the funnel plot ([Begg 1994](#)).

An alternative graphical test is available called Egger's technique which detects bias in meta-analyses ([Egger 1997](#)). Funnel plots can plot effect estimates against standard error in order to detect bias in meta-analyses. Egger uses a "simple" test of asymmetry of funnel plots in order to attempt to predict discordance of results among meta-analyses when they are compared to large trials. The degree of funnel plot asymmetry is assessed. This is based on imprecision of the intercept obtained through regression analysis for standard normal. Egger uses the effect sizes and precision, which differs from Beggs which uses ranks.

The Egger test uses the standard normal deviate (effect size divided by its standard error) and this is regressed upon precision (inverse of the standard error). The intercept in this regression corresponds to the slope in a weighted regression of the effect size on the standard error. By demonstrating that it is no different from 0 suggests that there is no asymmetry in the funnel plot ([Egger 1997](#)).

The trim and fill method was another alternative method considered. This method removes the most extreme small study studies from positive side of the funnel plot to evaluate what the effect estimate would be without them. This approach can add symmetrically mirror image extreme small studies to the negative side of the funnel plot to determine how that impacts the overall effect estimate. ([Duval 2000](#)).

Data synthesis

This systematic review included a meta-analysis using a random effects model. A random effects model was considered appropriate in this analysis since it is difficult to assume that an intervention has a singular fixed effect in complex biological organisms using healthcare interventions ([Cooper 2009](#); [Higgins 2008](#); [Schmidt 2009](#)). Treatment effects are expected to vary widely due to the wide variation in practices that constitute standards of care among the healthcare community. This is in addition to individual patient's biological variability.

A random effects model approach was considered because it provided a more conservative estimate of outcome effects when considering the variation in healthcare interventions. The more conservative larger confidence interval is likely more reflective of the broader range of treatment effects in healthcare interventions. There exists significant variability between individual subjects in their responses to interventions. There are variables that are not accounted for, since some mechanisms responsible for the effects of treatment in an individual remain poorly understood. These unknown prognostic factors are irrespective of efforts to use modeling to account for known modifying characteristics that may interact with the intervention or confound the intervention and effect. There may be hyper-responders that may be suggested by outliers. There is large biological complexity, making it is reasonable to infer that there likely exist numerous treatment effects among the population rather than a single fixed effect. Therefore, our analysis accounted for both conditional, and random variability ([Cooper 2009](#); [Higgins 2008](#), [Borenstein 2009](#)).

Sensitivity analysis

Efforts were made to determine whether the decisions made during the review process were robust, such as the inclusion/exclusion of particular studies from the meta-analyses with missing or insufficient data such as abstracts.

Studies that were restricted to unpublished abstracts ([Goretti 2008](#); [Roberts 2001](#)) were removed and a meta-analysis was then conducted separately in order to determine if the summary effect estimates were robust despite the exclusion of these two studies. This was considered appropriate since abstracts did not include the degree of information available in full study articles. Risk of bias assessments are difficult in light of the limited information provided by abstracts alone. Data were extracted from these abstracts for use in the systematic review.

However, it was important to determine if pooled effect size estimate were disproportionately influenced by the inclusion of these two abstracts.

The decision to use a random effects model for this systematic review was pre-specified. The effect estimates using a random effects model were compared to the effect estimates using a fixed effects model to determine if the findings were robust despite the model type used in the analysis.

Chapter 5

Results

Description of included studies

Upon retrieval of all full text studies a total of thirty studies met the Inclusion/Exclusion criteria for this systematic review [Figure 2](#); see [Characteristics of included studies](#) section. The studies were qualitatively and comprehensively summarized, see the [Characteristics of included studies](#) section of this systematic review. The accompanying risk of bias tables assessed the risk of bias in each of the 30 studies [Figure 3](#); [Figure 4](#). Collectively the included studies comprised a total of 2539 participants [Table 7](#); [Figure 5](#).

Inclusion / exclusion criteria for the individual included studies

See Inclusion and exclusion criteria for the individual included studies in the [Additional Tables](#) section of this review [Table 8](#). The list of inclusion/exclusion criteria in [Table 8](#) represent the criteria the authors of the individual studies used, and do not represent the inclusion/exclusion criteria used in this review. There was significant variability in the inclusion and exclusion criteria between studies [Table 8](#).

Study Characteristics for the 30 included studies

Study duration and follow up period

The study period ranged from 1992 - 2012 for the 30 included studies [Figure 6](#). The follow up period for the included studies ranged from 10 days to 24 weeks see [Characteristics of included studies](#).

Study Settings for the individual included studies

The study settings were primarily outpatient or specialized clinic settings (17 studies). However, 8 of the studies were reported in hospital settings, 2 studies included both inpatient-hospital and outpatient settings, and the setting was unclear in 5 studies.

The studies were conducted in the following countries (included in brackets () is the number of studies conducted in that respective country): Belgium (2), Brazil (1), Canada (1), Denmark (), France (1), Germany (2), Iran (1), Italy (5), Jordan (1 study), Malaysia (2), Pakistan (1), Saudi Arabia (1 study), Slovenia (1), Sweden (1), Switzerland (1), Tunisia (1), Turkey (1), UK (5), and US (7), Europe (2), Unclear (1) [Table 7](#). Four of the studies were conducted in more than one country and the adjacent study numbers are reflective of this.

Sample sizes for the individual included studies

The included studies ranged from sample sizes of 18 to 619 participants. [Table 9](#); [Figure 5](#). All 30 included studies reported total sample size. The mean sample size for the included studies was 85 (SD = 119) participants.

Study Participants in the included studies

See “Study year, sample sizes and study setting for included studies table” in the Additional Tables Section [Table 7](#).

a) Age

The mean ages for the included studies ranged from 52.1 through 69.3 years [Figure 7](#). A total of 23 studies reported on age. The mean age for the reported sample of studies was 59.01 (SD = 4.31) years.

b) Gender

In the majority of studies most participants were men with two studies reporting one or no female participants [Figure 8](#); [Figure 9](#). A total of studies 21/30 studies reported gender composition, 9 studies did not report gender [Table 9](#). The number of males ranged from 12 to 240. The total mean number of males was 49 (SD = 53) for the reported studies. The number of females ranged from 1 to 88 for the reported studies. The total mean number of females was 26 (SD = 22) for the reported studies.

c) Ethnicity

Ethnicity was reported in 4/30 studies. Four studies out of thirty reported on ethnicity including ([Shukrimi 2008](#), [Tallis 2013](#), [Singh 2006](#), and [Dhemecourt 1998](#)).

Study participants

d) Other participant data

BMI was reported in 5/30 studies. Socioeconomic status was reported in 1 study.

Wound specific characteristics for the included studies grading, surface area, and depth

Grading of the ulcer (severity) was used in 13 studies and included the use of the Wagner wound grading system and the University of Texas classification systems. The wounds were classified up to Wagner grade 4 or Texas classification grade 3. A total of 17 studies did not specify the wound classification and referred to the wounds as diabetic foot ulcers with partial or full thickness wounds. The initial size of the wound was specified in 20 out of the 30 studies using wound surface area. This was reported for both the intervention and control groups for each of these studies reporting. Depth of the wound was specified in 5 out of 30 studies. [Table 10](#); [Figure10](#); [Figure 11](#).

Wound duration at baseline for the included studies

Fourteen out of 30 studies reported on wound duration. Wound duration ranged from 1 week to 15.8 (SD = 10.7) years [Figure 12](#); [Figure 13](#).

Prognostic risk factors for the included studies

a) Mean Hemoglobin a1c, and duration of diabetes status at baseline for the included studies

The studies that reported on comorbidities that may impact wound healing included the following information: 8/30 studies reported on mean hemoglobin a1c, mean hgba1c ranged from 7.25% to 9.25% [Figure 14](#). 14/30 studies reported on mean duration of diabetes which ranged from 13 (SD= 10.6) years to 20.5 (SD = 13.5) years [Table 11 Figure 15](#).

b) Peripheral arterial disease (PAD) status at baseline for the included studies

The proportion of the sample with baseline arterial insufficiency was reported in 9 studies [Table 11, Figure 16](#).

c) Infection status at baseline for the included studies

The infection status at study onset was reported in 11 studies [Table 11, Figure 17](#)

d) Offloading status at baseline for the included studies

Offloading status was reported in 9 studies [Table 11, Figure 18](#).

e) Immunosuppression status at baseline for the included studies

Immunosuppression status was reported in 1 study [Table 11, Figure 19](#).

f) Nutritional status at baseline for the included studies

Two of the studies included nutritional status indicator at baseline using albumin [Table 11](#), [Figure 20](#).

g) Smoking status at baseline for the included studies

The proportion of smokers at baseline was reported in 5 studies [Table 11](#), [Figure 21](#).

h) Venous insufficiency status at baseline for the included studies

The proportion of the sample with baseline venous insufficiency was not reported [Table 11](#).

i) Industry support was reported in 13/30 of the included studies [Figure 22](#).

Results of the search

The three separate searches collectively retrieved a total of 3553 citations.

To these were added 160 citations retrieved through a hand search of the bibliographies of systematic reviews related to the research question that were among the full text studies retrieved. A hand search of the bibliographies of all 30 included studies along with 10 systematic reviews retrieved on a similar research question was conducted.

After duplicates were removed a total of 2625 citations remained. A total of 2513 citations were excluded based on title and abstract using the pre-specified eligibility criteria. 112 full text studies were retrieved for further review.

Upon scrutinizing 112 full-text articles, 82 of these studies did not meet the inclusion/exclusion criteria and were rejected, reasons for rejection are included in this systematic review, see [Characteristics of excluded studies](#) section of this review. A total of 30 studies met the pre-specified inclusion/exclusion criteria for this systematic review.

See Study selection Prisma flow diagram in [Figure 2](#).

Excluded studies

A total of 82 studies were excluded from this review. The main reasons cited for exclusion included: see [Characteristics of excluded studies](#)

- 1) The study was not randomized - 30 studies
- 2) The intervention was not classifiable as a recognized form of debridement - 30 studies
- 3) Other debridement intervention(s) besides the comparison interventions were applied to both treatment arms - 12 studies
- 4) Other reasons were reported for the remaining - 10 studies

Risk of bias in included studies

The risk of bias in included studies was appraised in 6 separate areas including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.

All of the included studies reported random sequence generation. However in most studies the method of randomization was unspecified with the exception of five studies ([Amini 2013](#); [Bowling 2011](#); [Jeffcoate 2009](#); [Munter 2006](#); [Tallis 2013](#)).

The method of sequence generation included simple randomization in ([Amini 2013](#)), and computer random sequence generation in the other four studies. See Risk of Bias [Figure 3](#) and [Figure 4](#).

Allocation concealment was assessed as a form of selection bias. Most of the included studies did not report whether allocation concealment was utilized with the exception of 5 studies; ([Bowling 2011](#), [Jeffcoate 2009](#), [Jude 2007a](#), [Munter 2006](#), and [Tallis 2013](#)). See Risk of Bias [Figure 3](#) and [Figure 4](#).

Blinding was assessed as a form of performance bias and detection bias. The blinding of outcome assessors was reported in 7 studies ([Ali 2013](#), [Goretti 2008](#), [Jeffcoate 2009](#), [Lalau 2002](#), [Piaggese 2001](#), [Shukrimi 2008](#), [Singh 2006](#)). Three studies ([Apelqvist 1990](#), [D'Hemecourt 1998](#), [Piaggese 1998](#)) reported double blinding including outcome assessors and the delivery of the intervention. However double blinding was not uniformly and clearly defined. Blinding was either not conducted or unclear in the remaining studies. This may have been attributable to the nature of the interventions (e.g. surgical debridement, mechanical jet irrigation). See Risk of Bias [Figure 3](#) and [Figure 4](#).

Incomplete outcome data were assessed as a form of attrition bias. Most of the studies did not report on the status of incomplete outcome data. One study ([Belcaro 2010](#)) reported that there were no drop outs in the study. Another study ([Whalley 2001](#)) reported withdrawals but reasons for withdrawals was unclear and method of addressing withdrawals was not specified.

Eight studies ([Markevich 2000](#), [Mazzone 1993](#), [Ogce 2007](#), [Piaggese 1998](#), [Rhaiem 1998](#), [Roberts 2001](#), [Shukrimi 2008](#), and [Singh 2006](#)), did not report whether there were any participant withdrawals nor was the method of addressing missing data specified. Eight studies ([Blackman 1994](#), [Clever 1995](#), [Foster 1994](#), [Hammouri 2004](#), [Jensen 1998](#), [Lalau 2002](#), [Piaggese 2001](#), and [Vandeputte 1997](#)), reported participant withdrawals or drop outs and cited reasons however the methods of addressing missing data were not specified.

Two studies ([D'Hemecourt 1998](#); [Donaghue 1998](#)) reported that an intention to treat analysis was conducted but did not specify the method that was used. Three studies ([Jeffcoate 2009](#), [Munter 2006](#), [Tallis 2013](#)), reported using an intention to treat analysis and specified that the method used was last observation carried forward.

Selective outcome reporting was assessed as a form of reporting bias. No pre-study protocols were available for any of the studies. Therefore, an assessment of selective reporting was based on discordance between pre-specified outcomes reported in the methods section not appearing in the results sections of the studies. Approximately 14 out of 30 studies were at low risk for selective reporting. Approximately 11 out of 30 studies were at high risk for selective reporting based on discordance between outcomes reported in the methods and results sections of the study.

17 out of the 30 studies were at high risk for other potential sources of bias. In the other 13 studies it was unclear whether other potential sources of bias were likely, since insufficient information was available to make this determination. Important sources of confounding were not addressed in the results section to determine if they were balanced in both treatment arms, especially since many of the studies included small sample sizes.

Randomization has a higher likelihood of balancing unknown or uncontrolled confounders in both treatment arms the greater the sample size. [Characteristics of included studies](#); Szklo 2007,

The studies had a broad range of follow up periods with some being as brief as 10 days and others being as long as 24 weeks [Characteristics of included studies](#).

13 of the 30 studies received private source of financial support, 2/30 reported not receiving any financial support, and in 15 other studies the source of financial support could not be determined or was not reported [Table 12](#); [Figure 22](#).

Effects of interventions

Twenty-two out of the 30 included studies collectively represent 19 separate comparisons that reported on a minimum of 1 of the 7 pre-specified outcomes of interest for this review.

These 19 comparisons included one study each in comparisons 1 – 5, 7, 8, 9, 11, 12, 14, 15, 16, 17, and 18; three studies in comparison 6; two studies in comparisons 10 and 13; and 10 studies in comparison 19 [Table 13](#).

The comparisons include effect sizes for each of the interventions per outcome of interest that were reported and include the results of the meta-analyses carried out on 4 comparisons including: comparison 6 (3 studies), 10 (2 studies), 13 (2 studies), and 19 (10 studies). The effects of the interventions are described under each of the primary outcomes of interest (proportion of participants with amputations, proportion of participants with complicating infections, and quality of life), and secondary outcomes of interest (proportion of ulcers healed, time to complete healing, proportion of ulcers recurring after healing, and cost of treatment).

8 out of the 30 studies, despite meeting our inclusion criteria for the review, did not report on any of the pre-specified outcomes of interest. These included the following studies [Ali 2013](#); [Baker 1993](#); [Bowling 2011](#); [Munter 2006](#); [Ogce 2007](#); [Shukrimi 2008](#); [Singh 2006](#); [Tallis 2013](#).

The studies are reported in the [Characteristics of Included Studies](#) section of this systematic review as they did meet our inclusion criteria but are not reported in this effects of interventions section since they did not include the outcomes of interest. These 8 studies were not pooled in any of the meta-analyses for this reason. The pre-specified outcomes of interest were not used as eligibility criteria as this would have restricted the number of studies captured in the search phase of this systematic review. They are summarized and included in the [Characteristics of Included Studies](#) section to prevent the introduction of biased reporting into this systematic review.

Comparison 1: Surgical debridement compared with conventional non-surgical management (1 trial, 42 participants)

This comparison included 1 trial ([Piaggese 1998](#)) with 42 participants. The follow up period was 24 weeks. The study period was 1995. There was significant risk of bias as many of the risk of bias considerations were unclear or high risk [Figure 3](#); [Figure 4](#).

Types of interventions

The surgical debridement group underwent surgical excision, eventual debridement or removal of bone segments underlying the lesion and surgical closure. The conventional management group received saline moistened gauze after an initial surgical debridement. Pressure relief was provided to both groups along with regular dressings. [Table 5](#); [Table 13](#).

Initial wound stage

The mean baseline maximum wound size depth was 1.58 (SD = 2.2) cm² in the sharp debridement group and 1.98 (SD = 1.07) cm² in the conventional non-surgical management group [Table 10](#).

Participant characteristics

The study comprised a total of 42 participants. The mean age for the study was 64.39 (SD = 11.67) years. The number of males and females was not reported [Table 9](#). The study setting included outpatients in Italy [Table 7](#). Baseline data were collected for the type and duration of diabetes, the age of patients, and their HBA1c [Table 11](#).

Primary outcomes

Proportion of participants with amputations

The proportion of individuals with amputations was lower in the surgical debridement group 0/22 as compared with the conventional non-surgical management group 1/24. (RR 0.36, 95% CI 0.02 to 8.46; participants = 46; studies = 1) [Analysis Table 1.1](#). No statistically significant difference was found.

Proportion of participants with complicating infections

The proportion of participants with complicating infections was lower (64% risk reduction) in the surgical debridement group 1/24 (5%) than the convention non-surgical treatment group 3/24 (13%) (RR 0.36, 95% CI 0.04 to 3.24; participants = 46; studies = 1) [Analysis Table 1.2](#) No statistically significant difference.

Quality of life

No data were reported although [Piaggese 1998](#) reported that patients reported a higher degree of satisfaction with surgical debridement as well as lower discomfort but did not report how this outcome was measured and whether a valid scale had been used. (MD -2.20, 95% CI -3.16 to -1.24; participants = 46; studies = 1) [Analysis Table 1.3](#)

Secondary outcomes

Proportion of ulcers completely healed

Conservative care healed 19/24 (79%) ulcers, compared with 21/22 (95%) of ulcers treated by surgical debridement. The number of ulcers healed was 15% greater in the surgical debridement group than in the conservative non-surgical treatment group. (RR 1.15, 95% CI 0.90 to 1.47; participants = 46; studies = 1) (No statistically significant difference was found) [Analysis Table 1.4](#).

Time to complete healing

The ulcers treated with conservative methods took longer to heal on average; 129 (+/- 87 days) compared with the surgically treated group whose healing time was 47 (+/- 39 days). It was unclear in the trial whether the figures in parentheses were ranges, standard errors or standard deviations as this was unspecified.

The mean difference in healing was approximately 82 days shorter in the sharp surgical treatment group as compared with the conventional non-surgical treatment group (MD 81.68, 95% CI 41.07 to 122.29; participants = 46; studies = 1) (statistically significant difference was observed). [Analysis Table 1.5](#).

Proportion of ulcers recurring after healing

In the non-surgical treatment group, 8/24 (33%) ulcers recurred within six months, compared with 3/22 (14%) in the surgical debridement group; There was a 59% reduction in ulcer recurrence favoring the sharp surgical debridement group. (RR 0.41, 95% CI 0.12 to 1.35; participants = 46; studies = 1) (No statistically significant difference) [Analysis Table 1.6](#).

No data were reported for the pre-specified outcome cost of treatment.

Analysis Table 1.1 – 1.6 Sharp Surgical Debridement compared to nonsurgical management				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Number of amputations reported	1	46	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.46]
1.2 Number of Infections reported	1	46	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.24]
1.3 Quality of life / Limitations	1	46	Mean Difference (IV, Random, 95% CI)	-2.20 [-3.16, -1.24]
1.4 Number of ulcers completely healed	1	46	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.90, 1.47]
1.5 Time to complete healing (days)	1	46	Mean Difference (IV, Random, 95% CI)	81.68 [41.07, 122.29]
1.6 Recurrence rates	1	46	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.12, 1.35]

Comparison 2: Superoxide solution compared with standard local treatment with povidone iodine (1 trial, 40 participants)

This included 1 trial [Goretti 2008](#) with 40 participants. The study was available in unpublished abstract form only. The range of follow up was 24 weeks. The study comparison period was not reported. There was significant risk of bias since the study information was limited to an unpublished abstract and much of the risk of bias considerations were unclear [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included superoxide solution as compared with standard local treatment with povidone iodine. Standard local treatment was not defined in the study [Table 5](#); [Table 13](#).

Initial Wound Stage

The mean wound size in the study was reported as greater than 5 cm². The mean wound depth, wound staging, and mean duration of ulcers in the study was not reported [Table 10](#).

Participant Characteristics

The studies comprised a total of 40 participants. The mean ages for the study was not reported. The number of males and females included were not reported [Table 9](#). The study setting included hospitalized patients and was conducted in Italy [Table 3](#).

[Goretti 2008](#)

Primary Outcomes

No data were reported for any of the primary outcomes of interest.

Secondary Outcomes

Proportion of participants with ulcers completely healed

Proportion of participants with ulcers healed was higher 17/20 (85%) in the superoxide solution group than the standard local treatment with iodine group 11/20 (55%). There was a 55% increase in ulcer healing favoring the superoxide solution group as compared to the standard local treatment with iodine group (RR 1.55, 95% CI 1.00 to 2.39; participants = 40; studies = 1) [Analysis 2.1](#). No statistically significant difference was observed.

Time to complete healing

Time to complete healing was reported to be 6 days shorter (MD -6.00, 95% CI -6.94 to -5.06; participants = 40; studies = 1) [Analysis 2.2](#) in the superoxide solution group 10.5 (SD = 1.3 days) than the standard local treatment with iodine group 16.5 (SD = 1.7days). A statistically significant difference.

No data were reported for the secondary outcomes proportion of ulcers recurring after healing, and cost of treatment.

Analysis Table 2.1 – 2.2 Superoxide solution dressing and standard local treatment as compared with standard local treatment with povidone iodine dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Number of ulcers completely healed	1	40	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.00, 2.39]
2.2 Time to complete healing (days)	1	40	Mean Difference (IV, Random, 95% CI)	-6.00 [-6.94, -5.06]

Comparison 3: Low frequency ultrasound compared with sharp debridement (1 trial, 40 participants)

This comparison included 1 trial [Amini 2013](#) with 40 participants. The range of follow up was 6 months or until complete wound healing. The study comparison period was March 2009 to May 2010. There was significant risk of bias since much of the risk of bias characteristics were not reported. [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included low frequency ultrasound debridement as compared with standard local sharp debridement [Table 5](#); [Table 13](#).

Initial Wound Stage

The mean wound size in the study was reported to be 6.8 (SD = 6) cm² in the ultrasound group and 9.9 (SD = 7.6) cm² in the sharp debridement group. The mean wound depth was not reported. The wound stage in the study was Wagner Grade 3. The mean duration of ulcers in the study was 15.6 (SD=16.8) weeks in the low frequency ultrasound group and 17.6 (SD = 18.8) weeks in the sharp debridement group [Table 10](#).

Participant Characteristics

The studies comprised a total of 40 participants. The mean age for the study was not 55.2 (SD = 9.4) years. The study included 24 males and 16 females [Table 9](#). The study setting was a diabetic foot ulcer clinic in Iran [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was 9% higher (RR 1.09, 95% CI 0.64 to 1.86; participants = 40; studies = 1) [Analysis 3.1](#) in the low frequency ultrasound debridement group 12/20 (60%) as compared with the sharp debridement group 11/20 (55%). No statistically significant difference.

Time to complete healing (days)

The mean time to complete healing was 19.6 days shorter (MD -19.60, 95% CI -69.96 to 30.76; participants = 40; studies = 1) [Analysis 3.2](#) in the low frequency ultrasound debridement group 61.6 (SD = 84 days) than in the sharp debridement group 81.2 (SD = 78.4). No statistically significant difference.

No data were reported for the secondary outcomes proportion of participants with ulcers recurring, or cost of treatment.

Analysis Table 3.1 – 3.2 Low frequency ultrasound debridement compared with sharp debridement				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Number of ulcers completely healed	1	40	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.64, 1.86]
3.2 Time to complete healing (days)	1	40	Mean Difference (IV, Random, 95% CI)	-19.60 [-69.96, 30.76]

Comparison 4: Larvae compared with hydrogel (1 trial, 140 participants)

This comparison included 1 study [Markevich 2000](#) and a total of 140 participants. The range of follow up was 10 days. The study period was not reported. The study was available in abstract form. The abstract reports follow up was 10 days whilst the trial was reported to be 30 months in duration. Attempts to contact the authors have been unsuccessful.

Types of Interventions

The interventions in these studies included maggot debridement therapy as compared with hydrogel [Table 5](#); [Table 13](#).

Initial Wound Stage

The baseline wound characteristics were reported as comparable between both groups but were not otherwise specified. The mean wound depth was not reported. The average ulcer duration at baseline was 15.8 (SD = 10.7) years. The wound grade or stage was not reported. The mean duration of ulcers in the study was not reported [Table 10](#).

Participant Characteristics

The studies comprised a total of 140 participants. The mean age for the study was not 53.6 (SD = 15.4) years. The number of males and females were not reported [Table 9](#). The study setting was conducted in Europe [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of ulcers completely healed

In the larvae group 5/70 (7%) patients achieved complete healing, compared with 2/70 (3%) patients from the hydrogel group. There was a 150% greater healing rate in the larvae group as compared with the hydrogel group (RR 2.50, 95% CI 0.50 to 12.46; participants = 140; studies = 1) (no statistically significant difference) [Analysis 4.1](#).

No were reported for the secondary outcomes time to complete healing, proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 4.1 Larvae compared with Hydrogel				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Number of ulcers completely healed	1	140	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.50, 12.46]

Comparison 5: Hydrogel purilon gel compared with hydrogel intrasite (1 trial, 74 patients)

This comparison included 1 trial [Whalley 2001](#) and a total of 74 participants ([Whalley 2001](#)).

The range of follow up was until ulcer healing or a maximum of 10 weeks. The study period was not reported and it was published in abstract form only. Attempts to contact the authors have been unsuccessful.

Types of Interventions

The interventions in these studies included hydrogel purilon gel as compared with hydrogel intrasite [Table 5](#); [Table 13](#).

Initial Wound Stage

The baseline wound size in surface area was 2.5 (SD = 3.2) cm² in the purilon hydrogel group and 2.4 (SD = 2.9) cm² in the intrasite hydrogel group. The mean wound depth was not reported. Wounds with wound grade 1 - 2 were included. The average ulcer duration at baseline was not reported. The mean duration of ulcers in the study was not reported [Table 10](#).

Participant Characteristics

The studies comprised a total of 74 participants. The mean age for the study was not reported. The number of males and females was not reported [Table 9](#). The study specific setting (outpatient or inpatient) was unreported. The study was conducted in Europe. [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary outcomes

Proportion of ulcers completely healed

66 people were evaluated for this outcome and in the first hydrogel group (Purilon) 35% achieved complete healing compared with 19% in the second hydrogel group (Intrasite) [Analysis 5.1](#) . The numbers of people in each group were not reported in the abstract, therefore no further analysis was possible.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 5.1 Hydrogel purilon compared with hydrogel intrasite				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Number of ulcers completely healed	1	74	Other data	No numeric data

Comparison 6: Hydrogel compared with gauze/good wound care (3 trials, 232 participants)

[D'Hemecourt 1998](#); [Jensen 1998](#); [Vandeputte 1997](#)

Trial 1: Hydrogel compared with wet to moist saline gauze (31 participants)

This comparison included 1 study ([Jensen 1998](#)) and a total of 31 participants. The range of follow up was 20 weeks. The study period was not reported.

Types of Interventions

The interventions in these studies included hydrogel as compared with wet to moist saline gauze [Table 5](#); [Table 13](#).

Initial Wound Stage

The study included all ulcers of at least 1 cm² mean wound surface area. The mean wound depth was not reported. The study included Wagner grade 2 wounds. The ulcer duration at baseline was not reported. The mean duration of ulcers was 32 weeks in the hydrogel group and 12 weeks in the wet to moist saline gauze group [Table 10](#). Good wound care and other ancillary care is defined in the characteristics of included studies tables for each of the respective studies.

Participant Characteristics

The studies comprised a total of 31 participants. The mean age for the study was not reported. The number of males and females in the study was not reported [Table 9](#). The hospital/outpatient study setting was unclear, and the study was conducted in Europe [Table 3](#).

Primary outcomes

Proportion of participants with amputations

0/14 or 0% amputations were reported in the hydrogel group as compared with 1/17 or 5.9% in the wet to moist saline group. There was a 60% reduction in amputations favoring the hydrogel group as compared with the control group (RR 0.40, 95% CI 0.02 to 9.12; participants = 31; studies = 1) No statistically significant difference was demonstrated.

Proportion of participants with complicating infections

2/14 or 14.3% of complicating wound infections were reported in the hydrogel group as compared with 1/17 or 5.9% in the wet to moist saline group. There was a 143% increase in complicating infections in the hydrogel group as compared with control (RR 2.43, 95% CI 0.24 to 24.07; participants = 31; studies = 1); No statistically significant difference was observed.

No data were reported for the primary outcome quality of life.

Secondary outcomes

Proportion of ulcers completely healed

In the hydrogel group 11/14 (79%) of patients healed completely compared with 6/17 (46%) in the control group. There was a 123% increase in ulcers healed in the hydrogel group as compared with the control group (RR 2.23, 95% CI 1.11 to 4.48; participants = 98; studies = 3). There was a statistically significant difference demonstrated.

Time to complete healing

Those ulcers treated with the hydrogel were reported as achieving healing in an average of 10 weeks, with the control group healing in an average of 12 weeks (no statistically significant difference was observed).

No data were reported for the secondary outcome proportion of participants with ulcers recurring after healing.

Cost of treatment

Insufficient reporting prevented the determination of whether the difference in cost between hydrogel (\$7/day) as compared with the control condition (\$12/day) was statistically significant.

Trial 2: Hydrogel (NaCMC aqueous based gel) compared with good wound care alone (172 participants)

This comparison included 1 study ([D'Hemecourt 1998](#)) and a total of 172 participants. The range of follow up was 20 weeks. The study period was not reported. In this trial the intention-to-treat population consisted of 172 patients.

Types of Interventions

The interventions in these studies included NaCMC aqueous based gel as compared with good wound care alone [Table 5](#); [Table 13](#).

Initial Wound Stage

The study included ulcers with a mean baseline wound surface area and depth of 3.5 (SD = 3.53) cm², 0.4 (SD = 0.52) cm in the aqueous based gel group as compared with 3.2 (SD = 2.75) cm², 0.4 (SD = 0.20) cm in the control group respectively. The study included Wagner grade 3 to 4 wounds. The mean duration of ulcers at baseline was 42 +/- 42 weeks and 52.8 (SD = 60.92) weeks in the aqueous based gel and control group respectively [Table 10](#).

Participant Characteristics

The studies comprised a total of 172 participants. The mean age for the study was 58.3 (SD = 12.13) years. There were 127 males and 45 females in the study [Table 9](#). The study setting was unclear and was conducted in the USA [Table 3](#).

Primary outcomes

Proportion of participants with complicating infections

21/70 or 30% of participants in the aqueous based gel group developed complicating wound infections as compared with 19/68 or 28% in the control group. There was a 7% increase in the proportion of participants with complicating wound infections in the aqueous based gel group as compared with the control group (RR 1.07, 95% CI 0.64 to 1.81); no statistically significant difference was observed.

No data were reported for the primary outcomes proportion of participants with amputations, quality of life.

In the control group 10/68 (15%) of patients reported an increase in pain compared with 11/70 (16%) in the hydrogel group, RR 1.07 (95% CI 0.49 to 2.35) (no statistically significant difference). It is not clear in the reporting of the trial how pain was measured or whether a valid scale was used.

Secondary outcomes

Proportion of ulcers completely healed

Within a 20-week study period 15/68 (22%) of patients healed with good wound care alone (daily dressing changes; sharp debridement of ulcer; systemic control of any present infection; off-loading of pressure) compared with 25/70 (36%) of patients healed with hydrogel. There was a 62% increase in proportion of healed participants as compared with the good wound care alone group, RR 1.62 (95% CI 0.94 to 2.80) (no statistically significant difference).

No data were reported for the secondary outcomes time to complete healing, proportion of participants with ulcers recurring after healing, cost of treatment

Trial 3: "Immunomodulating" hydrogel compared with dry gauze (29 participants)

This comparison included 1 study ([Vandeputte 1997](#)) and a total of 29 participants. The range of follow up was 12 weeks. The study period was not reported.

Types of Interventions

The interventions in these studies included hydrogel as compared with dry gauze; [Table 5](#); [Table 13](#).

Initial Wound Stage

The baseline wound size, depth, wound stage, and duration of ulcer was not reported for this study [Table 10](#).

Participant Characteristics

The studies comprised a total of 29 participants. The mean age for the study was 63.95 +/- 14.5 years. There were 13 males and 16 females in the study [Table 9](#). The study was conducted in the outpatient setting in Belgium [Table 3](#).

Primary outcomes

Proportion of participants with amputations

1/14 or 7.1% of amputations were reported in the hydrogel group as compared with 5/15 or 33.3% in the gauze group. There was a 79% reduction in amputations favoring the hydrogel group as compared with the gauze group (RR 0.21, 95% CI 0.03 to 1.61; participants = 29; studies = 1). No statistically significant difference was observed.

Proportion of participants with complicating infections

1/15 or 7% of complicating wound infections were reported in the hydrogel group as compared with 7/14 or 50% in the gauze group. There was an 87% reduction in complicating wound infections in the hydrogel group as compared with control (RR 0.13, 95% CI 0.02 to 0.95; participants = 29; studies = 1); there was a statistically significant difference. It was not reported that the study was stopped early.

No data were reported for the primary outcome quality of life.

Secondary outcomes

Proportion of ulcers completely healed

7/15 (47%) of ulcers were completely healed in the hydrogel group as compared with 5/14 (36%) in the gauze group. This was a 31% increase in proportion of participants with ulcers completely healed; RR 1.31, 95% CI 0.54 to 3.17). No statistically significant difference.

No data were reported for the secondary outcomes time to complete healing, proportion of participants with ulcers recurring after healing, and cost of treatment.

Summary: Hydrogel compared with gauze/good wound care alone

The three trials ([D'Hemecourt 1998](#); [Jensen 1998](#); [Vandeputte 1997](#)) comparing hydrogel with either gauze dressing or good wound care (dressing not specified) were considered sufficiently similar to pool, using a random effects model. They included a combined total of 232 participants. The follow up ranged from 12 - 20 weeks. The study period was not reported in the 3 studies. There was unclear to high risk of bias as many of the risk of bias considerations utilized in this review were either unclear or high [Figure 3](#); [Figure 4](#).

Proportion of participants with amputations

The two studies that reported number of amputations were pooled these included [Jensen 1998](#) and [Vandeputte 1997](#). Pooling these two studies yielded a relative risk for amputation of 0.26 (95% CI 0.05 to 1.40; participants = 60; studies = 2; in the presence of heterogeneity, $p = 0.74$, $I^2 = 0\%$) [Analysis 6.1](#). No statistically significant difference. This translates to 74% reduction in proportion of amputations for the hydrogel group as compared to gauze and a number needed to treat of 8 (95% CI 3 [NNTB], 12 [NNTH]): that is to prevent one additional patient with diabetic foot ulcer from having an amputation, eight patients must be treated with hydrogel instead of gauze or standard care (treatment time varied from 12 to 20 weeks). No statistical significant difference was observed [Figure 23](#).

Proportion of participants with complicating infections

All 3 studies reported on proportion of infections, and on the proportion of ulcers completely healed.

Pooling the three trials yielded a relative risk for infections with hydrogel of 0.74, (95% CI 0.18 to 2.99; participants = 198; studies = 3; in the presence of heterogeneity, $p = 0.09$, $I^2 = 59\%$) [Analysis 6.2](#). This translates to a 26% reduction in proportion of infections for the hydrogel group as compared to gauze, and a number needed to treat of 12 (95% CI 3 [NNTB], 6 [NNTH]): that is to prevent one additional patient with diabetic foot ulcer from having an infection, twelve patients must be treated with hydrogel instead of gauze or standard care (treatment time varied from 12 to 20 weeks). No statistically significant difference was observed [Figure 24](#).

Proportion of participants with ulcers healed

The proportion of ulcers healed yielded a relative risk of 1.71, 95% CI 1.16 to 2.52; participants = 198; studies = 3; in the absence of significant heterogeneity, $p = 0.62$, $I^2 = 0\%$) [Analysis 6.3](#).

This translates to a 71% increase in the proportion of ulcers healed in the hydrogel group as compared to gauze group, and a number needed to treat of 12 (95% CI 50 [NNTB] to 3 [NNTB]): that is to heal one additional patient with diabetic foot ulcer, twelve patients must be treated with hydrogel instead of gauze or standard care (treatment time varied from 12 to 20 weeks). No statistically significant difference was observed [Figure 25](#).

Quality of life index, proportion of participants with recurrent ulcers, time to complete healing, and cost of treatment were either not reported at all or not reported in at least two or more studies.

Analysis Table 6.1 – 6.3 Hydrogel compared with gauze or good wound care (gwc)				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Number of amputations reported	2	60	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.05, 1.40]
6.2 Number of Infections reported	3	198	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.18, 2.99]
6.3 Number of ulcers completely healed	3	198	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.16, 2.52]

Comparison 7 Polyurethane gel dressing compared with polyurethane foam dressing (1 trial, 40 participants)

This included 1 trial [Clever 1995](#) with 40 participants. The study was available in unpublished abstract form only. The range of follow included healing occurrence or a maximum of 16 weeks. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high risk [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Hydroactive polyurethane gel dressing (Cutinova Hydro) and standard therapy as compared with Hydrophilic polyurethane foam dressing (Allevyn) and standard therapy. Standard therapy was defined as offloading, infection control with antibiotics, wound cleansing with ringer's solution, and "debridement" with removal of callus if needed. The separate form of debridement was not defined [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area in the study was reported to be 2.05 (SD = 3.14) cm² in the polyurethane gel dressing group and 2.08 (SD = 2.72) cm² in the polyurethane foam dressing group. The initial mean depth of wound, or wound stage was not reported for either the intervention or comparison groups. The initial mean duration of ulcers in the study was 162.37 (SD = 325.55) days in the polyurethane gel dressing group and 165 (SD = 318.68) days in the polyurethane foam dressing group [Table 10](#).

Participant Characteristics

The studies comprised a total of 40 participants. The mean age for the study was 56 (SD = 13.13) years. There were 32 males and 8 females. The study setting included outpatients, and the study was conducted in Germany.

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of patients with ulcers completely healed was lower in the Polyurethane gel dressing group 14/20 (70%) as compared with the polyurethane foam dressing group 16/20 (80%) (RR 0.88, 95% CI 0.61 to 1.26; participants = 40; studies = 1) [Analysis 7.1](#) No statistically significant difference was observed.

Time to complete healing (days)

The time to complete healing was on average 4.76 days shorter in the Polyurethane gel dressing group as compared with the polyurethane foam dressing group (MD -4.76, 95% CI -16.93 to 7.41; participants = 40; studies = 1) [Analysis 7.2](#). No statistically significant difference was observed.

No data were reported for the secondary outcomes proportion of participants with ulcers recurring after healing, cost of treatment.

Analysis Table 7.1 -7.2 Polyurethane gel dressing compared with polyurethane foam dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Number of ulcers completely healed	1	40	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.26]
7.2 Time to complete healing (days)	1	40	Mean Difference (IV, Random, 95% CI)	-4.76 [-16.93, 7.41]

Comparison 8 Alginate dressing compared with gauze (2 Trials, 152 participants)

Trial 1: Calcium alginate as compared with Vaseline gauze (1 trial, 77 participants)

This comparison included 1 trial [Lalau 2002](#) with 77 participants. The range of follow up was 4 weeks this was reduced from the planned 6 week follow up period due to 13 withdrawals. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high risk. See [Figure 3](#); [Figure4](#).

Types of Interventions

The interventions in these studies included the calcium alginate dressing group as compared with Vaseline gauze. The study reported that no other treatments were permitted, except unrestricted saline solution and mechanical debridement was authorized "as needed" [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area was reported as 8.0 (SD = 10.5) cm² in the calcium alginate dressing group and 8.8 (SD = 16.0) cm² in the Vaseline gauze dressing group. The initial mean wound depth and wound staging were not reported. The mean duration of ulcers was 19.6 (SD = 31.2) weeks in the Calcium alginate group, and 36.4 (SD = 52.4) weeks in the Vaseline gauze group [Table 10](#).

Participant Characteristics

The studies comprised a total of 77 participants. The mean age reported was 62.2 (SD = 11.75) years. There were 45 males and 32 females in the study. [Table 9](#) The study was conducted at 13 outpatient settings "throughout" France. [Table 3](#)

Primary Outcomes

Proportion of participants with complicating infections

1/39 (2.6%) complicating wound infections were reported in the calcium alginate group as compared with 3/38 (7.9%) in the Vaseline gauze group. There was a 68% reduction in complicating wound infections in the calcium alginate group as compared with the Vaseline gauze group (RR 0.32, 95% CI 0.04 to 2.99; participants = 77; studies = 1) [Analysis 8.1](#). No statistically significant difference was observed.

No data were reported for the primary outcomes proportion of participants with amputations, and quality of life.

Secondary Outcomes

No data were reported for any of the secondary outcomes.

Trial 2: Collagen alginate as compared with moist gauze (1 trial, 75 participants)

This comparison included 1 trial [Donaghue 1998](#) with 75 participants. The follow up period was until the wound healed or a maximum of 8 weeks. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high risk. See [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included the collagen alginate dressing group as compared with moist gauze [Table 5](#); [Table 13](#). The study reported that in all participant's weight-bearing limitations for offloading were employed using self-adhesive felted foam with a window at the wound site, and "healing" sandals.

Initial Wound Stage

The initial mean wound surface area was reported as 2.6 (SD = 0.50) cm² in the collagen alginate dressing group and 2.99 (SD = 0.62) cm² in the moist gauze group. The initial mean wound depth was 0.4 (SD = 0.52) cm in the collagen alginate group, and 0.4 (SD = 0.20) cm in the moist gauze group. The wound staging reported as Wagner grade 1 to 3. The mean duration of ulcers was 20.86 (SD = 10.43) weeks in the collagen alginate group, and 32.14 (SD = 14.86) weeks in the Vaseline gauze group [Table 10](#).

Participant Characteristics

The studies comprised a total of 75 participants. The mean age reported was 59.5 years (no SD reported). There were 54 males and 21 females in the study. [Table 9](#) The study was conducted at outpatient settings in the US. [Table 3](#)

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of patients with ulcers completely healed were greater in the collagen alginate dressing group 24/50 (48%) as compared with the Vaseline gauze dressing group 9/25 (36%). There was a 33% increase in the proportion of ulcers healed in the collagen alginate group as compared with Vaseline gauze group (RR 1.33, 95% CI 0.73 to 2.42; participants = 75; studies = 1) [Analysis 8.2](#) No statistically significant difference was observed.

Time to complete healing (days)

The time to complete healing was on average 2.80 days shorter in the calcium alginate dressing group as compared with the Vaseline gauze dressing group. (MD 2.80, 95% CI 1.46 to 4.14; participants = 75; studies = 1) [Analysis 8.3](#). There was a statistically significant difference observed.

No data were reported for the secondary outcomes proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 8.1 – 8.3 Calcium alginate compared with moist gauze				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Number of Infections reported	1	77	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.04, 2.99]
8.2 Number of ulcers completely healed	1	75	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.73, 2.42]
8.3 Time to complete healing (days)	1	75	Mean Difference (IV, Random, 95% CI)	2.80 [1.46, 4.14]

Comparison 9 Hydrocolloid dressing compared with adhesive Zinc tape dressing (1 trial, 44 participants)

This included 1 trial [Apelqvist 1990](#) with 44 participants. The follow up period was 5 weeks. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were unclear. [Figure 3: Figure 4.](#)

Types of Interventions

The interventions in these studies included hydrocolloid dressing as compared with Zinc adhesive tape dressing (Allevyn). All patient received pressure relief offloading. All ulcers were cleaned with sterile saline [Table 5; Table 13.](#)

Initial Wound Stage

The initial mean wound surface area in the study was reported to be 2.2 cm² in the hydrocolloid dressing group and 2.2 cm² in the Zinc adhesive tape dressing group. The initial mean depth of wound, initial wound stage, and mean duration of ulcers were not reported in the study for either intervention arm [Table 10](#).

Participant Characteristics

The studies comprised a total of 40 participants. The mean age for the study was 63 (SD = 36) years. There were 26 males and 20 females. [Table 9](#) The study setting included outpatients, and the study was conducted in Sweden [Table 3](#).

Primary Outcomes

Proportion of participants with complicating infections

There were a greater number of complicating infections 1/22 (4.5%) in the hydrocolloid dressing group as compared with 0/22 (0%) of the Zinc adhesive tape dressing group. (RR 3.00, 95% CI 0.13 to 69.87; participants = 44; studies = 1) No statistically significant difference was observed.

No data were reported for the primary outcomes proportion of participants with amputations, and quality of life.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of patients with ulcers completely healed was lower in the Hydrocolloid dressing group 5/22 (22.3%) as compared with the Zinc adhesive tape dressing group 9/22 (40.9%). There was a 44% reduction in ulcers healed in the hydrocolloid dressing group as compared with the Zinc adhesive tape dressing group (RR 0.56, 95% CI 0.22 to 1.39; participants = 44; studies = 1)

[Analysis 9.2](#) No statistically significant difference was observed.

Time to complete healing (days)

No data were reported for the secondary outcomes proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 9.1 – 9.2 Hydrocolloid dressing compared with adhesive Zinc tape dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Number of Infections reported	1	44	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 69.87]
9.2 Number of ulcers completely healed	1	44	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.22, 1.39]

Comparison 10 Foam dressing compared with Wet to dry gauze dressing (2 trials, 37 participants)

Trial 1: Polymeric membrane foam dressing as compared with Wet to dry saline gauze (18 participants)

This comparison included 1 trial [Blackman 1994](#) with 18 participants. The follow up period was 6 months or until the ulcer healed. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high risk [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included a Polymeric membrane foam dressing group as compared with a Wet to dry saline gauze group. All the participants were "encouraged" to obtain orthotic foot wear [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area was reported as 2.67 (SD = 1.20) cm² in the calcium alginate dressing group and 1.81 (SD = 0.75) cm² in the wet to dry gauze dressing group. The initial mean wound depth was not reported. Wagner grade 1 and 2 wounds were included. The mean duration of ulcers was 25 (SD = 7) weeks in the Polymeric membrane group, and 28 (SD = 6) weeks in the Wet to dry saline group [Table 10](#).

Participant Characteristics

The studies comprised a total of 18 participants. The mean age reported was 55.9 (SD = 13.6) years. There were 17 males and 1 female in the study [Table 9](#). The inpatient/outpatient study setting was unclear, and the study was conducted in the US [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the Polymeric membrane dressing group 8/11 (73%) as compared with the Wet to dry saline dressing group 0/7 (0%). There was an increased risk of healing in the Polymeric membrane dressing group as compared with 0/7 (0%) in the Wet to dry saline dressing group (RR 11.33, 95% CI 0.76 to 170.03; participants = 37; studies = 1).

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, and cost of treatment.

Trial 2: Polymeric foam membrane dressing as compared with Wet to dry saline gauze mesh (19 participants)

This comparison included 1 trial [Mazzone 1993](#) with 19 participants. The follow up period was 8 weeks. The study comparison period was not reported. There was significant risk of bias as many of the risk of bias considerations were either unclear or high risk [Figure 3](#); [Figure 4](#). The study was only available as a published abstract.

Types of Interventions

The interventions in these studies included Polymeric foam membrane as compared with Wet to dry saline gauze mesh. No other treatments were reported [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area, initial mean wound depth, wound staging, and mean duration of ulcers was not reported [Table 10](#).

Participant Characteristics

The studies comprised a total of 19 participants. Age, and gender composition were not reported [Table 9](#). The study was conducted in an outpatient setting in the US [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of patients with ulcers completely healed was greater in the Polymeric foam membrane group 7/11 (48%) as compared with the Wet to dry saline gauze mesh dressing group 2/8 (36%). There was a 155% increase in the proportion of ulcers healed in the Polymeric foam membrane group as compared with Wet to dry saline gauze mesh dressing group (RR 2.55, 95% CI 0.71 to 9.16; participants = 19; studies = 1) No statistically significant difference was observed.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, cost of treatment

Summary: Foam compared with gauze/good wound care alone

The two trials ([Blackman 1994](#); [Mazzone 1993](#)) comparing Foam dressing with Wet to dry gauze dressing were considered sufficiently similar to pool, using a random effects model. They included a combined total of 37 participants. The follow up period ranged from 8 - 24 weeks. The study comparison period was not reported in the 2 studies. There was unclear to high risk of bias as many of the risk of bias considerations were either unclear or high [Figure 3: Figure 4](#).

Types of Interventions

The interventions in these studies included Foam dressing as compared with Wet to dry gauze [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area was reported in [Blackman 1994](#), but not in [Mazzone 1993](#). The mean wound depth was not reported in either study. The wound staging included in the studies were classified as Wagner grade 1 - 2 in the [Blackman 1994](#) but not reported in [Mazzone 1993](#). The mean duration of ulcers was 25 (SD = 7) weeks in the [Blackman 1994](#) study and not reported in [Mazzone 1993](#); [Table 10](#).

Participant Characteristics

The studies comprised a total of 37 participants. The mean ages for the studies were 55.9 (SD = 13.6) years in [Blackman 1994](#) and was not reported in [Mazzone 1993](#). There were a total of 17 males and 1 female in [Blackman 1994](#), while gender was not reported in [Mazzone 1993](#); [Table 4](#). The study setting was unclear in [Blackman 1994](#) and was conducted in an outpatient setting in [Mazzone 1993](#). Both studies were conducted in the US [Table 3](#).

Proportion of participants with ulcers healed

The proportion of ulcers healed yielded a relative risk of (RR 3.56, 95% CI 0.93 to 13.66; participants = 37; studies = 2); in the absence of significant heterogeneity, $p = 0.28$, $I^2 = 13\%$); [Analysis 10.1](#); No statistically significant difference was observed. This translates to a 256% increase in the proportion of ulcers healed in the foam membrane group as compared with the Wet to dry gauze group, and a number needed to treat of 2 (95% CI 2 [NNTB] to 5 [NNTB]); that is to heal one additional patient with a diabetic foot ulcer, two patients must be treated with foam dressing instead of Wet to dry gauze (treatment time varied from 8 to 24 weeks). No statistically significant difference was observed.

Proportion of participants with amputations, Proportion of participants with complicating infections, Quality of life index, Proportion of participants with recurrent ulcers, Time to complete healing, and Cost of treatment were either not reported at all or were not reported in both studies and therefore could not be pooled for a meta-analysis [Figure 26](#).

Analysis Table 10.1 Foam dressing compared with Wet to Dry Saline				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 Number of ulcers completely healed	2	37	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.93, 13.66]

Comparison 11 Foam dressing compared with saline nonadherent gauze dressing (1 trial, 30 participants)

[Roberts 2001](#)

This comparison included 1 trial with 30 participants. The follow up period was 13 weeks. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high [Figure 3; Figure 4](#).

Types of Interventions

The interventions in these studies included Foam dressing as compared with saline nonadherent Gauze dressing. All patient received "standard podiatric care" which was not defined [Table 5; Table 13](#).

Initial Wound Stage

The initial median wound surface area in the study was reported to be 1.1 cm² in the Foam dressing group and 1.45 cm² in the saline nonadherent Gauze dressing group. The initial depth of wound, wound stage were not reported in the study for either treatment arm. The mean duration of ulcers for the sample was 15.2 weeks. [Table 10](#)

Participant Characteristics

The studies comprised a total of 30 participants. The median age for the study was 59.5 years. There were 23 males and 7 females [Table 9](#). The study setting included hospitalized patients, and the study was conducted in UK [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the foam dressing group 6/14 (43%) as compared with the saline nonadherent gauze dressing group 4/16 (25%) (RR 1.71, 95% CI 0.60 to 4.86; participants = 30; studies = 1). There was a 71% increase in the proportion of participants with ulcers completely healed in the foam dressing group than in the nonadherent gauze dressing group. No statistically significant difference was observed.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring, and cost of treatment.

Analysis Table 11.1 Foam dressing compared with saline gauze dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 Number of ulcers completely healed	1	30	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.60, 4.86]

Comparison 12 Iodine impregnated fiber dressing compared with gauze dressing (1 trial, 214 participants)

This comparison included 1 trial [Jeffcoate 2009](#) with 214 participants. The follow up period was 24 weeks. The study comparison period was June 2003 to March 2007. There was some risk of bias however many of the risk of bias considerations were low. [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Iodine impregnated fiber dressing as compared with gauze dressing. All patient received ulcer management including regular use of debridement, and "recommended" fiberglass or polyester boot for offloading. It was not clear whether another alternate form of debridement was used or whether the study relied on the debridement effect of the dressing itself [Table 5](#); [Table 13](#).

Initial Wound Stage

The wound surface area included in the study ranged between 0.25 - 2.25 cm². It was further subdivided into 3 additional ranges that included 0.25 - 1 cm², 1.01 - 0.25 cm², and 2.5 - 25cm².

The number of participants in each subgroup was 48, 36, and 24 for the Inadine group; and 50, 34, and 22 for the gauze group, respectively. The initial depth of wound, wound stage, and wound duration were not reported in the study for either of the treatment arms [Table 10](#).

Participant Characteristics

The study comprised a total of 214 participants. The mean age for the study participants was reported was 59.6 (SD = 12.6) years. There were 159 males and 54 females [Table 9](#). The study setting included multidisciplinary outpatient centers, and the study was conducted in the UK [Table 3](#).

Primary Outcomes

Proportion of participants with amputations

The proportion of participants with amputations was lower in the Inadine dressing group 1/108 (1%) as compared with the gauze dressing group 2/106 (2%). There was a 51% reduction in amputations observed in the Inadine group as compared to control. (RR 0.49, 95% CI 0.05 to 5.33; participants = 214; studies = 1); No statistically significant difference was observed.

Proportion of participants with complicating infections

The proportion of participants with complicating infections was higher in the Inadine dressing group 71/108 (66%) as compared with the gauze dressing group 48/106 (45%). There was a 45% increase in complicating infection observed in the Inadine group as compared to control. (RR 1.45, 95% CI 1.13 to 1.86; participants = 214; studies = 1); a statistically significant difference was observed.

Quality of Life

The Quality of life Index was higher in the Inadine dressing group 0.3838 +/- 0.1085 as compared with the gauze dressing group 0.3939 +/- 0.1093. There was a - 0.01 Quality of life mean difference reduction in the Inadine group as compared to control. (MD -0.01, 95% CI -0.04 to 0.02; participants = 214; studies = 1); No statistically significant difference was observed.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the Inadine dressing group 48/108 (44%) as compared with the gauze dressing group 41/106 (39%). There was a 15% increase in the proportion of participants with ulcers completely healed in the Inadine dressing group as compared with the gauze-dressing group. (RR 1.15, 95% CI 0.84 to 1.58; participants = 214; studies = 1); No statistically significant difference was observed.

Time to complete healing (days)

The time to complete healing was lower in the Inadine dressing group as compared with the gauze dressing group. There was reduction of 2.9 days in time to complete healing in the Inadine dressing group 127.8 (SD = 54.2) days as compared with the gauze dressing group 130.7 (SD = 52.4) days; (MD -2.90, 95% CI -17.18 to 11.38; participants = 214; studies = 1); No statistically significant difference was observed.

The proportion of participants with ulcers recurring after healing

The proportion of participants with ulcers recurring after healing was higher in the Inadine dressing group 7/108 (6.5%) as compared with the gauze dressing group 3/106 (3%). There was a 129% increase in the proportion of participants with ulcers completely healed in the Inadine dressing group as compared with the gauze dressing group; (RR 2.29, 95% CI 0.61 to 8.62; participants = 214; studies = 1); No statistically significant difference was observed.

Cost of treatment

The cost of treatment was higher in the Inadine dressing group 183.60 (SD = 286.47) British Pounds as compared with the gauze dressing group 141.18 (SD = 171.31) British Pounds. The mean difference in cost of treatment was 42.42 British Pounds greater in the Inadine dressing group as compared with the gauze dressing group; (MD 42.42, 95% CI -20.69 to 105.53; participants = 214; studies = 1).

Analysis Table 12.1 – 12.7 Iodine impregnated fiber dressing compared with gauze dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 Number of amputations reported	1	214	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.05, 5.33]
12.2 Number of Infections reported	1	214	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.13, 1.86]
12.3 Quality of life	1	214	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.36, 0.18]
12.4 Number of ulcers completely healed	1	214	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.84, 1.58]
12.5 Time to complete healing (days)	1	214	Mean Difference (IV, Random, 95% CI)	-2.90 [-17.18, 11.38]
12.6 Recurrence rates	1	214	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.61, 8.62]
12.7 Treatment cost	1	214	Mean Difference (IV, Random, 95% CI)	42.42 [-20.69, 105.53]

Comparison 13 Hydrofiber compared with gauze dressing (2 trials, 229 participants)

[Jeffcoate 2009](#); [Piaggese 2001](#)

Trial 1: Hydrofiber dressing as compared with gauze dressing (209 participants)

This comparison included 1 study [Jeffcoate 2009](#) and a total of 209 participants. The follow up period was 24 weeks. The study comparison period was June 2003 to March 2007.

There was some risk of bias however many of the risk of bias considerations were low risk for bias [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included hydrofiber dressing as compared with gauze dressing. All patient received ulcer management including regular use of debridement, and "recommended" fiberglass or polyester boot for offloading. It was not clear whether another alternate form of debridement was used or whether the study relied on the debridement effect of the dressing itself [Table 5](#); [Table 13](#).

Initial Wound Stage

The wound surface area included in the study ranged between 0.25 - 2.25 cm². It was further subdivided into 3 additional ranges that included 0.25 - 1 cm², 1.01 - 0.25 cm², and 2.5 - 25cm². The number of participants in each subgroup was 53, 34, and 16 for the hydrofiber group; and 50, 34, and 22 for the gauze group, respectively. The initial depth of wound, wound stage, and wound duration were not reported in the study for either of the treatment arms [Table 10](#).

Participant Characteristics

The study comprised a total of 209 participants. The mean age for the study participants was reported was 59.6 +/- 12.6 years. There were 159 males and 49 females [Table 9](#). The study setting included multidisciplinary outpatient centers, and the study was conducted in the UK [Table 3](#).

Types of Outcomes

Primary Outcomes

Proportion of participants with amputations

The proportion of participants with amputations was higher in the Hydrofiber dressing group 4/103 (4%) as compared with the gauze dressing group 2/106 (2%). There was a 106% increase in the proportion of participants with amputations observed in the Hydrofiber group as compared to control. (RR 2.06, 95% CI 0.39 to 10.99; participants = 209; studies = 1); No statistically significant difference was observed.

Proportion of participants with complicating infections

The proportion of participants with complicating infections was higher in the Hydrofiber dressing group 54/103 (52%) as compared with the gauze dressing group 48/106 (45%). There was a 16% increase in proportion of participants with complicating infections observed in the Hydrofiber group as compared to the control group. (RR 1.16, 95% CI 0.88 to 1.53; participants = 209; studies = 1); No statistically significant difference was observed.

Quality of Life

The Quality of life Index was higher in the Hydrofiber dressing group 0.3822 (SD = 0.1085) as compared with the gauze dressing group 0.3939 (SD = 0.1093). There was a - 0.10 Quality of life mean difference reduction in the Hydrofiber group as compared to control. (MD -0.10, 95% CI -0.38 to 0.17; participants = 209; studies = 1); No statistically significant difference was observed.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the Hydrofiber dressing group 46/103 (45%) as compared with the gauze dressing group 41/106 (39%). There was a 15% increase in the proportion of participants with ulcers completely healed in the Hydrofiber dressing group as compared with the gauze-dressing group. (RR 1.15, 95% CI 0.84 to 1.59; participants = 209; studies = 1); No statistically significant difference was observed.

Time to complete healing (days)

The time to complete healing was lower in the Hydrofiber dressing group 125.8 (SD = 55.9) days as compared with the gauze dressing group 130.7 (SD = 52.4) days. There was a mean reduction of 4.9 days in time to complete healing in the Hydrofiber dressing group as compared with the gauze dressing group; (MD -4.90, 95% CI -19.60 to 9.80; (participants = 209; studies = 1); No statistically significant difference was observed.

The proportion of participants with ulcers recurring after healing

The proportion of participants with ulcers recurring after healing was higher in the Hydrofiber dressing group 3/103 (3%) as compared with the gauze dressing group 3/106 (3%). There was a small 3% increase in the proportion of participants with ulcers completely healed in the Hydrofiber dressing group as compared with the gauze dressing group; (RR 1.03, 95% CI 0.21 to 4.98; participants = 209; studies = 1); No statistically significant difference was observed.

Cost of treatment

The cost of treatment was higher in the Hydrofiber dressing group 191.33 (SD = 219.63 British Pounds) as compared with the gauze dressing group 141.18 (SD = 171.31). The mean difference in cost of treatment was 50.15 British pounds greater in the Hydrofiber dressing group as compared with the gauze dressing group; (MD 50.15, 95% CI -3.35 to 103.65; participants = 209; studies = 1), no statistically significant difference was observed.

Trial 2: Hydrofiber dressing as compared with gauze dressing (20 participants)

[Piaggese 2001](#)

This comparison included 1 study [Piaggese 2001](#) and a total of 20 participants. The follow up period was 8 weeks. The study period was 1998. There was significant risk of bias as many of the risk of bias considerations were unclear or high risk for bias [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included hydrofiber dressing as compared with gauze dressing. All patient received for post-operative shoes for pressure relief and were trained to walk on crutches until there was satisfactory healing [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound volume included in the study was 19.2 (SD = 6.4) cm³ in the Hydrofiber dressing group and 22.6 (SD = 8.4) cm³ in the gauze-dressing group. The initial mean wound depth was 2.9 (SD = 1.1) cm in the Hydrofiber dressing group and 2.3 (SD = 1.4) cm in the Saline moistened dressing group. The wound stage, and wound duration were not reported in the study for either of the treatment arms. [Table 10](#)

Participant Characteristics

The study comprised a total of 20 participants. The median age for the study participants was reported was 59.5. Gender composition was not reported. [Table 9](#) The study setting included outpatients, and the study was conducted in the Italy. [Table 3](#)

Types of Outcomes

Primary Outcomes

Proportion of participants with amputations

The proportion of participants with amputations was lower in the hydrofiber dressing group 0/10 (0%) as compared with the gauze dressing group 1/10 (10%). There was a decrease in the proportion of participants with amputations observed in the hydrofiber group as compared to control. (RR 0.33, 95% CI 0.02 to 7.32; participants = 20; studies = 1); No statistically significant difference was observed.

Proportion of participants with complicating infections

The proportion of participants with complicating infections was higher in the Hydrofiber dressing group 1/10 (10%) as compared with the Saline moistened gauze dressing group 3/10 (30%). There was a 67% decrease in the proportion of participants with complicating infections observed in the hydrofiber group as compared to the gauze group. (RR 0.33, 95% CI 0.04 to 2.69; participants = 20; studies = 1); No statistically significant difference was observed.

No data were reported for the primary outcome quality of life.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the hydrofiber dressing group 10/10 (100%) as compared with the saline nonadherent gauze dressing group 9/10 (90%). There was an 11% increase in the proportion of participants with ulcers completely healed in the Hydrofiber dressing group as compared with the gauze dressing group. (RR 1.11, 95% CI 0.85 to 1.44; participants = 20; studies = 1); No statistically significant difference was observed.

Time to complete healing (days)

The time to complete healing was less in the Hydrofiber dressing group 127 (SD = 46) days as compared with the gauze dressing group 234 (SD = 61) days. There was a mean reduction of 107 days in time to complete healing in the Hydrofiber dressing group as compared with the gauze dressing group; (MD -107.00, 95% CI -154.35 to -59.65; (participants = 20; studies = 1); Statistically significant difference was observed.

No data were reported for the secondary outcomes proportion of participants with ulcers recurring after healing, or cost of treatment.

Summary: Hydrofiber compared with saline moistened gauze

The two trials ([Jeffcoate 2009](#); [Piaggese 2001](#)) comparing hydrofiber with saline moistened gauze dressing were considered sufficiently similar to pool, using a random effects model. They included a combined total of 229 participants. The follow up ranged from 12 - 24 weeks. The study comparison period was 1998, and June 2003 - March 2007. There was significant risk of bias as many of the risk of bias characteristics were either unclear (unreported) or high risk of bias [Figure 3](#); [Figure 4](#).

Proportion of participants with amputations

The two studies on the number of amputations and were pooled. Pooling these two studies yielded a relative risk for amputation of (RR 1.34, 95% CI 0.29 to 6.10; participants = 229; studies = 2); in the absence of significant heterogeneity, $p = 0.31$, $I^2 = 3\%$) [Analysis 13.1](#). No statistically significant difference. This translates to 34% increase in the proportion of participants with amputations for the hydrofiber dressing group as compared to saline moistened gauze dressing group; and a number needed to treat [NNTB] of 100 (95% CI 25 [NNTB], 15 [NNTH]); that is to prevent one additional patient with diabetic foot ulcer from having an amputation, 100 patients must be treated with hydrofiber instead of saline moistened gauze. No statistically significant difference was observed [Figure 27](#).

Proportion of participants with complicating infections

Both studies reported on proportion participants with complicating infections.

Pooling the two trials yielded a relative risk for infections with hydrofiber of 0.96, (95% CI 0.40 to 2.31; participants = 229; studies = 2); in the absence of significant heterogeneity, $p = 0.24$, $I^2 = 27\%$); [Analysis 13.2](#). This translates to 4% reduction in the proportion participants with complicating infections for the hydrofiber dressing group as compared to saline moistened gauze dressing group, and a number needed to treat [NNTB] of 50 (95% CI 4 [NNTB] to 5 [NNTH]); that is to prevent one additional patient with diabetic foot ulcer from developing an infection, fifty patients must be treated with hydrofiber instead of gauze (treatment time varied from 8 to 24 weeks). Though no statistically significant difference was observed [Figure 28](#).

Proportion of participants with ulcers healed

The proportion participants with ulcers healed yielded a relative risk of (RR 1.13, 95% CI 0.92 to 1.38; participants = 229; studies = 2); in the absence of significant heterogeneity, $p = 0.79$, $I^2 = 0\%$). This translates to a 13% increase in the proportion of ulcers healed in the hydrofiber dressing group as compared to saline moistened gauze group, and a number needed to treat of 15 (95% CI 6 [NNTB], 20 [NNTH]): ([Analysis 13.4](#)) that is to heal one additional patient with diabetic foot ulcer, fifteen patients must be treated with hydrofiber instead of saline moistened gauze (treatment time varied from 8 to 24 weeks). No statistically significant difference was observed [Figure 29](#).

Time to complete healing

The Time to complete healing yielded a mean difference of 53.37 days less in the hydrofiber dressing group as compared to the saline moistened dressing group (MD -53.37, 95% CI -153.29 to 46.56; participants = 229; studies = 2); ([Analysis 13.5](#)) in the presence of significant heterogeneity, $p < 0.0001$, $I^2 = 94\%$) (treatment time varied from 8 to 24 weeks). No statistically significant difference was observed [Figure 30](#).

The primary outcome quality of life index, and the secondary outcomes proportion of participants with recurrent ulcers, and cost of treatment were not reported in one or both studies.

Analysis Table 13.1 – 13.7 Hydrofiber compared with gauze dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
13.1 Number of amputations reported	2	229	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.29, 6.10]
13.2 Number of Infections reported	2	229	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.40, 2.31]
13.3 Quality of life	1	209	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.38, 0.17]
13.4 Number of ulcers completely healed	2	229	Risk Difference (M-H, Random, 95% CI)	0.07 [-0.05, 0.19]
13.5 Time to complete healing (days)	2	229	Mean Difference (IV, Random, 95% CI)	-53.37 [-153.29, 46.56]
13.6 Recurrence rates	1	209	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.21, 4.98]
13.7 Treatment cost	1	209	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.02, 0.53]

Comparison 14: Hydrocellular polyurethane foam compared with Calcium

Alginate (1 trial, 30 participants)

This comparison included 1 trial ([Foster 1994](#)) with 30 participants. The follow up period was 8 weeks or the ulcer healing whichever came first. The study comparison period was not reported.

There was significant risk of bias since many of the risk of bias considerations were either unclear or high [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Hydrocellular foam dressing group as compared with Calcium alginate dressing group. Patients were prescribed "appropriate antibiotic cover" for prevention and control of infection [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial median wound surface area in the study was reported to be 0.88 cm² in the Hydrocellular foam dressing group and 0.79 cm² in the Calcium alginate dressing group. The initial depth of wound was not specified other than 12, and 13 without units for either respective groups respectively. The wound stage was not reported in the study for either treatment arm. The mean duration of ulcers for the sample was 15.3 weeks in the Foam dressing group and 24.3 weeks in the Calcium alginate group. [Table 10](#)

Participant Characteristics

The study comprised a total of 30 participants. The median age for the study was 65.5 years. There were 20 males and 10 females. [Table 9](#) The study setting included outpatients, and the study was conducted in UK. [Table 3](#)

Primary Outcomes

No data were reported for any the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was greater in the Hydrocellular polyurethane foam group 9/15 (60%) as compared with the calcium alginate group 8/15 (53%). (RR 1.13, 95% CI 0.60 to 2.11; participants = 30; studies = 1) [Analysis 14.1](#). There was a 13% increase in the proportion of participants with ulcers completely healed in the Foam dressing group as compared with the Calcium alginate dressing group. No statistically significant difference was observed.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, cost of treatment.

Analysis Table 14.1 Hydrocellular polyurethane foam compared with calcium alginate				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
14.1 Number of ulcers completely healed	1	30	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.60, 2.11]

Comparison 15 Honey soaked dressing compared with povidone iodine saline dressing (1 trial, 60 participants)

This comparison included 1 trial [EhsanUrRehman 2013](#) with 60 participants. The follow up period was 2 weeks. The study comparison period was from July to December 2012. There was significant risk of bias since many of the risk of bias considerations were either unclear or high.

[Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Honey soaked dressing group as compared with povidone iodine saline dressing group. Patient's in both groups had their wounds washed with copious normal saline [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial wound surface area, and initial wound depth in the study was not reported. The wound stage was reported as Wagner grade 1 - 2. The mean duration of ulcers was not reported. [Table 10](#)

Participant Characteristics

The study comprised a total of 30 participants. The median age for the study was 55.3 (SD = 3.89) years. There were 35 males and 25 females. [Table 9](#) The study setting included hospitalized patients, and the study was conducted in Pakistan. [Table 3](#)

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was greater in the honey soaked dressing group 24/30 (80%) as compared with the povidone iodine saline dressing group 22/30 (73%). There was a 9% increase in proportion of participants with ulcers completely healed in the honey soaked dressing group as compared with the povidone iodine saline dressing group (RR 1.09, 95% CI 0.82 to 1.44; participants = 60; studies = 1) [Analysis 15.1](#). No statistically significant difference was observed.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 15.1 Honey soaked dressing compared with povidone iodine saline dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
15.1 Number of ulcers completely healed	1	60	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.44]

Comparison 16 Honey/Normal saline dressing compared with povidone iodine saline dressing (1 trial, 200 participants)

This comparison included 1 trial [Hammouri 2004](#) with 200 participants. The follow up period was not pre-specified. The study comparison period was from 1996 to 2001. There was significant risk of bias since many of the risk of bias considerations were either unclear or high.

[Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Honey/saline dressing group as compared with povidone iodine/saline dressing group. All patients were debrided in advance in both treatment arms and washed with normal saline [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial wound surface area, initial wound depth, wound stage, and mean duration of ulcers was not reported. [Table 10](#)

Participant Characteristics

The study comprised a total of 200 participants. The mean age for the study was 58 years. There were 112 males and 88 females. [Table 9](#) The study setting included hospitalized patients, and the study was conducted in 4 district hospitals in Jordan. [Table 3](#)

Primary Outcomes

Proportion of participants with amputations

The proportion of participants with amputations were less in the honey/normal saline dressing group 10/100 (10%) as compared with the povidone iodine saline dressing group 20/100 (20%). There was a 50% decrease in the proportion of participants with amputations in the honey/normal saline dressing group as compared with the povidone iodine saline dressing group (RR 0.50, 95% CI 0.25 to 1.01; participants = 200; studies = 1); [Analysis 16.1](#). No statistically significant difference was observed.

No data were reported for the primary outcomes proportion of participants with complicating infections, and quality of life.

Secondary Outcomes

Cost of treatment

The cost of treatment was on average 334.00 Jordanian Dinar's less in the honey/normal saline dressing group as compared with the povidone peroxide/saline dressing group (MD -334.00, 95% CI -373.99 to -294.01; participants = 200; studies = 1) [Analysis 16.2](#). Whether this was total cost or cost per treatment was not specified.

No data were reported for the secondary outcomes proportion of participants with ulcers completely healed, time to complete healing (days), and proportion of participants with ulcers recurring after healing.

Analysis Table 16.1 – 16.2 Honey/normal saline dressing compared with povidone peroxide saline dressing				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
16.1 Number of amputations reported	1	200	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.25, 1.01]
16.2 Treatment cost	1	200	Mean Difference (IV, Random, 95% CI)	-334.00 [-373.99, -294.01]

Comparison 17 Sugar jam (with hydrogen peroxide and topical antibiotic) compared with (hydrogen peroxide and topical antibiotic) (1 trial, 80 participants)

This comparison included 1 trial [Rhaiem 1998](#) with 80 participants. The follow up period was not pre-specified. The study comparison period was from 1992 to 1995. There was significant risk of bias since many of the risk of bias considerations were either unclear or high. [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Honey/saline dressing group as compared with povidone iodine/saline dressing group [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial wound surface area, initial wound depth, wound stage, and mean duration of ulcers was not reported [Table 10](#).

Participant Characteristics

The study comprised a total of 80 participants. The mean age for the study was 56 (SD = 32) years. There were 59 males and 21 females [Table 9](#). The study setting included hospitalized patients, and the study was conducted in Tunisia [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the Sugar jam (with hydrogen peroxide and topical antibiotic) 19/40 (47.5%) as compared with the (hydrogen peroxide and topical antibiotic) 16/40 (40%). There was a 19% increase in the proportion of participants with ulcers completely healed in the Sugar jam (with hydrogen peroxide and topical antibiotic) as compared with the (hydrogen peroxide and topical antibiotic) (RR 1.19, 95% CI 0.72 to 1.96; participants = 80; studies = 1); [Analysis 17.1](#). No statistically significant difference was observed.

No data were reported for the secondary outcomes, time to complete healing (days), proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis Table 17.1 Sugar jam (hydrogen peroxide and topical antibiotic) dressing compared with (hydrogen peroxide and topical antibiotic)				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
17.1 Number of ulcers completely healed	1	80	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.96]

Comparison 18 Silver (standard cleaning and compression management methods) dressing group as compared with control group (standard cleaning and compression management methods without silver ointment) (1 trial, 66 participants)

[Belcaro 2010](#)

This comparison included 1 trial with 66 participants. The follow up period was 4 weeks. The study comparison period was not reported. There was significant risk of bias since many of the risk of bias considerations were either unclear or high. [Figure 3](#); [Figure 4](#).

Types of Interventions

The interventions in these studies included Silver (standard cleaning and compression management methods) dressing group as compared with control group (standard cleaning and compression management methods without silver ointment) [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial mean wound surface area was 2.22 (SD = 0.24) cm² in the Silver (standard cleaning and compression management methods) dressing group, and 2.18 (SD = 1.66) cm² in the control group. The initial wound depth, wound stage, and mean duration of ulcers was not reported.

[Table 10](#)

Participant Characteristics

The study comprised a total of 80 participants. The mean age for the study was 55.9 (SD = 3.8) years. There were 29 males and 37 females [Table 9](#). The study setting included hospitalized patients, and the study was conducted in Tunisia [Table 3](#).

Primary Outcomes

No data were reported for any of the primary outcomes.

Secondary Outcomes

Proportion of participants with ulcers completely healed

The proportion of participants with ulcers completely healed was higher in the Silver dressing group 13/34 (38%) as compared with the control group 5/32 (16%). There was a 145% increase in the proportion of participants with ulcers completely healed in the Silver dressing group as compared with the control group (RR 2.45, 95% CI 0.98 to 6.09; participants = 66; studies = 1); [Analysis 18.1](#). No statistically significant difference was observed.

No data were reported for the secondary outcomes time to complete healing (days), proportion of participants with ulcers recurring after healing, and cost of treatment.

Analysis 18.1 Silver dressing compared with control group (standard cleaning and compression management methods without silver ointment)				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
18.1 Number of ulcers completely healed	1	66	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.98, 6.09]

Comparison 19 Debridement (Any form of debridement against gauze or saline gauze) (10 trials, 807 participants)

Jeffcoate 2009; Jensen 1998; Piaggese 2001; Piaggese 1998; Vandeputte 1997; Lalau 2002; D'Hemecourt 1998; Donaghue 1998; Goretti 2008; Roberts 2001

Summary: Any form of debridement as compared with gauze

The 10 trials (D'Hemecourt 1998; Donaghue 1998; Goretti 2008; Jeffcoate 2009; Jensen 1998; Lalau 2002; Piaggese 1998; Piaggese 2001; Roberts 2001; Vandeputte 1997) comparing any form of debridement with gauze dressing were considered sufficiently similar to pool, using a random effects model. They included a combined total of 807 subjects. The follow up period ranged from 4 - 24 weeks. The study comparison period ranged from 1995 to March 2007, however the study period was not reported for 8/10 studies. There was significant risk of bias as many of the risk of bias characteristics were either unclear (unreported) or at high risk of bias. [Figure 3;](#) [Figure 4.](#)

Types of Interventions

The interventions in these studies included: Any (All) forms of debridement as compared with gauze or saline gauze. Gauze was the most frequently used method of control or "alternative" treatment arm. This was often paired with some form of standard treatment to both arms that when specified ranged from pressure relief/offloading, antiseptic or saline skin cleansing, secondary dressings, or infection control with antibiotics. Some of the studies used an alternate separate form of debridement that was not uniformly clearly defined in all studies. There were no details in the studies as to the extent this was done other than references to "as needed", "as required", or "regularly". If a study specified that a separate identical form of debridement was used on both intervention arms throughout the study it was excluded, as this would confound any debridement effect from the intervention and control groups [Table 5](#); [Table 13](#).

Initial Wound Stage

The initial wound size in the studies ranged from 0.21 cm² to 25 cm². The only study that did not report wound size was [Vandeputte 1997](#). The wound depth ranged from 0.4 cm to 2.9 cm. Four studies in this comparison reported wound depth [Table 10](#). The wound staging included in the studies were classified as Wagner grade 1 - 4. Four studies reported Wound stage in this comparison. The duration of ulcers in this comparison ranged from 5.9 weeks to 42 (SD = 42) weeks. There were 7 studies that reported duration of ulcers [Table 10](#).

Participant Characteristics

The studies comprised a total of 807 participants [Table 3](#). The mean ages for the studies ranged from 58.3 (SD = 12.13) years to 64.39 (SD = 11.67) years [Table 9](#). There were a total of at least 502 males in the studies that actually reported gender in this total sample [Table 9](#). The studies were conducted in a variety of settings including outpatient and inpatient (hospitalized) patients [Table 3](#). The studies were conducted in the following countries: Belgium, France, Italy, UK, and the US [Table 3](#). The risk of bias in the included studies was significant as most of the risk of bias characteristics used in this review were unclear or high for the studies used in this comparison [Figure 3](#), [Figure 4](#).

Types of Outcomes

Primary Outcomes

Proportion of participants with amputations

Five studies reporting on the number of amputations were pooled. There were fewer amputations using ANY form of debridement 6/272 as compared with gauze 10/171. Pooling these studies yielded a relative risk for amputation of (RR 0.48, 95% CI 0.17 to 1.37; participants = 443; studies = 5; $I^2 = 0\%$); in the absence of significant heterogeneity, $p = 0.75$, $I^2 = 0\%$) [Analysis 19.1](#). This translates to 52 % reduction in the proportion of participants with amputations in the Any debridement group as compared to gauze dressing group; and a number needed to treat for benefit [NNTB] of 50 (95% CI 15 [NNTB], 34 [NNTH]): that is to prevent one additional patient with diabetic foot ulcer from having an amputation, 50 patients must be treated with Any form of debridement instead of gauze. No statistically significant difference was determined [Figure 31](#).

Proportion of participants with complicating infections

The seven studies reporting on the number of infections were pooled. There were more infections using ANY form of debridement 152/381 as compared with gauze 84/278. Pooling these studies yielded a relative risk for amputation of (RR 1.07, 95% CI 0.76 to 1.52; participants = 659; studies = 7); in the absence of significant heterogeneity, $p = 0.15$, $I^2 = 35\%$) [Analysis 19.2; Figure 32](#).

This translates to 7% increase in the proportion of participants with infections in the Any debridement group as compared to the gauze dressing group; and a number needed to treat [NNT] of 50 (95% CI 9 [NNTB], 12 [NNTH]): that is to prevent one additional patient with diabetic foot ulcer from having an infection, 50 patients must be treated with Any form of debridement instead of gauze. No statistically significant difference was determined [Figure 32](#).

Secondary Outcomes

Proportion of participants with ulcers healed

The ten studies reporting on the number of patients with ulcers completely healed were pooled. There were more ulcers healed using ANY form of debridement 213/462 as compared with gauze 134/336. Pooling these studies yielded a relative risk for amputation of (RR 1.22, 95% CI 1.04 to 1.44; participants = 798; studies = 10); in the absence of significant heterogeneity, $p = 0.18$, $I^2 = 28\%$) [Analysis 19.3](#).

This translates to 22% increase in the proportion of participants with infections in the Any debridement group as compared to the gauze dressing group; and a number needed to treat [NNTB] of 10 (95% CI 5 to 100 [NNTB]); that is to heal one additional patient with diabetic foot ulcer, 10 patients must be treated with Any form of debridement instead of gauze. Statistically significant difference was determined [Figure 33](#).

Proportion of participants with ulcers healed - Subgroup analysis excluding the two abstracts

A subgroup analysis was performed excluding two studies that were only available as abstracts including: [Goretti 2008](#); [Roberts 2001](#).

The eight studies reporting on the number of patients with ulcers completely healed were pooled. There were more ulcers healed using ANY form of debridement 190/428 as compared with gauze 119/300. Pooling these studies yielded a relative risk for amputation of (RR 1.18, 95% CI 0.99 to 1.41; participants = 728; studies = 8); in the absence of significant heterogeneity, $p = 0.14$, $I^2 = 35\%$) [Analysis 19.3](#).

This translates to an 18% increase in the proportion of participants with infections in the Any debridement group as compared to the gauze dressing group; and a number needed to treat to benefit [NNTB] of 12 (95% CI 6 [NNTB], 50 [NNTH]); that is to heal one additional patient with diabetic foot ulcer, 12 patients must be treated with Any form of debridement instead of gauze. No statistically significant difference was determined when excluding the two studies available as abstracts only.

Quality of Life Index

One study with 3 arms reported on this outcome. The mean difference was 0.01 points lower in the Any debridement group (using either Hydrofiber or Iodine impregnated fiber dressing) as compared with the gauze dressing group (MD -0.01, 95% CI -0.04 to 0.01; participants = 317; studies = 1); in the absence of significant heterogeneity, $p < 0.95$, $I^2 = 0\%$; [Analysis 19.4](#). No statistically significant difference was demonstrated [Figure 34](#).

Time to complete healing

Four studies reported on this outcome. Time to complete healing yielded a mean difference of -27.88 days less time to achieve healing in the Any debridement dressing group as compared to the gauze dressing group (MD -27.88, 95% CI -52.53 to -3.23; participants = 458; studies = 4); in the presence of significant heterogeneity, $p < 0.0001$, $I^2 = 90\%$); [Analysis 19.5](#). No statistically significant difference was observed [Figure 35](#).

Proportion of participants with recurrent ulcers

Two studies reporting on the proportion of patients with recurrent ulcers were pooled. There were less recurrent ulcers using ANY form of debridement group 13/232 as compared with gauze dressing group 11/125. Pooling these studies yielded a relative risk for recurrent ulcers of (RR 0.81, 95% CI 0.25 to 2.58; participants = 357; studies = 3); in the absence of significant heterogeneity, $p = 0.18$, $I^2 = 39\%$); [Analysis 19.6](#).

This translates to 19% reduction in the proportion of participants with recurrent ulcers in the Any debridement group as compared to the gauze dressing group; and a number needed to treat [NNTB] of 100 (95% CI 10 [NNTB], 13 [NNTH]); that is to prevent one additional patient with diabetic foot ulcer from developing a recurrent ulcer, 100 patients must be treated with Any form of debridement instead of gauze. No statistically significant difference was demonstrated [Figure 36](#).

Cost of treatment was either not reported at all or not reported in at least 2 out of the 10 studies used in this comparison.

Analysis Table 19.1 – 19.6 Any debridement compared with saline gauze control				
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
19.1 Number of amputations reported	5	443	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.17, 1.37]
19.1.1 Any debridement compared with saline gauze	5	443	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.17, 1.37]
19.2 Number of Infections reported	7	659	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.52]
19.2.1 Any debridement compared with saline gauze	7	659	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.52]
19.3 Number of ulcers completely healed	10	798	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
19.3.1 Any Debridement vs Saline Gauze	8	728	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.32]
19.3.2 SA w/o Abstracts	2	70	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.04, 2.42]
19.4 Quality of life	1	317	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
19.5 Time to complete healing (days)	4	458	Mean Difference (IV, Random, 95% CI)	-27.88 [-52.53, -3.23]
19.6 Recurrence rates	2	357	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.58]

Summary of Results, Overall Effect sizes, and Heterogeneity

Table 14 below summarizes the overall results, effect sizes discussed in this section, along with heterogeneity that were reported for all meta-analyses done in this review.

Table 14 Summary of Results, Overall Effect Sizes, and Heterogeneity								
Intervention comparison	Outcome	k	RR (95% CI) **MD (95% CI)		Heterogeneity of Outcome Effects Summary Statistics ^b			
			Fixed-Effects	Random-Effects	τ^2	χ^2	I ² (%)	p-value
Hydrogel vs. Gauze	Proportion of Amputations	2	0.26 (0.05, 1.37)	0.26 (0.05, 1.40)	0.00	0.11	0	0.74
	Proportion of Infections	3	0.87 (0.54, 1.40)	0.74 (0.18, 2.99)	0.91	4.89	59	0.09
	Proportion of Ulcers Healing	3	1.68 (1.14, 2.49)	1.71 (1.16, 2.52)	0.00	0.95	0	0.62
Foam vs. Wet to Dry	Proportion of Ulcers Healing 2 studies	2	4.35 (1.33, 14.29)	3.56 (0.93, 13.66)	0.18	1.15	13	0.28
Hydrofiber vs. Gauze	Proportion of Amputations 2 studies	2	1.31 (0.33, 5.16)	1.34 (0.29, 6.10)	0.05	1.03	3	0.31
	Proportion of Infections 2 studies	2	1.11 (0.84, 1.46)	0.96 (0.40, 2.31)	0.21	1.37	27	0.24
	Proportion of Ulcers Healing 2 studies	2	0.06 (0.06, 0.19)	0.07 (0.05, 0.19)	0.00	0.09	0	0.76
	Mean Time to Complete Healing 2 studies	2	** -13.87 (-27.91, 0.16)	** -53.37 (-153.29, 46.56)	4892.23	16.29	94	< 0.0001
Any debridement vs. Gauze	Proportion of Amputations 5 studies (n=6)	5	0.49 (0.19, 1.27)	0.48 (0.17, 1.37)	0.00	2.67	0	0.75
	Proportion of Infections 7 studies (n=8)	7	1.10 (0.89, 1.36)	1.07 (0.76, 1.52)	0.07	10.82	35	0.15
	Quality of Life 1 study (n=2)	1	-0.01 (-0.04, 0.01)	-0.01 (-0.04, 0.01)	0.00	0.00	0	0.95
	Proportion of Ulcers Healing 10 studies (n=11)	3	1.17 (1.00, 1.36)	1.22 (1.04, 1.44)	0.02	13.89	28	0.18
	Proportion of Ulcers Healing (two studies available only as abstracts)	10	1.12 (0.95, 1.32)]	1.18 (0.99, 1.41)	0.02	12.26	35	0.14
	Proportion of Ulcer Recurrence 2 studies (n=3)	2	0.77 (0.34, 1.71)	0.81 (0.25, 2.58)	0.42	3.29	39	0.19
	Mean Time to Complete Healing 4 studies (n=5)	4	2.54 (1.20, 3.87)	-27.88 (-52.53, -3.23)	614.40	39.33	90	< 0.00001
<p>Note:</p> <p>** indicates a significant effect; k represents the number of studies for each outcome included in the analysis; Q represents Cochran's Q indicating significance of heterogeneity; I² represents the magnitude of heterogeneity; p-value represents the significance of heterogeneity.</p> <p>b) Relative risk (RR) was the effect estimate for proportion of amputations, proportion of infections, and proportion of ulcers healed, and proportion of recurrence. Mean difference (MD) was the effect estimate for the outcomes Quality of life, and Time to complete healing.</p>								

Sensitivity Analysis

A sensitivity analysis was conducted by removing the two studies that were only available as abstracts ([Goretti 2008](#); [Roberts 2001](#)). This was performed in order to determine if the results were robust despite their exclusion from the analysis. Prior to removing the studies there was a statistically significant increase in proportion of ulcers healed using a random effects model. When the studies were removed there was no statistically significant difference in the proportion of ulcers healed. The fixed effects model demonstrated no statistically significant benefit irrespective of whether the abstracts were included or not.

[Table 14](#) contrasts the fixed effects versus random effects model estimates. The findings were generally robust despite model used. The exception was in the comparisons Wet to Dry debridement versus Foam dressing for the outcome proportion of ulcers healed where the fixed effects model demonstrated a statistically significant increase in proportion of ulcers healed whereas the random effects model did not demonstrate a statistically significant difference. The Any debridement as compared with the control condition demonstrated the mean Time to complete healing to be longer in the intervention group using the fixed effects model but shorter in duration using the random effects model.

Publication bias investigation

The studies used in this comparison of any debridement against gauze for the outcome proportion of ulcers healed. These 10 studies were plotted in a funnel plot to investigate publication bias. The funnel plot suggested slight asymmetry favoring disproportionately positive studies to the right side of the graph including the smaller studies which suggests publication bias [Figure 37](#).

This analysis included the Beggs and Eggers tests which did not detect any significant asymmetries using these statistical tests [Table 15](#). 13/30 (43%) studies retrieved in this review received funding through private sources though despite this fact few significant associations were found further suggesting a lack of publication bias [Figure 22](#).

Chapter 6 Meta-regression Analysis

Introduction

Moderator analysis is an important part of any comprehensive SR and meta-analysis. It is utilized in a manner similar to the way regression analysis is conducted in an individual study. Moderators or covariates may result in effect modification, or interact with the intervention of interest. This may include confounding, magnifying or diminishing the interventions effect.

Efforts were made to understand any unexplained heterogeneity. This systematic review and meta-analysis demonstrated relatively low heterogeneity as evidenced by the statistical tests reported in [Table 14](#).

The tests for homogeneity including τ^2 , χ^2 , and I^2 demonstrated large and significant heterogeneity in one outcome (mean time to complete healing) for the interventions Hydrofiber and “Any debridement”, both as compared with gauze. Moderate heterogeneity though not statistically significant was suggested in the outcome proportion of infections for the intervention Hydrogel as compared with gauze. The outcomes proportion of infections, proportion of ulcers healed, and proportion of ulcer recurrence, demonstrated moderate heterogeneity for the intervention “Any debridement” as compared with gauze, though these were not found to be statistically significant. If the degree of heterogeneity reached significance based on our statistical test results; then efforts were made to explain it. Therefore, this meta-regression analysis was conducted on prognostic variables or moderators with the goal of explaining any significant heterogeneity between the studies.

This portion of the analysis was limited. The optimal number of covariates is 10 studies per moderator/covariate for each of the outcomes of interest. This is a similar threshold used in multivariate regression analysis. Therefore, this analysis was limited to Comparison 19 where the number of studies per covariate included 10 studies.

The moderators that were used for analysis included the sample and risk specific characteristics age, peripheral arterial disease, duration of diabetes, proportion of females. These prognostic factors are suspected of having an association with wound healing. The study specific characteristics data collection year, and study duration follow up were also investigated.

There were two outcomes that satisfied the minimal studies per covariate requirement these included proportion of infections and proportion of ulcers healed. The outcome included 10 studies though not all studies reported on every moderator of interest. See [Tables 7, 9, 10, and 11](#) for the 30 respective studies which include information on which of the studies reported on the moderators of interest for this review.

Methods

Assessment of heterogeneity

Design heterogeneity was discussed and summarized in the Characteristics of Included studies tables. Methods for identifying statistical heterogeneity included visual graphical analysis of Forest plots, the use of the Q-statistic, tau-squared, χ^2 test, and the I^2 test statistic).

Assessment of heterogeneity included using visual assessment of the Forest Plots generated whenever 2 or more studies were available for analysis to meet the study objectives. Evaluation for heterogeneity included the use of the Q-test, τ^2 , and the I^2 test statistics.

These statistical techniques were utilized to both detect the presence and magnitude of heterogeneity, respectively (Higgins 2002; Higgins 2003; Higgins 2008). The homogeneity statistic, Q, determines whether each set of the weighted mean effect sizes (d+s) shared a common effect size, a significant Q indicates a lack of homogeneity and an inference of heterogeneity of the effect sizes between studies (Higgins 2002; Higgins 2003; Higgins 2008).

To assess the extent or magnitude to which studies' outcomes were consistent, the I^2 index and its corresponding 95% confidence intervals (CIs) were calculated; I^2 varies between 0 (homogeneous) and 100% (non-homogeneous/heterogeneous). If the CI around I^2 includes zero, the set of effect sizes (ES's) is considered homogeneous. The I^2 has been demonstrated as a statistic used to complement the Q-test statistic, but is not used in lieu of it (Huedo-Medina 2006).

In order to address residual unexplained heterogeneity that is not a function of a single outlier effect or exaggerated idiosyncratic effects among outlying responders, the study reports were reviewed. This was done to determine whether the authors of the studies described how they addressed these outliers, and their explanations for any outlier effects. The effects of outliers were either not reported or the threshold for defining outliers were not standardized across studies. This information would be helpful at the individual study level since the respective authors have access to these raw data.

This systematic review relied on the summary statistics which poses greater challenges in determining the reasons for within study variance. The unit of analysis or observation in this systematic review is the study not the individual which compounds this challenge.

This systematic review used clinical, methodological, and statistical heterogeneity to help decide whether to conduct a meta-regression analysis. We relied on visual graphical methods by analyzing the Forest plots, the Q statistic, tau-squared (τ^2), χ^2 statistic, and the I^2 statistic. Tau-squared (τ^2) is defined as the between-studies variance or the variance of the effect size parameter across the population of studies. The risk of bias tables and the characteristic of included studies tables served as the basis for methodological considerations ([Borenstein 2009](#), [Higgins 2008](#), [Cooper 2009](#)).

Meta-regression was performed on moderators/covariates in order to explain any remaining variability between studies for the 7 outcomes of interest. The approach to variability present in the primary and secondary outcomes and for the comparison interventions was standardized for all moderators. This was conditional on a sufficient number of studies to permit this type of analysis.

Meta-regression and moderator analysis was limited since there were too few comparisons with sufficient studies for the recommended 10 studies per moderator ratio. This restricted the analysis to 2 of the 19 pairwise comparisons that were made. The 19 comparisons grouped studies accordingly based on the same intervention against an alternate control/comparison intervention. Comparison 19 grouped “any” form of debridement intervention against the same control group (see effects of interventions section).

Besides varying in the type of debridement comparisons the studies varied in some characteristics including design-specific, and sample-specific characteristics.

There were sample-specific factors that were considered to influence wound healing. These are considered higher risk and include severity of diabetes, age, peripheral arterial disease and offloading, among others that were previously discussed. These moderators are considered high priority and clinically significant based on content expert opinion. There were also study-specific factors including the duration of the intervention that might influence these clinical and public health outcomes that warrant further study. However, many of the covariates of interest that were originally sought in this systematic review were not reported adequately to allow for a comprehensive meta-regression analysis.

This segment of the analysis includes modeling each of the moderators specified above in order to determine if there is any effect on the between study variance irrespective of the lack of significant heterogeneity. This will facilitate hypothesis generation and provide insight into future areas for research.

The analysis included a series of models that utilize one covariate per model. The use of more than one moderator in a model is precluded by the limitation in the information reported in the studies and the finite number of studies available for more detailed meta-regression analysis. The moderators are analyzed for purposes of hypothesis generation as well as to determine whether they help explain heterogeneity. This approach was scrutinized to avoid over-reliance on allowing the availability of data to drive the meta-regression analysis. Therefore, the Meta-regression analysis proceeds with an effort to limit any broad conclusions on moderator effect under these circumstances as a result of the limited information reported.

The multivariate approach was not possible for all the reasons discussed. Weighted mean effect size by the inverse of the variance of each study was calculated across all studies under the random effects assumptions for the Meta-regression analysis. The random effects model assumes that these data are coming from different populations and accounts for both within and between-study variance. The random effects assumption is arguably more consistent with biological and clinical variability in complex health systems. The fixed effects model assumes that all effect sizes are from the same population and accounts strictly for within study variance. To test for heterogeneity, Cochran's Q and I^2 were calculated. The Q test evaluates for the significance of heterogeneity. I^2 calculates the magnitude of heterogeneity with a range from 0%-100%.

In order to assess whether the moderators explain the heterogeneity of the effect sizes, moderator analysis using weighted mixed-effects models with maximum likelihood estimation of the random effects weights was performed.

This systematic review tested each variable for study where sufficiently reported information was available and if clinically warranted based on known risk factors. Moderator analysis was conducted by using CMA ([CMA 2005](#)).

Results

The Meta analyses portion of the systematic review reported previously was conducted on comparisons 6, 10, 13, and 19. Of these 4 comparisons conducted, comparison 19 was the sole comparison out of the four where an adequate number of studies were available for meta-regression analysis on moderators ([Analysis 19](#)). The moderator analysis for Comparison 19 included 9 – 10 studies per covariate for two outcomes.

The two outcomes included the proportion of complicating Infections ([Analysis 19.2](#)), and the proportion of ulcers healed ([Analysis 19.3](#)). The meta analyses for these two respective outcomes involved the comparison “any debridement” against the pre-specified control condition. Please refer to [Tables 16 – 31 concurrently](#).

Age

A model was generated in order to determine what effect if any does the moderating variable age have on the outcome variables of interest including number of Infection, number of ulcers healed.

There was no significant association or effect using age as a moderator for either outcomes of interest including number of infections and number of ulcers healed. ($B_{\text{infection}} = -0.2131$, $p < 0.0651$; $B_{\text{ulcerhealed}} = -0.0130$, $p < 0.6873$ for number of infections, and ulcers healed respectively). Therefore, the coefficient or slope of the effect of the moderator age on the outcomes interest is no different from 0.

The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest no significant effect on heterogeneity by including the moderator age. These results are presented in [Table 16](#) and [Table 17](#) respectively with associated scatterplots ([See also summary tables 28, 39, and 30 below](#)). Each circle on the scatterplot represents the point estimate of the effect for that study. The size or area of that circle represents the weighting for that respective study in the scatterplot.

Peripheral Arterial Disease (PAD)

A model was generated in order to determine what effect if any does the moderating variable PAD have on the outcome variables of interest including number of Infection, number of ulcers healed, and the effect of heterogeneity. There was no significant association or effect using PAD as a moderator for either outcomes of interest including number of infections and number of ulcers healed. ($B_{\text{infection}} = 3.3706$, $p = 0.3023$; $B_{\text{ulcerhealed}} = -0.4095$, $p = 0.6191$ for number of infections, and ulcers healed respectively). Therefore, the coefficient or slope of the effect of the moderator PAD on the outcomes interest is no different from 0. The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest no significant effect on heterogeneity by including the moderator PAD. These results are presented in [Table 18](#) and [Table 19](#) respectively with associated scatterplots ([See also summary tables 28, 29, and 30 below](#)).

Duration of Diabetes

A model was generated in order to determine what effect if any does the moderating variable Duration of Diabetes have on the outcome variables of interest including number of Infection, number of ulcers healed, and the effect of heterogeneity. There was no significant association or effect using duration of diabetes as a moderator for either outcomes of interest including number of infections and number of ulcers healed. ($B_{\text{infection}} = -0.1528$, $p = 0.5460$; $B_{\text{ulcerhealed}} = 0.0419$, $p = 0.5625$ for number of infections, and ulcers healed respectively). Therefore, the coefficient or slope of the effect of the moderator diabetes duration on the outcomes interest is no different from 0. The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest no significant effect on heterogeneity by including the moderator duration of diabetes.

These results are presented in [Table 20](#) and [Table 21](#) respectively with associated scatterplots. The moderator analysis displayed in [Table 28](#) demonstrates no statistically significant effect on the outcomes proportion of infections or proportion of ulcers healed for all but one of the moderators. This analysis was conducted for the intervention any debridement as compared with saline gauze and the proportion of females demonstrates a statistically significant reduction in the proportion of infections ([See also summary tables 28, 29, and 30 below](#)).

Proportion of Females

A model was generated in order to determine what effect if any does the moderating variable Proportion of females have on the outcome variables of interest including number of Infection, number of ulcers healed, and the effect of heterogeneity. There was a statistically significant effect on the proportion of infections. No significant association or effect using proportion of females as a moderator for number of ulcers healed was found. ($B_{\text{infection}} = -6.1651$, $p = 0.0264$; $B_{\text{ulcerhealed}} = 0.2486$, $p = 0.8683$ for number of infections, and ulcers healed respectively).

Therefore, the coefficient or slope of the effect of the moderator proportion of females on the outcomes interest is different from 0. The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest a significant effect on heterogeneity by including the moderator proportion of females. These results are presented in [Table 22](#) and [Table 23](#) respectively with the associated scatterplots ([See also summary tables 28, 29, and 30 below](#)).

Data collection year

A model was generated in order to determine what effect if any does the moderating variable Data Collection Year have on the outcome variables of interest including number of Infection, number of ulcers healed, and the effect of heterogeneity.

There was no significant association or effect using data collection year as a moderator for either outcomes of interest including number of infections and number of ulcers healed. ($B_{\text{infection}} = 0.0246$, $p = 0.3890$; $B_{\text{ulcerhealed}} = 0.0013$, $p = 0.9274$ for number of infections, and ulcers healed respectively). Therefore, the coefficient or slope of the effect of the moderator data collection year on the outcomes of interest is no different from 0. The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest no significant effect on heterogeneity by including the moderator data collection year. These results are presented in [Table 24](#) and [Table 25](#) respectively with associated scatterplots ([See also summary tables 28, 29, and 30 below](#)).

Study duration follow up

A model was generated in order to determine what effect if any does the moderating variable Study duration follow up have on the outcome variables of interest including number of Infection, number of ulcers healed, and the effect of heterogeneity. There was no significant association or effect using study duration of follow up as a moderator for either outcomes of interest including number of infections and number of ulcers healed. ($B_{\text{infection}} = 0.0482$, $p = 0.1857$; $B_{\text{ulcerhealed}} = 0.0048$, $p = 0.6043$ for number of infections, and ulcers healed respectively). Therefore, the coefficient or slope of the effect of the moderator follow up period on the outcomes interest is no different from 0. The comparison of the new model with the null model for Tau^2 , I^2 , Q , and R^2 suggest no significant effect on heterogeneity by including the moderator follow up period. These results are presented in [Table 26](#) and [Table 27](#) respectively with associated scatterplots ([See also summary Tables 28, 29, and 30 below](#)).

Table 28 Moderators of effect size magnitude for the “Any debridement vs. gauze^a” comparison.					
Outcome(s)	Moderator(s)Characteristic(s)/Level(s)	RR (95% CI)	K^b	Coefficient	p-value
	Participant-specific demographic characteristics				
Proportion of infections	Age	1.07 (0.76, 1.52)	7	-0.2132	0.0651
	Risk-specific characteristics				
Proportion of infections	PAD ^c	1.07 (0.76, 1.52)	7	3.3706	0.3023
Proportion of infections	Duration of diabetes (yrs.)	1.07 (0.76, 1.52)	7	-0.1528	0.5460
Proportion of infections	Proportion of females	1.07 (0.76, 1.52)	7	-6.1651	0.0264
	Study-specific characteristics				
Proportion of infections	Data collection year	1.07 (0.76, 1.52)	7	0.0246	0.3890
Proportion of infections	Duration of follow up	1.07 (0.76, 1.52)	7	0.0482	0.1857
Proportion of Ulcers healed	Age	1.17 (1.00, 1.36)	10	-0.0130	0.6873
Proportion of Ulcers healed	PAD(c)	1.17 (1.00, 1.36)	10	-0.4095	0.6191
Proportion of Ulcers healed	Duration of diabetes (yrs.)	1.17 (1.00, 1.36)	10	0.0419	0.5626
Proportion of Ulcers healed	Proportion of females	1.17 (1.00, 1.36)	10	0.2486	0.8683
	Study-specific characteristics				
Proportion of Ulcers healed	Data collection year	1.17 (1.00, 1.36)	10	0.0013	0.9247
Proportion of Ulcers healed	Duration of follow up	1.17 (1.00, 1.36)	10	0.0048	0.6043
<p>a. Each moderator listed is evaluated individually without controlling for the other listed moderators. Effect sizes are based on random effects assumptions for the comparison and respective outcome listed in two columns. In this analysis there was 1 comparison (“any debridement” as compared with gauze) and 2 outcomes (proportion of infections, and Proportion of ulcers healed) that approximated a sufficient (number of studies): moderator ratio in order to facilitate moderator analysis.</p> <p>b. k = number of studies</p> <p>c. PAD = proportion with initial baseline peripheral arterial disease.</p>					

Table 29 Non-Significant Moderators
Non-Significant Moderators
All the following moderators assessed were non-significant.
Age
PAD (Peripheral arterial disease)
Duration of diabetes
Data collection year
Duration of follow up

Table 30 Moderators that were Unable to be analyzed due to lack of Reported Information
Out of the 235 coded variables on our data extraction form, 138 of these were non-effect size related variables. These were reviewed as candidate variables for regression analysis and most were unable to be analyzed due to the lack of reported information on the outcomes of interest for this systematic review. See Data extraction form Appendix 2 .

Chapter 7

Discussion

Summary of main results

This systematic review included a comprehensive, exhaustive, and transparent search of the literature accordingly using established standards. This systematic review retrieved, identified, extracted, synthesized, and appraised all available evidence from randomized controlled studies on the debridement of diabetic foot ulcers. The evidence included direct and indirect fundamental clinical and public health outcomes on established and widely used forms of debridement in the treatment of diabetic foot ulcers. A total of 19 comparisons were made in the 30 studies included in this review. This included variable reporting on all 7 pre-specified outcomes of interest that have both clinical and public health implications. The comparisons were based on data from the individual studies that were extracted in order to conduct both a qualitative and quantitative systematic review (meta-analysis). There were a total of four comparisons where evidence was pooled into meta-analyses for the pre-specified outcomes to help answer our research question.

There was no statistically significant beneficial difference in amputation frequency, or infection frequency in any of the comparisons that were analyzed with meta-analyses [Table 14](#), for the studies that reported on these outcomes.

Quality of life was reported in 3 studies ([Piaggese 1998](#); [D'Hemecourt 1998](#); [Jeffcoate 2009](#)) and there was no significant difference found between the debridement and the control/comparison condition ([Jeffcoate 2009](#)) utilized the (SF-36) questionnaire.

In the studies that reported on ulcers healed, no evidence of any difference in ulcer healing was found between the specific forms of debridement when compared to each other except between hydrogel as compared with gauze/good wound care. There was evidence of an increase in ulcers healed in the comparison any form of debridement as compared with gauze dressing though this was not statistically significant. However when the two studies ([Goretti 2008](#); [Roberts 2001](#)) that were available only as abstracts were excluded in a sensitivity analysis there was less significant difference in complete healing found, see [Table 14](#).

There was no evidence of any difference in time to complete healing for diabetic foot ulcers healed except in 3 analyses, the superoxide solution as compared with standard local treatment with povidone iodine which was 6 days shorter ([Goretti 2008](#)). The time to complete healing was 2.8 days longer in the alginate dressing group as compared with the gauze ([Donaghue 1998](#)). The Any debridement versus saline gauze group demonstrated a significant reduction of approximately 28 days in healing time using the random effects model whereas there was a 2.5-day increase in healing time using the fixed effects model, see [Table 14](#).

The random effects model was pre-specified for this systematic review. However, the fixed effects model was used for purposes of sensitivity analysis. The findings were relatively robust irrespective of model used with one exception where the fixed effect model demonstrated a significant beneficial effect on the proportion of ulcers healed in the Foam as compared to the Wet to dry intervention; whose benefit was not significant under the random effects model.

The other exception was in the Any debridement group as compared with gauze that found a significant beneficial effect in proportion of ulcers healed using the random effects model but not the fixed effects model. When the two studies available exclusively as abstracts were removed both models failed to demonstrate a beneficial difference for the outcome proportion of ulcers healed. See [Table 14](#), [Analysis Tables 1.1 through 19.6](#), Results section.

The meta-analysis using foam as compared with wet to dry debridement demonstrated no beneficial effect in the random effects model though a significant beneficial difference was found in fixed effects model for the outcome proportion of ulcers healed.

In the studies that reported recurrence rates there was no significant beneficial difference between the competing forms of debridement or between any debridement and gauze dressing.

Cost of treatment was reported in 3 studies ([Jensen 1998](#); [Jeffcoate 2009](#); [Hammouri 2004](#)) the Iodine impregnated fiber dressing group, the Hydrofiber group, and the honey normal saline dressing group as compared with the gauze dressing group. No statistically significant difference was found. The hydrogel group as compared with the gauze dressing group suggested a reduced daily cost for hydrogel however this was not found to be statistically significant ([Jensen 1998](#)).

The studies retrieved in this review included trials that used relatively smaller sample sizes which may have been statistically underpowered. This would create difficulty in detecting small treatment effects.

A Meta-regression analysis found that none of the candidate moderators demonstrated a beneficial effect on the respective outcomes of interest. The coefficients were not significantly different from the null value with one exception, the proportion of females.

This correlates with the coherent understanding that an observed gender predilection favors males in the development of wounds and amputations. There was no significant study heterogeneity that was explained with any of univariate models that were performed. (See [Tables 16 – 30](#)).

This finding may be a function of the variability in reporting that limited the moderator analysis through meta-regression to a small sub sample of studies retrieved in this systematic review. The effects of these moderators on the outcomes of interest may be better delineated as the standardization of reporting across studies improves. This would increase sample size for meta-regression analysis and improve detection of significant effect interactions.

Overall completeness and applicability of evidence

The clinical and public health indicators included seven pre-specified outcomes of interest that were defined in the methods section of this review. Quality of life and cost of treatment were not well defined. For example, an acceptable robust standardized quality of life measure such as SF-36 or a similarly acceptable measurement tool was universally under-utilized in the included studies.

Quality of life and treatment cost are fundamental considerations in comparing the various debridement methods. Standardized reporting should include quality of life and economic data. The other five outcomes of interest were variably reported between studies including outcomes with very serious public health and clinical implications such as amputation and infection.

Applicability of the evidence is dependent on the four primary outcomes (amputations, complicating infections, quality of life, and cost) being universally reported as they have direct public health and clinical implications.

Indirect evidence that is applicable to the primary outcomes of interest are provided by the 3 pre-specified secondary outcomes (recurrence rates, complete healing, and time to complete healing) as they have clinical and public health bearing ([SVD 1990](#)).

The pre-specified outcomes were variably reported throughout the 30 included studies making meaningful and comprehensive synthesis and analysis challenging.

Quality of the evidence

All 30 studies included in this review were classifiable as unclear or high risk of bias for many of the risk of bias characteristics utilized in this systematic review [Characteristics of included studies; Figure 3, Figure 4](#). Though randomization was reported throughout most of the included studies did not report the method of randomization utilized. Allocation concealment was unclear in greater than 75% of studies. Due to the nature of the interventions blinding may not have been possible in the participants and the personnel delivering the intervention. Blinding of outcome assessors was unclear or high risk in approximately 70% of studies. Incomplete outcome data reporting was unclear or high risk in over 75% of the included studies. Selective reporting of outcomes was unclear or high risk in 50% of the included studies. Other bias was either unclear or high risk in the included studies.

The studies did not follow established reporting practice conduct such as the CONSORT guidelines ([CONSORT](#)). Major considerations consistent with these guidelines include appropriate random sequence generation and allocation concealment. The 30 studies reported randomization, though most studies did not report the specific method of randomization that was used i.e. computer generated, coin toss, except in 5/30 studies ([Amini 2013](#); [Bowling 2011](#); [Jeffcoate 2009](#); [Munter 2006](#); [Tallis 2013](#)) . Allocation concealment was universally unreported except in 5/30 studies ([Bowling 2011](#), [Jeffcoate 2009](#), [Jude 2007a](#), [Munter 2006](#), and [Tallis 2013](#)).

Blinding was often either absent or incomplete. This could have been a function of the nature of applying the specific debridement intervention. For example, in some cases it would be challenging for the investigator delivering the intervention to be blinded from the intervention they were using e.g. sharp/surgical debridement. It is difficult to blind the patient from the debridement method used e.g. sharp debridement or maggot debridement therapy. The studies that did report blinding/masking did not clearly define what was meant by "double-blinding" ([Devereaux 2002](#)). It was unclear whether the principal investigator, and/or the participants, and/or the outcome assessor were blinded.

The studies that did report blinding of the outcome assessor included the following 8 studies ([Ali 2013](#); [Apelqvist1990](#); [D'Hemecourt 1998](#); [Jeffcoate 2009](#); [Lalau 2002](#); [Piaggese 2001](#); [Shukrimi 2008](#); [Singh 2006](#)).

All study authors should report on these quality considerations. Study authors should anticipate that their respective study might be considered for inclusion in systematic reviews.

The Consort guidelines were meant to standardize reporting guidelines for study authors in order to help better define and reduce the variability in what is reported in the medical and public health literature. Universal standardized reporting guidelines would make it less difficult for authors synthesizing the evidence in systematic reviews and meta-analyses.

Methods of addressing incomplete outcome data were not clearly reported in most of the studies. Intention to treat analysis (ITT) was not reported in the majority of studies. The 4 studies that reported an ITT analysis used last observation carried forward ([D'Hemecourt 1998](#); [Jeffcoate 2009](#); [Munter 2006](#); [Tallis 2013](#)).

Other methods of Intention to Treat Analysis (ITT) such as Bayesian methods and imputation (imputing values for missing data) were not utilized. Fundamentally better efforts should be made before and during the conduct of the study to prevent or limit the amount of missing data to the maximum degree possible. This is the most ideal approach and lessens the reliance of researchers on the use of ITT methods to make up for missing data. ITT methods are not universally standardized and the specific methods used are variable. However irrespective of ITT method utilized, the reporting of method used should still be mandatory.

Selective reporting of outcomes was difficult to determine as all studies did not provide a pre-study protocol. Efforts were made to determine whether all of the outcomes defined and reported in the methods sections were subsequently reported in the results sections of the included studies. This was conducted as an alternative surrogate method of detecting selective reporting by the authors. Many of the studies were characterized as unclear or high risk of bias with respect to selective reporting of outcomes.

Authors should specify every outcome of interest in the methods section and these should be summarily reported in the results. Any deviation from this approach should be clearly explained.

All studies were characterized as high risk or unclear risk of bias (See [Characteristics of Included Studies Table Section and Risk of Bias Table section for individual studies](#)), [Figure 1 – 2](#). This was in part due to the variability of inclusion/exclusion criteria, and patient/study specific characteristics which were under-reported by the investigators of the included studies e.g. disease severity, variable methods of measurement e.g. variable methods of determining the presence of arterial insufficiency [Table 7 - 11](#). The majority of studies were industry supported 13/30 [Table 12](#). Publication bias was suggested graphically in the funnel plot. However other statistical tests for publication bias including Beggs, and Eggers test did not demonstrate significant evidence of publication bias. Publication bias assessment was limited to the Any debridement as compared with the control condition for the outcome number of ulcers healed. This was the only condition that met the recommended 10 studies threshold for publication bias testing.

Potential biases in the review process

This systematic review made efforts to include studies that were not published in English language journals. These studies were translated using Google Translate, and the reviewers relied on outside translators only when needed information was not translated by Google translate.

Efforts were made to contact authors of the studies that were only available as abstracts but were unsuccessful. We conducted a sensitivity analysis with and without the studies that were only available as abstracts in order to determine what the impact that would have on the effect estimates if they were excluded. This resulted in a smaller effect size and nonsignificance when the two abstracts were not included as reported above.

The potential for bias in translating the studies that were screened and included is possible. Though this risk is likely to be limited in this review given the negative findings in the translated studies are concordant with other similar findings that have been published.

Many of the studies paired both intervention treatment arms with sharp debridement on an as needed basis, even if sharp debridement was not one of the primary treatment arms. These studies were included unless they specified regular use sharp debridement in both intervention treatment arms, as this would have made it impossible to determine the inherent efficacy of the primary alternate forms of debridement used in the respective study. This could have introduced bias in that “as needed periodic” use of an alternative form of debridement conducted in both treatment arms could still have confounded the effect of the primary debridement methods of interest or debridement against control.

Studies with short-term follow-up periods were compared alongside studies that included longer follow up periods e.g. 10 days to 24 weeks. Length of study was not used as inclusion/exclusion criteria to prevent missing pertinent studies as a result of relying on narrower and more restrictive search criteria.

An additional study on Ultrasound debridement is currently underway and based on its description would meet eligibility criteria for inclusion in future updates of this review.

Three studies are presently designated as “studies awaiting classification”. Three studies in a previous review that were awaiting classification were assessed for inclusion during the course of this review and have been designated to the excluded studies section.

The designation “studies awaiting classification” indicates that a study is unclassifiable until further information is made available that can clarify whether or not it meets the inclusion/exclusion criteria. It cannot be classified as included, or excluded until there is sufficient additional information.

Agreements and disagreements with other studies or reviews

The objectives in this review included the search and retrieval of all other systematic reviews focusing on the same research question utilizing similar eligibility criteria. These other systematic reviews could then be compared and contrasted with this review. The search retrieved 10 related systematic reviews that were compared with our findings, see [Table 31](#) below. The first row represents collective ranges and summary data of the 10 systematic reviews that were retrieved. The first row is a condensed summary form of [Table 6](#), see [Table 6](#) for further details on each of the other 10 respective systematic reviews. The systematic reviews that included nonrandomized studies in addition to RCT’s made comparable conclusions to reviews restricted to randomized studies.

This summary table of the 10 systematic reviews retrieved that shared similar eligibility criteria (i.e. Type 1 or 2 Diabetic participants with foot ulcers, randomized studies, and any debridement method) are contrasted with the findings in this systematic review below:

Table 31 Comparison of systematic reviews preceding this current systematic review													
#	[Review]	[# Studies included]	[Study Type(s)]	[Total sample size]	Follow up period	Study period	Type of wound	[Participant Type]	[Intervention Type]	Outcomes	SR/MA methodology Evidence Grading	[Conclusions]	
10	SR's	4 – 10	4 – 8 RCT's 2 – 4 Pooled	149 - 575	10 days to 24 weeks	1989 - 2007	DFU Ischemic Venous	Diabetic Nondiabetic	1.Alginates 2.Foam 3.Film 4.Hydrogel 5.Hydrocolloid 6.Hydrotherapy 7.Larva 8.Sharp 9.LFU	1.Amputation 2.Infection 3.HRQoL 4.Ulcer healing 5.Time to complete healing 6.Recurrence 7.Adverse events	5 CR/GRADE AND 5 Other SR No Meta-Regression	“No evidence Insufficient evidence Low evidence Moderate Evidence for Hydrogel uncertain Moderate for Hydrocolloid but not strong evidence”	
1	SR	30	30 RCT's (10 pooled)	2539	10 days to 24 weeks	1992 - 2012	DFU	Diabetic	Alginates Foam Film Hydrogel Hydrocolloid Hydrotherapy Larva Silver dressing Sharp LFU 19 comparisons	1.Amputations 2.Infection 3.HRQoL 4.Ulcer healing 5.Time to complete healing 6. Recurrence 7.Cost	SR/MA AND Meta-regression AND GRADE approach	Very low to low evidence.	

The 10 systematic reviews retrieved in the search phase of this systematic review included Type 1 and Type two diabetics with one review restricted to Type 2 diabetics ([Mason 1999](#)). The studies all included participants with diabetic foot ulcers with 2/10 systematic reviews including venous and ischemic wound types ([Game 2012](#), [Voight 2011](#)). These reviews reported their results under the different wound types separately. The reviews included a range of 4 - 10 studies. The studies all included randomized studies with 3/10 systematic including nonrandomized studies ([Mason 1999](#); [Game 2012](#); [Hinchliffe 2008](#)). If the systematic reviews included nonrandomized studies the comparison with this systematic review was restricted to the summary findings of the included randomized studies. The number of participants ranged from 149 - 575 participants. The follow up period in the retrieved systematic reviews ranged from 10 days to 24 weeks. The study period for the studies included in the systematic reviews ranged from 1989 – 2007. The number of comparisons ranged from 1 - 9 methods of debridement including: Alginates, Foam, Film, Hydrogel, Hydrocolloid, Hydrotherapy, Larva, Sharp, and Low frequency ultrasound.

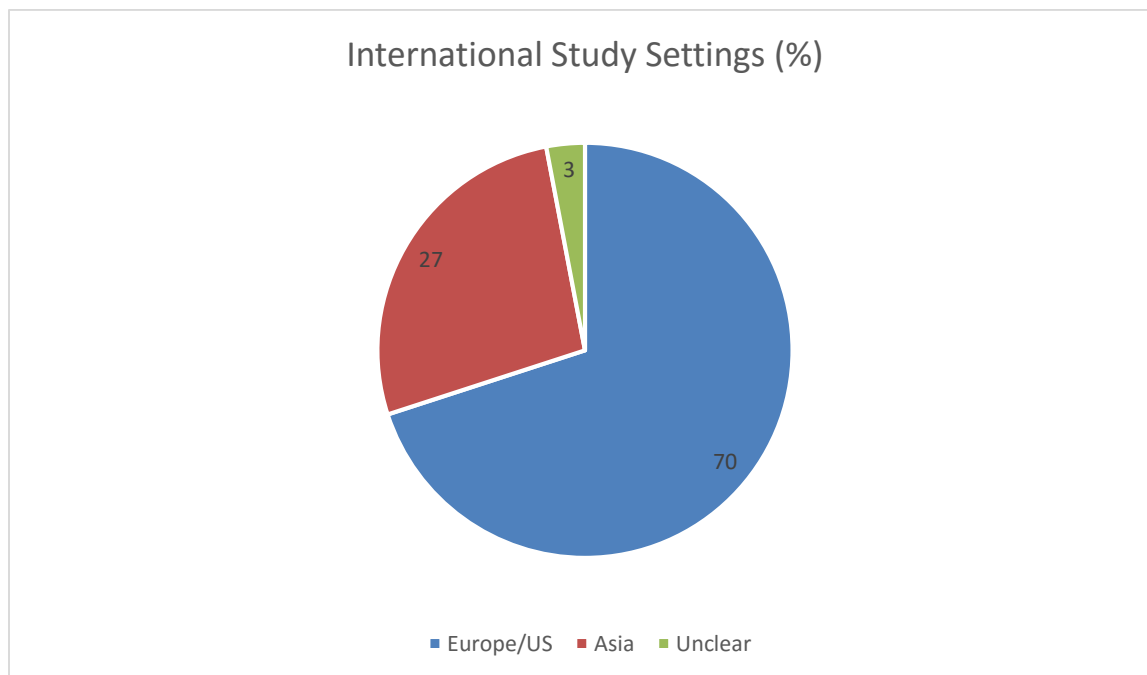
The outcomes reported in the retrieved systematic reviews included amputations, infections, quality of life, ulcer healing, time to complete healing, recurrence. Frequently amputation, and infection were reported as an adverse effect. It was unclear whether this was attributed to the debridement intervention in these reviews or in the studies themselves as amputation and infection are an inherent risk in the non-healing wound irrespective of method of debridement used. This systematic review did not attribute these outcomes to either the intervention or to the wound as this would be difficult to discern. This systematic review treated infection and amputation not necessarily as adverse outcomes to the intervention as outcomes inherent in chronic wounds that could also be averted through debridement interventions.

Five out of the 10 systematic reviews utilized a standardized approach to summarizing their findings. These were all Cochrane reviews and the method used was the Grade approach ([Grade Working Group 2010](#)). The 10 systematic reviews pooled a range of 2 – 6 of their included studies in their respective analyses. The systematic reviews findings were collectively consistent in concluding no, low, to weak evidence that one form of debridement was superior to another alternate form of debridement or superior to the control or standard condition. One systematic review reported moderate evidence of efficacy for hydrogel as compared with basic wound contact dressing, although this was uncertain due to risk of bias considerations ([Dumville 2013](#)). None of the 10 systematic reviews utilized Meta-regression or conducted any type of moderator analysis.

In contrast this review retrieved a total of 30 studies. 10 of these studies were pooled. This review included a total of 2539 participants, a follow up period of 10 days to 24 weeks, and a study period from 1992 – 2012. The studies included were exclusively RCT's. The wound type focus was exclusively diabetic foot ulcers in type 1 and type 2 diabetics. The methods of debridement included: Alginates, Foam, Film, Hydrogel, Hydrocolloid, Hydrotherapy, Larva, Silver dressing, Sharp, low frequency ultrasound. There were a total of 19 debridement comparison types reported. The outcomes of interest in this review included: amputations, infections, quality of life, ulcer healing, time to complete healing, recurrence, and cost. This review included a qualitative systematic review, meta-analyses, and meta regression. Summarizing of this reviews findings were based on the Grade approach ([Grade Working Group 2010](#)).

Many of the conclusions reached in our review regarding the direction of future trials were similar to these preceding reviews with respect to the need for larger sample sizes, and standardized reporting.

The findings in this review are consistent with other similar systematic reviews that found low evidence that any dressing type was more effective than others in healing diabetic foot ulcers. There was low evidence for Hydrogel, and for Any debridement as compared with gauze but this was unclear due to risk of bias. The geographic scope of the 30 studies in this review includes: 70% Europe/North America, 27% from Asia, with 1 study 3% not reporting international setting see pie chart below.



Chapter 8 Conclusion

Implications for practice

Based on a comprehensive systematic review of all the currently available evidence, any debridement method (i.e. any and all forms of the debridement types described) used as an intervention in the treatment of diabetic foot ulcers do not appear to increase the healing rates of diabetic foot ulcers compared with any other form of debridement or standard practice. Most of the included studies evaluated debridement interventions on participants who appeared to have a wide variation in foot ulcers including size and duration. However, disease severity and co-morbidities may not have been balanced between both intervention groups. This may have been more apparent in smaller studies despite the use of randomization to balance for confounding.

Grade assessments were made on the 4 Meta-analyses comparisons and the utilized in this data synthesis. These included the Hydrogel compared with gauze/good wound care [Summary of findings Table 32](#), Foam dressing compared with wet to dry saline dressings [Summary of findings Table 33](#) Hydrofiber compared with gauze dressing [Summary of findings Table 34](#), and Any debridement compared with gauze dressing [Summary of findings Table 35](#).

The grading of the evidence is either **High quality:** Further research is very unlikely to change our confidence in the estimate of effect, **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, and **Very low quality:** We are very uncertain about the estimate. The use of the GRADE approach ([Grade Working Group 2010](#)) to evaluate the evidence includes the following considerations: the quality of evidence includes all of the following:

1) Risk of bias/study limitations, 2) Directness, 3) Consistency of results, 4) Precision, 5) Publication bias, 6) Magnitude of the effect, 7) Dose-response gradient, and 8) Influence of residual plausible confounding.

The quality of the evidence is low to very low for these comparisons using the Grade approach. There was one outcome that was given a moderate evidence rating regarding the quality of life indicator for any debridement compared with gauze. This comparison included two arms of the same study ([Jeffcoate 2009](#)). The control condition was divided in half to avoid double counting the participants. The reduction in quality of life index was modestly lower in the intervention group for Any debridement compared with gauze [Summary of findings Table 35](#).

The evidence was found to be weak based on several considerations that are utilized in the GRADE approach ([Grade Working Group 2010](#)):

- 1) Downgraded as substantial risk of bias characteristics were either unclear or high.
- 2) Downgraded due to the 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. (GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.)
- 3) Downgraded due to total (cumulative) sample size being lower than the calculated optimal information size (OIS) and/or total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of less than 0.2 SD, representing a small effect).
- 4) 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit or harm.
- 5) Downgraded due to widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect.

These findings collectively do not support the endorsement of any single form of debridement over any other form of debridement. Nor do the findings support the use of ANY form of debridement over the frequently used control comparison gauze. This systematic review may be considered a non-inferiority study.

The confidence intervals for the point estimates have been large, frequently including thresholds that would include equivalence and the threshold of inferiority making this a reasonable conclusion.

Practitioners may therefore elect to consider other characteristics such as individualization of therapy, tolerability, indications/contraindications, cost, when choosing between the alternative methods of debridement. Alterations in practice habits with respect to the wide choices of debridement types available to clinicians may be based on clinical experience, biological plausibility, mechanistic and animal data, individual patient characteristics, tolerability. Relying on information from individual nonrandomized human studies which are available may have more biased effect estimates as a function of their design. These challenges should be appreciated along with the consideration that uncertainty exists around this treatment decision due to the quality of data used to inform clinical decision making.

Implications for research

Currently inadequate evidence exists to conclude that there is any difference, advantage or benefit between the various competing forms of debridement or against standard care.

It is of critical importance that future studies include better standardized reporting of outcomes including quality of life and cost-effectiveness analyses. There needs to be less variability and more uniform reporting of specific outcomes that clearly have direct implications on clinical decision making and critical public health implications including amputation frequency, infection frequency, and quality of life.

Future research clearly needs to be optimized to be of greater value to all stakeholders including patients, physicians, allied health providers, public health professionals, and policy makers.

There exist numerous choices of debridement available and the design of future studies should be guided by findings reached in this systematic review to help meet the needs of all stakeholders.

The comprehensive set of outcomes utilized in this systematic review include important direct and indirect clinical and public health indicators e.g. diabetics account for most of the amputations and this can be directly extrapolated to mortality risk.

It is important to view the ulcer or wound as a determinant or risk factor for these adverse outcomes, rather than viewing the ulcer or wound strictly as a disease state. Future research studies should qualify what constitutes standard care, and address patient lifestyle issues. The standard of care in diabetic foot ulcers includes offloading, nutritional services, infection eradication, smoking status and cessation, and addressing arterial insufficiency. The status of these other interventions should be universally reported in future studies.

Studies should be conducted in accordance with standardized uniform good practice guidelines in the design, conduct, and reporting of randomized controlled trials. This would afford researchers the opportunity to design and conduct better quality systematic reviews of the evidence. The synthesis could potentially be more comprehensive and include both qualitative and quantitative components in the systematic review for all comparisons. This will undoubtedly aid in the decision making about the competing forms of debridement.

The costs associated with complicating amputations, infections, premature mortality, quality of life and mortality transcends monetary costs. These complications are rising and disproportionately burden the individual, healthcare resources, society, the family unit, the workplace, the employer, along with government and private services for the disabled. The obesity epidemic, diabetes incidence rates, and non-healing wounds qualify as an imminent and growing pandemic with serious public health and clinical implications. Methods of prevention and intervention including debridement require further investigation to determine efficacy. Systematic reviews that are undertaken are a useful tool in Evidence based Medicine. They require summarizing and pooling studies of high quality in order to make broader inference and can identify knowledge gaps. This will not only summarize and make broader inference on the state of current evidence but help direct future research efforts as this systematic review has highlighted.

Contributions of authors

David Dayya developed this expanded and revised review and coordinated its development including the study search, appraisal, retrieval, study identification, data extraction form and tools development, data extraction and data cleaning, reliability testing, data analysis, and completed the drafts of this review, made an intellectual contribution, approved the final version prior to submission and is the guarantor of the review.

Tania Huedo-Medina edited the review, mentored and served as a methodology consultant throughout the entire review process, made an intellectual contribution and approved the final version of the review prior to submission.

Owen J O'Neill edited the review and served as a content expert throughout the entire review process, made an intellectual contribution and approved the final version of the review prior to submission.

Nusrat Habib ensured redundancy in the appraisal, retrieval, study identification, and data extraction phases, made an intellectual contribution to the review, advised on the review and approved the final version prior to submission.

Declarations of interest

None to declare. The authors report no conflicts of interest.

Differences between protocol and review

This systematic review was a significant expansion and revision on the subject of Debridement of Diabetic Foot Ulcers. The creation of a new protocol was necessary in order to make the expansion and revision transparent and reduce the risk of bias in this review. The review expanded the outcomes from 4 to 7 including amputation risk, infection frequency risk, and cost. These were added in addition to the 4 other variables. One of the 3 searches conducted included a comprehensive search without any date restrictions. The other two searches relied on finite search dates from the dates of the last review on this research question.

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Characteristics of included studies/Risk of bias summaries

Characteristics of included studies

1. Ali 2013	Methods	Randomized Clinical Trial Texas classification used.
	Participants	A) 35 (25M/10F, age <50 yrs. = 10, age > 50 yrs. = 25, 7 smoking, 10 HgbA1c <= 7) B) 35 (23M/12F, age < 50yrs = 12, age > 50 yrs. = 23, 8 smoking, 9 HgbA1c <= 7) No statistical difference in demographics between both groups nor in initial glycemic or cholesterol control.
	Interventions	A) Cutimed Sorbact B) Standard Dressing (Saline cleansed povidone soaked gauze dressing)
	Outcomes	No outcomes were reported that were targeted in this review.
	Notes	Outcomes reported in this study include comparison of foot inspection pre and post intervention (i.e. edema, pulse, temperature, skin color). Other outcomes included comparison of wound granulation and grade pre and post intervention, and wound changes and pain pre and post intervention (i.e. wound size, wound depth, and exudates). Reported that edema, impaired pulse, cold extremities, and abnormal skin color demonstrated better improvements in the study group.

		<p>Improvements in granulation tissue and wound grade were reported in the study group.</p> <p>Reported that the study group patients had higher wound grades than control at study onset.</p> <p>These findings were found to be statistically significant differences. Wound size but not depth improved in the study group and was found to be statistically significant.</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study Reports randomization of subjects but does not specifically identify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports blind assessment of the outcomes was done by trained nurses not involved in the study.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Unclear if a protocol was prepared for this study. The outcomes discussed in the methods section were reported in the results. The point estimates reported in this study included dichotomous nominal cutoff values in lieu of mean point estimates it is unclear if the cutoffs assigned were arbitrary.
Other Bias	Unclear risk	The study text reports that 60 patients were enrolled in the study however the tables suggest that 70 were enrolled in the study.

2. Amini 2013	Methods	Randomized Clinical Trial 6 months' duration or until complete wound healing Weekly wound evaluations (photo documentation) Plain x-rays and bone scan to exclude osteomyelitis
	Participants	40 patients from a diabetic foot ulcer clinic HgbA1c = 8.9 +/- 2.3 #patients, gender, mean age +/-SD, diabetes duration, smoker, BMI, PVD A) 20, 14M/6F, 55.3 +/- 9.5 yrs., 14.4 +/- 8.2 yrs., 0.05, 27.9, 0.60 B) 20, 10M/10F, 55 +/- 9.6 yrs., 15.2 +/- 6.2 yrs., 0.10, 28.7, 0.40 Reported that the only statistically significant difference was more heart disease in the ultrasound group.
	Interventions	A) Low frequency (20-60kHz) ultrasound assisted wound therapy + standard wound care B) Standard wound care alone (All wounds reported to be initially surgically debrided and thereafter as needed. Daily dressing changes All patients received offloading and antibiotics.
	Outcomes	1) Proportion Healed A) 0.60 B) 0.55

		<p>Not statistically significant difference</p> <p>2) Complete healing Time</p> <p>A) 61.6 +/- 84 days</p> <p>B) 81.2 +/- 78.4 days</p>
	Notes	<p>Other outcomes reported included:</p> <p>Mean wound size reduction at 6 months</p> <p>A) 0.879 +/- 0.338</p> <p>B) 0.824 +/- 0.33</p> <p>No statistically significant difference</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT reported. Specific method of sequence generation reported as simple randomization.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Preselected outcomes in the methods section were reported in the results section. No pre-specified protocol was reported.
Other Bias	Unclear risk	Sharp debridement reportedly performed initially and as needed.

3. Apelqvist 1990	Methods	<p>-Open randomized controlled study</p> <p>5-week study</p> <p>Blinded evaluation</p> <p>Weekly evaluation included color photos and evaluation by combined foot care team (diabetologist, orthopedist, orthotist, podiatrist, and a nurse)</p> <p>Study reports foot wear corrected when necessary.</p> <p>Intervention stopped for surgical debridement, hospitalization, noncompliance, increase in size or necrosis of the ulcer by 50%, and reaction to dressing.</p>
	Participants	<p>44 outpatients 26M/18F, mean age 63 yrs. (23-86), HgbA1c = 8.2 mean duration of diabetes = 20 yrs. (2 - 54),</p> <p>A) 22, 8.4 +/- 1.4, 22 +/- 15,</p> <p>B) 22, 8.0 +/- 2.1, 19 +/- 12,</p>
	Interventions	<p>A) Hydrocolloid</p> <p>B) Adhesive Zinc Oxide tape</p> <p>Ulcers cleaned with sterile saline.</p> <p>Dressing changes daily for 1st week then every 3 days afterwards where wound and surrounding area inspected and assessed.</p>
	Outcomes	<p>1) Proportion healed</p> <p>A) $5/22 = 0.227$</p> <p>B) $9/22 = 0.409$</p>

		2) Proportion of Infections A) $1/22 = 0.045$ B) $0/22 = 0$ Not statistically significant difference 2) Complete healing Time A) 61.6 +/- 84 days B) 81.2 +/- 78.4 days
	Notes	Changes in necrotic ulcer area were also reported.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized study reported. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	Blinded evaluation was reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Prespecified protocol not reported. Prespecified outcomes in the methods section reported in the results.
Other Bias	Unclear risk	Study financially supported by industry.

4. Baker 1993	Methods	RCT - Pilot Study Duration - 12 weeks Limited - Abstract available only
	Participants	19 with neuropathic foot ulcers, number of participants in each intervention group not reported. Age, sex, grade or duration of wounds, severity of peripheral arterial disease, presence of infection and diabetes disease severity not reported.
	Interventions	A) Allevyn Hydrocellular dressing B) Sorbsan Calcium-Alginate dressings
	Outcomes	1) Proportion of ulcers healed 90% vs 44% at 12 weeks 2) Median time to healing 28 days vs. 84 days
	Notes	Allevyn Hydrocellular reported as significantly more absorbent ($p=0.001$) and less adherent or easier to remove ($p=0.011$) than the alginate dressing.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported. Specific method of sequence generation was unspecified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Unclear risk	No protocol reported or clearly pre-specified outcomes in methodology. Only abstract available.
Other Bias	High risk	Other significant covariates and differences between intervention groups not reported.

5. Belcaro 2010	Methods	Open-label registry randomized pilot study. 4 weeks Categorized: venous ulcers and diabetic ulcers
	Participants	148 patients A) 34 patients, 16M/18F, Mean Age 56.5 +/- 4.4 years B) 32 patients, 13M/19F Mean Age 55.3 +/- 3.2 years
	Interventions	A) Multivalent silver oxide Ag4O4 ointment + elastic compression B) Control group (standard cleaning and elastic compression management methods without silver ointment)
	Outcomes	Complete closure of the ulceration A) 39% b) 16% (p <=0.05).
	Notes	Notes The study also reported the following outcomes of noninvasive vascular investigations to exclude major vascular problems that could result in decreased perfusion. These include Skin PO2 and Skin flux. perimalleolar Skin (P02) (Oxygenation in the skin of the affected limb) Baseline at 4 weeks A) 43 mmHg 53 mmHg (increase of 23.3%)

		<p>B) 44 mmHg 48mmHg (increase of 9.1 %)</p> <p>(p <= 0.05)</p> <p>Laser Doppler flowmetry perimalleolar Skin flux (RF)</p> <p>Baseline at 4 weeks</p> <p>A) 3.22 flux units 2.36 flux units (decrease of -26.7%)</p> <p>B) 3.21 flux units 3.01 flux units (decrease of -6.2%)</p> <p>(p <= 0.05)</p> <p>Total surface area reduction of the ulcer</p> <p>A) -89.0%</p> <p>B) -23.9%</p> <p>(p <= 0.05)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports that the patients were randomly assigned however method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	The study reported no dropouts.
Selective outcome reporting (reporting bias)	High risk	No protocol was available for this study and the outcomes were not all clearly pre-specified in the methods section of the study.
Other Bias	Unclear risk	The study does not compare the intervention groups on other risk factors that could influence outcomes. No further detail was

		provided on how balanced both intervention groups were.
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6. Blackman 1994	Methods	<p>RCT</p> <p>Surface area tracings of wound margins.</p> <p>Foot ulcer measurements every 3 weeks for a follow up period of 24 weeks.</p> <p>Cross-over design after two months to group A</p> <p>Subjects encouraged to obtain orthotic footwear</p> <p>Subjects followed until ulcer healed, or until 6 months had elapsed.</p>
	Participants	<p>18 subjects Type 1 and 2 DM</p> <p>#, gender, mean age, HgbA1c,</p> <p>A) 11, 11M/0F, 59 +/- 5yrs, 8.4 +/- 0.9</p> <p>B) 7, 6M/1F, 51 +/- 4yrs, 9.5 +/- 1.1</p> <p>No statistical significant difference</p>
	Interventions	<p>A) Polymeric dressing</p> <p>B) Wet to dry saline dressing</p> <p>Dressing changes at minimum once daily or when saturated.</p> <p>4 wounds surgically debrided in group A and 3 in group B prior to start.</p>
	Outcomes	<p>1) Proportion healed</p> <p>A) 0.73 OR 0.27</p> <p>B) 0</p> <p>(p <=0.05).</p>

	Notes	<p>Other outcomes reported included:</p> <p>Ulcer size reduction</p> <p>A) 35 +/- 16%</p> <p>B) 105 +/- 28% -> 35 +/- 11% (post-crossover, $p < 0.02$, 5 subjects were crossed over from conventional treatment to polymeric membrane after two months of treatment)</p> <p>Statistically significant difference ($p < 0.03$)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Reported that subjects were randomly assigned. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	2 patients from each group progressed to Wagner grade 3 and were not included in the study.
Selective outcome reporting (reporting bias)	Low risk	Prespecified protocol not reported. Prespecified outcomes in the methods section were reported in the results.
Other Bias	High risk	2 patients in underwent debridement in their referring physician's office during the study. No patient obtained new orthotic footwear. The study was industry supported.

7. Bowling 2011	Methods	<p>Prospective randomized, controlled, double blind, pilot study.</p> <p>Weekly treatments for 4 weeks.</p> <p>Semi-quantitative wound tissue cultures post-debridement at baseline and week 4.</p> <p>Maximum wound size Length X Width</p>
	Participants	<p>20 patients</p> <p>#, Gender M/F, Type 1/2, Duration of diabetes, HgbA1c %</p> <p>A) 10, 6/4, 3/7, 21.2 +/- 9.0 yrs., 9.3 +/- 1.7,</p> <p>B) 10, 6/4, 2/8, 17.5 +/- 7.2 yrs., 8.1 +/- 1.9,</p>
	Interventions	<p>A) Jet lavage debridement with superoxide aqueous solution + hydrogel</p> <p>B) Jet lavage debridement with saline solution + hydrogel</p> <p>All dressing changes every 3-4 days, specified treating physician</p> <p>Superoxide solution or saline applied at every dressing change.</p>
	Outcomes	<p>The study qualitatively reports no adverse effects were recorded. The study did not report that 15% of the study ulcers were healed. The study reported no statistically significant results between the two treatments ($p>0.05$). No further information was specified on the outcomes of interest for this review.</p>
	Notes	<p>Wound bio-burden (bacterial load) was reported on an</p>

		<p>ordinal scale as scattered (0/+), light (+), medium (++), heavy (+++)</p> <p>Reduction in bacterial load at week 4</p> <p>A) 1.6 +/- 1.3 -> 1.1 +/- 1.2</p> <p>B) 1.7 +/- 1.4 -> 1.2 +/- 1.2</p> <p>No statistically significant difference (p = 0.9)</p> <p>The study reports trend toward a 75% reduction in necrotic tissue in the study group (p>0.05)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized controlled pilot study. Method of sequence generation reported as computer-generated block randomization scheme.
Allocation concealment (selection bias)	Low risk	Reported that medical centers were provided with sealed randomization envelopes for conducting the treatment assignment.
Blinding participants	Unclear risk	The authors report that this was a double blind study, however it is not specified which combination of participants, personnel delivering the intervention, or outcome assessors was blinded.
Blinding personnel delivering intervention	Unclear risk	The authors report that this was a double blind study, however it is not specified which combination of participants, personnel delivering the intervention, or outcome assessors was blinded.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	No pre-specified protocol was reported. The outcomes pre-specified in the methods section were reported in the outcomes. However full numeration for both groups was not reported in the results.
Other Bias	Unclear risk	Offloading status was not reported.
Notes		

<p>8. Clever 1995</p>	<p>Methods</p>	<p>Open, randomized, controlled study</p> <p>comparing two polyurethane dressings</p> <p>40 patients</p> <p>Objective clinical evaluation: ulcer tracings, photographs and date of healing.</p> <p>At end of treatment, both the investigator and patient evaluated the wound care product subjectively.</p>
	<p>Participants</p>	<p>A) 20 patients, 15M/5F, age 58.85 +/- 11.64 years</p> <p>B) 20 patients, 17M/3F, age 53.15 +/- 14.62 years No statistically significant difference was reported in gender or age.</p> <p>Sample age range 18 - 80</p> <p>Pure neuropathic superficial diabetic ulcer of 1-5 cm in diameter.</p> <p>No clinical or radiological signs of osteomyelitis or tendon involvement.</p> <p>Study reports no statistically significant differences between intervention groups in terms of ankle-brachial pressure index, threshold of vibration, average duration of ulcer before entering study, and number of recent recurrences.</p> <p>Number of Smokers (9 vs 4, $p < 0.01$) was statistically significant.</p>

	Interventions	<p>A) Hydroactive polyurethane gel dressing Cutinova Hydro + standard therapy*</p> <p>B) Hydrophilic polyurethane foam dressing Allevyn + standard therapy*</p> <p>"Dressing changes reportedly performed as often as required, but at least once a week."</p> <p>*Standard therapy included:</p> <p>(i) pressure relief comprising a half-shoe or so-called "heel sandal" therapeutic footwear with cushioned insoles and crutches as required to meet individual needs.</p> <p>(ii) infection control with systemic antibiotics if required,</p> <p>(iii) wound cleansing with Ringer's solution, and</p> <p>(iv) debridement with removal of callus if needed</p>
	Outcomes	<p>Time to Healing</p> <p>A) 25.19 ± 23.52 days</p> <p>B) 20.43 ± 14.74 days ($p > 0.2$)</p> <p>Proportion healed</p> <p>A) $14/20 = 0.70$</p> <p>B) $16/20 = 0.80$</p> <p>Excluding dropouts, 88% of the patients were healed in an average of 23 days, 50% within 16 days.</p>
	Notes	Dressing changes by patient's in-between the weekly assessments:

		<p>A) 2.23 ± 2.19 times</p> <p>B) 2.37 ± 2.18 times, No statistically significant difference ($p > 0.2$)</p> <p>The study reported "subjective product evaluation" including ease of showering with dressing ($p > 0.1$), absorption capacity ($p > 0.1$), handling and suitability (lack of side-effects or skin problems) ($p > 0.2$), and all were found to not be statistically significant. No details on the subjective evaluation was specified.</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization reported but method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	2 patients in group A and 4 patients in group B were reported to not have completed the study. It is unclear how the missing data were addressed.
Selective outcome reporting (reporting bias)	High risk	The study broadly reported outcomes in the methods section but did not specify all outcomes that were reported in the results. No protocol specified.
Other Bias	High risk	Unclear if both groups were adequately balanced for confounders or other risk factors including disease severity. Prospective wound healing study was possible due to financial support from manufacturer.
Notes		

9. D'Hemecourt 1998	Methods	<p>RCT Multi-centered (10 sites); Evaluator-blind</p> <p>Study period was not reported. Follow up period was 140 days.</p>
	Participants	<p>172 patients</p> <p>A) 68</p> <p>B) 70</p> <p>C) 34</p> <p>45 women/127 men; 19 years or older; Type 1 / Type 2 diabetes. At least one full thickness Stage 3 or Stage 4 chronic diabetic ulcer of the lower extremity.</p> <p>Wound size (area and depth) measured at baseline.</p>
	Interventions	<p>A) Good wound care*</p> <p>B) Good wound care & NaCMC hydrogel</p> <p>C) Good wound care & Becaplermin</p> <p>Off-loading of pressure and systemic control of infection for all wounds.</p> <p>*'Good wound care' was defined by the study authors as follows: "this regimen consisted of daily dressing changes, sharp debridement of the ulcer when deemed necessary by the investigator, systemic control of infection if present, and off-loading of pressure".</p>
	Outcomes	<p>1. Proportion with complete wound healing at 20 weeks</p> <p>A) 15 / 68 (22%)</p> <p>B) 25 / 70 (36%)</p> <p>2. Time to complete healing</p>

		<p>A) 141 days *</p> <p>B) 98 days *</p> <p>3. Proportion with Infection</p> <p>A) 0.28</p> <p>B) 0.30</p>
	Notes	<p>Largest trial with regard to patient numbers</p> <p>* It is unclear if these are mean or median times to healing.</p> <p>Two other indicators reported in the study included:</p> <p>Pain reported as adverse event</p> <p>A) 10 / 68 (15%)</p> <p>B) 11 / 70 (16%)</p> <p>Wound related adverse events</p> <p>A) 25 / 68 (37%)</p> <p>B) 19 / 70 (27%)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The method of sequence generation procedure was not specified: "patients were randomly assigned in a 2:2:1 ratio to one of three treatment groups".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Statement by authors from published study: "both the NaCMC gel and Becaplermin gel treatment groups were conducted in double-blind fashion; the group receiving good wound care alone was blinded to the investigator by a third party".
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel delivering the intervention: yes - control group;

		unclear - intervention groups (see statement from authors above).
Blinding outcome assessors	Low risk	Blinding of outcomes assessor: yes. Study described as "evaluator-blind".
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis was conducted. However, the specific Intention to treat analytic method was not reported.
Selective outcome reporting (reporting bias)	Low risk	Four parameters pre-specified as outcomes, all of which were reported
Other Bias	High risk	<p>Baseline differences in group size and ulcer characteristics (mean area, depth, and duration):</p> <p>Good wound care (n=68): n=65 at stage III; 3.5 cm²; 67cm; 24 weeks.</p> <p>NaCMC gel (n=70): n=70 at stage III; 3.2 cm²; 69 cm; 24 weeks.</p> <p>Becaplermin gel (n=34): n=32 at stage III; 2.4 cm²; 33cm; 11 weeks.</p> <p>The group receiving Becaplermin gel were not comparable with the two other groups.</p> <p>'Good wound care' included "sharp debridement of the ulcer when deemed necessary by the investigator". No other data reported on diabetes disease severity or other risk factors.</p>
Notes		

10. Donaghue 1998	Methods	<p>75 patients enrolled in an open-label design with random assignment to two groups in 2:1 ratio.</p> <p>Wagner classification used.</p> <p>Offloading prescribed to all patients with self-adhesive felted foam and window at wound site, and use of healing sandals.</p> <p>Seen weekly until target ulcer healed or maximum of 8 weeks.</p> <p>Exit interview to determine satisfaction level.</p>
	Participants	<p># Gender Age (range) Duration of DM(range) Weight Creatinine Albumin Proportion</p> <p>M/F yrs. (yrs.) (lbs.) (mg/dl) (gms/dl) Retinopathy</p> <p>A) 50, 33/17, 59 (30-81), 19 (4-47), 195 +/- 45, 1.2 +/- 0.6, 3.72 +/- 0.07 0.56</p> <p>B) 25, 21/4, 60 (33-79), 17 (2-25), 214 +/- 49, 1.14 +/- 0.06, 3.79 +/- 0.11 0.76</p> <p>No statistically significant difference in any of these baseline participant characteristics was reported in the study.</p>
	Interventions	<p>A) Collagen Alginate</p> <p>B) Saline gauze</p> <p>Patients or caregivers given instructions to change as often as required.</p>
	Outcomes	<p>1) Proportion healed</p> <p>A) $24/50 = 0.48$</p>

		<p>B) $9/25 = 0.36$</p> <p>No statistically significant difference ($p=0.3933$)</p> <p>2) Mean time to complete healing</p> <p>A) 43.4 ± 2.8 days</p> <p>B) 40.6 ± 2.8 days</p> <p>The study authors reported that there were no differences in the number or severity of adverse effects ($p=0.453$) No other information was provided.</p>
	Notes	<p>The study also reported:</p> <p>Baseline values:</p> <p>Additional outcome included:</p> <p>Mean percent reduction of the wound area at the end of the study was reported as:</p> <p>A) $80.6 \pm 6\%$</p> <p>B) $61.1 \pm 26\%$</p> <p>No statistically significant difference ($p=0.4692$)</p> <p>The study reported wound size reduction rate in a multivariate analysis to be statistically significant in favor of Collagen alginate over saline gauze ($p=0.049$). No other information was provided.</p> <p>Subgroup analysis was reported for wounds of less</p>

		than 6 month's duration and the authors report a faster healing rate for Collagen alginate over saline gauze but the result was not statistically significant.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Random assignment to treatment groups was reported but method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	75 patients enrolled, 61 completed study, 14 withdrawals (6 patients in group A and 8 in group B did not complete the study, 5 withdrew no reason reported, 3 patients missed > 2 visits, and 6 patients experienced adverse events). The authors report that all 75 patients enrolled were included in the intention to treat analysis. The method used in the intention to treat analysis to address the 14 withdrawals was unspecified.
Selective outcome reporting (reporting bias)	High risk	No protocol was specified in the report. The outcomes reported in the results section were not explicitly prespecified outcomes in the methods section.
Other Bias	Unclear risk	The study reported adverse effects were not statistically significant between both groups. Specific information on adverse effects was not reported.
Notes		

11. EhsanUrRehman 2013	Methods	<p>60 subjects randomly assigned to two groups.</p> <p>non-probability purposive sampling</p> <p>Wound measurements were done on day 15.</p> <p>Wagner grade I & II ulcers.</p> <p>Length, width and maximum perpendicular depth of ulcer were measured and multiplied post-surgical debridement</p>
	Participants	Not reported.
	Interventions	<p>A) Honey soaked dressing</p> <p>B) Povidone-iodine/normal saline dressing</p> <p>Daily dressing changes</p> <p>All wounds washed with saline prior to</p> <p>Surgical debridement at the time of presentation.</p>
	Outcomes	<p>1) Proportion healed</p> <p>A) $24/50 = 0.48$</p> <p>B) $9/25 = 0.36$</p> <p>No statistically significant difference ($p=0.3933$)</p> <p>2) Mean time to complete healing</p> <p>A) 43.4 ± 2.8 days</p> <p>B) 40.6 ± 2.8 days</p> <p>The study authors reported that there were no differences in the number or severity of adverse effects ($p=0.453$) No</p>

		other information was provided, Proportion healed A) 0.867 B) 0.733
	Notes	Other outcomes reported include: % decrease in wound size A) 80.81 +/- 17.27% B) 54.63 +/- 3.42%
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Subjects reported randomly assorted into two groups. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	The study reports swab and culture would be carried out in the methods section but infection not reported in the results. Other outcomes reported in the results section were not pre-specified in the methods section.
Other Bias	High risk	Prespecified outcomes not reported in methods section. Comorbidities used as exclusion criteria reported in methods section but not specified. No patient baseline characteristics reported unclear whether both groups balanced for confounding. Non-probability purposive sampling which could produce sampling bias.
Notes		

12. Foster 1994	Methods	<p>RCT, Stratified according to neuropathic or ischemic diabetic foot ulcers</p> <p>Study length 8 weeks or until the ulcer.</p> <p>Weekly clinic assessments of wounds and dressings, and where ulcers were debrided.</p>
	Participants	<p>30 Patients</p> <p>A) 15 patients, 12M/3F, mean age 61, DMT1 = 6</p> <p>B) 15 patients 8M/7F, mean age 70, DMT1 = 4</p>
	Interventions	<p>A) Hydrocellular polyurethane foam dressing Allevyn</p> <p>B) Calcium sodium alginate dressing changes</p> <p>All wounds washed with saline prior to</p> <p>Surgical debridement at the time of presentation.</p>
	Outcomes	<p>Proportion Healed</p> <p>A) $9/15 = 0.60$</p> <p>B) $8/15 = 0.533$</p> <p>No statistically significant difference in time to healing between both intervention groups.</p>
	Notes	<p>Study reported that some evidence ulcer more likely to heal if IDDM as opposed to NIDDM ($p=0.07$).</p> <p>Also smaller ulcers or ulcers of neuropathic origin more likely to heal.</p>

		<p>A statistically significant difference was reported favoring Polyurethane foam dressings over Calcium alginate dressings in 1) time taken for application (2.1 +/- 0.6 minutes vs 3.2 +/- 1.0 minutes), and in subjective ordinal scales including ease of application (p<0.001), absorbency (p<0.01), patient comfort (p<0.01), non-adherence (p<0.01), and ease of removal (0.001). % decrease in wound size</p> <p>A) 80.81 +/- 17.27%</p> <p>B) 54.63 +/- 3.42%</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study reports randomization but method of sequence generation is unspecified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	<p>4 patients from the alginate group withdrew due to:</p> <p>severe pain (1); plugged lesion prevented free drainage of exudate (3) with one becoming infected. Unclear how incomplete outcome data were addressed.</p>
Selective outcome reporting (reporting bias)	High risk	Study pre-specified a number of "ideal" parameters in the introduction including infection however these were not all were reported in the results section. No parameters were pre-specified in the methods section.
Other Bias	High risk	The study reported stratification was conducted in order to ensure that a more equitable number of individuals with neuropathic, ischemic ulcers, traumatic wounds in each intervention group.

		However, no mention was made on whether other risk factors such as diabetes disease severity was balanced in both intervention groups. Duration of ulcer was longer in the calcium alginate group (170 days vs 107 days).
Notes		

13. Goretti 2008	Methods	RCT; Randomized into two groups.
	Participants	<p>A) 20</p> <p>B) 20</p> <p>Wounds > 5 cm², ABI \geq 0.9 and two arteries in the ankle palpable by pulse or Doppler.</p> <p>Age, gender, diabetes type, duration of diabetes, proportion of wounds infected, or other data not provided.</p>
	Interventions	<p>A) Super-oxidized solution (SOS) treatment</p> <p>B) Standard local treatment with povidone iodine</p> <p>Frequency or number of times intervention used was not reported.</p> <p>The study abstract mentions that the patients received metabolic control, systemic antibiotics, and offloading as necessary, but no further detail was provided.</p>
	Outcomes	<p>1. Proportion Healed</p> <p>A) 0.85</p> <p>B) 0.53</p> <p>($p < 0.01$, statistically significant difference)</p> <p>2. Healing Time</p> <p>A) 10.5 +/- 1.3 weeks</p> <p>B) 16.5 +/- 1.7 weeks</p> <p>($p < 0.01$, statistically significant difference)</p> <p>The study reports weekly visits to record lesions clinical signs of infection, microbiological sampling,</p>

		eventual new debridement procedures, and adverse events. No further detail is available.
	Notes	<p>Other outcomes that were reported include:</p> <p>Sterilization of lesions (ST)</p> <p>A) 5.5 +/- 2.1 weeks</p> <p>B) 16.2 +/- 6.6 weeks</p> <p>(p<0.01, statistically significant difference)</p> <p>Number of Debridement procedures (ND)</p> <p>A) 3/20</p> <p>B) 9/20</p> <p>(p<0.01, statistically significant difference)</p> <p>Adverse Events (NA)</p> <p>A) 4</p> <p>B) 9</p> <p>No other information provided other than a statement that no differences were observed in (NA)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only. Randomization reported but the method of sequence generation used was not specified
Allocation concealment (selection bias)	Unclear risk	Published abstract only. Not reported.
Blinding participants	Unclear risk	Published abstract only. Not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only. Not reported.

Blinding outcome assessors	Unclear risk	Published abstract only. The study reports weekly visits to "blindly" record lesions clinical signs of infection, microbiological sampling, eventual new debridement procedures, and adverse events. Unclear if other outcomes were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only. Not reported.
Selective outcome reporting (reporting bias)	Low risk	Published abstract only. Results were available for all outcomes reported in the methods section however unclear if protocol was written ahead of the study.
Other Bias	Unclear risk	Published abstract only. Other sources of bias not discernible.
Notes		

14. Hammouri 2004	Methods	203 patients allocated randomly to two groups, 3 excluded.
	Participants	200 patients, 112M/88F, Mean age = 58 A) 100 58M/42F, (24-100), B) 100 54M/46F, (22-100)
	Interventions	A) Honey/Normal Saline, washed with normal saline post-debridement B) Povidone Iodine/H2O2 (3:1) washed with same solution post-debridement All dressings applied 3 times daily then declined as treatment progresses in both groups.
	Outcomes	1) Time to healing A) Median 21 days, (7-70 days), SD = 15.97 B) Median 32 days, (7-90 days), SD = 20.89 Statistically significant difference (p<0.001) 2) Treatment Cost A) 282 +/- 66.33 Jordan Dinar, B) 616 +/- 192.97 Jordan Dinar, Statistically significant difference (p<0.001) 3) Proportion amputations A) 0.10 B) 0.20

		Statistically significant difference ($p < 0.05$)
	Notes	<p>Other outcomes reported:</p> <p>Hospital stay</p> <p>A) Median 23 days (7-42 days), SD = 8.26</p> <p>B) Median 13 days (7-56 days), SD = 14.54</p> <p>Statistically significant difference ($p < 0.001$)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The authors report random allocation. Method of sequence generation is not specified in the report.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	The authors report that 3 patients were excluded from the analysis that died from other medical illness.
Selective outcome reporting (reporting bias)	High risk	No protocol is reported. The study authors report healing, hospital stay, and cost as the respective outcomes of interest in the methods section. These were reported in the results section. The study reported amputation proportion, bioburden reduction which were not explicitly pre-specified in the methods section.
Other Bias	High risk	The study authors did not report exclusion criteria and reported only diabetic foot ulcers as inclusion criteria. Baseline characteristics of the ulcers in each group were not reported. Disease severity indicators including HgbA1c, duration of diabetes were not reported. Grade of diabetic foot ulcers not reported. Debridement under anesthesia is reported but study authors do not specify whether this was an initial

		debridement only or if debridements were conducted throughout the course of the study.
Notes		

15. Jeffcoate 2009	Methods	<p>A multicenter, prospective, observer-blinded, parallel group, randomized controlled trial.</p> <p>Research nurse monitored every two weeks.</p> <p>Primary endpoint number of ulcers healing in each group within 24 weeks.</p> <p>Ulcers monitored by nurses every two weeks. Blinded wound assessments made at baseline, 12 weeks, 24 weeks, 4 weeks after healing, and 12 weeks after the 24-week assessment.</p> <p>Healing defined as complete epithelialization with no drainage for 4 weeks and confirmed by a blinded assessor. If an ulcer was assessed as healed at any point the authors stated that ulcer was reassessed at 2 and 4 weeks after healing. If the ulcer recurred within 4 weeks or at any point up to 24 weeks, the patient was re-entered into the study using the allocated dressing.</p> <p>The study reported on ulcer-related endpoints, patient-related endpoints, and process related endpoints.</p> <p>A health economics evaluation which included the direct costs associated with dressings used and patient travel costs was reported. The quality of life assessment</p>
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		included SF-36 questionnaire, a visual analogue scale for pain, and the CWIS (Cardiff wound impact schedule).
	Participants	<p># Gender M/F Age (yrs.) DM Type 1/2 DM duration (yrs.)</p> <p>Total 317, 240/76, 59.6 +/- 12.6, 240/76, 15.7 +/- 10.8</p> <p>A) 103, 81/22, 59.5 +/- 11.5, 22/81, 16.0 +/- 11.4</p> <p>B) 108, 81/27, 58.8 +/- 13.2, 25/83, 15.3 +/- 9.8</p> <p>C) 106, 78/27, 61.9 +/- 12.8, 78/27, 15.8 +/- 11.4</p>
	Interventions	<p>A) Hydrofiber dressing Aquacel</p> <p>B) Iodine impregnated gauze</p> <p>C) Non-adherent viscous filament gauze</p> <p>Other care reported to include: regular use of debridement, offloading,</p> <p>The study reports dressings were changed daily, on alternate days, and 3X/week depending on the need by the patient or caregiver who received training, or by the nurse. If patient changed the dressing, then nursing oversight was conducted every two weeks.</p> <p>The study reported that off-loading was variable, and 42% of participants were issued the preferred casting device, two centers issued no casting devices, one center issued 1.</p>
	Outcomes	<p>1) Proportion of ulcers healed</p> <p>A) 46/103 = 0.447</p> <p>B) 48/108 = 0.444</p>

		<p>C) $41/106 = 0.387$</p> <p>No statistically significant difference (p=0.38)</p> <p>2) Proportion of ulcers recurring</p> <p>A) $3/103 = 0.029$</p> <p>B) $7/108 = 0.065$</p> <p>C) $3/106 = 0.028$</p> <p>3) Time to healing</p> <p>A) 125.8 +/- 55.9 days</p> <p>B) 127.8 +/- 54.2 days</p> <p>C) 130.7 +/- 52.4 days</p> <p>No statistically significant difference (p=0.80)</p> <p>4) Proportion amputated</p> <p>A) $4/103 = 0.039$</p> <p>B) $1/108 = 0.009$</p> <p>C) $2/106 = 0.019$</p> <p>Statistical significance not reported.</p> <p>5) Proportion infected</p> <p>A) $54/103 = 0.524$</p> <p>B) $71/108 = 0.657$</p> <p>C) $48/106 = 0.453$</p>
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		<p>Statistical significance not reported</p> <p>6) Treatment cost</p> <p>A) 194.03</p> <p>B) 184.17</p> <p>C) 141.1</p> <p>Statistical significance not reported</p> <p>7) Quality of life index</p> <p>A) 0.382</p> <p>B) 0.384</p> <p>C) 0.394</p> <p>No statistically significant difference (p=NS)</p>
	Notes	<p>Other outcomes reported:</p> <p>Hospital stay</p> <p>A) Median 23 days (7-42 days), SD = 8.26</p> <p>B) Median 13 days (7-56 days), SD = 14.54</p> <p>Statistically significant difference (p<0.001)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported to be stratified by center, size, using block size of nine design. Randomization was also stratified across the whole population by ulcer area in three groups. The study reports that randomization lists were created using statistical software.

Allocation concealment (selection bias)	Low risk	The randomization lists and records of the allocation details were reported to be held at a central location and each recruiting center telephoned.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports that the clinician in charge of care and assessing for healing was blinded to the randomization group.
Incomplete outcome data (attrition bias)	Low risk	<p>The authors reported that 88 participants (27.8%) out of the 317 enrolled were withdrawn. The reasons for withdrawal were reported as:</p> <p>Adverse event = 35</p> <p>Protocol violation = 24</p> <p>Loss to follow up = 7</p> <p>Consent withdrawal = 16</p> <p>Death = 5</p> <p>Other = 1</p> <p>Intention to treat analysis was carried out using last observation carried forward.</p>
Selective outcome reporting (reporting bias)	Low risk	No protocol was available or referred to in the study. The outcomes reported in the results were pre-specified in the methods section.
Other Bias	High risk	The study reported 88 withdrawals out of 317 participants, last observation carried forward was utilized as intention to treat. This may have biased the results in either direction.
Notes		

16. Jensen 1998	Methods	<p>RCT; Randomized into 2 groups.</p> <p>Study period was not reported. Follow up period was 20 weeks.</p>
	Participants	<p>31 patients</p> <p>A) 14</p> <p>B) 17</p> <p>No description of age, sex, type of diabetes, or disease severity was reported.</p> <p>Wound area measured at baseline.</p> <p>Average duration of ulceration</p> <p>A) 8.9 months</p> <p>B) 3 months</p>
	Interventions	<p>A) Carrasyn hydrogel wound dressing (CHWD) cleansed with ULTRAKLENZ wound cleanser.</p> <p>B) Wet-to-moist saline gauze cleansed with ULTRAKLENZ wound cleanser.</p> <p>Adjunctive wound care included all patients who initially received sharp debridement to remove all non-viable (dead) tissue and all patients received custom made healing sandals for pressure redistribution. Dressings changes were conducted daily. Saline moist gauze remoistened as needed. Patients evaluated weekly using wound tracings and computer planimetry.</p>
	Outcomes	<p>1. Proportion with complete wound healing at 16 weeks (Defined as 100% wound re-epithelialization)</p> <p>A) 11/13 84.6%</p> <p>B) 6/13 46.1% P=0.05</p>

		<p>2. Time to complete healing</p> <p>A) 10.3 weeks *</p> <p>B) 11.69 weeks *</p> <p>3. Proportion with amputation</p> <p>A) 0/14 = 0</p> <p>B) 1/17 = 0.059</p> <p>4. Proportion with Infection</p> <p>A) 2/14 = 0.143</p> <p>B) 1/17 = 0.059</p> <p>5. Cost</p> <p>A) 7.01 - (\$/day)</p> <p>B) 12.28 - (\$/day)</p>
	Notes	<p>* It is unclear if these are mean or median times to healing. 13/14 patients completed the study in the Hydrogel group whereas 13/17 completed the study in the control group.</p> <p>Other outcomes that were reported in this study included:</p> <p>Complications</p> <p>A) 2/14 (14%)</p> <p>B) 4/17 (24%)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported but method of sequence generation not specified.

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	5 patients dropped out (n=1 in Group A; n=4 in Group B): no intention-to-treat analysis or other method of handling missing data were specified.
Selective outcome reporting (reporting bias)	Unclear risk	No protocol available. No parameters clearly pre-specified as outcomes in the methods section.
Other Bias	High risk	No Group A and Group B data reported on ulcer size, depth, on entry to trial other than ulcer with minimum of 1cm diameter; and Wagner grade II thickness. However, the trial report suggests that Group A had average ulcer duration of 8.9 months compared with 3 months for group B. Study supported by an educational grant from Carrington Laboratories, Inc. (the manufacturers of Carrasyn).
Notes		

17. Lalau 2002	Methods	<p>Open - label multicenter randomized controlled trial.</p> <p>Study reported 13 centers throughout France participated.</p> <p>Number of wound dressings and adverse events recorded weekly. Follow up visits scheduled at weeks 1, 2, 4, 6 to monitor healing efficacy and safety.</p> <p>Planimetric evaluation used for surface area.</p> <p>The study reported a 6-week treatment period, though efficacy analysis was reduced to 4 weeks due to premature cessation of treatment in 13 patients. Reported that there was no revision to efficacy criteria.</p> <p>The study reported that conservative management was carried out using pressure relieving methods.</p>
	Participants	<p>77 patients enrolled, 13 withdrawn</p> <p>#, Gender, Age, BMI, DM type, Diabetes duration, HgbA1c, # revascularizations, TcPO2,</p> <p>A) 39, 22M/17F, 60.8 +/- 10.7 yrs., 27.6 +/- 5.11, 15/24, 19.2 +/- 11.8 yrs., 7.6 +/- 2.0, 13, 44.6 +/- 12.3</p> <p>B) 38, 23M/25F, 63.5 +/- 12.8 yrs., 27.3 +/- 5.52, 16/22, 16.9 +/- 8.9 yrs., 7.9 +/- 1.5, 4, 42.6 +/- 10.3</p> <p>No statistically significant difference in participants except for # revascularizations.</p>
	Interventions	A) Calcium Alginate

		<p>B) Vaseline Gauze</p> <p>The study reported daily dressing changes initially until thoroughly debrided, then once granulation occurred, every 2 - 3 days depending on exudate amount as determined by nurses. The authors reported no other local treatments except unrestricted saline.</p> <p>The study reported that mechanical debridement was authorized as necessary.</p>
	Outcomes	<p>Proportion of infections</p> <p>A) $1/39 = 0.026$</p> <p>B) $3/38 = 0.079$</p>
	Notes	<p>Proportion of patients with granulation tissue > 75% of wound area, and a 40% decrease in wound surface area. Secondary outcomes included: pain on dressing changes, cumulative number of dressing changes, and number of adverse events. All were reported not to be statistically significant except for pain and cumulative number of dressing changes in favor of calcium alginate.</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization of participants was reported. The method of random sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reported that an independent investigator, blind to the allocated treatment, was assigned to analyze wound surface areas. Analysis reportedly performed two times for each patient, and a third as warranted.

Incomplete outcome data (attrition bias)	Unclear risk	77 patients enrolled, and 64 completed the study for the full 6 weeks. 13 withdrawals - 1 consent withdrawal, and 4 adverse events in the Calcium Alginate group, 1 ineffective treatment, 1 aggravation, and 6 adverse events in the Vaseline group. The study reports that due to the loss of data as a result of the 13 withdrawals the study was shortened to efficacy analysis at 4 weeks.
Selective outcome reporting (reporting bias)	Low risk	No protocol was reported in the study. Outcomes pre-specified in the methods section were reported in the results section.
Other Bias	High risk	The revascularizations were reportedly higher in the Calcium Alginate group. Sub group analysis on acute versus chronic lesions was also reported but demonstrated no statistically significant difference. Most of the lesions were chronic and reportedly may have been more refractory to treatment.
Notes		

18. Markevich 2000	Methods	RCT; Multi-centered; Double-blind Study period not reported, follow up period was 10 days
	Participants	140 patients, A) 70 B) 70 Average Age: 53.6 +/- 15.4 years. Average duration of Diabetes: 15.8 +/- 10.7 years No description of sex, type of diabetes, disease severity, infection status, offloading status, or wound grade, other than qualitative statement that depth and volume were comparable at baseline between both groups.
	Interventions	A) Larval therapy (green bottle fly - <i>Lucilia sericata</i> 6-10 larva per 1 cm ² of wound surface area) removed after 72 hours B) Hydrogel (no data on frequency of dressing change)
	Outcomes	Complete healing (no data as to time this took) A) 5/70 (7.1%) B) 2/70 (2.8%) (no report of whether this was a statistically significant difference was mentioned)
	Notes	A) Average Surface area of wound 14.9 cm ² B) Average Surface area of wound 15.14 cm ² (no statistically significant difference)

		<p>Qualitatively reported in abstract that surface area, depth and volume, surrounding skin, tissue quality, exudate, odor, and glucose levels were comparable at baseline but no numerical data were provided.</p> <p>Assessments reported every 3 days during first 10 days.</p> <p>At 10 days granulation tissue covering 50% of wound was higher in larval therapy (60% vs 34.3%; $p<0.001$ statistically significant difference)</p> <p>Proportion of patients with greater than 50% reduction in wound area was higher in the larval group than in the hydrogel group (51.1% vs 27.1% $p<0.05$, statistically significant difference)</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only - Randomization reported but method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	<p>N.B. RCT described as "double-blind" by study authors but no further detail given.</p> <p>Blinding of participants - not reported (published abstract only): This may be difficult due to nature of treatments - larval therapy vs. hydrogel.</p>
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel - not reported (published abstract only): This may be difficult due to nature of treatments - larval therapy vs. hydrogel.

Blinding outcome assessors	Unclear	Blinding of outcome assessors: not reported (published abstract only).
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data were not reported, if incomplete outcome data were present then assessment and how outcome data were addressed is not discernible.
Selective outcome reporting (reporting bias)	Unclear risk	Published abstract only - selective reporting not discernible.
Other Bias	Unclear risk	Published abstract only - other bias not discernible.
Notes		

19. Mazzone 1993	Methods	RCT, Method of random sequence generation was not reported.
	Participants	19 A) 11 B) 8 No data on age, sex, or other patient specific demographics or characteristics were reported.
	Interventions	A) Polymeric membrane foam dressing B) Wet to Dry saline gauze mesh dressing
	Outcomes	Complete healing (no data on the time to this endpoint reported) A) 5/70 (7.1%) B) 2/70 (2.8%) (no report of whether this was a statistically significant difference was mentioned)
	Notes	Wound size reduction was reported as well. No other information on other risk factors such as diabetes type, duration, or disease severity was reported. No data reported on wound size or grade between treatment groups.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports randomization however method of random sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported

Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Unclear risk	Not discernible; abstract only available.
Other Bias	High risk	No data were reported on study participant characteristics between treatment groups, nor on other risk factors such as diabetes type, duration, or disease severity. No data reported on wound size or grade between treatment groups.
Notes		

20. Munter 2006	Methods	<p>Randomized controlled trial</p> <p>Duration = 4 weeks</p> <p>Reported that patients were assessed weekly at wound clinic as judged necessary.</p> <p>Study reports that participating clinics used same clinical guidelines and data-collection forms.</p>
	Participants	<p>619 patients, Multi-etiology ulcers</p> <p>Mean age = 55.2 +/- 9.4 yrs., Duration of diabetes = 14.8 yrs.</p> <p># Age Gender M/F (%),</p> <p>A) 326, 69.8 +/- 13.7 yrs., 38/62</p> <p>B) 293, 68.8 +/- 14.1 yrs., 39/61</p>
	Interventions	<p>A) Silver releasing hydrophilic polyurethane foam dressing</p> <p>Mean dressing changes = 3.1 days</p> <p>B) Local Best Practice (Study reports that this ranged from gauze, moist wound healing, wound healing products, to antimicrobial treatments)</p> <p>Mean dressing changes = 2.1 days</p> <p>Wound management included compression therapy.</p> <p>DFU's comprised 8% of Silver and 8% Local best practice group</p>
	Outcomes	<p>The study conducted a subgroup analysis for diabetic foot ulcers. The study reported one of the outcomes of interest for this review, quality of life. The authors did not specify the results of this outcome for the subgroup of diabetic foot ulcers instead</p>

		it was reported that the results were comparable for all parameters between the two treatment groups, except for wound progress, exudate, and odor.
	Notes	The study reported other outcomes such as ulcer area reduction, slough, wound progress, maceration, exudate, leakage, ease of dressing use and time spent, malodor, pain, and cost effectiveness.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports open prospective parallel, block randomized evaluation. Specific method of sequence generation was a computer generated list.
Allocation concealment (selection bias)	Unclear risk	The study reports that the computer generated sequence list was in sealed envelopes.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	The study reports that in order to include patients in the analysis all missing data were addressed with last observation carried forward and obtained data were analyzed as intention to treat.
Selective outcome reporting (reporting bias)	Low risk	There was no protocol available or reported in the study. The outcomes reported in the outcomes section were pre-specified in the methods section.
Other Bias	High risk	The study reports private financial support.
Notes		

21. Ogce 2007	Methods	<p>Randomly assigned</p> <p>30 days' study duration</p> <p>Weekly follow up with 4 follow ups. Study reports that participating clinics used same clinical guidelines and data-collection forms.</p>
	Participants	<p>60 patients, Gender = 36M/24F, mean age = 59.85, Hgb1c = 7.73, BMI = 25.06 24.47</p> <p>#, DM Type (1/2) Mean Age Hgb1c</p> <p>A) 30, 0.867/0.133 59.47 yrs., 7.60%,</p> <p>B) 30, 0.733/0.267 60.23 yrs., 7.86%</p>
	Interventions	<p>A) Hydrocolloid dressing (combined with paste for wound cavities, and powder for infection)</p> <p>B) Classic wound dressing</p> <p>Daily dressing changes</p>
	Outcomes	The study reported that healing was much better and faster in the experimental group.
	Notes	The article was only available in Turkish and was translated through the use of Google translate as were all non-English language publications that were retrieved through our search and accepted in this review. The translation was of higher quality for some languages and difficult in others. This study was among those that was difficult to translate. This posed a limitation in data extraction.
Risk of bias table		
Bias	Authors' judgment	Support for judgment

Random sequence generation (selection bias)	Low risk	Random assignment reported but method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	No protocol was available or reported in the study. The outcomes reported in the results were not explicitly pre-specified in the methods section.
Other Bias	Unclear risk	Limited reporting.
Notes		

22. Piaggese 2001	Methods	<p>Study duration = 8 weeks</p> <p>All subjects initial surgical debridement + postoperative pressure relieving shoes + crutches</p> <p>Weekly assessments:</p> <p>Photographed lesions traced on acetate film to measure maximal dimensions.</p> <p>Wound depth measured by probe and volume by gel.</p>
	Participants	<p>24 identified, 20 enrolled, 4 withdrawn</p> <p>A) 10, 61.3 +/- 7.5 years</p> <p>Duration of diabetes = 16.1 +/- 8.9 years</p> <p>HgbA1c = 8.9 +/- 3.1%</p> <p>ABPI = 1.0 +/- 0.2</p> <p>B) 10, 63.1 +/- 4.6 years,</p> <p>Duration of diabetes = 14.8 +/- 6.2 years</p> <p>HgbA1c = 8.1 +/- 2.7%</p> <p>ABPI = 1.1 +/- 0.3</p>
	Interventions	<p>A) Saline moistened gauze (renewed twice daily with saline to prevent drying)</p> <p>B) Sodium Carboxy-Methyl Cellulose Hydrofiber (Aquacel) changed every 2nd or 3rd day depending on extent of exudate produced by wound.</p> <p>Dressing changes by trained relative or visiting nurse.</p>
	Outcomes	1) Proportion healed

		<p>A) $10/10 = 1$</p> <p>B) $9/10 = 0.90$</p> <p>2) Healing Time</p> <p>A) 234 +/- 61 days</p> <p>B) 127 +/- 46 days</p> <p>Statistically significant difference</p> <p>3) Proportion with Infection</p> <p>A) $1/10 = 0.30$</p> <p>B) $3/10 = 0.10$</p> <p>4) Proportion amputations</p> <p>a) $1/10$</p> <p>b) $0/10$</p> <p>No statistically significant difference</p>
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study reports random assignment but specific method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	Reported that blindly evaluated by one of the authors.
Incomplete outcome data (attrition bias)	High risk	24 eligible patients, 20 enrolled and randomized. 2 refused consent, 1 due to missed visits, 1 due to neuro-osteoarthropathy.
Selective outcome reporting (reporting bias)	Low risk	The study states a protocol was written and submitted to an ethics committee however this was unavailable, however the methods section reported the outcomes to be studied including: 1) rate of

		reduction in lesion volume, 2) rate of granulation tissue, 3) infective complications, and 4) healing time. These outcomes are reported in the results section. Proportion requiring amputation was also reported that was not in methods section.
Other Bias	Unclear risk	Reported that manufacturers not involved in any part of experiment. Amputations reported but difficult to determine if in same individuals or different individuals based on the report. Unclear if groups were balanced for other risk factors.
Notes		

23. Piaggese 1998	Methods	<p>Randomized into 2 treatment groups</p> <p>Study period 1995. Follow up period was 24 weeks. Patients were followed twice a week.</p>
	Participants	<p>42 patients with 46 ulcers</p> <p>A) 22 patients, (17 NIDDM / 3 IDDM), 24 ulcers</p> <p>Mean age = 63.24 +/- 13.46 years</p> <p>Duration of diabetes = 18.2 +/- 8.41 years</p> <p>HgbA1c = 9.5 +/- 3.8%</p> <p>B) 24 patients, (19 NIDDM / 2 IDDM), 22 ulcers</p> <p>Mean age = 65.53 +/- 9.87</p> <p>Duration of diabetes = 16.84 +/- 10.61 years</p> <p>HgbA1c = 8.9 +/- 2.2%</p> <p>No description of sex</p> <p>Baseline wound area measurement not reported.</p>
	Interventions	<p>A) Control - Non-surgical conventional treatment including pressure relief and regular dressing (type of dressing not reported).</p> <p>B) Treatment - Surgical debridement, removal of bone segments</p>
	Outcomes	<p>1. Complete healing at 6 months: Group A = complete re-epithelialization of lesions; Group B = formation of continuous scar</p> <p>A) 19/24 (79%)</p> <p>B) 21/22 (95%)</p>

		<p>2. Healing time</p> <p>A) 48.7 +/- 36.99 days</p> <p>B) 130.38 +/- 90.49 days</p> <p>4. Recurrence rate</p> <p>A) 8/24 (33%)</p> <p>B) 3/22 (14%)</p> <p>5. Infective complications</p> <p>A) 3/24 (13%)</p> <p>B) 1/22 (5%)</p> <p>6) Amputations</p> <p>A) 1/24 = 0.04</p> <p>B) 0/22 = 0</p>
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Exact sequence generation not reported: "a table of randomization".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	<p>Non-surgical debridement and pressure relief vs. surgical debridement.</p> <p>Blinding of participants difficult due to nature of treatments – nonsurgical control vs. surgical intervention.</p>
Blinding personnel delivering intervention	Unclear risk	<p>Blinding of personnel: difficult due to nature of treatments - non-surgical control vs. surgical intervention.</p> <p>Yes - Group A. Physicians and nurses treating Group A (control) patients were unaware of their patients' involvement in the trial: "the whole treatment course of group A patients from initial</p>

		<p>debridement to follow-up visit was performed by physicians and nurses unaware of the participation of patients in the study, and did not differ from the standard protocol of treatment of non-complicated neuropathic ulcerations in our foot clinic".</p> <p>Unclear - Group B. It was not reported if personnel for the Group B (intervention) were aware of their patients' participation in the trial.</p>
Blinding outcome assessors	Unclear risk	Blinding of outcome assessors: unclear who conducted outcome assessment for both Groups (A and B).
Incomplete outcome data (attrition bias)	Unclear risk	Patient numbers at follow-up were not reported.
Selective outcome reporting (reporting bias)	Low risk	Four parameters were pre-specified as outcomes, all of which were reported.
Other Bias	High risk	Group B given antibiotics 5 days after surgery: "general therapy for group B patients differed from group A in that systemic parenteral therapy with wide-spectrum antibiotics was given 5 days after surgery, according to the protocols of our hospital for the prophylaxis of nosocomial infection".
Notes		

24. Rhaiem 1998	Methods	Randomization of subjects into 3 groups Study period was 1992 - 1995, Follow-up period was 40 +/- 13 days
	Participants	80 patients, Gender 59M/21F, DM type 1/2 = 61/19, mean age = 56 +/- 32 yrs. (26 - 89), diabetes duration = 13 +/-10.6 yrs. (1 - 26) yrs., peripheral neuropathy 74.6%, smokers 55%, Alcohol users 21%, infected wounds at baseline = 51.7% G1: 16 patients G2: 24 patients G3: 40 patients
	Interventions	3 treatment groups: A) G2: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy + local applied Jam sugar B) G3: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy (40 patients) C) G1: cleaning ulcers with hydrogen peroxide 3% + local applied Jam sugar
	Outcomes	In groups 1 and 2 (using sugar): 47.5% of ulcers healed, compared with group 3 in which 40% of ulcers healed with a mean delay respectively of 6 and 9 weeks. Proportion healed A) G1 and G2 = 0.475 B) G1 = 0.40 Not a statistically significant difference.

	Notes	This study was translated using Google translate from French into English.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports randomization, but does not specify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	High risk	The study does not report whether a protocol was pre-established. The methods section of the study does not pre-specify the outcomes reported in the results section.
Other Bias	High risk	The study does not explicitly report whether the subjects received off-loading. It is not mentioned in the study how the determination of ischemic wounds was established. The study does not clarify. The study reports the combined healing proportion for the G1 and G2 groups, it does not report the proportion separately. The study reports that 51.7% of wounds were infected, no information was provided on whether infected or ischemic wounds were balanced between the 3 treatment groups.
Notes		

25. Roberts 2001	Methods	<p>RCT</p> <p>Dressing changed and wound assessment with tracings were reported to occur weekly.</p> <p>Study duration was 13 weeks</p>
	Participants	<p>30 patients 23M/7F</p> <p>Type 1 DM</p> <p>Median Age = 59.5 years Range (37-77)</p> <p>Neuropathic ulcers of the plantar surfaces.</p> <p>Median wound size for sample was 123 mm², range (21 - 350 mm²)</p> <p>Median wound size for Hydrocellular foam was 114.5 mm² and 144.5 mm² for saline soaked low adherent dressing.</p> <p>Median Wound duration 15.2 weeks, range (1 week - 6 years)</p> <p>ABPI < 0.8</p> <p>A) 14</p> <p>B) 16</p>
	Interventions	<p>A) Allevyn hydrocellular foam dressing</p> <p>B) Saline soaked (low adherent) dressing and standard podiatric care</p>
	Outcomes	<p>1) Proportion healed over 13 weeks</p> <p>A) 6/14 = 43%</p> <p>B) 4/16 = 25%</p> <p>2) Time to healing - Not significantly different between both groups p = 0.325</p>

	Notes	<p>The study also reported the proportion of patients in each group that demonstrated a 50% area reduction over 13 weeks:</p> <p>A) $13/14 = 93\%$</p> <p>B) $12/16 = 75\%$</p> <p>The study reports that after adjusting for covariate risk factors: age, sex, ulcer size and duration, the hydrocellular dressing was associated with a significantly faster response ($p=0.013$), than saline soaked (low adherent) dressing.</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported however method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	Published abstract only - blinding not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only - blinding not reported.
Blinding outcome assessors	Unclear risk	Published abstract only - blinding not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data not reported.
Selective outcome reporting (reporting bias)	High risk	Not clear that a protocol was available and methods did not pre-specify outcomes reported.
Other Bias	High risk	<p>Published abstract only - other bias not discernible.</p> <p>Unclear if risk factors such as diabetes disease severity or others were balanced between the two intervention groups. Depth of wound between intervention groups was not reported. Study supported by an educational grant from manufacturer Smith & Nephew - Group Research Centre).</p>

Notes		
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26. Shukrimi 2008	Methods	Wagner grade II diabetic foot ulcers Wound assessments every other day by a surgeon blinded to the material of the dressing.
	Participants	30 patients (31-51 yrs.), 15M/15F, mean age = 52.1 yrs. (31-65 yrs.), TcPO2 mean = 39 mmHg (36 - 42 mmHg)
	Interventions	A) Honey dressing B) Standard dressing (Povidone Iodine/Normal saline, 1:10) All patients received antibiotics and ulcers debrided initially surgically (debridement specimens were sent for culture) Wound dressing started on first postoperative day by nurses and reported as daily dressing changes.
	Outcomes	The outcomes of interest for this review were not reported in this study. The study reported the cost to buy a bottle of commercial honey. The study reported that a bottle of honey could be used for the entire period of study. No other information on cost was provided on the standard dressing.
	Notes	Other outcomes reported include: Time to healing for surgical closure A) 14.4 days (7-26 days) B) 15.4 days (9-36 days) Statistically significant difference (p<0.005) The study reported all patients had less pain in the honey group.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The authors report randomization. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.

Blinding participants	Unclear risk	Not reported.
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Low risk	The study authors reported blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	High risk	No protocol was reported in the study. The outcomes reported in the results section including wound culture results and time to healing for surgical wound closure was reported in the methods section. Cost was reported in the results section but was not pre-specified in the methods section.
Other Bias	Unclear risk	No information on diabetes disease severity such as HgbA1c or duration of diabetes was reported.
Notes		

27. Singh 2006	Methods	<p>Randomized clinical trial</p> <p>Ulcers x-ray to exclude Osteomyelitis</p> <p>Duration: two weeks</p> <p>First assessment at first day of debridement and again at day fourteen.</p>
	Participants	<p>59 patients - 60 ulcers, 33M/27F, DM type 1/2 = 5/55, mean age = 56.87 +/- 11.06 yrs.</p> <p>A) 33, 5/28</p> <p>B) 27 0/27</p>
	Interventions	<p>A) Non-contact Ultrasonic debridement (24 KHz) performed every other day</p> <p>B) Sharp/surgical debridement conducted every other day</p>
	Outcomes	None of the outcomes of interest for this systematic review were reported in the study.
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports the subjects were randomized into the two treatment groups. The specific method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports that assessment was done by two independent observers who were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	Low risk	No protocol was available or reported in the study. The outcomes reported in the results section were pre-specified in the methods section.

Other Bias	Unclear risk	The authors did not report other important risk factors for wound healing including disease severity and off-loading status.
Notes		

28. Tallis 2013	Methods	<p>Randomized controlled parallel group multicenter open-label study</p> <p>Duration 12 weeks, patients seen weekly.</p> <p>Wounds are measured with length of long axis times greatest width perpendicular to long axis.</p>
	Participants	<p>48 patients, 32M/16F, 61 +/- 11.8 yrs., 45 Caucasian 3 AA</p> <p>A) 24, 16M/8F, 58.5 +/- 13.3 yrs., 22 Caucasian 2 AA</p> <p>B) 24 16M/8F, 63.5 +/- 9.8 yrs., 23 Caucasian 1 AA</p> <p>No statistically significant difference in demographics, including race.</p>
	Interventions	<p>A) Clostridial Collagenase Ointment (CCO)</p> <p>B) Saline Moistened Gauze (SMG) + Selective Sharp Debridement</p> <p>Randomized to both groups after baseline surgical debridement and 6.9 mean debridement in total for the SMG group.</p>
	Outcomes	<p>1) Direct mean costs per responder</p> <p>Physician office Wound clinic facility</p> <p>A) \$832 \$1607</p> <p>B) \$1042 \$1980</p> <p>Cost effectiveness analysis was used.</p>
	Notes	.
Risk of bias table		
Bias	Authors' judgment	Support for judgment

Random sequence generation (selection bias)	Low risk	The study reports a computer-generated randomization sequence.
Allocation concealment (selection bias)	Low risk	The study reports randomization was centralized and for or each qualified patient investigative sites contacted the central call center for the next sequential pre-determined treatment assignment.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	The study reports that 8 patients discontinued the study. The authors reported that an Intention to treat analysis was used. Specifically, last observation carried forward was utilized for missing wound area measurements at any of the weeks resulting from wound healing, early discontinuations, or for any other reasons.
Selective outcome reporting (reporting bias)	Low risk	No protocol was available for review or was reported in the study. The outcomes reported in the results section were pre-specified in the methods section.
Other Bias	High risk	The study reports that a total of 23 patients (28 in the CCO group, and 33 in the SMG group) in the study experienced 61 treatment-emergent adverse events. The specific nature of the events was not specified other than the adverse events were reported to be similar in the treatment groups and unrelated to the treatment.
Notes		

29. Vandeputte 1997	Methods	Pre-prepared randomization listing Study period was not reported. Follow up period was 12 weeks. Patients were followed up every 4 weeks.
	Participants	29 patients with 30 wounds A) 15 patients (15 wounds) B) 14 patients (15 wounds) No description of age, sex or type of diabetes. Baseline wound area measurement not reported.
	Interventions	A) Hydrogel B) Dry gauze (control) includes moistened gauze with antiseptic. Other ancillary wound care measures not reported.
	Outcomes	Complete Healing at 3 months A) 14/15 (93%) B) 7/14 (50%) Infective complications A) 1/15 (7%) B) 7/14 (50%) Amputations A) 1/15 B) 5/14
	Notes	Other outcomes reported included: Peri-ulcer maceration A) 11.6% B 22.1% Low grade skin reactions/allergies reported

		qualitatively in both groups, no numerical data provided.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Specific sequence generation procedure was not reported: "patients were allocated to treatment groups according to a pre-prepared randomization listing".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Blinding of participants was unclear in the report.
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel delivering intervention was unclear.
Blinding outcome assessors	High risk	Blinding of outcome assessors: no - same nurses as personnel and outcome assessors.
Incomplete outcome (attrition bias)	Unclear risk	<p>Lack of clarity concerning patient deaths in control group.</p> <p>Methods and Results sections report control group as n=14. Results section states: "one patient of the control group died. One patient had a wound on both legs. The number of legs treated was 30 (15 in each group)".</p> <p>Two deaths in the control group are reported in the 'Overall healing time' Table 5 in the Results section: '2 - died during trial' in the control group, although the total participants remains stated as n=14.</p>
Selective outcome reporting (reporting bias)	Low risk	Nine parameters were pre-specified as outcomes, all of which were reported.
Other Bias	High risk	Author had an affiliation with wound product manufacturer.
Notes		

30. Whalley 2001	Methods	RCT Randomized into 2 comparison groups Study period not reported, follow up period was 10 weeks.
	Participants	74 patients; (66 patients evaluated) no further data were available including how many patients allocated to each group. Age 55.2 +/- 9.4
	Interventions	A) Purilon Hydrogel B) Intrasite Hydrogel using Biatain Non-adhesive dressing (Coloplast A/S) as a secondary dressing Dressings changed at least every second day
	Outcomes	1. Complete healing at 10 weeks A) 35% healed B) 19% healed No report of whether this was a statistically significant difference. 2. Change in mean wound area A) 2.5 cm ² (SD 3.2) to 0.6 cm ² (SD 1.1) B) 2.4 cm ² (SD 2.9) to 1.0 cm ² (SD 1.8)
	Notes	Offloading reported in both groups. Abstract only; limited data Other outcomes reported included: Peri-ulcer maceration

		<p>A) 11.6%</p> <p>B 22.1%</p> <p>Low grade skin reactions/allergies reported qualitatively in both groups, no numerical data provided.</p>
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only - Randomization reported but method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding outcome assessors	Unclear risk	Published abstract only - allocation concealment not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data were reported but assessment and how outcome data were addressed is not discernible. "66 patients were evaluable" from the 74 patients recruited.
Selective outcome reporting (reporting bias)	Unclear risk	Published abstract only - selective reporting not discernible.
Other Bias	Unclear risk	Published abstract only - other bias not discernible.
Notes		

Characteristics of excluded studies

Abbruzzese 2009

Reason for exclusion	Both groups received debridement.
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Abdelatif 2008

Reason for exclusion	Nonrandomized study
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Aceechurovai 2003

Reason for exclusion	Nonrandomized study
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Aftab 2010

Reason for exclusion	Soft tissue laser intervention in this study was not used as a form of debridement.
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Ahroni 1993

Reason for exclusion	Surgical debridement was reported as being carried out routinely throughout study on both treatment arms.
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Apelqvist 1994

Reason for exclusion	Varidase is used as a debriding agent but no separate data were available for this group of patients. If such data had been available, the size of the study (n=17) is unlikely to be sufficiently powered.
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Apelqvist 1996

Reason for exclusion	Authors report that both treatment groups received surgical debridement performed during the course of the study indicating that debridement was not the primary focus of this study.
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Armstrong 2000

Reason for exclusion

Although all wounds were debrided the primary intervention measured was a foot compression system, there was no comparison or conclusions drawn regarding the debridement methods used.

Ashry 1998

Reason for exclusion

Not an RCT on debridement but a cost related archival analysis on amputations among in diabetic minority groups.

Bahrami 2008

Reason for exclusion

Intervention was not a form of debridement but an oral herbal preparation.

Berry 1996

Reason for exclusion

Randomized study on the debridement of cavity wounds not diabetic foot ulcers.

Biliaieva 2009

Reason for exclusion

This was a non-randomized study investigating absorptive dressings.

Bowling 2007

Reason for exclusion

This was a non-randomized study - case series investigating larval therapy.

Brenes 2011

Reason for exclusion

This was a non-randomized study - case series on hyaluronate iodine.

Caputo 2009

Reason for exclusion

The study does not report outcomes separately for diabetic and other wound types.

Cardinal 2009

Reason for exclusion	Non-randomized retrospective study of healing rates as predictors of complete wound closure.
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Chan 2007

Reason for exclusion	Systematic review of Maggot debridement therapy not RCT.
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Chiglashvili 2004

Reason for exclusion	Non-randomized study - case series not on debridement but IV infusion of complex medical regimen.
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Clavel 2008

Reason for exclusion	Narrative review article on preventing amputations in diabetics.
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Davydov 2011

Reason for exclusion	Narrative review article on Larval therapy.
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Dekhtiar 1995

Reason for exclusion	Non-randomized case series.
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Dereure 2012

Reason for exclusion	RCT on Venous leg ulcers and Mixed etiology ulcers using Hyaluronic acid.
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Ennis 2005

Reason for exclusion	Study utilized another form of debridement in both treatment arms.
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Freeman 2010

Reason for exclusion	Non-randomized study of bee honey.
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Gelunenko 2000

Reason for exclusion

The intervention under study is an oral immune modulating agent not a form of debridement.

Gottrup 2001

Reason for exclusion

This is a cost evaluation paper. Not an RCT.

Gough 1997

Reason for exclusion

RCT which compares granulocyte stimulating factor, with a placebo. There is no debriding agent included in the trial.

Graham 2014

Reason for exclusion

The study involved wounds of varying etiologies and was a non-randomized case series study on Oakin dressing.

Grayson 1994

Reason for exclusion

RCT assessing the effectiveness of Imipenem / Cilastatin against ampicillin / Sulbactam in the treatment of pedal infections in diabetic. No debriding agent was considered.

Holtzer 1998

Reason for exclusion

This study was not an RCT but an archival data analysis.

Jan 2012

Reason for exclusion

This study was not an RCT but was reported as a quasi-experimental study.

Jude 2007

Reason for exclusion

Standardized surgical debridement was used regularly in both treatment arms concurrently as part of standard care.

Jude 2004

Reason for exclusion

RCT of 120 people that compares silver based fiber dressing with an alginate, alternate form of debridement confounded both arms.

Kaviani 2011

Reason for exclusion

The laser therapy was not used here for debridement but to stimulate growth. Debridement was carried out separately.

Khramilin 2011

Reason for exclusion

Narrative review article not an RCT.

Krupski 1991

Reason for exclusion

RCT which compared platelet derived wound healing with a placebo. Although all wounds were extensively debrided initially, there were no debriding agents included in the trial. The trial sample was 'mixed ulcers' - with leg ulcers mainly identified.

Krymets 2013

Reason for exclusion

Non-randomized study not an RCT.

Kuo 2012

Reason for exclusion

Randomized study on the use of herbal botanical anti-inflammatory creams. These herbal botanicals were not used as a form of debridement.

Li 2006

Reason for exclusion

Growth factors as focus of RCT. (Debridement to aid growth factor only).

Logachev 2001

Reason for exclusion

Nonrandomized study - Case series.

Macleod 1991

Reason for exclusion	Not an RCT.
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Martinez-de-Jesus 1997

Reason for exclusion	RCT where all foot ulcers underwent surgical debridement and were then treated with either topical Ketanserin or normal saline (placebo). Excluded as the topical treatment, although gel based was compounded by the fact that it contained Ketanserin gel.
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Metha 1999

Reason for exclusion	Review article on cost using claims data.
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Mohajeri 2014

Reason for exclusion	Though topical Kiwifruit possesses debridement properties both treatment arms of the study were subjected regularly to surgical debridement concurrently throughout the study.
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Moore 2011

Reason for exclusion	Systematic review on Silver dressings but in mixed etiology wounds, not restricted to diabetic foot ulcers.
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Moretti 2009

Reason for exclusion	Study on shock wave therapy which was not used for debridement but for angiogenesis. Debridement was conducted similarly in both groups.
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Motley 2014

Reason for exclusion	Serial sharp debridement was carried out on both treatment arms with and without enzymatic debridement.
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Mulder 1994a

Reason for exclusion

RCT comparing lamin gel with standard care and vehicle gel. The lamin gel contains a peptide copper complex, which has been shown to be a chemoattractant for capillary endothelial cells and stimulates angiogenesis. It is therefore not a debriding agent.

Mulder 2005

Reason for exclusion

RCT comparing lamin gel with standard care and vehicle gel. The lamin gel contains a peptide copper complex, which has been shown to be a chemoattractant for capillary endothelial cells and stimulates angiogenesis. It is therefore not a debriding agent.

Naidu 2005

Reason for exclusion

Study did not pertain to debridement but on off-loading of callus.

Nielsen 2012

Reason for exclusion

Nonrandomized study on surgical wounds and not specific to diabetic patients.

Oluwatosin 2000

Reason for exclusion

Intervention was not a comparison between forms of debridement but included a comparison Phenytoin.

Pettican 2012

Reason for exclusion

This study was not an RCT but a Non-randomized study on larval therapy, specifically a case series.

Pollak 1997

Reason for exclusion

RCT which assesses the effectiveness of human dermis replacement against conventional treatment. There is initially sharp debridement, but there is no debriding agent assessed in the trial.

Ramsey 1999

Reason for exclusion

Nonrandomized study on healthcare costs of foot ulcers in diabetes.

Razzak 1997

Reason for exclusion

RCT including 24 patients, dividing patients into treatment with either antibiotics or local insulin application. No debriding agent was assessed in this trial.

Ricci 2010

Reason for exclusion

Nonrandomized study on unspecified leg wounds.

Richard 2012

Reason for exclusion

Nonrandomized study on Immunomodulating NOSF dressing.

Saap 2002

Reason for exclusion

Fulfills the inclusion criteria for RCT and diabetic foot ulcers. The paper, however, is concerned with measuring the standard of debridement and the effectiveness of a debridement scale rather than the effectiveness of debridement as a treatment.

Saied 2011

Reason for exclusion

RCT of low intensity laser therapy as biostimulation not as a form of debridement.

Sanchez 2006**Reason for exclusion**

This was a retrospective non-randomized study on collagen matrix.

Santra 2012**Reason for exclusion**

The comparison in the study was not form of debridement.

Schindl 1998**Reason for exclusion**

RCT of Low intensity laser therapy for use as biostimulation not a form of debridement.

Schindl 2002**Reason for exclusion**

An RCT of Low intensity laser therapy for use as biostimulation not a form of debridement.

Sedlarik 1969**Reason for exclusion**

This is a Non-randomized study - case series.

Seidel 1994**Reason for exclusion**

RCT which assess the use of short term retrograde transvenous leg perfusion. The trial is concerned with infection of foot ulcers; wound healing was not an outcome.

Siavash 2015**Reason for exclusion**

Though Royal Jelly could be considered a form of autolytic debridement both treatment arms received a regular form of debridement that was unspecified.

Singh 2004**Reason for exclusion**

Systematic review on using hydrocolloids in chronic wounds not strictly diabetic foot ulcers.

Solway 2011

Reason for exclusion

Non-randomized study. Sharp debridement was done on both groups.

Soos 2003

Reason for exclusion

Narrative review article on diabetic foot ulcer management.

Steed 1996

Reason for exclusion

RCT of 118 patients which compares treatment of human-derived growth factor against a placebo. The influence of debridement was evaluated by reviewing the records of the trial. This paper was used in the discussion section of this review.

Steenvoorde 2007

Reason for exclusion

Non-randomized study - prospective case series on larval therapy.

Tennvall 2000

Reason for exclusion

Non-randomized study on cost of care in diabetics with deep foot infections.

Van Acker 2000

Reason for exclusion

Costs for prevention and treatment of foot lesions in diabetics in Belgium not on debridement.

Van Houtum 1995

Reason for exclusion

The study investigates cost of amputations in the Netherlands not cost of debridement.

Varma 2006

Reason for exclusion

RCT undertaken on people whose wounds had already been debrided, and the effectiveness of the post debridement dressing was the focus of the trial.

Wieman 1998

Reason for exclusion	RCT of 382 patients which assessed the efficacy and safety of topically applied recombinant human platelet derived growth factor at two strengths, either Becaplermin 30 mg or Becaplermin 100 mg.
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Wolff 2003

Reason for exclusion	Nonrandomized study - case series of larval therapy.
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Zgonis

Reason for exclusion	Expert opinion narrative review not RCT.
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Zimny 2008

Reason for exclusion	RCT of competing methods of off-loading including felted foam dressing versus pressure relief half-shoe. The debridement method was the same in both groups.
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Characteristics of studies awaiting classification

Callaghan 1993

Callaghan DP. Assessment of the effectiveness of Debrisan in healing ulceration on pressure areas of diabetic patients' feet. In: 2nd European Conference on Advances in Wound Management; 1992, 20-23 October; Harrogate, UK. 1993:82.

Dolynchuk 2001

Dolynchuk K. The use of collagenase in the debridement of diabetic foot ulcers: a double-blind prospective randomized study. In: 7th Annual Conference of the Canadian Association of Wound Care 1-3 November 2001 London, Ontario, Canada. 2001:56.

Mulder 1994b

Mulder GD, Jensen JL, Seeley JE, Peak Andrews K. A controlled randomized study of an amorphous hydrogel to expedite closure of diabetic ulcers. In: 4th European Tissue Repair Society Meeting; 1994, 25-28 August; Oxford, England. 1994:130 (Abstract 90).

Characteristics of ongoing studies

Michaeldis 2014

Michailidis L, Williams CM, Bergin SM, Haines TP. Comparison of healing rate in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomized trial protocol. Journal of foot and ankle research. 2014;7(11):1 - 10.

Additional tables

Table 1 of Descriptive Statistics	
Total number of studies	30
Total number of participants	2564
Sample size range	18 to 619
Average sample size per study	152
Total Range of follow up	10 days to 24 weeks
Total Study period or duration	1992 - 2012
Studies reporting age	24/30 (70%)
Mean age (range)	52.1 – 69.3 years
Total number of studies reporting gender	21/30 (70%)
Range of number of males	12 to 240
Range of number of females	1 to 88
Number of studies reporting ethnicity	5/30 (16.7%)
Number of studies reporting socioeconomic status	1/30 (3.3%)
Geographic setting	Europe and US (70%)
Publication Language	English 93%
Healthcare setting	Hospital 8/30 (26.7%) Outpatient 17/30 (56.7%) Both 2/30 (6.7%)
Studies reporting wound size (area)	20/30 (67%)
Studies reporting wound duration	14/30 (70%)
Studies reporting Hemoglobin a1c (Hgb a1c)	8/30 (26.7%)
Hgb a1c (range)	7.25% - 9.25%
Studies reporting on duration of diabetes	14/30 (70%)
Duration of diabetes (range)	13 to 21 years
Studies reporting baseline peripheral arterial insufficiency	9/30 (30%)
Studies reporting BMI	5/30 (16.7%)

Table 2 IWGDF 2012 (Reproduced here with permission from the IWGDF)					
Costs of Treating Foot Ulcers and Amputations					
Reference	Country	Number of Patients	Costs (year of costing)	USD 2005 equivalent	Comments
Ulcers not requiring amputation					
Apelqvist et al, 1994	Sweden	197	Sweden 197 SEK 51,000 (1990)	8,654	All ulcer types; total
Harrington, et al, 2000	USA	400,000	USA 400,000 USD 3,999-6 (1996)	4,982-7,821	Inpatient and outpatient costs
Holzer et al, 1998	USA	1846 c	USD 1,929 (1992)	2,695	Inpatient and outpatient costs, those >64 yr. excluded
Metha et al, 1999	USA	5149	USA 5149 USD 900-2,600 (1995)	1,150-3,322	Private insurance charges; mean age 51 yr.
Ragnarson Tennvall et al, 2000	Sweden	88	Sweden 88 SEK 136,600 (1997)	18,719	Deep foot infection; total direct costs
Ramsey et al, 1999	USA	514 d	USD 27,987 (1995)	35,758	Including 2 yr. after diagnosis
Van Acker et al 2000	Belgium	120	Belgium 120 USD 5,227 (1993)	7,039	Inpatient and outpatient costs
Costs of lower extremity amputations					

Apelqvist et al 1994	Sweden	27	Sweden 27 SEK 258,000 (1990)	43,778	All ulcer types; minor LEA; total direct costs
Apelqvist et al 1994	Sweden	50	Sweden 50 SEK 390,000 (1990)	66,176	All ulcer types; major LEA; total direct Costs
Ashry et al 1998	USA	5062	USA 5062 USD 27,930 (1991)	39,891	Hospital charges Only
Holzer et al, 1998	USA	504 c	USD 15,792 (1992)	22,062	Gangrene/amputation, those >64 yr. excluded
van Houtum et al, 1995	Netherlands	1575 e	NLG 28,433 (1992)	19,052	Hospital costs only
Panayiotopoulos et al, 1997	UK	20	UK 20 GBP 15,500 (1994-95)	33,587	Inpatient and prostheses costs (46% diabetics)
Ragnarson Tennvall et al, 2000	Sweden	77	Sweden 77 SEK 261,000 (1997)	35,767	Deep infection; minor LEA; total direct costs
Ragnarson Tennvall et al, 2000	Sweden	19	Sweden 19 SEK 234,500 (1997)	32,136	Deep infection; major LEA; total direct costs
Van Acker et al, 2000	Belgium	7	Belgium 7 USD 18,515 (1993)	24,933	Inpatient and outpatient costs; minor LEA

Van Acker et al, 2000	Belgium	9	Belgium 9 USD 41,984 (1993)	56,538	Inpatient and outpatient costs; major LEA
<p>Footnotes</p> <p>For comparison of the results, costs were first adjusted for inflation to 2005 prices with the consumer price index f and then converted to USD with the appropriate currency exchange rate for 2005.</p> <p>NA = not applicable.</p> <p>LEA = Lower Extremity Amputation.</p> <p>Minor = amputation below the ankle;</p> <p>Major = amputation above the ankle.</p> <p>a Based on data from observational studies</p> <p>b Based on data from databases and other secondary sources</p> <p>c Number of episodes</p> <p>d Includes 80 amputations</p> <p>e Number of hospitalizations</p>					

Table 3 Wagner Wound Grade Classification System					
Grade					
0	1	2	3	4	5
No ulcer in a high risk foot	Wound involving full skin thickness	Wound extending to ligament and muscle	Wound with cellulitis or abscess	Localized gangrene	Extensive gangrene involving the whole foot

Table 4 University of Texas Wound Classification System				
	Grade			
Stage	0	1	2	3
	Pre or Post ulcerative lesion completely epithelialized	Superficial wound not involving tendon, muscle, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
A No Infection, or Ischemia	0A	1A	2A	3A
B Infection but no ischemia	0B	1B	2B	3B
C Ischemia but no infection	0C	1C	2C	3C
D Infection and ischemia are present	0D	1D	2D	3D

Table 5 Methods of debridement			
Debridement Method	Explanation	Advantages	Disadvantages
Mechanical			
Surgical (scalpel)	The technique is considered a rapid means of debriding a wound, requiring the use of sterile scissors, a scalpel, or curette, it does require a certain amount of skill and may slightly enlarge the wound.	Allows rapid removal of devitalized tissue.	Can be complicated by infection, and bleeding. Expensive
Wet-to dry	The wound is soaked in saline to moisten the hardened wound material before the application of a moist gauze pad is placed over the affected area. As both the gauze and wound tissue dry, the wound tissue and gauze adhere to each other. When the dressing is removed it non-selectively pulls off the tissues.	Allows rapid removal of hardened devitalized tissue Inexpensive	It is not discriminating/non-selective and may remove healing granulation tissue. It also may be painful for the patient.
Aqueous High Pressure Lavage or Irrigation	This involves a pressurized stream of aqueous solution such as saline to mechanically dislodge devitalized tissue from a wound. Whirlpool is also a form of lavage irrigation that is carried out with the affected wound immersed in the solution.	Allows for rapid removal of devitalized tissue.	It is non-selective and can dislodge healing granulation tissue. This procedure may be painful. Cross contamination and infection is possible.
Low frequency Ultrasound	This process uses sound waves through a contact or noncontact form of transducer to dislodge devitalized tissue.	Permits a rapid removal of devitalized tissue.	Nonselective and can remove healthy granulation tissue. Cost implication Aerosolizing pathogens
Bio-Surgery Maggot Debridement therapy (larva, maggots)	Sterile maggots of the green bottle fly <i>Lucilia sericata</i> are placed directly on to the wound (loose) and covered by a dressing, or held within a closed net dressing against the wound (bagged). The larvae have a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue. They also use enzymes to digest devitalized tissue and are believed to secrete antimicrobial and tissue-growth promoting substances. Therefore, they are considered a complete system of wound care.	They discriminate between the nonviable and the viable granulating tissue.	There is at present no conclusive evidence of effectiveness in foot ulcers, there may also be a reluctance to use this treatment by patients and clinicians. There is a cost implication but other treatments discussed above may be costlier.

Debridement Method	Explanation	Advantages	Disadvantages
Non-Mechanical These treatments are easy to apply and have additional properties that may be beneficial for wound healing			
Enzyme Preparations	The only formulation available in the UK contains Streptokinase and Streptodornase. This enzyme digests the proteins fibrin, collagen & elastin, which are commonly found in the necrotic exudate of a wound. This includes the enzymes Matrix Metalloproteinases contained within the wound and promoting auto-digestion or self-digestion of the wound. Other enzymatic preparations include trypsin and collagenase, are licensed in other countries including the U.S.	They can be applied directly onto the necrotic area. Nonpainful	Streptokinase can be systemically absorbed and is therefore contraindicated in patients at risk of an MI. There is a cost implication.
Non-Mechanical Primarily facilitating Autolytic Debridement			
Hydrogels	These gels are biologically inert and have significant water content. They complement the body's natural debridement process by providing a moist environment, which promotes autolytic debridement, while still acting to preserve living healthy tissue. (Bradley 1999)	Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue.
Alginates	These are absorbent, biodegradable dressings derived from seaweed. The high absorptivity is due to the hydrophilic gel formation that is formed when in contact with wounds. Alginate dressings are used for moderate to heavily exudating wounds	Widely available in a wide variety of healthcare settings and can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required. Not associated with pain as mechanical forms of debridement may be.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue. Cost factor.
Hydrocolloids	Hydrocolloids contain gel-forming substances, such as sodium carboxymethylcellulose (NaCMC) and gelatin. They can be combined with elastomers and adhesives and associated with a carrier such as polyurethane foam or film dressing. The result is an absorbent, self-adhesive, waterproof adherent dressing. When they contact wound exudate, hydrocolloids are hydrophilic and form a gel. Hydrocolloids are impermeable to water	Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required. Not associated with pain as mechanical forms of debridement may be.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue. Cost Factor

	vapor initially but subsequently become more permeable.		
Foam	These are absorbent dressings made from a hydrophilic polyurethane foam. Foams can absorb exudate absorbing it from the wound and can decrease maceration to the surrounding tissue. The direct contact between the foam and the wound will maintain a moist wound environment. Used for exudative wounds.	Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required. Not associated with pain as mechanical forms of debridement may be.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue. Cost factor
Film	Film dressings are made of thin polyurethane membrane coated with a layer of acrylic adhesive. They are flexible and allow direct visualization of the wound without always needing to remove the dressing. They do not absorb wound exudate.	They are believed to limit friction and shearing forces that may be more common with other dressings. Film dressings should not be used for infected, deep, or significantly exudative wounds. Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required. Not associated with pain as mechanical forms of debridement may be.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue. Cost factor
Honey	Honey provides an osmotic hydrophilic environment that allows the rehydration of devitalized tissue, among other benefits.	Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement. Minimal level of skill required. Not associated with pain as mechanical forms of debridement may be.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue. Cost factor
Saline gauze	Moist saline gauze is often widely utilized and can potentially serve as a control or standard form of debridement.	Can be applied to a wound at any stage, promotes moist wound healing and autolytic debridement as long as it is kept from drying Minimal level of skill required.	Promotes a slow process of debridement. If the surrounding skin is not masked properly they may macerate the surrounding tissue.

Table 7 Study year, sample sizes and study settings of included studies							
#	[Study ID]	Year	[Total Sample Size]	[Primary Intervention] (# patients preceding)	[Comparator/Control] (# patients preceding)	Study Setting	Country
1	Ali 2013	2013	70	A) Cutimed Sorbact 35 patients	B) Standard Dressing (Saline cleansed povidone soaked gauze dressing) 35 patients	Hospital	Saudi Arabia
2	Amini 2013	2013	40	A) Low frequency (20-60kHz) ultrasound assisted wound therapy + standard wound care 20 patients	B) Standard wound care alone 20 patients	Clinic	Iran
3	Apelqvist 1990	1990	44	A) Hydrococolloid 22 patients	B) Adhesive Zinc Oxide tape 22 Patients	Outpatient	Sweden
4	Baker 1993	1993	19	A) Allevyn Hydrocellular dressing ? patients	B) Sorbsan Calcium-Alginate dressings ? patients	Clinic	Unclear
5	Belcaro 2010	2010	66	A) Multivalent silver oxide Ag ₄ O ₄ ointment + elastic compression 34 patients	B) Control group (standard cleaning and elastic compression management methods without silver ointment) 32 patients	Unclear	Italy
6	Blackman 1994	1994	18	A) Polymeric dressing 11 patients	B) Wet to dry saline dressing 7 Patients	Unclear	US
7	Bowling 2011	2011	20	A) Jet lavage debridement with superoxide aqueous solution + hydrogel 10 patients	B) Jet lavage debridement with saline solution + hydrogel 10 patients	Hospital, Outpatient	US, UK
8	Clever 1995	1995	40	A) Hydroactive polyurethane gel dressing Cutinova Hydro + standard therapy* 20 patients	B) Hydrophilic polyurethane foam dressing Allevyn + standard therapy* 20 patients	Outpatient	Germany
9	D'Hemeourt 1998	1998	138	A) Good wound care + Sodium Carboxymethylcellulose Hydrogel 70 patients	B) Good wound care* alone 68 patients	Unclear	USA
10	Donaghue 1998	1998	75	A) Collagen Alginate	B) Saline gauze	Outpatients	USA

				50 patients	25 patients		
11	EhsanUrRehman 2013	2013	60	A) Honey soaked dressing ? patients	B) Povidone-iodine/normal saline dressing ? patients	Hospital, ED	Pakistan
12	Foster 1994	1994	30	A) Hydrocellular polyurethane foam dressing Allevyn 15 patients	B) Calcium sodium alginate dressing 15 patients	Outpatient	UK
13	Goretti 2008	2008	40	A) Super-oxidized solution (SOS) treatment 20 patients	B) Standard local treatment with povidone iodine 20 patients	Hospital	Italy
14	Hammouri 2004	2004	203	A) Honey/Normal Saline, washed with normal saline post-debridement 100 patients	B) Povidone Iodine/H ₂ O ₂ (3:1) washed with same solution post-debridement 100 patients	Hospital	Jordan
15	Jeffcoate 2009	2009	317	A) Hydrofiber 103 patients B) Iodine Gauze 108 patients	C) Gauze 106 patients	Multidisciplinary Outpatient 9 centers	UK
16	Jensen 1998	1998	31	A) Carrasyn hydrogel wound dressing (CHWD) cleansed with ULTRAKLENZ wound cleanser. 14 patients	B) Wet-to-moist saline gauze cleansed with ULTRAKLENZ wound cleanser 17 patients	Outpatient	USA
17	Lalau 2002	2002	77	A) Calcium Alginate 39 patients	B) Vaseline Gauze 38 patients	Outpatients	France
18	Markevich 2000	1998	140	A) Larval therapy (green bottle fly - Lucilia sericata 6-10 larva per 1 cm ² of wound surface area) removed after 72 hours 70 patients	B) Hydrogel (no data on frequency of dressing change) 70 patients	Unclear	Europe
19	Mazzone 1993	1993	19	A) Polymeric membrane foam dressing 11 patients	B) Wet to Dry saline gauze mesh dressing 8 patients	Outpatient	USA
20	Munter 2006	2006	619	A) Silver releasing hydrophilic	B) Local Best Practice (study reports that this ranged from gauze, moist wound healing, wound healing products,	Outpatient	Germany UK

				polyurethane foam dressing 326 patients	to antimicrobial treatments) 293 patients		Denmark Italy Switzerland Belgium Slovenia Brazil Canada
21	Ogce 2007	2007	60	A) Hydrocolloid dressing (combined with paste for wound cavities, and powder for infection) 30 patients	B) Classic wound dressing 30 patients	Hospital	Turkey
22	Piaggese 2001	2001	24	A) Sodium Carboxy-Methyl Cellulose Hydrofiber (Aquacel) changed every 2nd or 3rd day depending on extent of exudate produced by wound. 10 patients	B) Saline moistened gauze (renewed twice daily with saline to prevent drying) 10 patients	Outpatient	Italy
23	Piaggese 1998	1998	46	A) Treatment - Surgical debridement 22 patients	B) Control - Non-surgical conservative treatment and pressure relief 24 patients	Outpatient	Italy
24	Rhaiem 1998	1998	80	A) G1: cleaning ulcers with hydrogen peroxide 3% + local applied Jam sugar 16 patients	B) G2: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy 24 patients C) G3: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy 40 patients	Hospital	Tunisia
25	Roberts 2001	2001	30	A) Allevyn hydrocellular foam dressing 14 patients	B) Saline soaked (low adherent) dressing and standard podiatric care 16 patients	Hospital	UK
26	Shukrimi 2008	2008	30	A) Honey dressing ? patients	B) Standard dressing (Povidone Iodine/Normal saline, 1:10) ? patients	Hospital	Malaysia

27	Singh 2006	2006	60	A) Non-contact Ultrasonic debridement (24 KHz) performed every other day 33 patients	B) Sharp/surgical debridement conducted every other day 27 patients	Hospital	Malaysia
28	Tallis 2013	2013	48	A) Clostridial Collagenase Ointment (CCO) 24 patients	B) Saline Moistened Gauze (SMG) + Selective Sharp Debridement 24 patients	Outpatient	USA
29	Vandeputte 1997	1997	29	A) Hydrogel 15 patients	B) Dry gauze (control) 14 patients	Outpatient	Belgium
30	Whalley 2001	2001	66	A) Purilon Hydrogel ? patients	B) Intrasite Hydrogel using Biatain Non-adhesive dressing (Coloplast A/S) as a secondary dressing Dressings changed at least every second day ? patients	Unclear	Europe
Footnotes: G1 = Group 1, G2 = Group 2							

Table 8 Inclusion & exclusion criteria for included studies		
Trial Author	Inclusion Criteria	Exclusion Criteria
1) Ali 2013	1) Texas 2nd grade diabetic foot ulcer	Not reported.
2) Amini 2013	1) Diabetes (type 1 and type 2) 2) Diabetic foot ulcer 3) Wagner Grade 3 chronic (>1 month)	1) $0.6 \leq \text{ABI}^* \leq 1.2$ (*Ankle Brachial Index)
3) Apelqvist 1990	1) Previous diabetes mellitus 2) Superficial skin ulcer below the ankle 3) Systolic toe pressure > 45 mmHg or an absence of cutaneous erythema. 4) Ulcers between 1 - 25 cm ² and > 50% covered by dry or wet necrotic tissue. 5) Only one ulcer the largest was chosen for study in each patient.	1) Patch test positive individuals. 2) Clinical signs of cellulitis. 3) Ulcers where application of intervention dressings would be inappropriate.
4) Baker 1993	1) Patients with neuropathic foot ulcer in a diabetic foot center Type of DM unspecified	Not reported
5) Belcaro 2010	1) Patients who had ulcers resulting from chronic venous insufficiency or diabetes	Not reported.
6) Blackman 1994	1) Diabetes Type 1 or Type 2 2) Partial or full thickness open wound or foot ulcer free; free of hard eschar	1) Ulcers with Wagner stage 3 or higher 2) Ulcers progressing to Wagner stage 3 or higher 3) Subjects needing vascular surgery 4) Ulcers from Charcot joints 5) Ulcers of non-diabetic origin
7) Bowling 2011	1) Type 1 or Type 2 DM 2) Foot ulcer, full thickness, distal to malleoli 2) Chronic > 4 weeks 3) Non-clinically infected foot ulcers 4) Necrotic tissue present and mechanical debridement indicated. 5) One ulcer per patient included	1) Ulcers larger than 25 cm ² 2) Texas Classification grade 3 3) Osteomyelitis 4) Peripheral arterial disease (ABI < 0.8/absent pulses. 5) Prescription use of anticoagulants, immunosuppressive drug treatment 6) Allergies to chlorine 7) Clinically infected wounds excluded on grounds of antibiotic use.

8) Clever 1995	<p>1) Age 18 - 80 years</p> <p>2) Pure neuropathic superficial ulcer 1-5 cm in diameter</p>	<p>Diabetics with an ankle-brachial pressure index < 0.8 (measured using Doppler ultrasound)</p> <p>Clinical or radiological signs of osteomyelitis or tendon involvement.</p> <p>Large vessel disease Ulcers requiring additional topical treatment</p> <p>Known allergies to any product used</p>
9) D'Hemecourt (1998): written consent needed	<p>1) 19 years or older</p> <p>2) Type 1 or type 2 diabetes</p> <p>3) At least 1 full thickness ulcer (stage 3 or 4) chronic diabetic foot ulcer present for at least 8 weeks.</p> <p>4) Target area (Length x Width) 1cm²-10cm² post debridement 5) Transcutaneous oximetry in the affected limb (TcpO₂) >= 30 mmHg</p>	<p>1) Osteomyelitis affecting area of ulcer</p> <p>2) Target area < 1cm² OR > 10 cm² post-debridement</p> <p>3) More than 3 ulcers present at baseline</p> <p>4) A cause of ulcer other than diabetes e.g. electrical, chemical or radiation</p> <p>5) Patients with cancer at time of enrollment</p> <p>6) Concomitant medication known to affect wound healing e.g. corticosteroids, chemotherapy, immunosuppressant's</p> <p>7) Pregnant, nursing or of child bearing potential not using acceptable contraception.</p>
10) Donaghue 1998	<p>1) At least 21 years of age</p> <p>2) Adequate nutritional intake (albumin > 2.5 gms/dl)</p> <p>3) Adequate blood flow to lower extremity (palpable pulses, normal noninvasive tests)</p> <p>4) Foot ulceration at least 1 cm² post-debridement.</p>	<p>1) Severe renal impairment (creatinine >)</p> <p>2) Severe liver impairment (liver function tests >= 2 times normal levels.</p> <p>3) Serious medical disorder that can interfere with wound healing.</p> <p>4) Osteomyelitis (deep ulcer probing to bone, or radiographic evidence)</p> <p>5) Clinical signs of infection</p> <p>6) History of alcohol or drug abuse.</p>
11) EhsanUrRehman 2013	<p>1) Diabetic patients of either gender</p> <p>2) All age groups</p> <p>3) Diabetic foot ulcers Wagner grade I & II</p>	<p>1) Nonconsenting patients</p> <p>2) Systemic infection and other comorbidities</p>
12) Foster 1994	<p>1) At least 18 years' old</p> <p>2) A clean diabetic foot ulcer</p> <p>3) Willing and able to comply with study protocol</p>	<p>1) Slough, necrotic, or infected ulcer</p>

13) Goretti (2008)	1) Infected foot lesions post-surgical debridement 2) surgical outcomes > 5 cm ² 3) ankle-brachial index > 0.9, 4) presence of at least two arteries in the ankle documented by palpable pulses or Doppler CW	Not reported
14) Hammouri 2004	1) Diabetic foot ulcers	Not reported
15) Jeffcoate 2009	1) Type 1 and type 2 Diabetes 2) Age > 18 yrs. 3) Chronic (>= 6 weeks) full thickness foot ulcer on or below malleoli 4) Cross sectional area 25 mm ² - 2500 mm ² 5) Able and willing to give informed consent 6) Reasonably accessible by car to the hospital	1) Known allergy to treatment preparations 2) Ulcer extending to tendon, periosteum, or bone 3) Osteomyelitis 4) Soft tissue infection requiring systemic antibiotics 5) Ulcer on a limb being considered for revascularization 6) Management with a non-removable cast without a dressing window. 7) Gangrene on affected foot 8) Eschar not removable by clinical debridement 9) Sinus or deep track 10) Hallux amputation preventing toe pressure measurement 11) ABI < 0.7 or toe systolic pressure < 30 mmHg 12) Ulceration by disease other than diabetes 13) Any other serious disease likely to compromise outcome 14) Cr > 300 µMol/L 15) Immunosuppressant's, systemic steroids other than inhalation, or any other preparation that could interfere with healing. 16) Living > 10 miles from clinic 17) Those withholding consent
16) Jensen (1997): written consent needed	1) Diabetic foot ulcer of at least 1cm diameter	No exclusion criteria specified

	<p>2) No evidence of infection in ulcer or peri-wound tissue</p> <p>3) Wagner grade 2 ulcer, full thickness into subcutaneous tissue, not involving tendon, joint capsule, or bone</p> <p>4) Documented blood supply consistent with the ability to heal (palpable pulses, non-invasive vascular study)</p> <p>5) Willingness to comply with protocol.</p>	
17) Lalau 2002	<p>1) Age < 75 yrs.</p> <p>2) Diabetes either Type 1 or Type 2</p> <p>3) Foot lesion in the phase of cleansing (granulation tissue < 50% for wound area)</p> <p>4) Surface area between 1 - 50 cm².</p> <p>Acute (< 2 months) and Chronic lesions</p> <p>2) Surface area of 1 - 50 cm²</p>	<p>1) HgbA1c > 10%</p> <p>2) Presence of clinical infection (redness, swelling, warmth, periwound erythema)</p> <p>3) Osteomyelitis (on plain radiography, or probing of bone)</p> <p>4) Tunneled wound</p> <p>5) Severe hypo-vascularization (TcPO₂ < 30mmHg)</p>
18) Markevich (2000)	Diabetic Neuropathic Foot wounds	No exclusion criteria specified
19) Mazzone 1993	<p>1) Diabetic subjects with chronic foot ulcers</p> <p>Type of DM unspecified.</p> <p>No other inclusion criteria pre-specified.</p>	No exclusion criteria specified.
20) Munter	<p>1) 18 years or older</p> <p>2) Not pregnant or lactating</p> <p>3) Chronic wounds</p> <p>4) Mixed etiology wounds including: burns, donor sites, post-operative wounds, but most reported as leg ulcers, pressure ulcers, and Diabetic foot ulcers (Wagner grade 1 - 3)</p> <p>5) Ulcer depth < 0.5 cm</p>	Not reported
21) Ogce 2007	<p>1) Type 1 or Type 2 Diabetes</p> <p>2) Wagner grade 2 or grade 3 diabetic foot ulcers</p>	Not reported
22) Piagessi 2001	<p>1) All patients presenting to foot clinic in 1998</p> <p>2) Age 18 - 75</p> <p>3) Type 1 or Type 2 diabetes > 5 years</p> <p>4) Ulcer deeper than 1 cm for 3 weeks</p>	<p>1) Active infection: Local signs (purulent discharge, redness, swelling, tenderness or odor) OR systemic signs (fever, malaise, leukocytosis) + confirmed culture exams</p> <p>2) Plasma creatinine > 2 mg/dl</p> <p>3) Recent episode of ketoacidosis</p>

	<p>5) Palpable peripheral pulses or ABPI > 0.9</p> <p>6) Ulcers due to diabetic neuropathy or surgical drainage of previous infection or both.</p>	<p>4) Malignancies</p> <p>5) Any therapy of pathology that might interfere with healing process</p> <p>6) Candidates for a major amputation</p>
23) Piaggese (1998)	<p>1) All patients newly presenting to the diabetic foot clinic between January - December 1995</p> <p>2) One or more diabetic neuropathic ulcer</p> <p>3) Diabetes type 1, type 2, at least 5 years duration uncomplicated.</p>	<p>1) Presence of symptomatic claudication OR absence of foot pulses</p> <p>2) Recent ketoacidosis</p> <p>3) Renal Failure Cr > 177 micromole/L</p> <p>4) Presence of Infection</p> <p>5) Congenital foot deformities or diabetic neuroarthropathy</p> <p>6) BMI > 30</p> <p>7) Clinical history of stroke, cardiac failure, cancer, HIV, Mental Illness</p> <p>8) ABPI < 0.9</p> <p>9) Osteomyelitis</p>
24) Rhaïem 1998	1) Diabetic hospitalized patients from 1992 - 1995	Not reported
25) Roberts 2001	<p>1) Type 1 diabetics with neuropathic foot ulcers of the plantar surface.</p> <p>No other inclusion criteria pre-specified.</p>	ABPI < 0.8 No exclusion criteria specified.
26) Shukrimi 2008	<p>1) All NIDDM patients with Wagner grade II ulcers admitted for surgery.</p> <p>2) Age 35 - 65</p> <p>3) TcPO₂ > 30 mmHg</p> <p>4) Albumin > 35 g/dl</p>	<p>1) Multiple medical comorbidity</p> <p>2) Steroid therapy</p> <p>3) Neutrophil count < 2000/mm³</p>
27) Singh 2006	<p>1) Diabetic foot ulcers admitted to orthopedic wards.</p> <p>2) Wagner type 1 and type 2</p> <p>3) Known cases of DM Type 1 or Type 2 treated medically</p> <p>4) Glycemic control during hospitalization with insulin.</p> <p>5) Sensate feet based on Modified Neuropathic Disability Score (NDS)</p>	<p>1) Wagner grade 3 or grade 4 diabetic foot ulcers</p> <p>2) Ulcers covered with hard scab</p> <p>3) Peripheral neuropathy based on modified NDS</p> <p>4) Patients without at least one of the foot pulses palpable (dorsalis pedis or posterior tibial)</p>

	6) At least one of the foot pulses palpable (dorsalis pedis or posterior tibial arteries)	
28) Tallis 2013	1) 18 yrs. or older, any race, either sex 2) Type 1 or Type 2 DM requiring diabetic medications. 3) Full thickness neuropathic ulcers between 0.5 cm ² - 10 cm ² 4) Ulcer duration 1 month 5) Willing and able to perform daily dressing changes at home. 6) Willing and able to use off-loading 7) Adequate perfusion to target foot ulcer (TcPO ₂ > 40 mmHg, or toe pressure > 40 mmHg or Doppler waveform consistent with adequate flow) 8) Adequate nutrition (albumin >= 2.0 g/dL and pre-albumin > 15 mg/dL) 9) No active infection 10) No target wound tunneling 11) Target could not be on heel or over a Charcot deformity	Not reported
29) Vandeputte (1997): written consent needed	Diabetic wound on foot	Patient receiving systemic antibiotics
30) Whalley (2001)	1) Diabetic neuropathic foot ulcer 2) Type 1 and Type 2 Diabetics	No exclusion criteria specified
Foot notes TcPo2 – Transcutaneous oximetry in mmHg ABI – Ankle Brachial Index Hga1c = Hemoglobin a1c BMI – Body Mass Index		

Table 9 Patient demographics for Included studies			
#	[Study ID]	[Mean Age yrs. +/- SD]	[Gender M/F]
1	Ali 2013	Not reported	48/22
2	Amini 2013	55.2 +/- 9.4	24/16
3	Apelqvist 1990	63 +/- 36	26/20
4	Baker 1993	Not reported	Not reported
5	Belcaro 2010	55.9 +/- 3.8	29/37
6	Blackman 1994	55.9 +/- 13.6	17/1
7	Bowling 2011	53.1 +/- 12.6	12/8
8	Clever 1995	56 +/- 13.13	32/8
9	D'Hemeourt 1998	58.3 +/- 12.13	127/45
10	Donaghue 1998	59.5	54/21
11	EhsanUrRehman 2013	55.3 +/- 3.89	35/25
12	Foster 1994	65.5	20/10
13	Goretti 2008	Not reported	Not reported
14	HammouriJRMS2004	58	112/88
15	Jeffcoate 2009	59.6 +/- 12.6	240/76
16	Jensen 1998	Not reported	Not reported
17	Lalau 2002	62.2 +/- 11.75	45/32
18	Markevich 2000	53.6 +/- 15.4	Not reported
19	Mazzone 1993	Not reported	Not reported
20	Munter 2006	69.3 +/- 13.90	Not reported
21	Ogce 2007	59.85	36/24
22	Piaggese 2001	62.2 +/- 6.05	Not reported
23	Piaggese 1998	64.39 +/- 11.67	Not reported
24	Rhaïem 1998	56 +/- 32	59/21
25	Roberts 2001	59.5 Median	23/7
26	Shukrimi 2008	52.1	15/15
27	Singh 2006	56.87 +/- 11/06	33/27
28	Tallis 2013	61 +/- 11.8	32/16
29	Vandeputte 1997	63.95 +/- 14.5	13/16
30	Whalley 2001	Not reported	Not reported

Table 10 Baseline wound size and duration characteristics of included studies			
Surface Area of wound ** ** Expressed as means +/- SD unless otherwise noted	Depth of wound **	Wound Staging (Wagner Wound Grade 0 - 5 OR Texas classification 1 - 3, A, B, C, or D) (Staging indicates maximum stage or grade accepted for study.)	Duration of ulcer **
1) Ali 2013 Reported as: < 4 cm ² 4+ cm ² A) 0 35 B) 8 27	Reported only as: < 3 cm 3+ cm A) 0 35 B) 19 16	Texas 1A -> 2D (Texas 2D)	Total Sample Mean duration of foot ulcers = 9 weeks (1 - 105)
2) Amini 2013 A) 6.8 +/- 6 cm ² B) 9.9 +/- 7.6 cm ²	Not reported	Wagner Grade 3	A) 3.4 +/- 3.5 months (15.6 +/- 16.8 weeks) B) 4.4 +/- 4.7 months (17.6 +/- 18.8 weeks)
3) Apelqvist 1990 A) median 2.2 cm ² (1 - 10.5) B) median 2.2 cm ² (0.9 - 20.4)	Not reported	Not reported	Not reported
4) Baker 1993 No baseline data reported.	Not reported	Not reported	Not reported
5) Belcaro 2010	Not reported	Not reported	Not reported

Baseline at 4 weeks A) 2.22 cm ² 0.24 cm ² B) 2.18 cm ² 1.66 cm ² p<0.05 statistically significant difference			
6) Blackman 1994 A) 2.67 +/- 1.20 cm ² B) 1.81 +/- 0.75 cm ² No statistically significant difference	Not reported.	Wagner Grade 1-2 (Wagner 3)	A) 25 +/- 7 weeks B) 28 +/- 6 weeks
7) Bowling 2011 A) 3.0 +/- 3.7 cm ² B) 1.8 +/- 1.6 cm ²	Not reported	Texas Grade 1-2 (Texas 2)	A) 13.7 +/- 12.0 weeks B) 9.7 +/- 8.1 weeks
8) Clever 1995 Initial After 4 weeks A) 2.05 +/- 3.14 cm ² A) 0.32 ± 0.54 cm ² B) 2.08 +/- 2.72 cm ² B) 0.34 ± 0.75 cm ² (p > 0.2) Not statistically significant	Not reported	Not reported	A) 162.37 +/- 325.55 days (23.2 ± 46.5 weeks) B) 165.00 +/- 318.68 days (23.6 ± 42.5 weeks)
9) D'Hemecourt (1998) A) (Good Wound Care alone) 3.5 +/- 3.53 cm ² B) (Good Wound Care + NaCMC) 3.2 +/- 2.75 cm ²	A) 0.4 +/- 0.52 cm B) 0.4 +/- 0.20 cm Full thickness Stage 3 or 4	Wagner Grade 3 - 4 (Wagner 4)	A) 42 +/- 42 weeks B) 52.8 +/- 60.92 weeks

Target area 1 cm ² to 10 cm ² post-debridement			
10) Donaghue 1998 A) 2.6 +/- 0.50 cm ² B) 2.99 +/- 0.62 cm ² No statistically significant difference (p=0.6237)	Not reported	Wagner Grade 1 - 3 (Wagner 3)	A) 146 +/- 73 days (20.86 +/- 10.43 weeks) B) 225 +/- 104 days (32.14 +/- 14.86 weeks) No statistically significant difference (p=0.5369)
11) EhsanUrRehman 2013 Not reported	Not reported	Wagner Grade 1 - 2 (Wagner 2)	Not reported
12) Foster 1994 A) 0.88 cm ² B) 0.79 cm ²	Superficial Deep A) 12 3 B) 13 2	Not reported	A) 107 days (15.3 weeks) B) 170 days (24.3 weeks)
13) Goretti (2008) Surgical outcomes > 5 cm ² No other baseline data specified	Not reported	Not reported	Not reported
14) Hammouri 2004 Not reported	Not reported	Not reported	Not reported
15) Jeffcoate 2009 0.25-1 cm ² 1.01- 0.25 cm ² 2.5-25 cm ² A) 53 34 16	Not reported	Not reported	Not reported

B) 48 36 24			
C) 50 34 22			
16) Jensen (1997) All ulcers at least 1 cm ² No other baseline data specified	No other baseline data specified	Wagner Grade 2	A) 8 months (32 weeks) B) 3 months (12 weeks)
17) Lalau 2002 A) 8.0 +/- 10.5 cm ² B) 8.8 +/- 16.0 cm ²	Not reported	Not reported	A) 4.9 +/- 7.8 months (19.6 +/- 31.2 weeks) B) 9.1 +/- 13.1 months (36.4 +/- 52.4 weeks)
18) Markevich (2000) A) 14.90 cm ² B) 15.14 cm ²	Reported as comparable at baseline, but not otherwise specified	Not reported	Average duration reported for total sample as 15.8 +/- 10.7 years. (821.6 +/- 556.4 weeks) Not reported separately for each intervention group.
19) Mazzone 1993 Not reported	Not reported	Not reported	Not reported
20) Munter 2006 A) 52.9 +/- 90 cm ² B) 36.6 +/- 64.4 cm ²	Not reported	Wagner Grade 1 - 3 (Wagner grade 3)	Not reported
21) Ogce Not reported	Not reported	Not reported	Not reported
22) Piagessi 2001	A) 2.9 +/- 1.1 cm	Not reported	A) 5.9 +/- 1.3 weeks

A) 19.2 +/- 6.4 cm ³ B) 22.6 +/- 8.4 cm ³ No statistically significant difference	B) 2.3 +/- 1.4 cm No statistically significant difference		B) 6.8 +/- 2.6 weeks No statistically significant difference
23) Piagessi 1998 Not reported	A) 1.58 +/- 2.20 cm B) 1.98 +/- 1.07 cm	Wagner Grade 1 - 2 (Wagner Grade 2)	A) 32.74 +/- 19.25 days (4.7 +/- 2.75 weeks) B) 39.43 +/- 18.92 (5.6 +/- 2.7 weeks)
24) Rhaiem 1998 Not reported	Not reported	Not reported	Not reported
25) Roberts 2001 Sample median 1.23 cm ² Sample median range (0.21 - 3.50 cm ²) A) Median 1.1 cm ² B) Median 1.45 cm ²	Not reported	Not reported	Sample 15.2 weeks Range (1 week - 6 years)
26) Shukrimi 2008 Not reported	Not reported	Wagner Grade 2	Not reported
27) Singh 2006 Not reported	Not reported	Wagner Grade 1 - 2 (Wagner Grade 2)	Not reported
28) Tallis 2013 A) 3.0 +/- 2.1 cm ² B) 2.4 +/- 2.1 cm ²	Not reported	Not reported	Not reported
29) Vandeputte 1997 Not reported	Not reported	Not reported	Not reported
30) Whalley 2001 A) 2.5 +/- 3.2 cm ²	Not Reported	Wagner Grade 1 - 2 (Wagner grade 2)	Not reported

B) $2.4 \pm 2.9 \text{ cm}^2$			
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Table 11 Baseline participant complicating risk factors for delayed healing in the included studies

[#]	[Study ID]	[Mean HgbA1c (%)]	[Mean Duration of DM (yrs.)]	[Proportion of sample with baseline PAD/PVD]	[Proportion of sample with baseline Infection]	[Offloading] Reported Y/N	[Proportion with Baseline Immune-suppression]	[Nutritional status]	Proportion of sample Smoking	Proportion of sample with Venous Insufficiency
1	Ali 2013	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	0.214	Not reported
2	Amini 2013	8.9 +/- 2.3	14.8 +/- 7.3	0.50	Not reported	Yes	Not reported	Not reported	0.075	Not reported
3	Apelqvist 1990	8.2 +/- 1.75	20.5 +/- 13.5	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported
4	Baker 1993	Not reported	Not reported	Not reported	Not reported	Not Reported	Not reported	Not reported	Not Reported	Not Reported
5	Belcaro 2010	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
6	Blackman 1994	8.95 +/- 1	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported
7	Bowling 2011	8.7 +/- 1.8	19.35 +/- 8.1	0	0	Not reported	Not reported	Albumin	Not reported	Not reported
8	Clever 1995	Not reported	Not reported	Not reported	0.725	Yes	Not reported	Not reported	0.325	Not reported
9	D'Hemecourt 1998	Not reported	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported
10	Donaghue 1998	Not reported	18	Not reported	0	Yes	Not reported	Alb	Not reported	Not reported
11	EhsanUrRehman 2013	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	3.76 +/- 0.09	Not reported	Not reported
12	Foster 1994	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
13	Goretti 2008	Not reported	Not reported	0	1	Not reported	Not reported	Not reported	Not reported	Not reported
14	Hammouri 2004	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
15	Jeffcoate 2009	Not reported	15.7 +/- 10.8	0.196	0	Yes	0	Not reported	0.170	Not reported
16	Jensen 1998	Not reported	Not reported	0	0	Yes	Not reported	Not reported	Not reported	Not reported
17	Lalau 2002	7.75 +/- 1.75	18.05 +/- 10.35	0.22	Not reported	Yes	Not reported	Not reported	Not reported	Not reported
18	Markevich 2000	Not reported	15.8 +/- 10.7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
19	Mazzone 1993	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
20	Munter 2006	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
21	Ogce 2007	7.73	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
22	Piaggese 2001	8.5 +/- 2.9	15.45 +/- 7.55	0	0	Yes	Not reported	Not reported	Not reported	Not reported
23	Piaggese 1998	9.2 +/- 3.0	17.52 +/- 9.51	0	0	Yes	0	Not reported	Not reported	Not reported
24	Rhaïem 1998	Not reported	13 +/- 10.6	Not reported	0.517	Not reported	Not reported	Not reported	0.55	Not reported

25	Roberts 2001	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
26	Shukrimi 2008	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
27	Singh 2006	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
28	Tallis 2013	Not reported	Not reported	0	0	Yes	Not reported	Not reported	Not reported	Not reported
29	Vandeputte 1997	Not reported	Not reported	Not reported	0.069	Not reported	Not reported	Not reported	Not reported	Not reported
30	Whalley 2001	Not reported	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported
Footnotes Study ID = Study Identification Hgba1c % = Hemoglobin A1c in percent Duration of DM = Duration of Diabetes in years PAD/PVD = Peripheral arterial disease/Peripheral vascular disease										

Table 12 Table of industry supported included studies		
[#]	[Study ID]	[Industry support] 0 = No, 1 = Yes, 2 = Unclear
1	Ali 2013	2
2	Amini 2013	0
3	Apelqvist 1990	1
4	Baker 1993	1
5	Belcaro 2010	2
6	Blackman 1994	1
7	Bowling 2011	1
8	Clever 1995	1
9	D'Hemeourt 1998	2
10	Donaghue 1998	1
11	EhsanUrRehman 2013	2
12	Foster 1994	2
13	Goretti 2008	1
14	Hammouri 2004	2
15	Jeffcoate 2009	2
16	Jensen 1998	1
17	Lalau 2002	1
18	Markevich 2000	2
19	Mazzone 1993	1
20	Munter 2006	1
21	Ogce 2007	2
22	Piaggese 2001	0
23	Piaggese 1998	2
24	Rhaem 1998	2
25	Roberts 2001	1
26	Shukrimi 2008	2
27	Singh 2006	2
28	Tallis 2013	1
29	Vandeputte 1997	2
30	Whalley 2001	2

Table 13 Table of study debridement types																
	Study															
		[Sur gical]	[W et to Dr y]	[Aqu eous Lava ge]	[Ultras ound]	[Biosurge ry/MDT]	[Enzy matic]	[Saline Gauze]	[Hydr ogels]	[Algi nates]	[Hydroc olloids]	[Fo am]	[Fi lm]	[Ho ney]	[Zi nc]	[Topica l Antimi crobial]
23	Piaggese 1998	Exp						Comp								
2	Amini 2013				Exp			Comp								
28	Tallis 2013						Exp	Comp								
20	Munter 2006							Comp								Exp
5	Belcaro 2010							Comp								Exp(Sil ver)
11	EhsanUr Rehman 2013							Comp						Exp		
14	Hammou ri 2004							Comp						Exp		
26	Shukrimi 2008							Comp						Exp		
25	Roberts 2001							Comp				Exp				
15	Jeffcoate 2009							Comp			Exp					
21	Ogce 2007							Comp			Exp					
22	Piaggese 2001							Comp			Exp					
10	Donaghu e 1998							Comp		Exp						
17	Lalau 2002							Comp		Exp						
9	D'Heme ourt 1998							Comp	Exp							
16	Jensen 1998							Comp	Exp							
17	Lalau 2002							Comp		Exp						
18	Markevi ch 2000					Exp			Comp							
19	Mazzone 1993		Co mp									Exp				
20	Munter 2006							Comp								Exp
21	Ogce 2007							Comp			Exp					
22	Piaggese 2001							Comp			Exp					
23	Piaggese 1998	Exp						Comp								
24	Rhaiem 1998													Exp		
25	Roberts 2001							Comp				Exp				
26	Shukrimi 2008							Comp						Exp		
27	Singh 2006	Com p			Exp											
28	Tallis 2013						Exp	Comp								
29	Vandepu tte 1997		Co mp						Exp							
30	Whalley 2001								Exp- Comp							

Table 14 Summary of Results, Overall Effect Sizes, and Heterogeneity								
			RR (95% CI) **MD (95% CI)		Heterogeneity of Outcome Effects Summary Statistics ^b			
Intervention comparison	Outcome	k	Fixed-Effects	Random-Effects	τ^2	χ^2	I ² (%)	p-value
Hydrogel vs. Gauze	Proportion of Amputations	2	0.26 (0.05, 1.37)	0.26 (0.05, 1.40)	0.00	0.11	0	0.74
	Proportion of Infections	3	0.87 (0.54, 1.40)	0.74 (0.18, 2.99)	0.91	4.89	59	0.09
	Proportion of Ulcers Healing	3	1.68 (1.14, 2.49)	1.71 (1.16, 2.52)	0.00	0.95	0	0.62
Foam vs. Wet to Dry	Proportion of Ulcers Healing 2 studies	2	4.35 (1.33, 14.29)	3.56 (0.93, 13.66)	0.18	1.15	13	0.28
Hydrofiber vs. Gauze	Proportion of Amputations 2 studies	2	1.31 (0.33, 5.16)	1.34 (0.29, 6.10)	0.05	1.03	3	0.31
	Proportion of Infections 2 studies	2	1.11 (0.84, 1.46)	0.96 (0.40, 2.31)	0.21	1.37	27	0.24
	Proportion of Ulcers Healing 2 studies	2	0.06 (0.06, 0.19)	0.07 (0.05, 0.19)	0.00	0.09	0	0.76
	Mean Time to Complete Healing 2 studies	2	** -13.87 (-27.91, 0.16)	** -53.37 (-153.29, 46.56)	4892.23	16.29	94	< 0.0001
Any debridement vs. Gauze	Proportion of Amputations 5 studies (n=6)	5	0.49 (0.19, 1.27)	0.48 (0.17, 1.37)	0.00	2.67	0	0.75
	Proportion of Infections 7 studies (n=8)	7	1.10 (0.89, 1.36)	1.07 (0.76, 1.52)	0.07	10.82	35	0.15
	Quality of Life 1 study (n=2)	1	-0.01 (-0.04, 0.01)	-0.01 (-0.04, 0.01)	0.00	0.00	0	0.95
	Proportion of Ulcers Healing 10 studies (n=11)	3	1.17 (1.00, 1.36)	1.22 (1.04, 1.44)	0.02	13.89	28	0.18
	Proportion of Ulcers Healing (two studies available only as abstracts)	10	1.12 (0.95, 1.32)]	1.18 (0.99, 1.41)	0.02	12.26	35	0.14
	Proportion of Ulcer Recurrence 2 studies (n=3)	2	0.77 (0.34, 1.71)	0.81 (0.25, 2.58)	0.42	3.29	39	0.19
	Mean Time to Complete Healing 4 studies (n=5)	4	2.54 (1.20, 3.87)	-27.88 (-52.53, -3.23)	614.40	39.33	90	< 0.00001
<p>Note:</p> <p>** indicates a significant effect; k represents the number of interventions for each outcome included in the analysis; Q represents Cochran's Q indicating significance of heterogeneity; I² represents the magnitude of heterogeneity; p-value represents the significance of heterogeneity.</p> <p>b) Relative risk (RR) was the effect estimate for proportion of amputations, proportion of infections, and proportion of ulcers healed, and proportion of recurrence. Mean difference (MD) was the effect estimate for the outcomes Quality of life, and Time to complete healing.</p>								

Table 15 Tests for Publication Bias			
Intervention	Outcome	Egger's	Begg's
Any debridement as compared with gauze	Proportion of Ulcers Healing	*p = 0.8958	**p = 0.5858
Footnote *2 tailed p-value * Beggs performed without continuity correction, 2 tailed p-value. Beggs and Eggers test for publication bias performed on outcomes and interventions that included 10 or more studies.			

Table 16 with scatterplot. Model for outcome Proportion of complicating infections using Age as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	12.8688	6.8830	-0.6217	26.3593	1.87	0.0615
age	-0.2132	0.1156	-0.4397	0.0133	-1.84	0.0651

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 3.40, df = 1, p = 0.0651

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0014, Tau = 0.0376, I² = 13.57%, Q = 6.94, df = 6, p = 0.3263

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 32.11%, Q = 10.31, df = 7, p = 0.1717

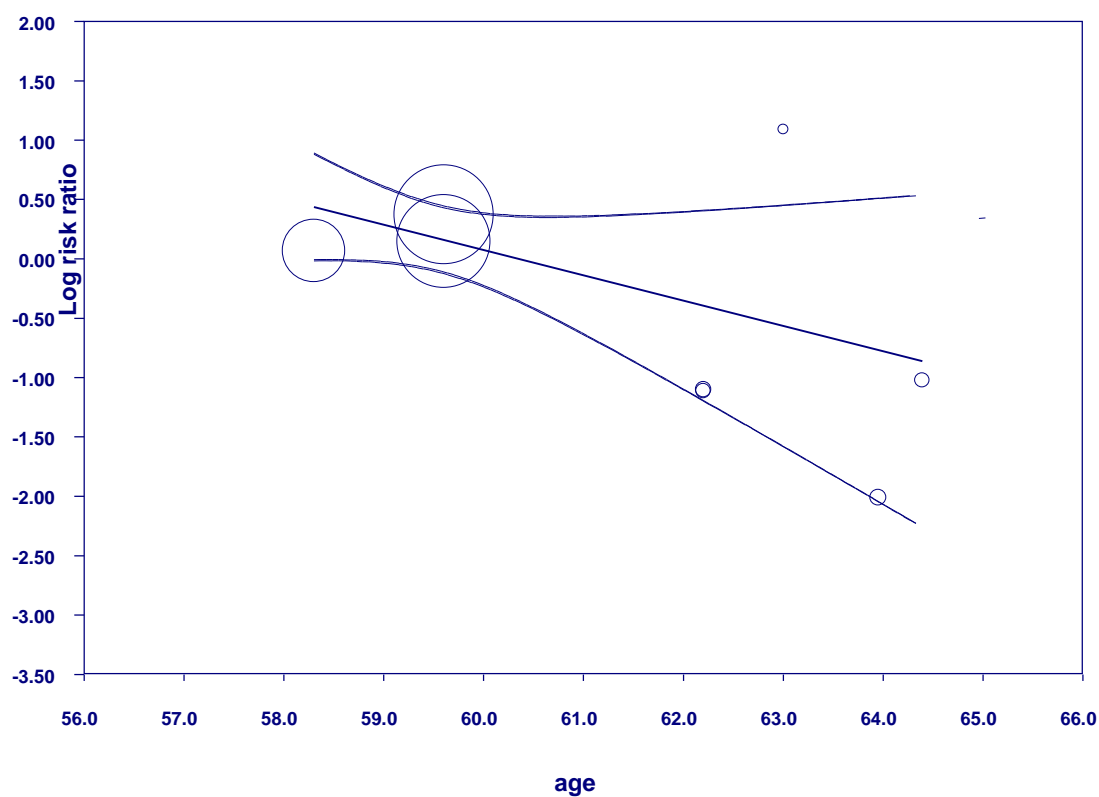
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 8

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Age(yrs.)	-0.2132	0.1156	3.40	0.0651	0.00	0.0014	6.94	13.57	0.3263

Regression of Log risk ratio on age



Age (years)

Coeff = -0.2132, CI = (-0.4397, 0.0133), $R^2 = 0.00$

Table 17 with scatterplot. Model for outcome proportion of ulcers healed using age as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.9828	1.9981	-2.9333	4.8989	0.49	0.6228
age	-0.0130	0.0322	-0.0760	0.0501	-0.40	0.6873

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.16, df = 1, p = 0.6873

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 1.68, df = 5, p = 0.8917

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 1.84, df = 6, p = 0.9338

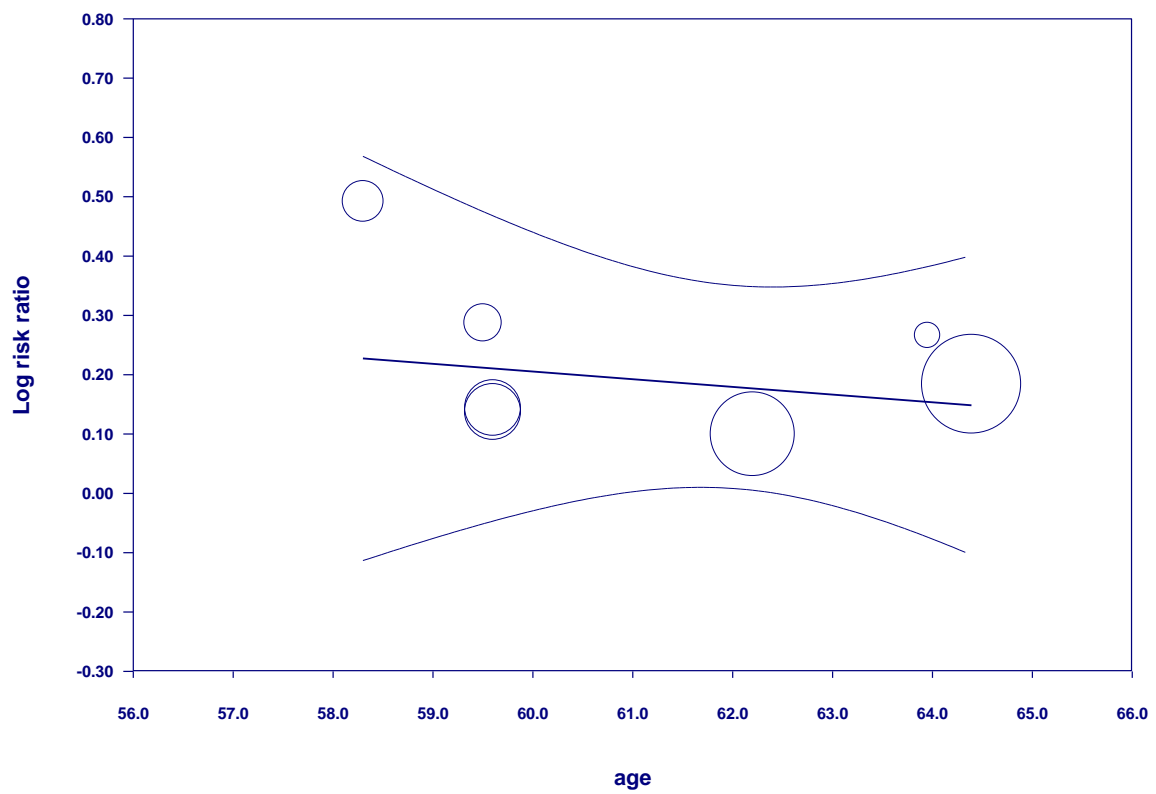
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 7

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Age (yrs.)	-0.0130	0.0322	0.16	0.6873	0.00	0.00	1.68	0.00	0.8917

Regression of Log risk ratio on age



Age (years)

Coeff = -0.0130, CI = (-0.0760, 0.0501), $R^2 = 0.00$

Table 18 with scatterplot. Model for outcome Proportion of complicating infections using Peripheral Arterial Disease (PAD) as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.4240	0.6431	-1.6844	0.8365	-0.66	0.5097
prop_pad	3.3706	3.2676	-3.0338	9.7750	1.03	0.3023

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 1.06, df = 1, p = 0.3023

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 9.82%, Q = 4.44, df = 4, p = 0.3502

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 9.09%, Q = 5.50, df = 5, p = 0.3580

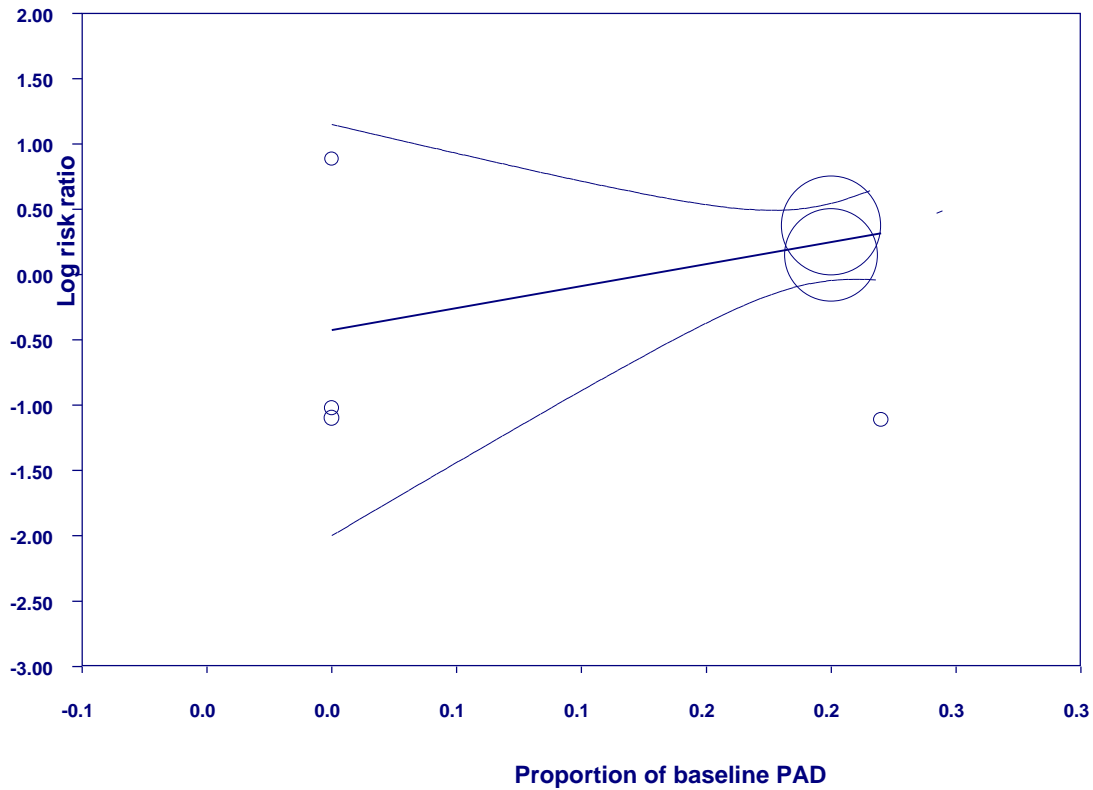
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 6

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Proportion with peripheral arterial disease	3.3706	3.2676	1.06	0.3023	0.00	0.00	4.44	9.82	0.3502

Regression of Log risk ratio on proportion of baseline PAD



Proportion of sample with Peripheral arterial disease

Coeff = 3.3706, CI = (-3.0338, 9.7750), $R^2 = 0.00$

Table 19 with scatterplot. Model for outcome ulcers healed using Peripheral Arterial Disease (PAD) as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	0.2227	0.0794	0.0671	0.3782	2.81	0.0050
prop_pad	-0.4095	0.8237	-2.0240	1.2050	-0.50	0.6191

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.25, df = 1, p = 0.6191

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 3.89, df = 4, p = 0.4206

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 4.14, df = 5, p = 0.5293

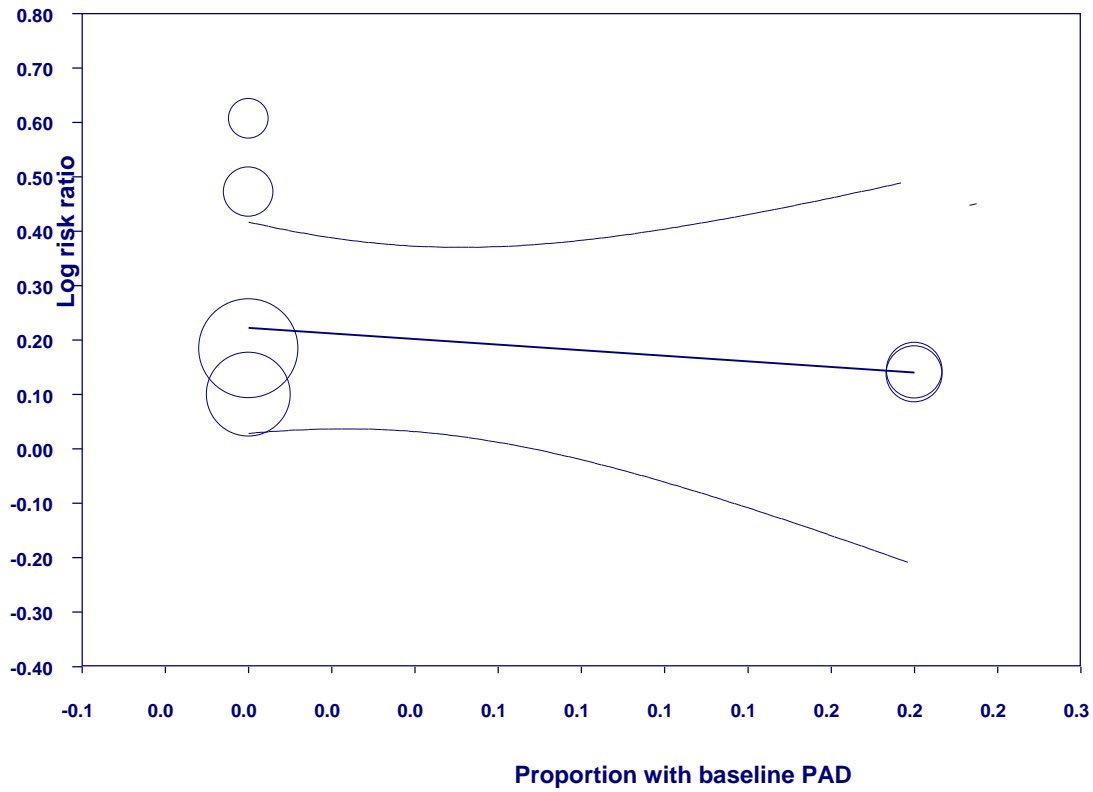
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 6

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Proportion of baseline with peripheral arterial disease	-0.4095	0.8237	0.25	0.6191	0.00	0.00	3.89	0.00	0.4206

Regression of Log risk ratio on Proportion with baseline PAD



Proportion of sample with peripheral arterial disease

Coeff = -0.4095, CI = (-2.0240, 1.2050), $R^2 = 0.00$

Table 20 with scatterplot. Model for outcome proportion of complicating infections using diabetes duration as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	2.6351	3.9921	-5.1893	10.4595	0.66	0.5092
diabetes_duration	-0.1528	0.2530	-0.6487	0.3432	-0.60	0.5460

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.36, df = 1, p = 0.5460

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 21.68%, Q = 5.11, df = 4, p = 0.2764

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 8.63%, Q = 5.47, df = 5, p = 0.3610

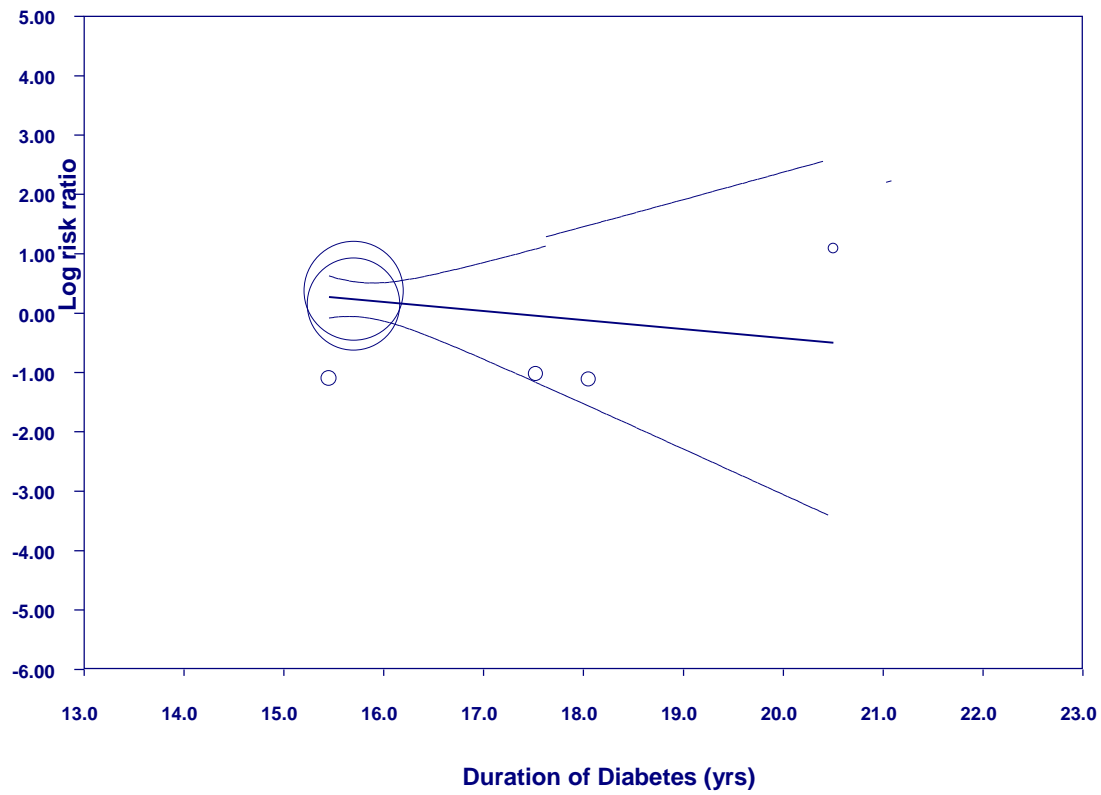
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 6

Outcome	Moderator	Coeff	Standard error	Q	p-value	R ²	Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Duration of diabetes (years)	-0.1528	0.2530	0.36	0.5460	0.00	0.00	5.11	21.68	0.2764

Regression of Log risk ratio on Duration of Diabetes



Duration of Diabetes (years)

Coeff = -0.1528, CI = (-0.6487, 0.3432), $R^2 = 0.00$

Table 21 with scatterplot. Model for outcome number of ulcers healed using duration of diabetes as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	-0.5355	1.1946	-2.8768	1.8058	-0.45	0.6539
diabetes_duration	0.0419	0.0723	-0.0999	0.1836	0.58	0.5625

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.34, df = 1, p = 0.5625

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 0.09, df = 3, p = 0.9930

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 0.43, df = 4, p = 0.9803

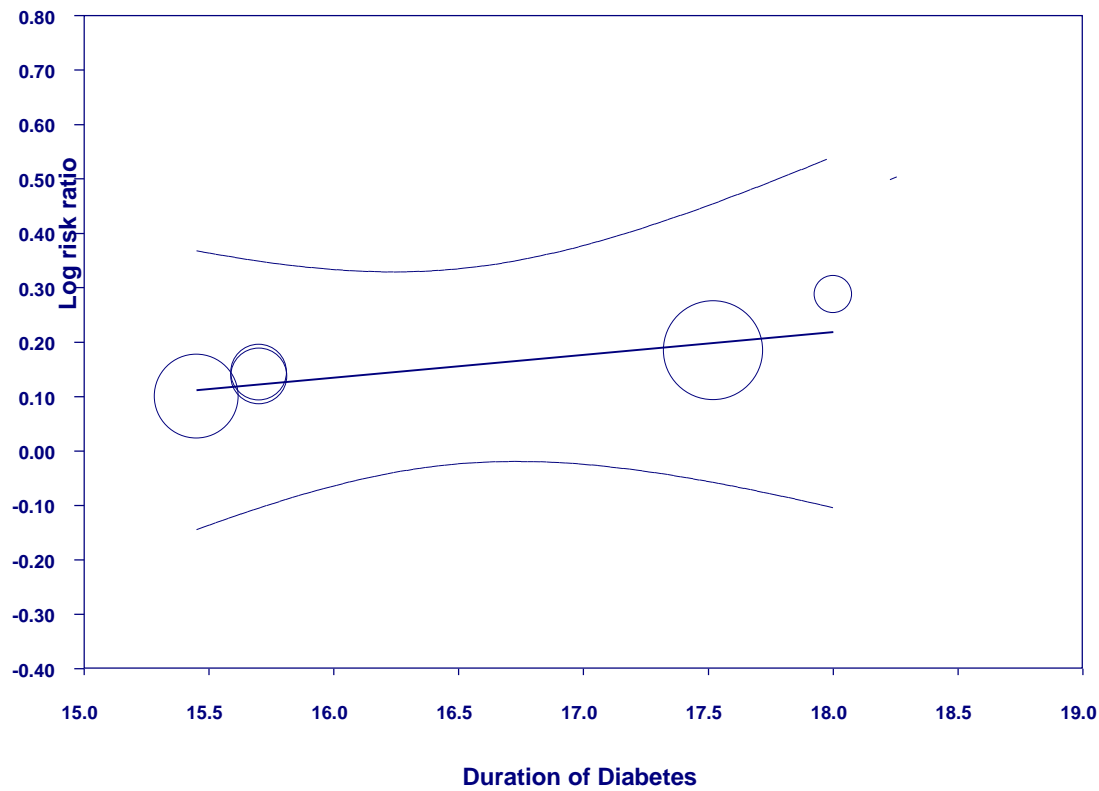
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 5

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Diabetes duration (years)	0.0419	0.0723	0.34	0.5625	0.00	0.00	0.09	0.00	0.9930

Regression of Log risk ratio on Duration of Diabetes



Diabetes Duration (years)

Coeff = 0.0419, CI = (-0.0999, 0.11836), $R^2 = 0.00$

Table 22 with scatterplot. Model for outcome proportion of complicating infections using proportion of females as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	1.7382	0.7012	0.3639	3.1125	2.48	0.0132
prop_fem	-6.1651	2.7765	-11.6070	-0.7232	-2.22	0.0264

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 4.93, df = 1, p = 0.0264

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 2.76, df = 4, p = 0.5995

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 34.95%, Q = 7.69, df = 5, p = 0.1744

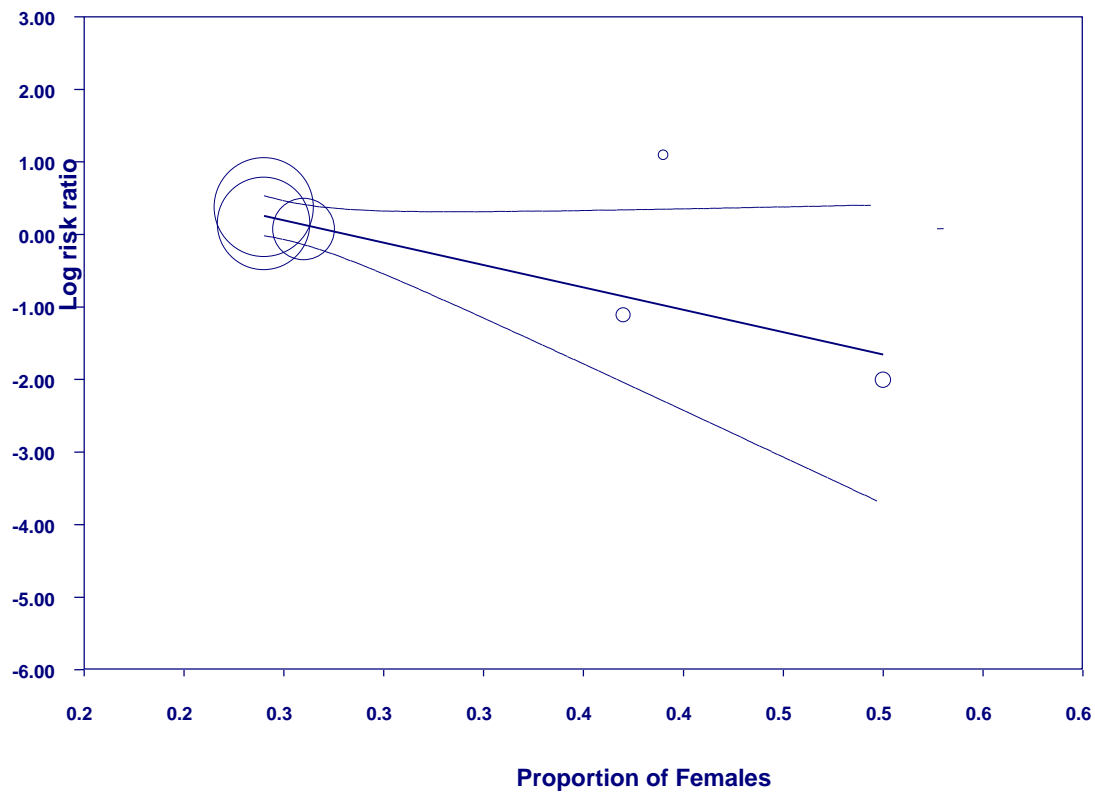
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 6

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Proportion of females	-6.1651	2.7765	4.93	0.0264	0.00	0.00	2.76	0.00	0.5995

Regression of Log risk ratio on Proportion of Females



Proportion of sample with females

Coeff = -6.1651, CI = (-11.6070, -0.7232), $R^2 = 0.00$

Table 23 with scatterplot. Model for outcome number of ulcers healed using proportion of females as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	0.1761	0.4165	-0.6402	0.9925	0.42	0.6724
prop_fem	0.2486	1.4998	-2.6909	3.1882	0.17	0.8683

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.03, df = 1, p = 0.8683

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 1.62, df = 4, p = 0.8053

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 1.65, df = 5, p = 0.8956

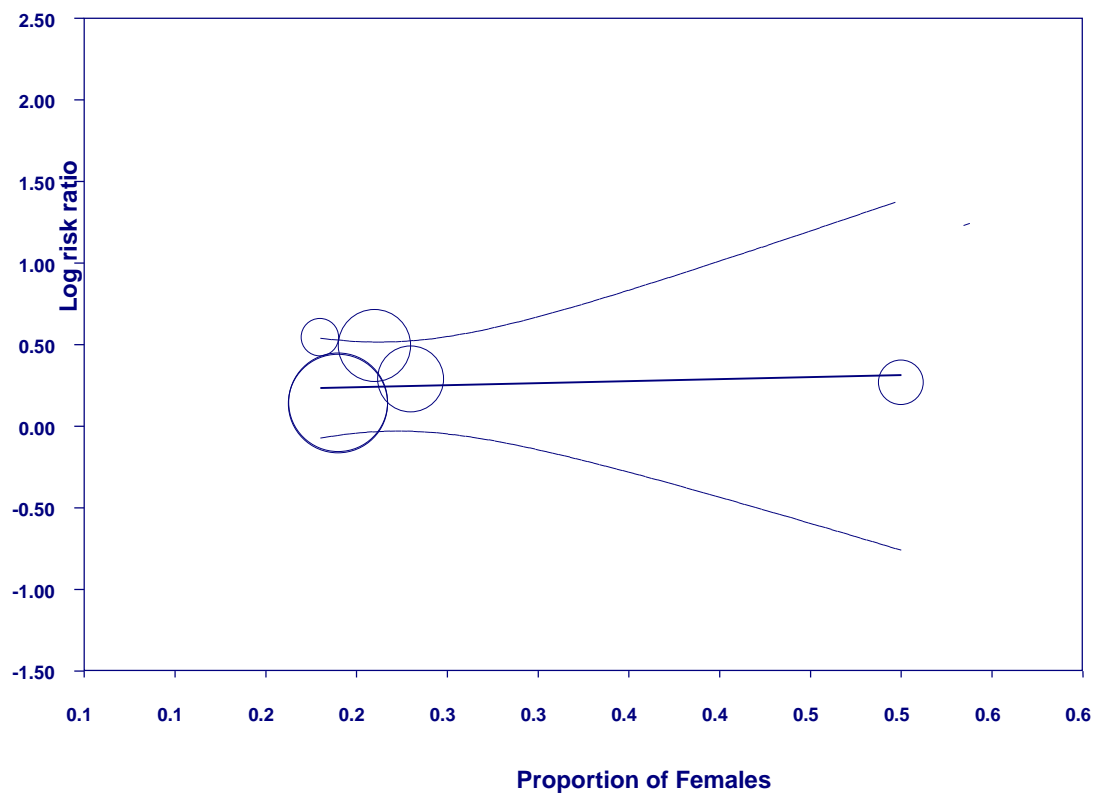
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 6

Outcome	Moderator	Coefficient	Standard error	Q	p-value	R ²	Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Proportion of females	0.2486	1.4998	0.03	0.8683	0.00	0.00	1.62	0.00	0.8053

Regression of Log risk ratio on Proportion of Females



Proportion of sample with females

Coeff = 0.2486, CI = (-2.6909, 3.1882), $R^2 = 0.00$

Table 24 with scatterplot. Model for outcome proportion of complicating infections using data collection year as moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-49.1028	57.2510	-161.3127	63.1072	-0.86	0.3911
data_yr	0.0246	0.0286	-0.0314	0.0806	0.86	0.3890

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.74, df = 1, p = 0.3890

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 3.98, df = 5, p = 0.5526

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 4.72, df = 6, p = 0.5802

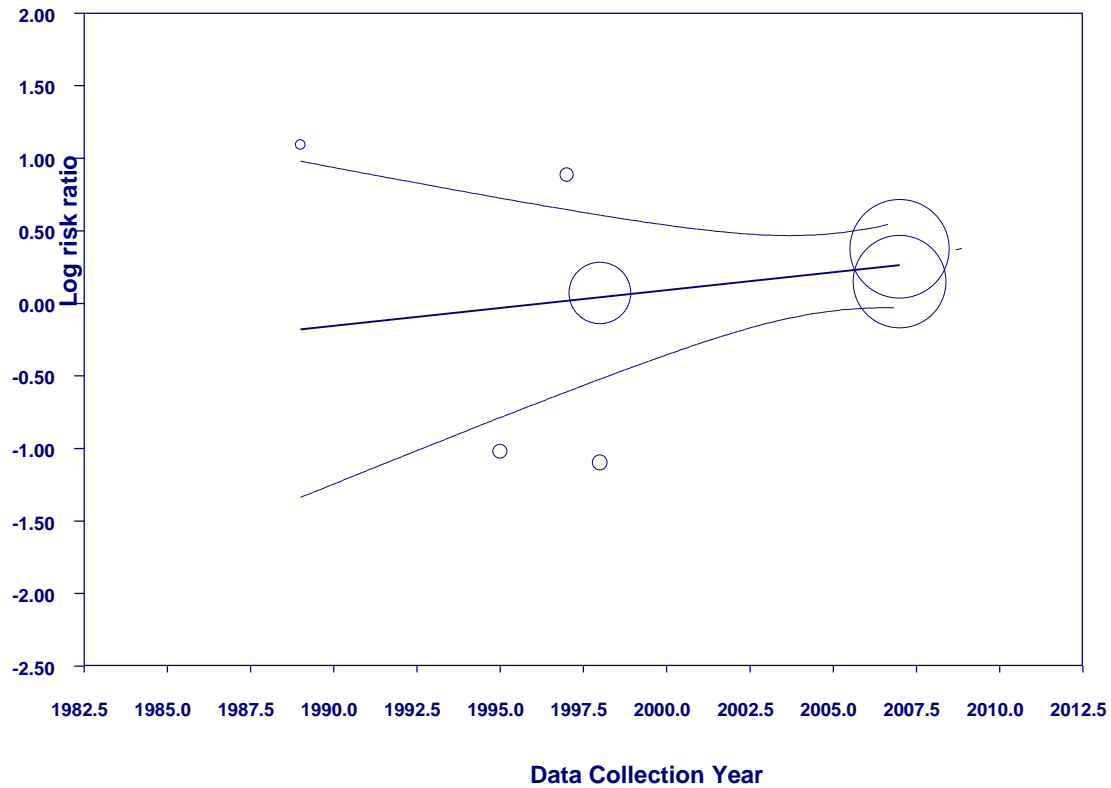
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 7

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Data collection year	0.0246	0.0286	0.74	0.3890	0.00	0.00	3.98	0.00	0.5526

Regression of Log risk ratio on Data Collection Year



Data Collection year

Coeff = 0.0246, CI = (-0.0314, 0.0806), $R^2 = 0.00$

Table 25 with scatterplot. Model for outcome number of ulcers healed using data collection year as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-2.2702	27.4233	-56.0190	51.4785	-0.08	0.9340
data_yr	0.0013	0.0137	-0.0256	0.0281	0.09	0.9274

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.01, df = 1, p = 0.9274

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 5.55, df = 8, p = 0.6972

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 5.56, df = 9, p = 0.7829

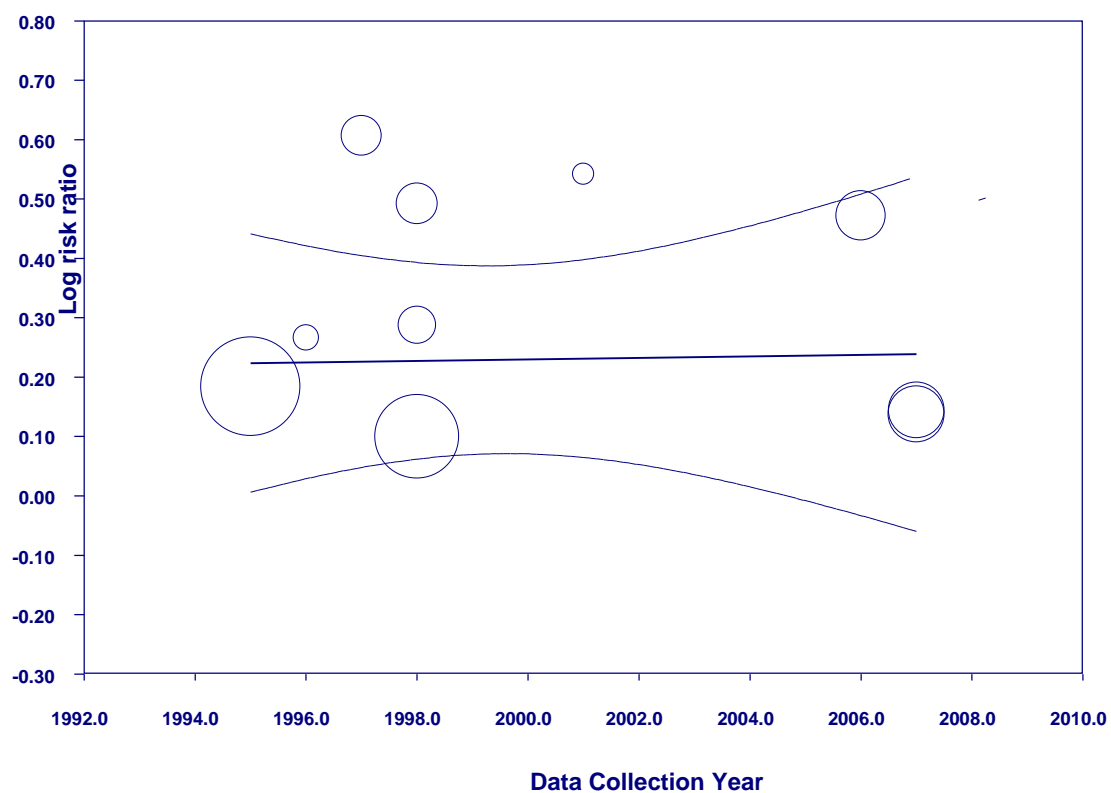
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 10

Outcome	Moderator	Coefficient	Standard error	Q	p-value	R ²	Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Data collection year	0.0013	0.0137	0.01	0.9274	0.00	0.00	5.55	0.00	0.6972

Regression of Log risk ratio on Data Collection Year



Data collection Year

Coeff = 0.0013, CI = (-0.0256, 0.0281), $R^2 = 0.00$

Table 26 with scatterplot. Model for outcome proportion of complicating infections using duration of follow up as moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.8985	0.8414	-2.5477	0.7506	-1.07	0.2856
short_f/u	0.0482	0.0365	-0.0232	0.1197	1.32	0.1857

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 1.75, df = 1, p = 0.1857

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 4.35, df = 6, p = 0.6294

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 6.10, df = 7, p = 0.5280

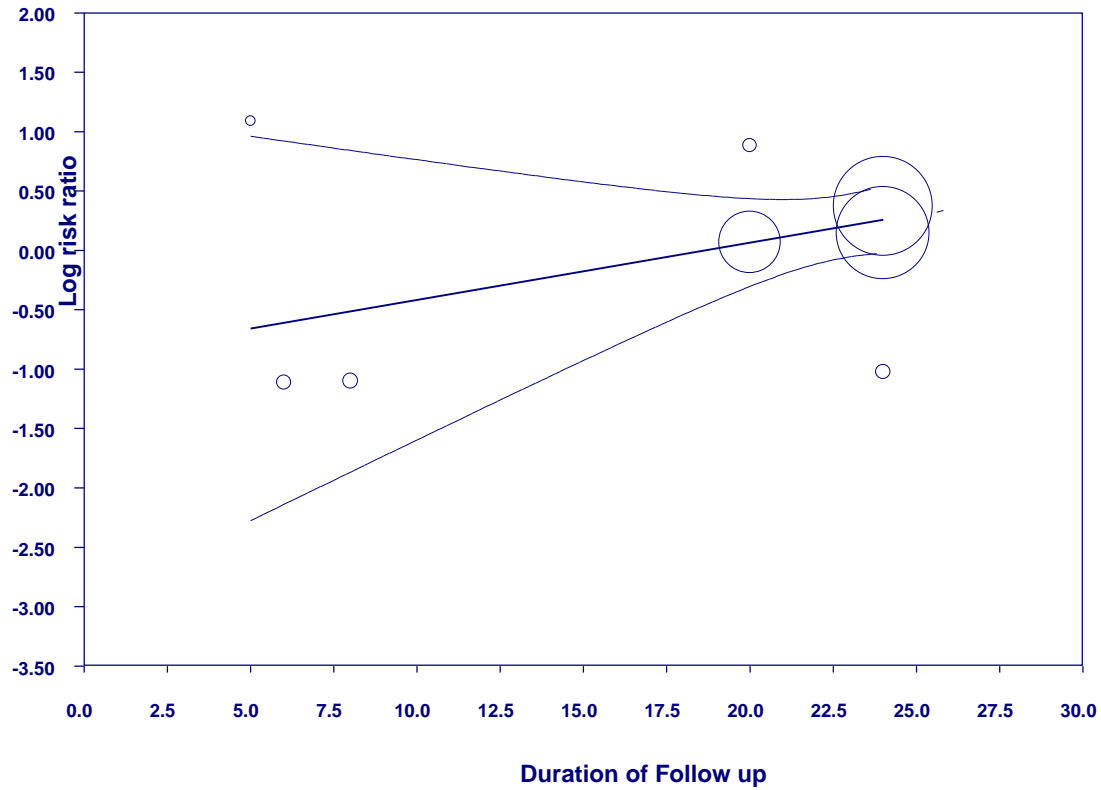
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 8

Outcome	Moderator	Coeff	Standard error	Model		R ²	Goodness of fit			
				Q	p-value		Tau ²	Q	I ² (%)	p-value
Proportion of Complicating Infections	Duration of follow up	0.0482	0.0365	1.75	0.1857	0.00	0.00	4.35	0.00	0.6294

Regression of Log risk ratio on Duration of Follow up



Follow up period (days)

Coeff = 0.0482, CI = (-0.0232, 0.1197), $R^2 = 0.00$

Table 27 with scatterplot. Model for outcome number of ulcers healed using duration of follow up as a moderator. Any debridement vs Moistened gauze.

Main results for Model 1, Random effects (ML), Z-Distribution, Log risk ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided p-value
Intercept	0.1365	0.1892	-0.2343	0.5074	0.72	0.4705
short_f/u	0.0048	0.0093	-0.0135	0.0232	0.52	0.6043

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.27, df = 1, p = 0.6043

Goodness of fit: Test that unexplained variance is zero

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 5.29, df = 7, p = 0.6252

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 5.55, df = 8, p = 0.6971

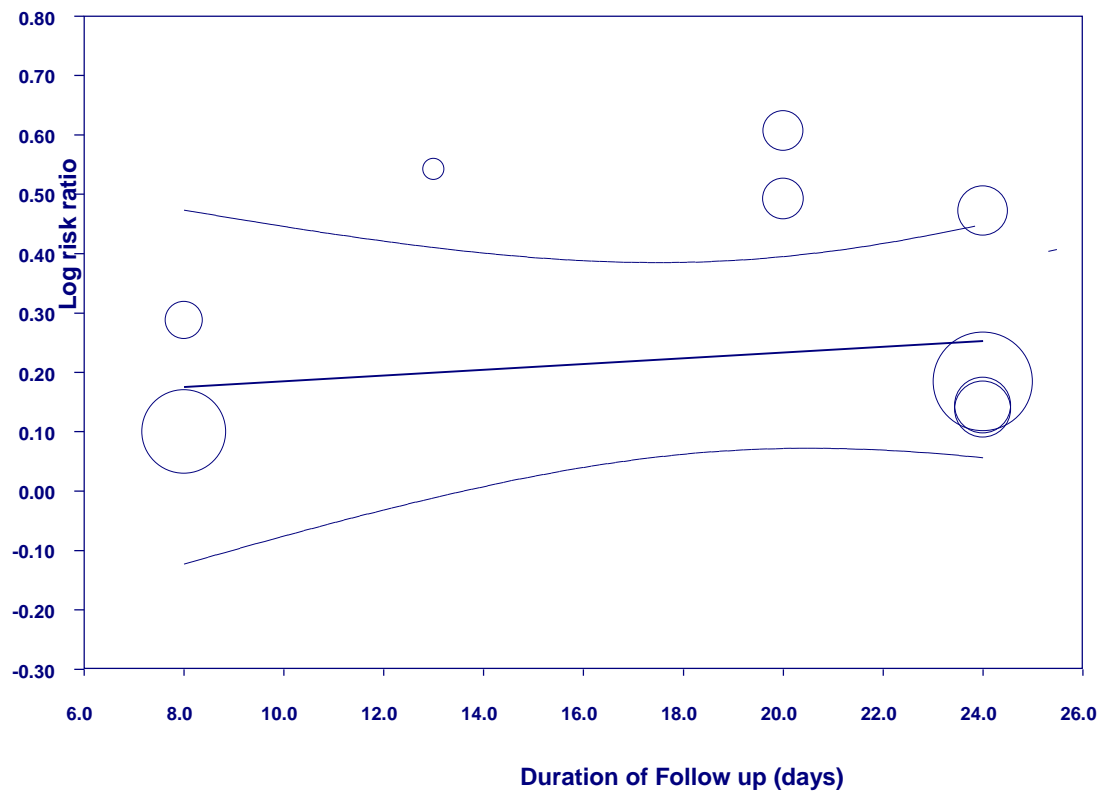
Proportion of total between-study variance explained by Model 1

R² analog = 0.00

Number of studies in the analysis 9

Outcome	Moderator	Coefficient	Standard error	Q	p-value	R ²	Tau ²	Q	I ² (%)	p-value
Proportion of ulcers healed	Duration of follow up	0.0048	0.0093	0.27	0.6043	0.00	0.00	5.29	0.00	0.6252

Regression of Log risk ratio on Duration of Follow up



Follow up period (days)

Coeff = 3.3706, CI = (-3.0338, 9.7750), $R^2 = 0.00$

Table 28 Moderators of effect size magnitude for the “Any debridement vs. gauze^a” comparison.					
Outcome(s)	Moderator(s)Characteristic(s)/Level(s)	RR (95% CI)	K^b	Coefficient	p-value
	Participant-specific demographic characteristics				
Proportion of infections	Age	1.07 (0.76, 1.52)	7	-0.2132	0.0651
	Risk-specific characteristics				
Proportion of infections	PAD ^c	1.07 (0.76, 1.52)	7	3.3706	0.3023
Proportion of infections	Duration of diabetes (yrs.)	1.07 (0.76, 1.52)	7	-0.1528	0.5460
Proportion of infections	Proportion of females	1.07 (0.76, 1.52)	7	-6.1651	0.0264
	Study-specific characteristics				
Proportion of infections	Data collection year	1.07 (0.76, 1.52)	7	0.0246	0.3890
Proportion of infections	Duration of follow up	1.07 (0.76, 1.52)	7	0.0482	0.1857
Proportion of Ulcers healed	Age	1.17 (1.00, 1.36)	10	-0.0130	0.6873
Proportion of Ulcers healed	PAD(c)	1.17 (1.00, 1.36)	10	-0.4095	0.6191
Proportion of Ulcers healed	Duration of diabetes (yrs.)	1.17 (1.00, 1.36)	10	0.0419	0.5626
Proportion of Ulcers healed	Proportion of females	1.17 (1.00, 1.36)	10	0.2486	0.8683
	Study-specific characteristics				
Proportion of Ulcers healed	Data collection year	1.17 (1.00, 1.36)	10	0.0013	0.9247
Proportion of Ulcers healed	Duration of follow up	1.17 (1.00, 1.36)	10	0.0048	0.6043
<p>a. Each moderator listed is evaluated individually without controlling for the other listed moderators. Effect sizes are based on random effects assumptions for the comparison and respective outcome listed in two columns. In this analysis there was 1 comparison (“any debridement” as compared with gauze) and 2 outcomes (proportion of infections, and Proportion of ulcers healed) that approximated a sufficient (number of studies): moderator ratio in order to facilitate moderator analysis.</p> <p>b. k = number of studies</p> <p>c. PAD = proportion with initial baseline peripheral arterial disease.</p>					

Table 29 Non-Significant Moderators
Non-Significant Moderators
All the following moderators assessed were non-significant.
Age
PAD (Peripheral arterial disease)
Duration of diabetes
Data collection year
Duration of follow up

Table 30 Moderators that were Unable to be analyzed due to lack of Reported Information
<p>235 coded variables on our data extraction form</p> <p>138 of these were non-effect size related variables.</p> <p>These were thoroughly reviewed as candidate variables for regression analysis and most were unable to be analyzed due to lack of reported information as either none of the studies reported certain outcomes or only very few did. Many had as few as 1 or no study reporting information. See Data extraction form Appendix 2.</p>

32 Summary of Finding Tables (SoF)

Hydrogel compared to Gauze/Good wound care (gwc) for Diabetic foot ulcers (DFU)

Hydrogel compared to Gauze/Good wound care (gwc) alone for Diabetic foot ulcer

Patient or population: patients with Diabetic foot ulcer

Settings: Outpatient

Intervention: Hydrogel

Comparison: Gauze/Good wound care (gwc) alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Gauze/Good wound care (gwc) alone	Hydrogel				
Number of amputations reported Follow-up: 20 weeks	Study population		RR 0.26 (0.05 to 1.4)	60 (2 studies)	⊕⊕⊕⊕ low ^{1,2,3}	
	19 per 100	5 per 100 (1 to 26)				
	Moderate					
	20 per 100	5 per 100 (1 to 27)				
Number of Infections reported Follow-up: 12 - 20 weeks	Study population		RR 0.74 (0.18 to 2.99)	198 (3 studies)	⊕⊕⊕⊕ very low ^{1,2,4,5,6}	
	27 per 100	20 per 100 (5 to 82)				
	Moderate					
	28 per 100	21 per 100 (5 to 83)				
Number of ulcers completely healed Follow-up: 12 - 20 weeks	Study population		RR 1.71 (1.16 to 2.52)	198 (3 studies)	⊕⊕⊕⊕ low ^{1,7}	
	26 per 100	45 per 100 (30 to 66)				
	Moderate					
	35 per 100	60 per 100 (41 to 89)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Many of the risk of bias characteristics were either unclear or high.

² The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit.

³ 2/3 did not mention whether industry support was sought and the studies yet all had negative findings.

⁴ No explanation was provided

⁵ Point estimates are far apart and confidence intervals do not overlap.

⁶ The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable harm.

⁷ The total (cumulative) sample size is lower than the calculated OIS.

Table 33 Summary of Findings Table

Foam dressing compared with Wet to Dry Saline for DFU

Foam dressing compared to Wet to Dry Saline for Diabetic foot ulcer

Patient or population: patients with Diabetic foot ulcer

Settings:

Intervention: Foam dressing

Comparison: Wet to Dry Saline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Wet to Dry Saline	Corresponding risk Foam dressing				
Number of ulcers completely healed Follow-up: 8 to 24 weeks	Study population		RR 3.56 (0.93 to 13.66)	37 (2 studies)	⊕⊕⊖⊖ low ^{1,2,3}	
	13 per 100	47 per 100 (12 to 100)				
	Moderate					
	12 per 100	44 per 100 (12 to 100)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Many of the risk of bias characteristics were either unclear or high.

² The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit.

³ The total (cumulative) sample size is lower than the calculated Optimal Information Size OIS and/or total number of events is less than 300 (a threshold rule-of-thumb value) (based on: Mueller et al. Ann Intern Med. 2007;146:878)

Table 34 Summary of Findings Table

Hydrofiber compared to Gauze dressing for DFU

Hydrofiber compared to Gauze dressing for Diabetic foot ulcers						
Patient or population: patients with Diabetic foot ulcers						
Settings: Outpatient						
Intervention: Hydrofiber						
Comparison: Gauze dressing						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Gauze dressing	Hydrofiber				
Number of amputations reported	Study population		RR 1.34 (0.29 to 6.1)	229 (2 studies)	⊕⊕⊖⊖ low ^{1,2,3}	
	3 per 100	3 per 100 (1 to 16)				
	Moderate					
	6 per 100	8 per 100 (2 to 36)				
Number of Infections reported Follow-up: 8 - 24 weeks	Study population		RR 0.96 (0.4 to 2.31)	229 (2 studies)	⊕⊕⊖⊖ low ^{1,2,3}	
	44 per 100	42 per 100 (18 to 100)				
	Moderate					
	38 per 100	36 per 100 (15 to 87)				
Number of ulcers completely healed Follow-up: 8 - 24 weeks	Study population		RR 1.13 (0.92 to 1.38)	229 (2 studies)	⊕⊕⊖⊖ low ^{1,2,4}	
	43 per 100	49 per 100 (40 to 59)				
	Moderate					
	64 per 100	73 per 100 (59 to 89)				
Time to complete healing (days) Scale from: 0 to 295. Follow-up: 8 to 24 weeks	The mean time to complete healing (days) ranged across control groups from 78.3 to 295 days	The mean time to complete healing (days) in the intervention groups was 53.37 lower (153.29 lower to 46.56 higher)		229 (2 studies)	⊕⊖⊖⊖ very low ^{1,5,6,7}	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						
CI: Confidence interval; RR: Risk ratio;						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						
¹ Many of the risk of bias characteristics were either unclear or high.						
² The total (cumulative) sample size is lower than the calculated optimal information size (OIS) and total number of events is less than 300 (a threshold rule-of-thumb value) (based on: Mueller et al. Ann Intern Med. 2007;146:878-881).						
³ The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit and appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.						
⁴ The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.						
⁵ There exists widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggesting true differences in underlying treatment effect.						
⁶ The total (cumulative) sample size is lower than the calculated Optimal Information Size (OIS) and/or total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β, and an effect size of 0.2 SD, representing a small effect).						
⁷ The 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit or harm (Note: if the MID is not known or the use of different outcomes measures required calculation of an (ES), we suggest downgrading if the upper or lower confidence limit crosses an effect size of 0.5 in either direction).						

35 Any debridement compared to Gauze control for Diabetic Foot Ulcers

Any debridement compared to Saline gauze for Diabetic Foot Ulcers						
Patient or population: patients with Diabetic Foot Ulcers						
Settings:						
Intervention: Any debridement						
Comparison: Saline gauze						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Saline gauze	Any debridement				
Number of amputations reported Follow-up: 8 to 24 weeks	Study population		RR 0.48 (0.17 to 1.37)	443 (5 studies)	⊕⊕⊖⊖ low ^{1,2}	
	6 per 100	3 per 100 (1 to 8)				
	Moderate					
	5 per 100	2 per 100 (1 to 7)				
Number of Infections reported Follow-up: 4 to 24 weeks	Study population		RR 1.07 (0.76 to 1.52)	659 (7 studies)	⊕⊕⊖⊖ low ^{1,2}	
	30 per 100	32 per 100 (23 to 46)				
	Moderate					
	29 per 100	31 per 100 (22 to 44)				
Number of ulcers completely healed Follow-up: 4 to 24 weeks	Study population		RR 1.22 (1.04 to 1.44)	798 (10 studies)	⊕⊖⊖⊖ very low ^{1,2,3}	
	40 per 100	49 per 100 (41 to 57)				
	Moderate					
	40 per 100	48 per 100 (41 to 57)				
Number of ulcers completely healed - Any Debridement vs Saline Gauze Follow-up: 4 to 24 weeks	Study population		RR 1.18 (0.99 to 1.41)	728 (8 studies)	⊕⊕⊖⊖ low ²	
	40 per 100	47 per 100 (39 to 56)				
	Moderate					
	40 per 100	47 per 100 (39 to 56)				
Number of ulcers completely healed - SA w/o Abstracts Follow-up: 13 to 24 weeks	Study population		RR 1.57 (1.05 to 2.35)	70 (2 studies)	⊕⊕⊖⊖ low ^{1,2}	
	42 per 100	65 per 100 (44 to 98)				
	Moderate					
	40 per 100	63 per 100 (42 to 94)				
Quality of life Scale from: 0 to 100. Follow-up: 13 to 24 weeks		The mean quality of life in the intervention groups was 0.01 lower (0.04 lower to 0.01 higher)		317 (1 study)	⊕⊕⊖⊖ low ^{1,4}	
Time to complete healing (days) Follow-up: 8 to 24 weeks		The mean time to complete healing (days) in the intervention groups was 27.88 lower (52.53 to 3.23 lower)		458 (4 studies)	⊕⊕⊖⊖ low ^{1,5}	
Recurrence rates	Study population		RR 0.81 (0.25 to 2.58)	357 (2 studies)	⊕⊕⊖⊖ low ^{1,2}	
	88 per 1000	71 per 1000 (22 to 227)				
	Moderate					
	38 per 1000	31 per 1000 (9 to 98)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded as substantial risk of bias characteristics were either unclear or high.

² Downgraded due to the 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

³ Downgraded for asymmetric funnel plot distribution around the null value is observed favoring a positive effect that includes studies with smaller sample sizes.

⁴ Downgraded due to total (cumulative) sample size is lower than the calculated optimal information size (OIS) and/or total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β , and an effect size of less than 0.2 SD, representing a small effect). 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm.

⁵ Downgraded due to widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect.

Figures

Figure 1 Serial images depicting measurements of wound progress over the course of sequential combined forms of debridement lasting 12 weeks including sharp, enzymatic, and autolytic.



Figure 2 Study selection Prisma flow diagram.

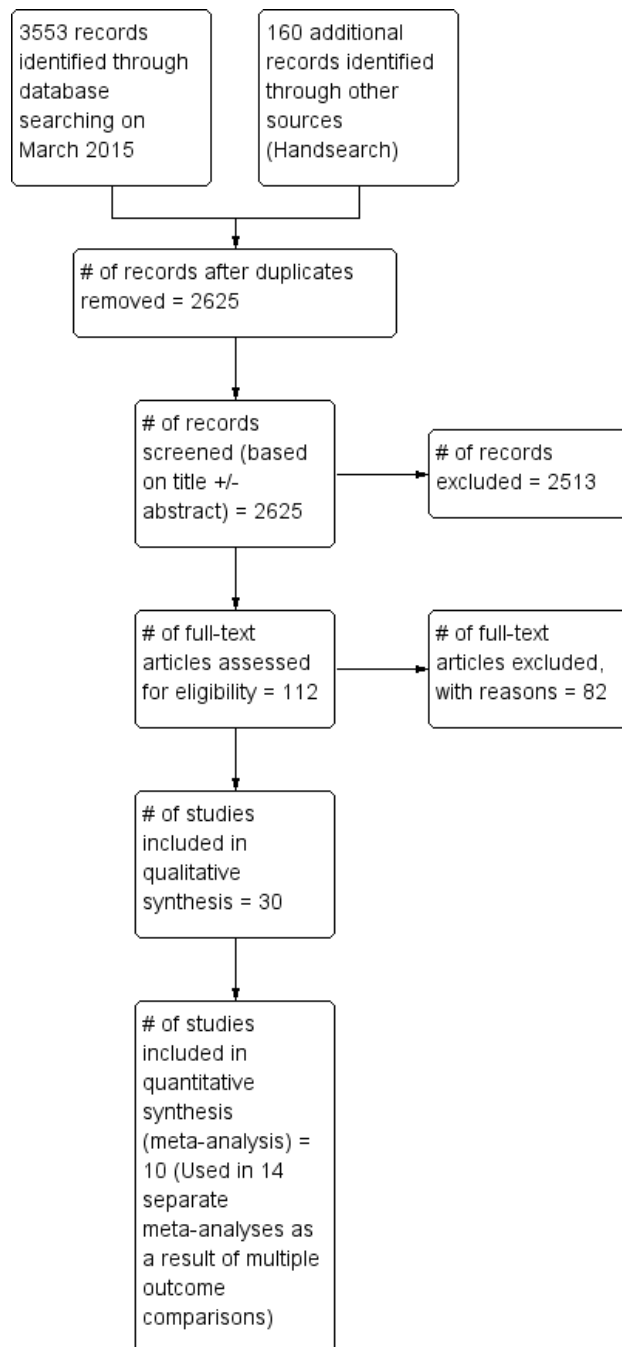
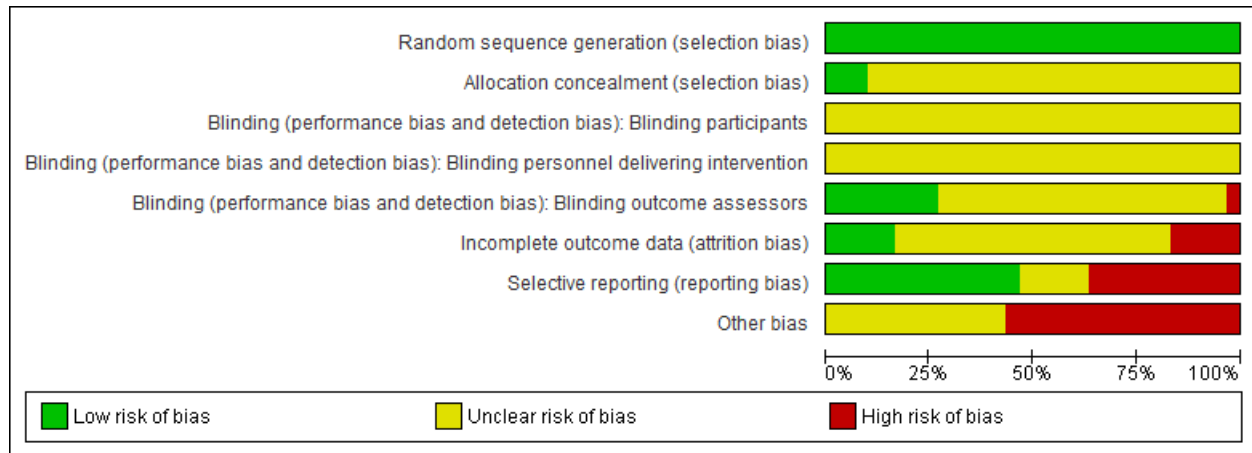


Figure 3 Methodological quality graph across all studies



Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 4 Methodological quality summary review of risk of bias tables across all studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Blinding participants	Blinding (performance bias and detection bias): Blinding personnel delivering intervention	Blinding (performance bias and detection bias): Blinding outcome assessors	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2013	+	?	?	?	+	?	+	?
Amini 2013	+	?	?	?	?	?	+	?
Apelqvist 1990	+	?	?	?	+	?	+	?
Baker 1993	+	?	?	?	?	?	?	+
Belcaro 2010	+	?	?	?	?	+	+	?
Blackman 1994	+	?	?	?	?	+	+	+
Bowling 2011	+	+	?	?	?	?	+	?
Clever 1995	+	?	?	?	?	+	+	+
D'Hemecourt 1998	+	?	?	?	+	+	+	+
Donaghue 1998	+	?	?	?	?	?	+	?
EhsanUrRehman 2013	+	?	?	?	?	?	+	+
Foster 1994	+	?	?	?	?	+	+	+
Goretti 2008	+	?	?	?	?	?	+	?
Hammouri 2004	+	?	?	?	?	?	+	+
Jeffcoate 2009	+	+	?	?	+	+	+	+
Jensen 1998	+	?	?	?	?	+	?	+
Lalau 2002	+	?	?	?	+	?	+	+
Markevich 2000	+	?	?	?	?	?	?	?
Mazzone 1993	+	?	?	?	?	?	?	+
Munter 2006	+	?	?	?	?	+	+	+
Ogce 2007	+	?	?	?	?	?	+	?
Piaggese 1998	+	?	?	?	?	?	+	+
Piaggese 2001	+	?	?	?	+	+	+	?
Rhalem 1998	+	?	?	?	?	?	+	+
Roberts 2001	+	?	?	?	?	?	+	+
Shukrimi 2008	+	?	?	?	+	?	+	?
Singh 2006	+	?	?	?	+	?	+	?
Tallis 2013	+	+	?	?	?	+	+	+
Vandeputte 1997	+	?	?	?	+	?	+	+
Whalley 2001	+	?	?	?	?	?	?	?

Methodological quality summary:
review authors' judgements about
each methodological risk of bias
quality item for each included
study.

Figure 5 Distribution of sample sizes for included studies

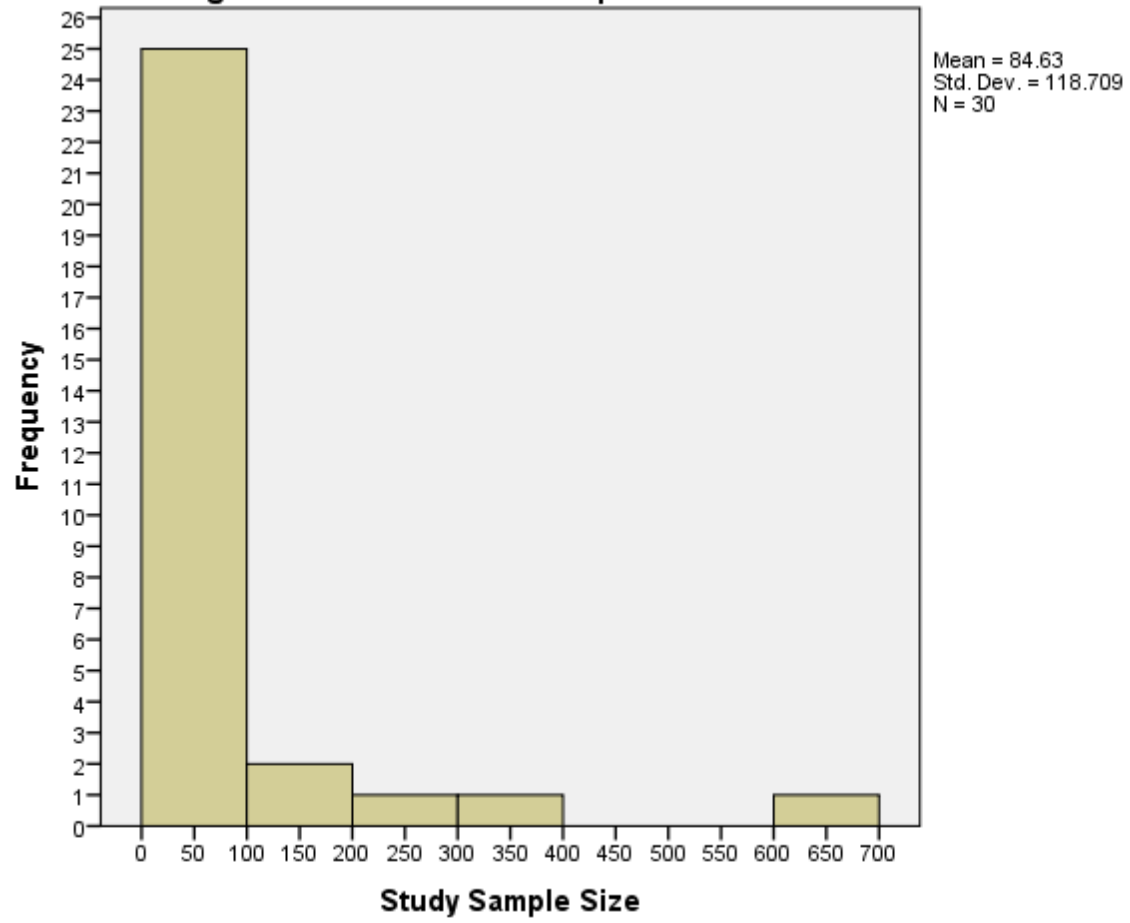


Figure 6 Distribution of year data collection was completed

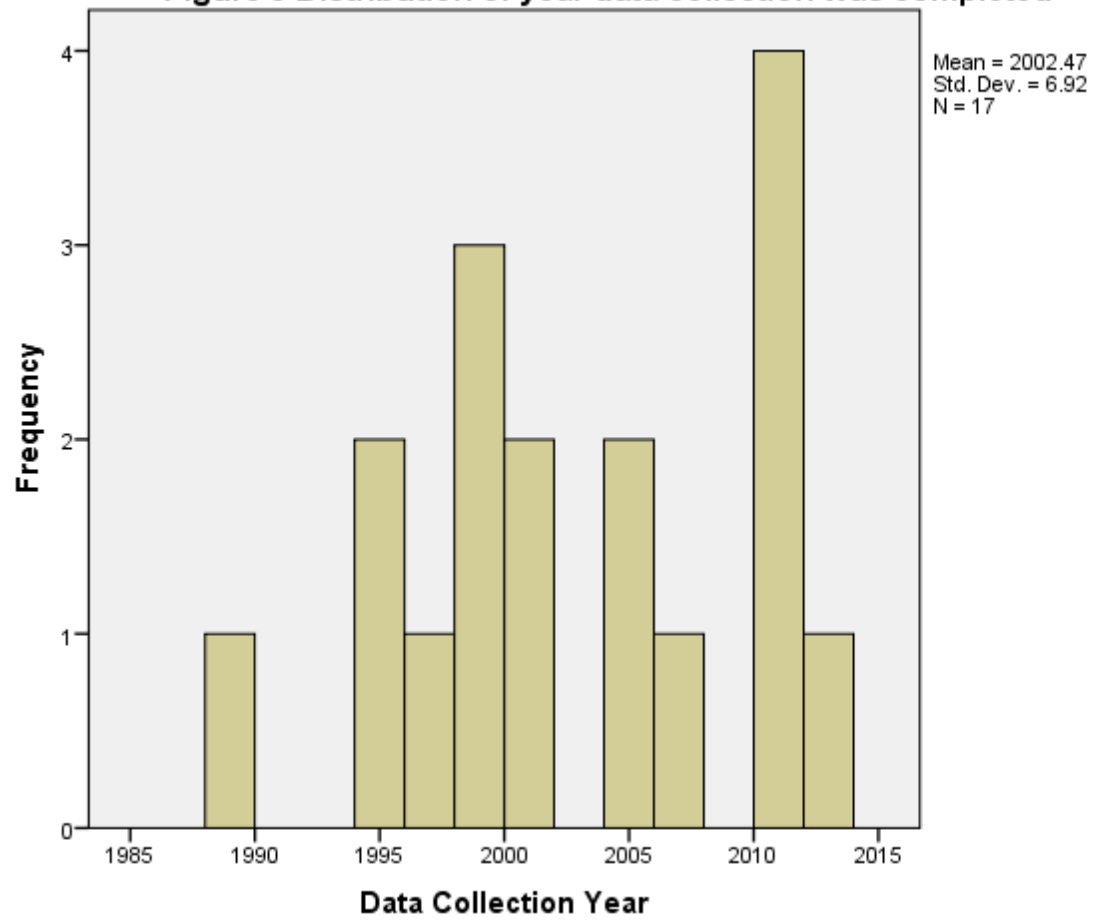


Figure 7 Distribution of mean sample ages for the included studies

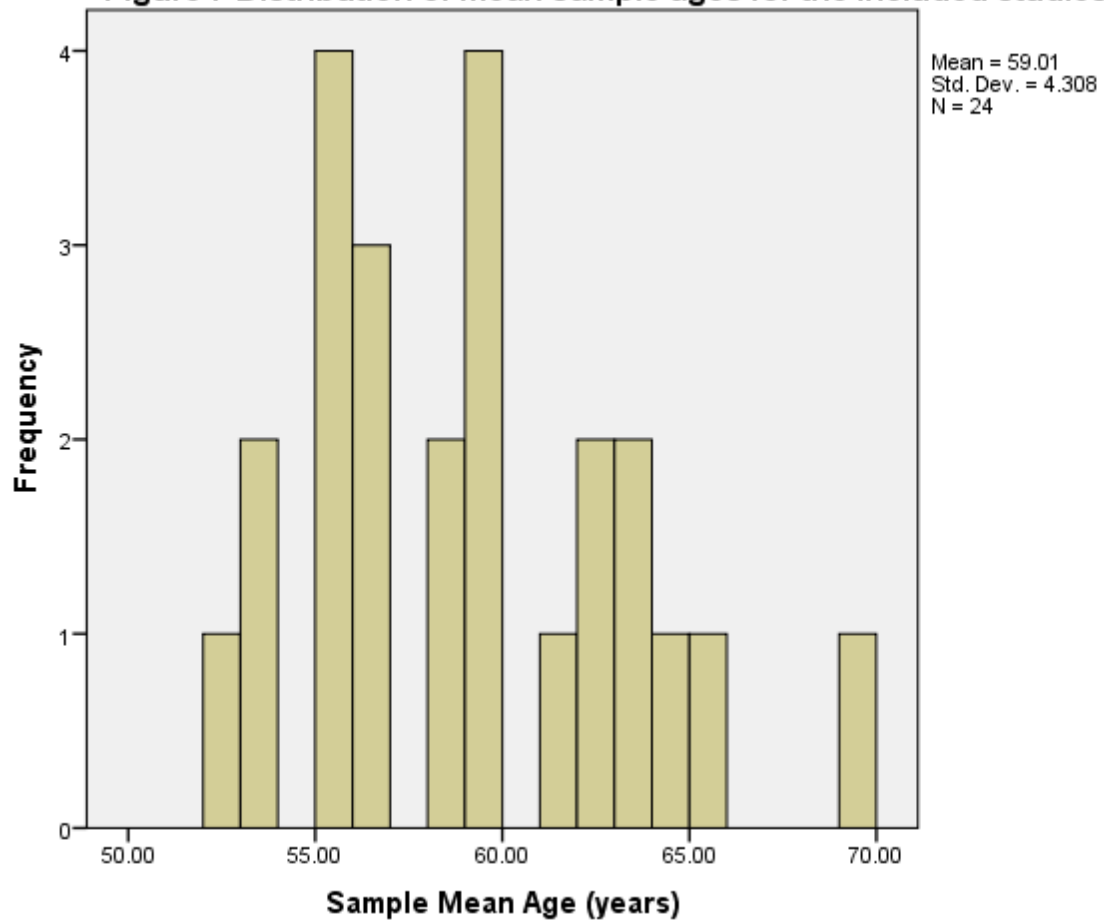


Figure 8 Frequency distribution for number of females in the included studies

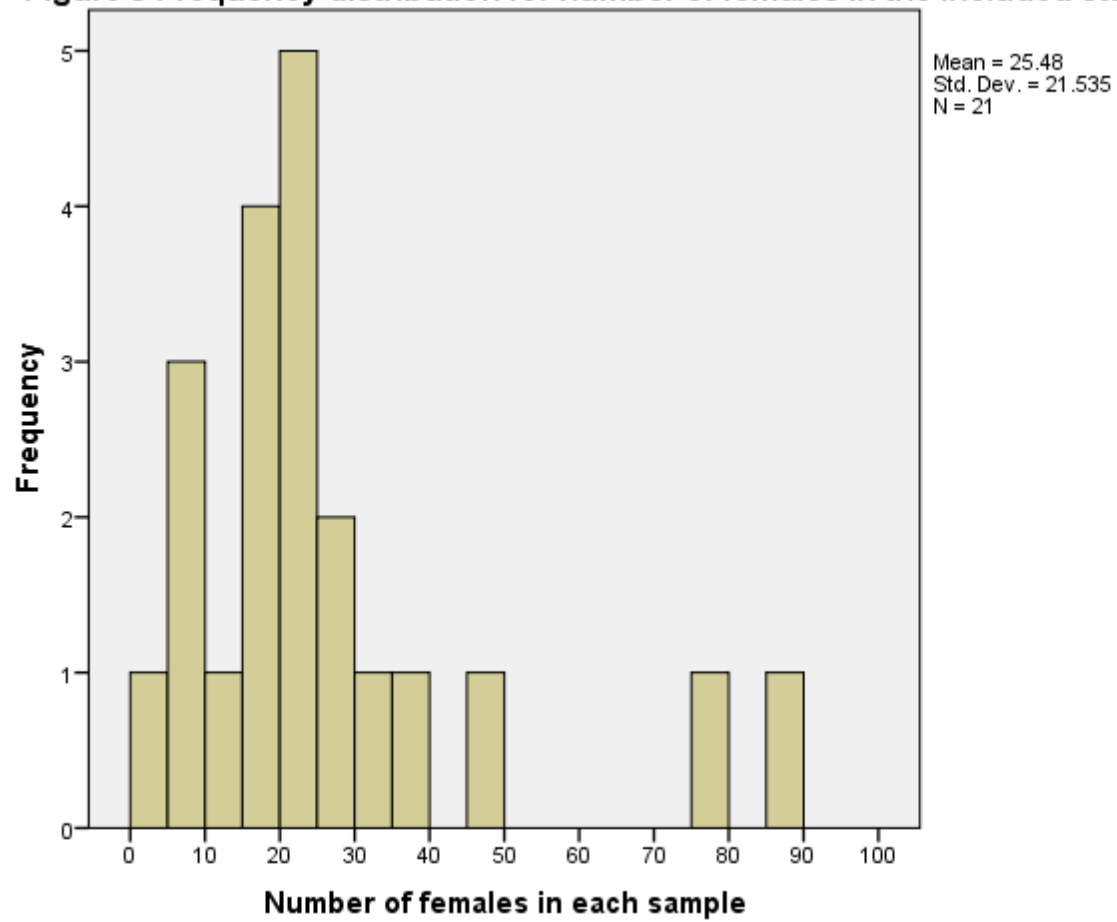


Figure 9 Frequency distribution for the number of males in the included studies

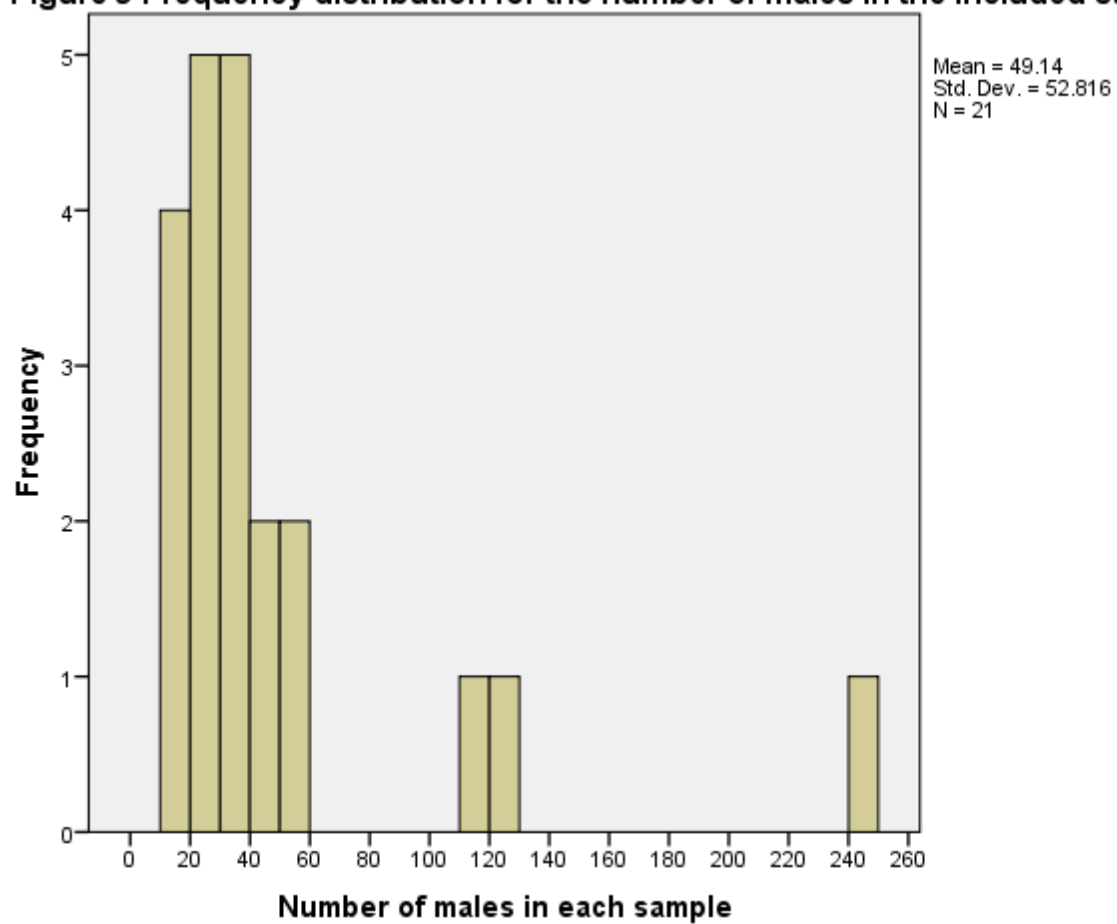


Figure 10 Frequency distribution of baseline mean surface area (cm2) in the experimental groups for the included studies

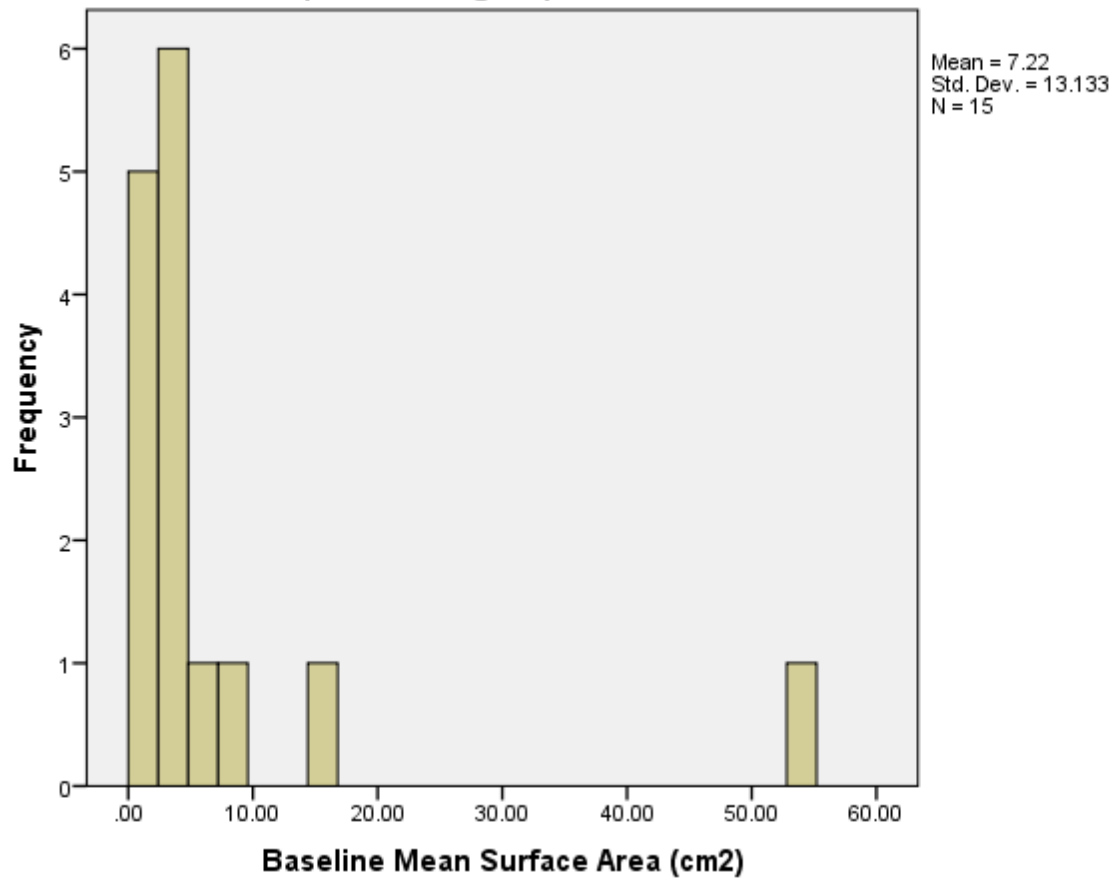


Figure 11 Frequency distribution of baseline mean wound surface area (cm²) in the control groups for the included studies

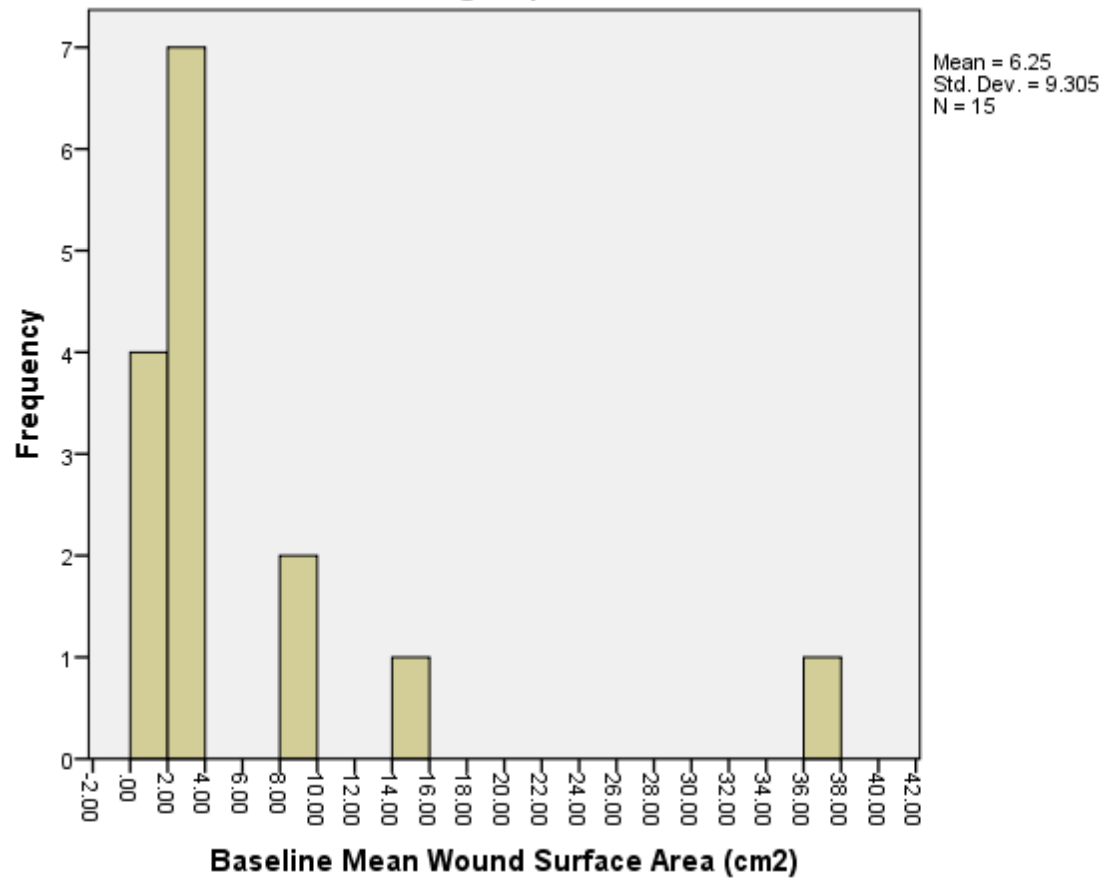


Figure 12 Frequency distribution of the baseline mean wound duration (weeks) in the experimental groups for the included studies

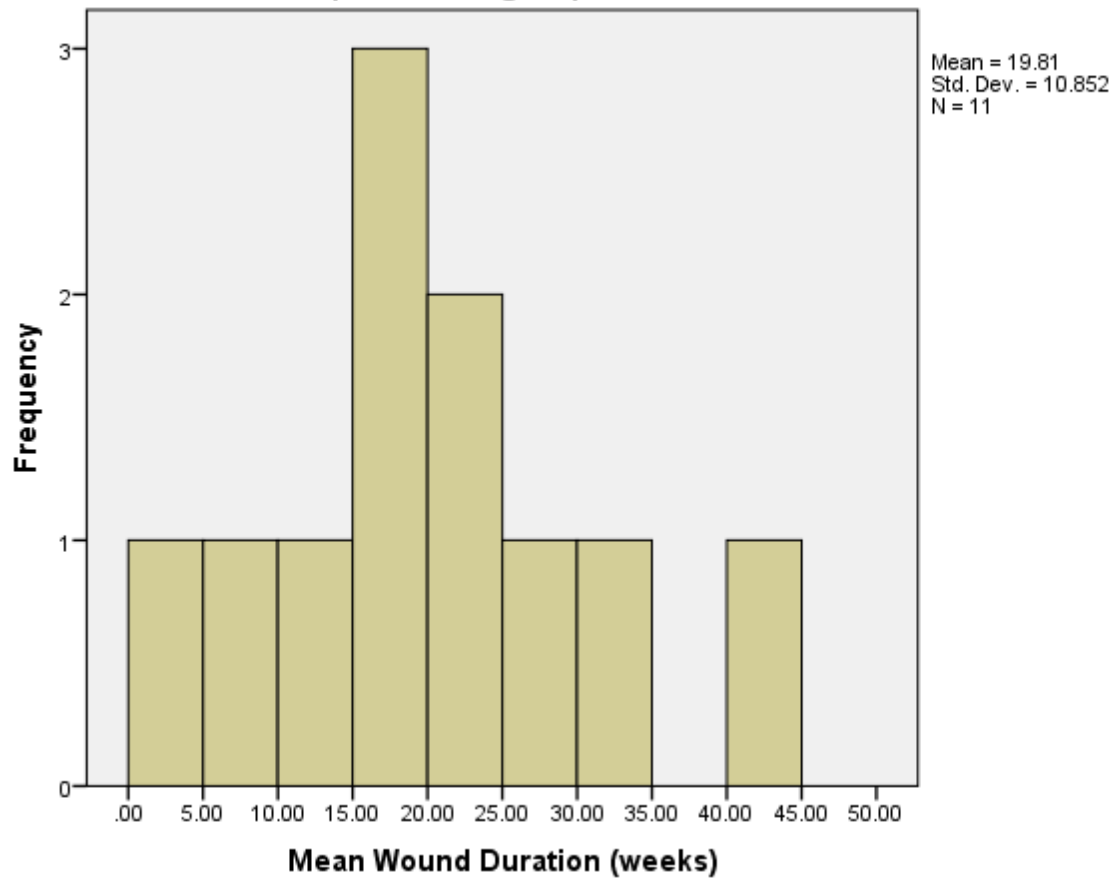


Figure 13 Frequency distribution of the baseline mean wound duration in the control groups for the included studies

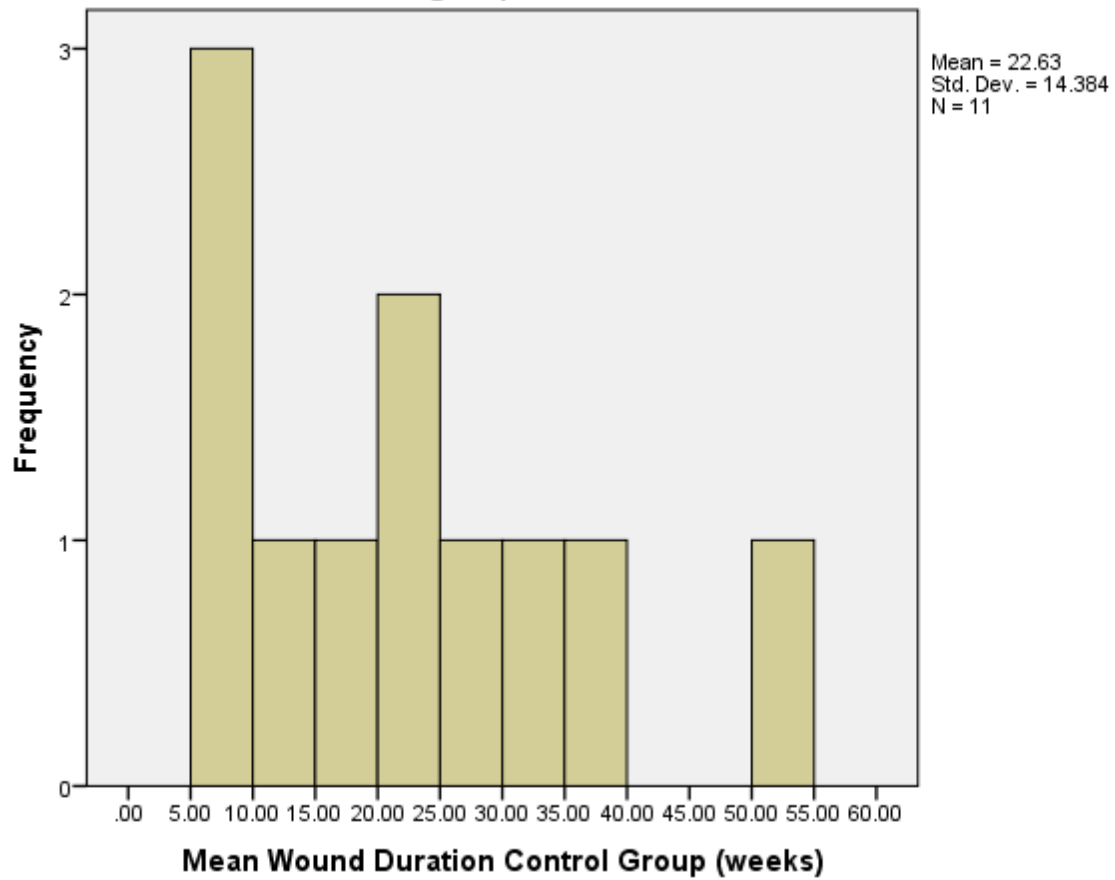


Figure 14 Frequency distribution of the baseline Hgba1c sample means

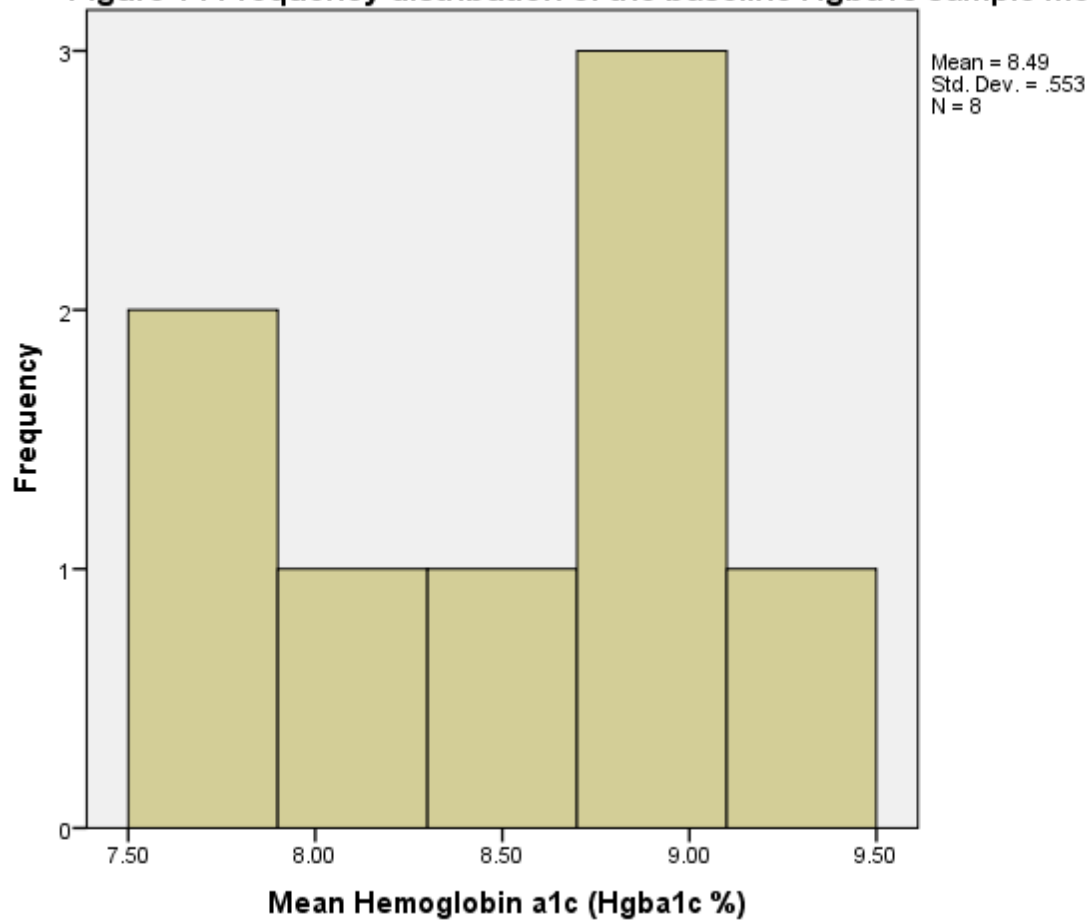
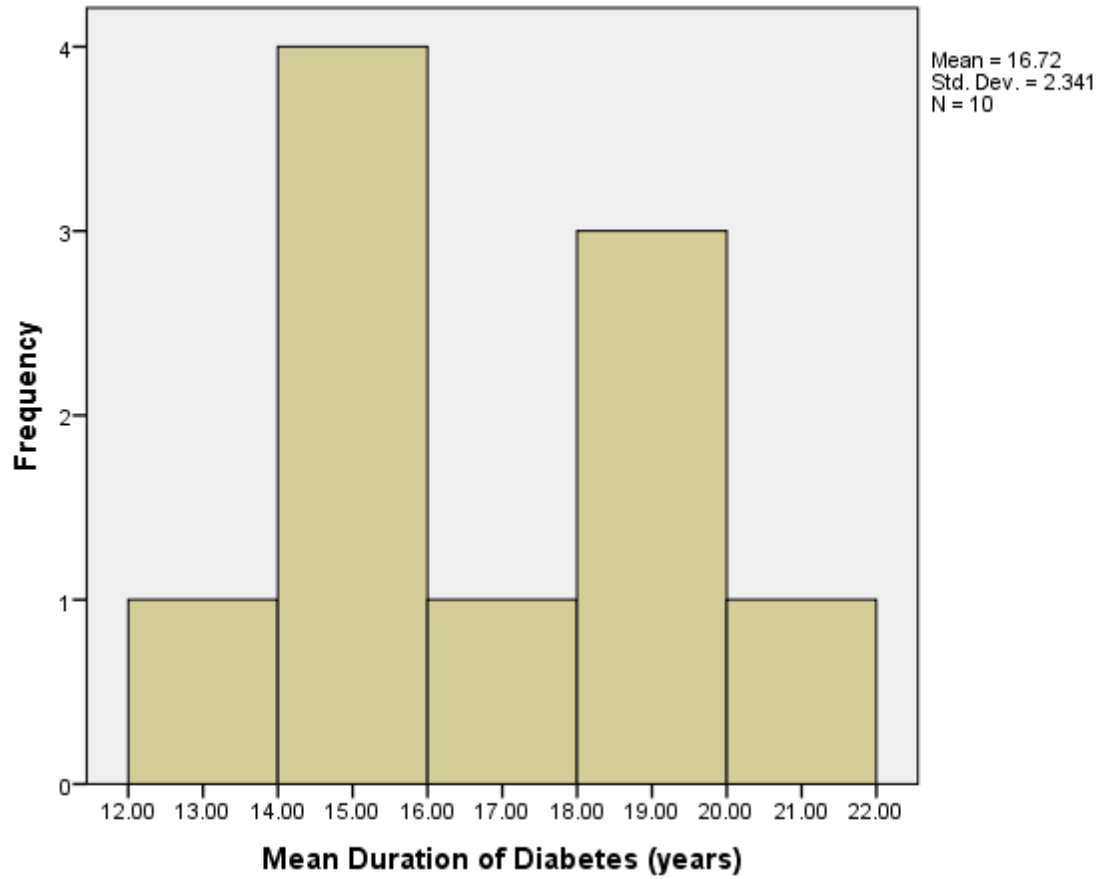


Figure 15 Frequency distribution of the mean duration of diabetes (years) for the samples in the included studies



**Figure 16 Proportion of baseline peripheral arterial disease (PAD) in the samples
for the included studies**

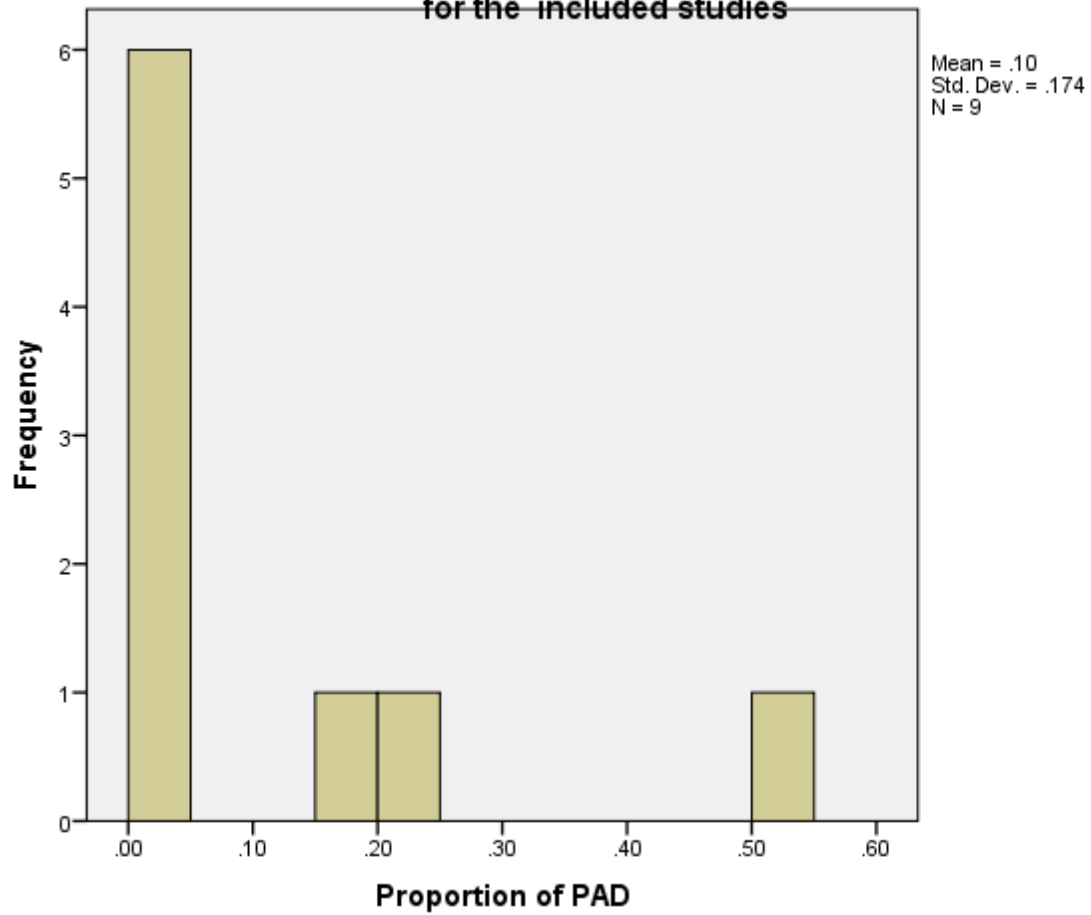


Figure 17 Proportion of baseline infection in the samples for the included studies

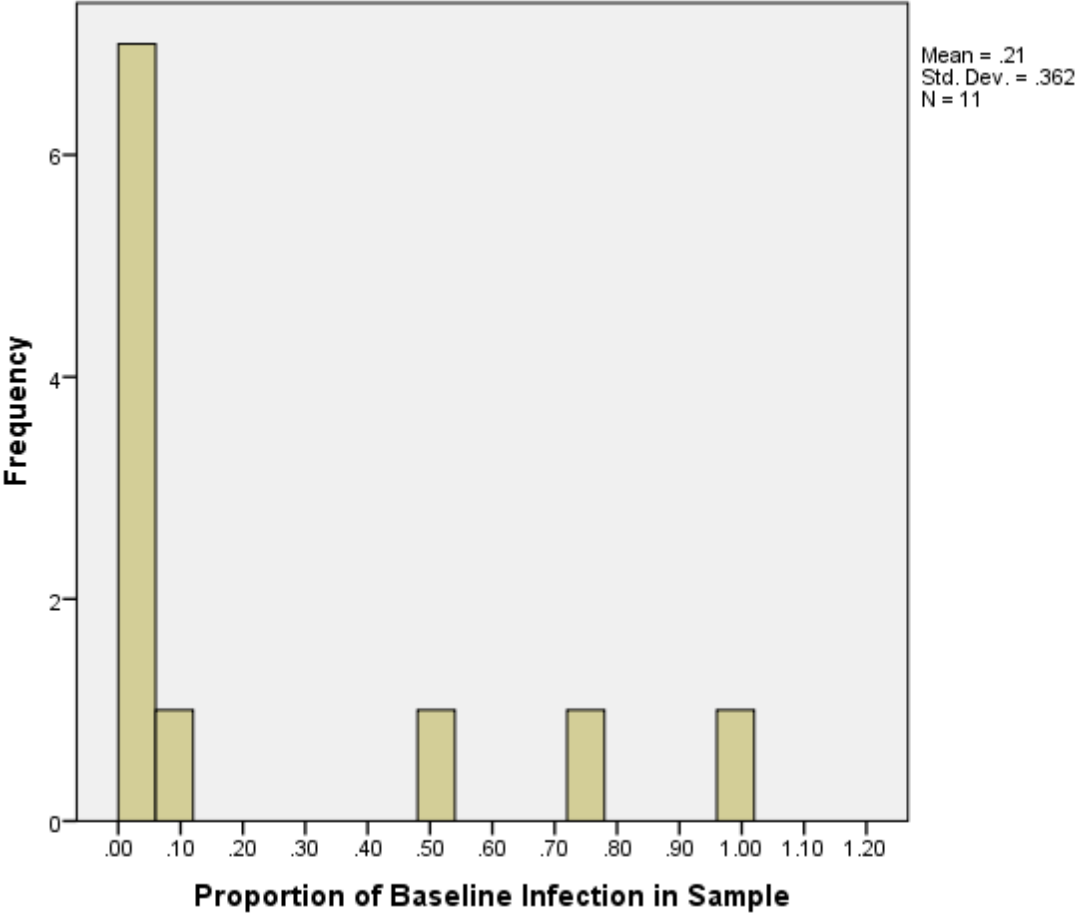


Figure 18 Frequency of reporting offloading in the samples for the included studies

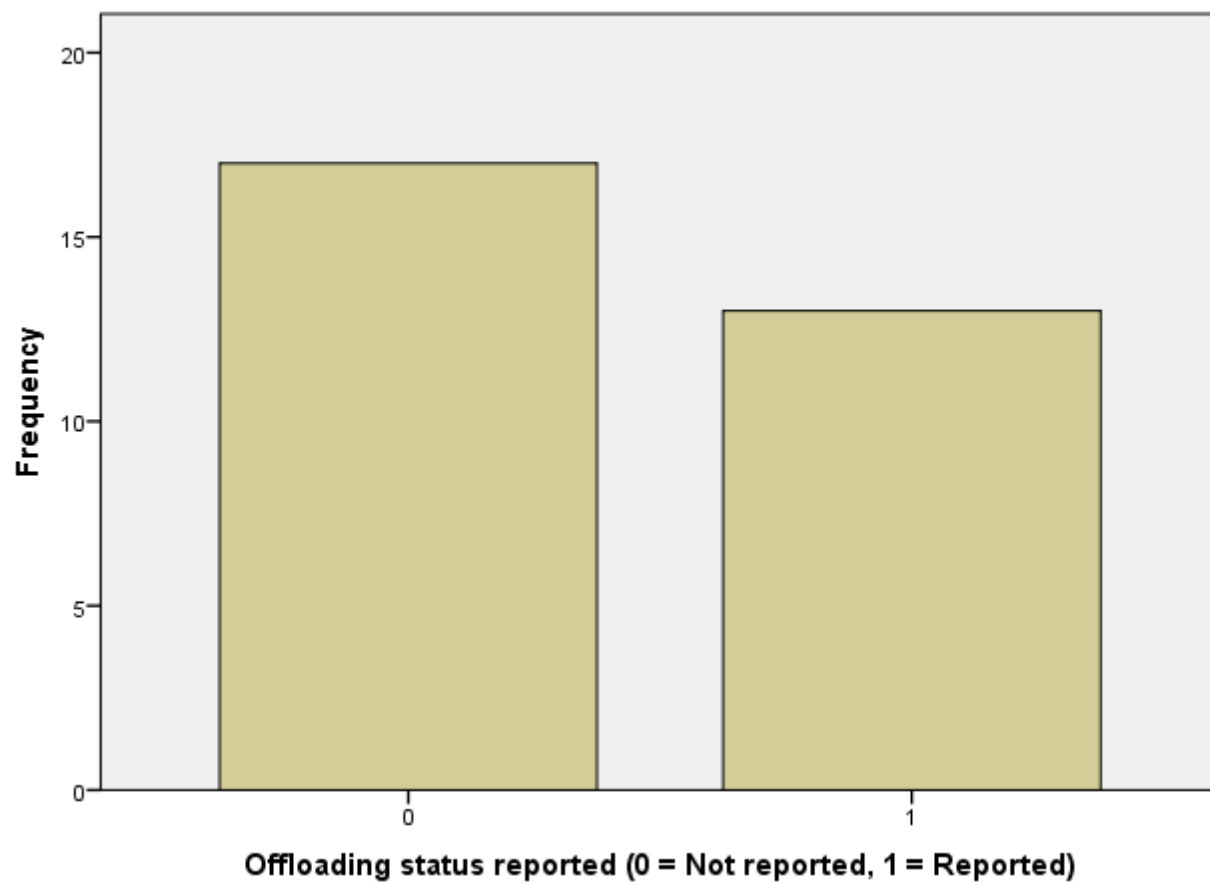


Figure 19 Frequency of reporting immunosuppression in the samples for the included studies

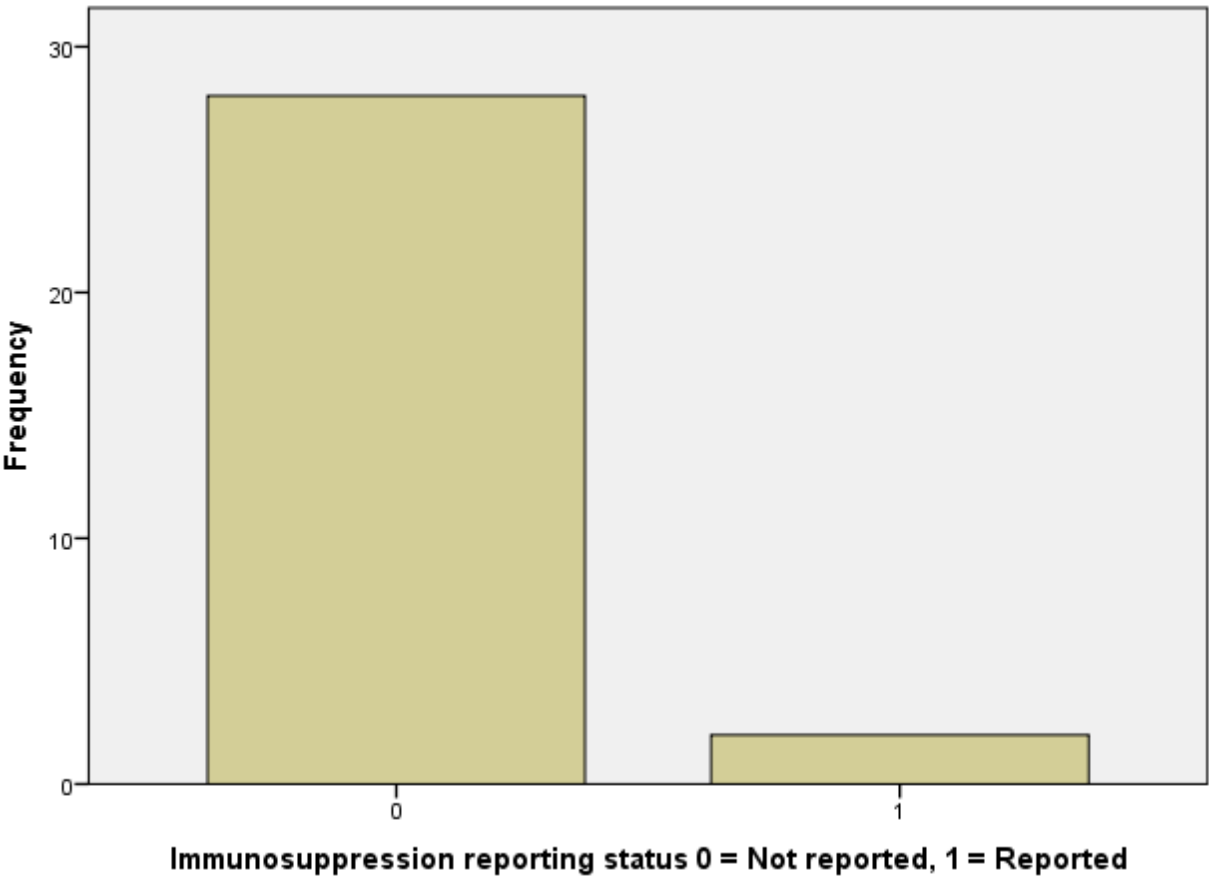


Figure 20 Frequency of reporting nutritional status in the samples for the included studies

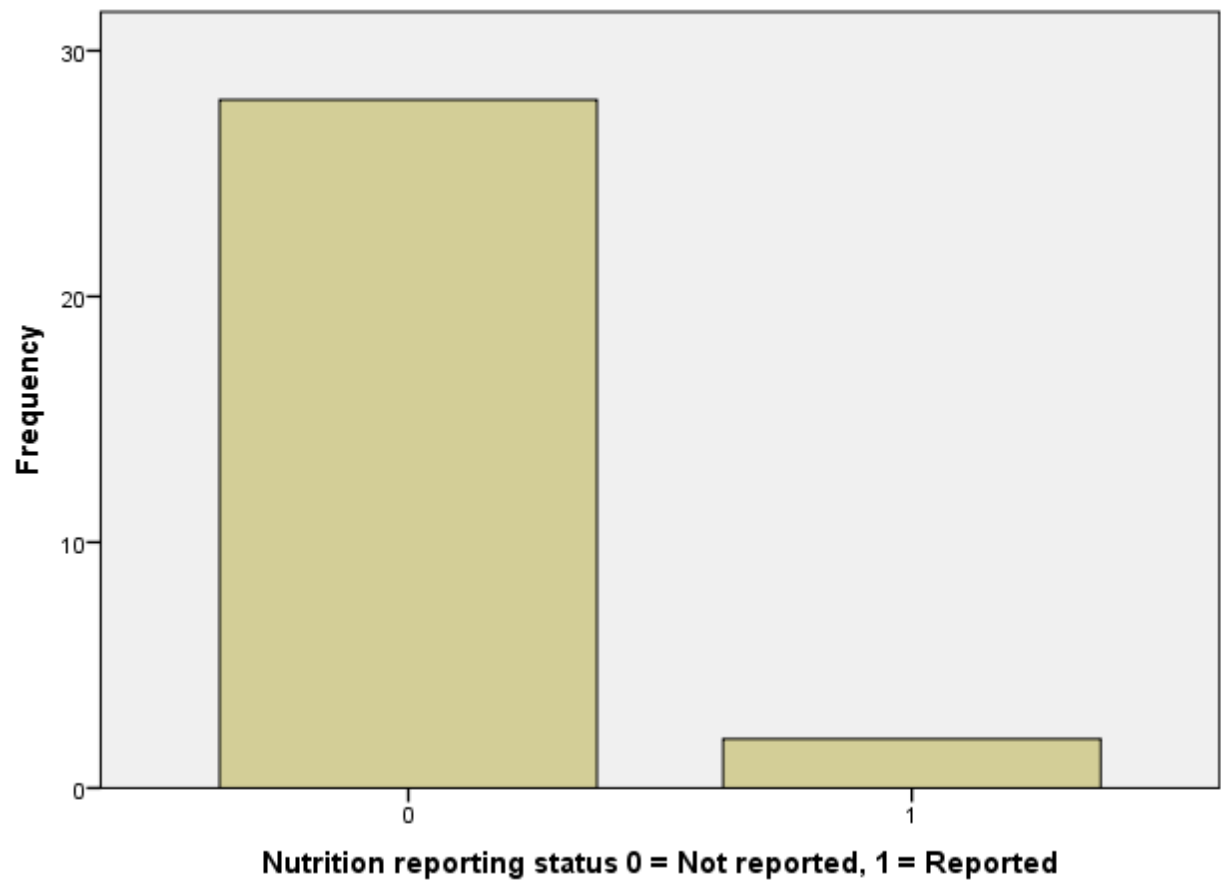


Figure 21 Frequency distribution of the proportion of smokers in the samples for the included studies

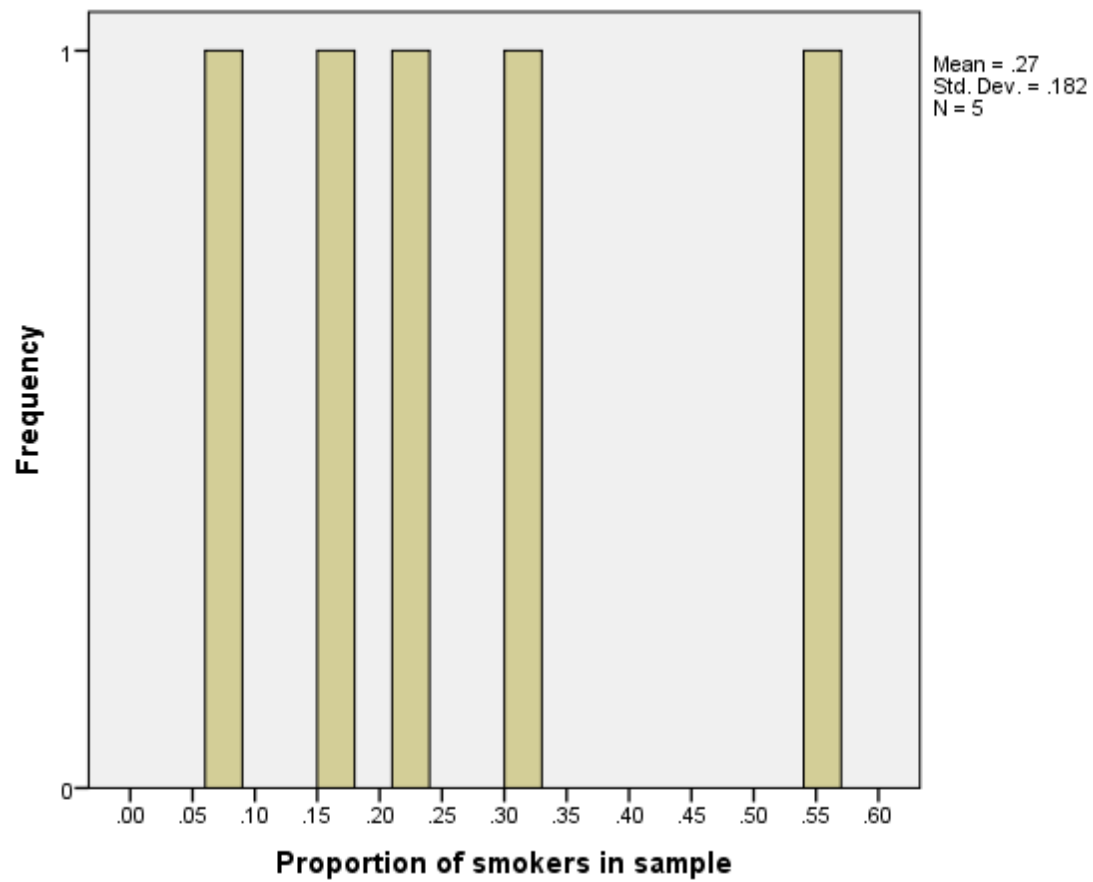


Figure 22 Frequency of industry support in the samples for the included studies

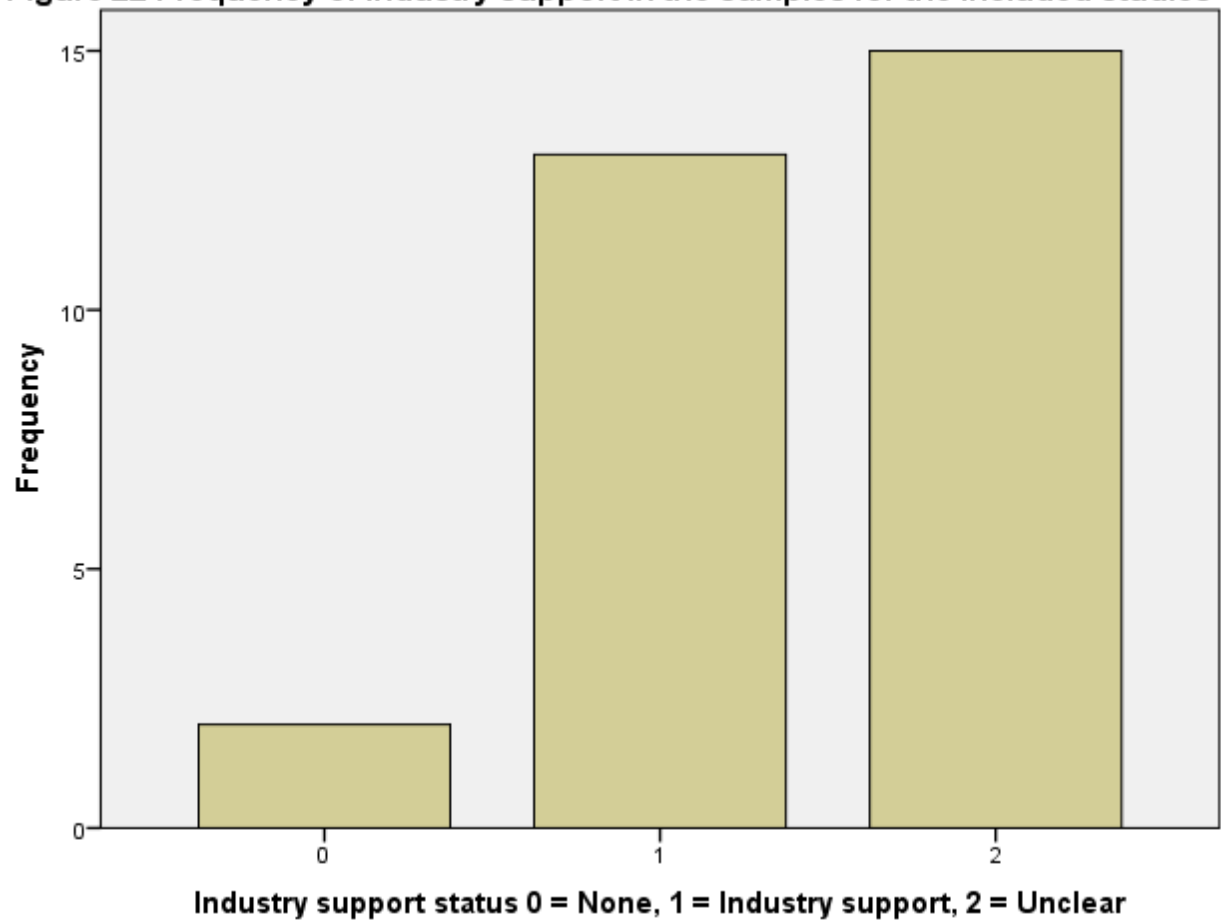
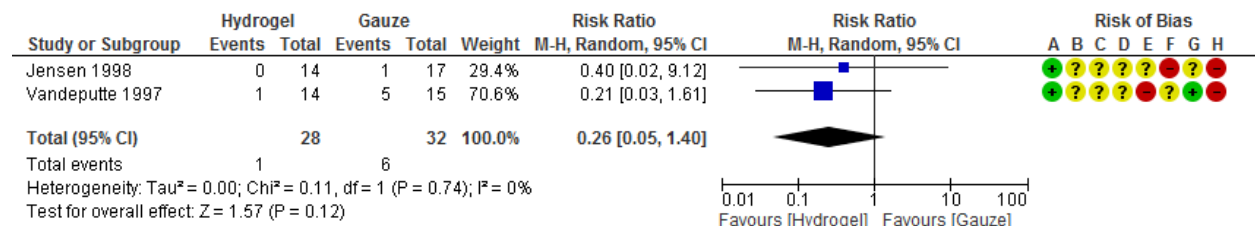


Figure 23 (Analysis 6.1)

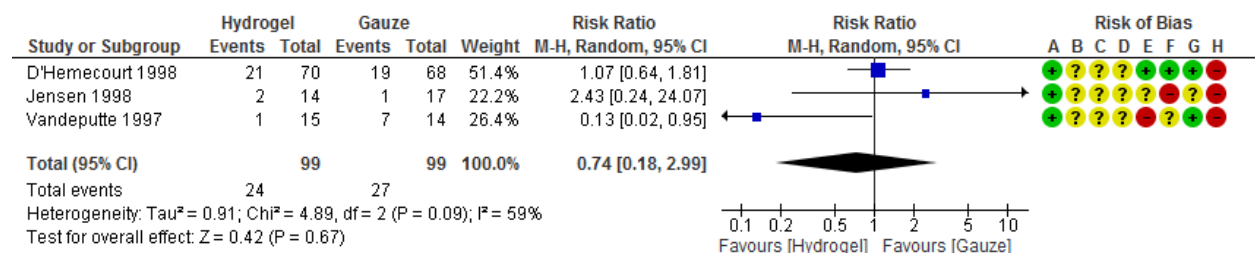


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 6 Hydrogel compared with gauze or good wound care (gwc), outcome: 6.1 Number of amputations reported.

Figure 24 (Analysis 6.2)

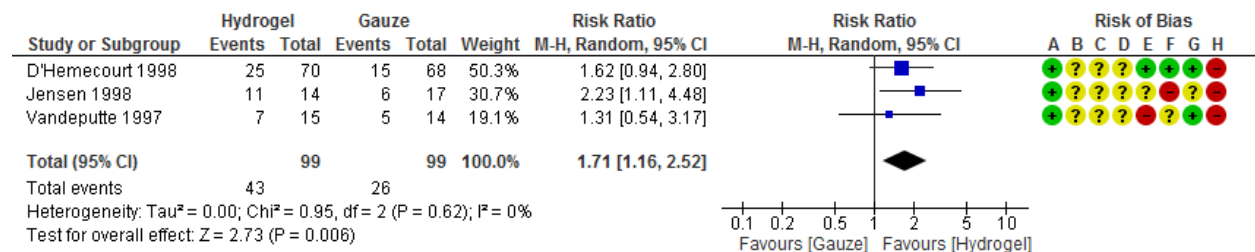


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 6 Hydrogel compared with gauze or good wound care (gwc), outcome: 6.2 Number of Infections reported.

Figure 25 (Analysis 6.3)

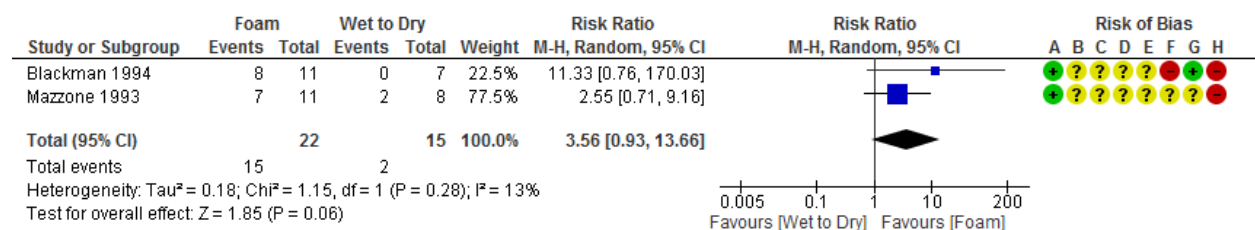


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 6 Hydrogel compared with gauze or good wound care (gwc), outcome: 6.3 Number of ulcers completely healed.

Figure 26 (Analysis 10.1)

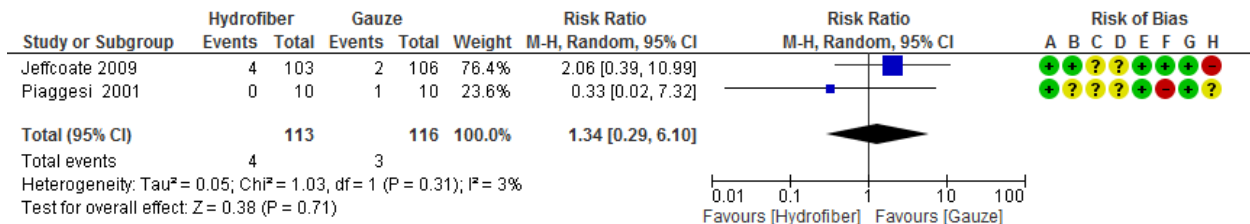


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 10 Foam dressing compared with Wet to Dry Saline, outcome: 10.1 Number of ulcers completely healed.

Figure 27 (Analysis 13.1)

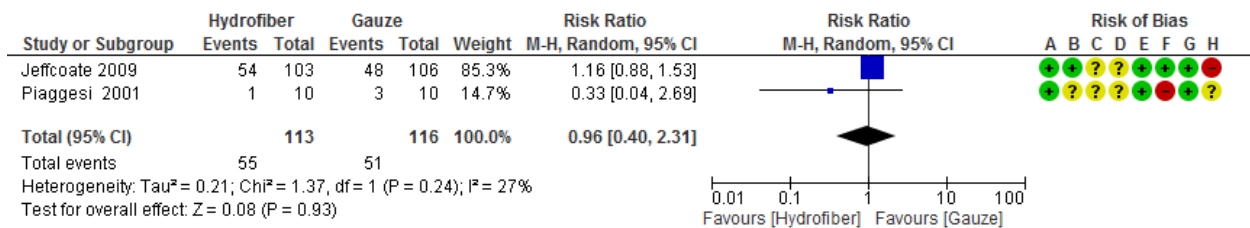


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 13 Hydrofiber compared with gauze dressing, outcome: 13.1 Number of amputations reported.

Figure 28 (Analysis 13.2)

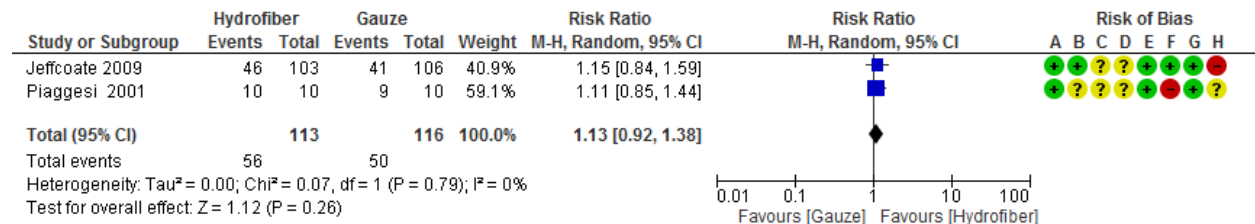


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 13 Hydrofiber compared with gauze dressing, outcome: 13.2 Number of Infections reported.

Figure 29 (Analysis 13.4)

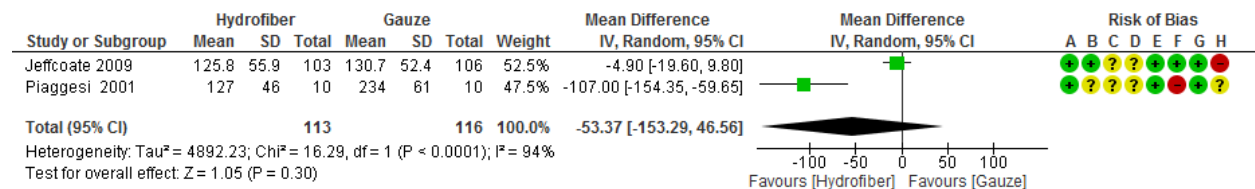


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 13 Hydrofiber compared with gauze dressing, outcome: 13.4 Number of ulcers completely healed.

Figure 30 (Analysis 13.5)

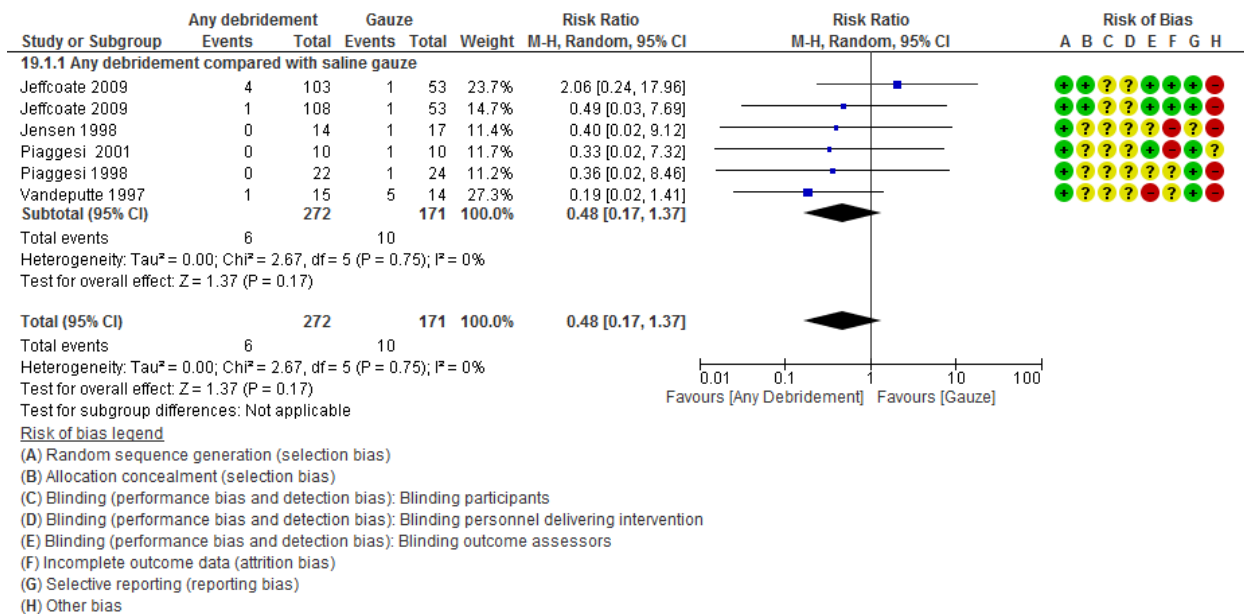


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

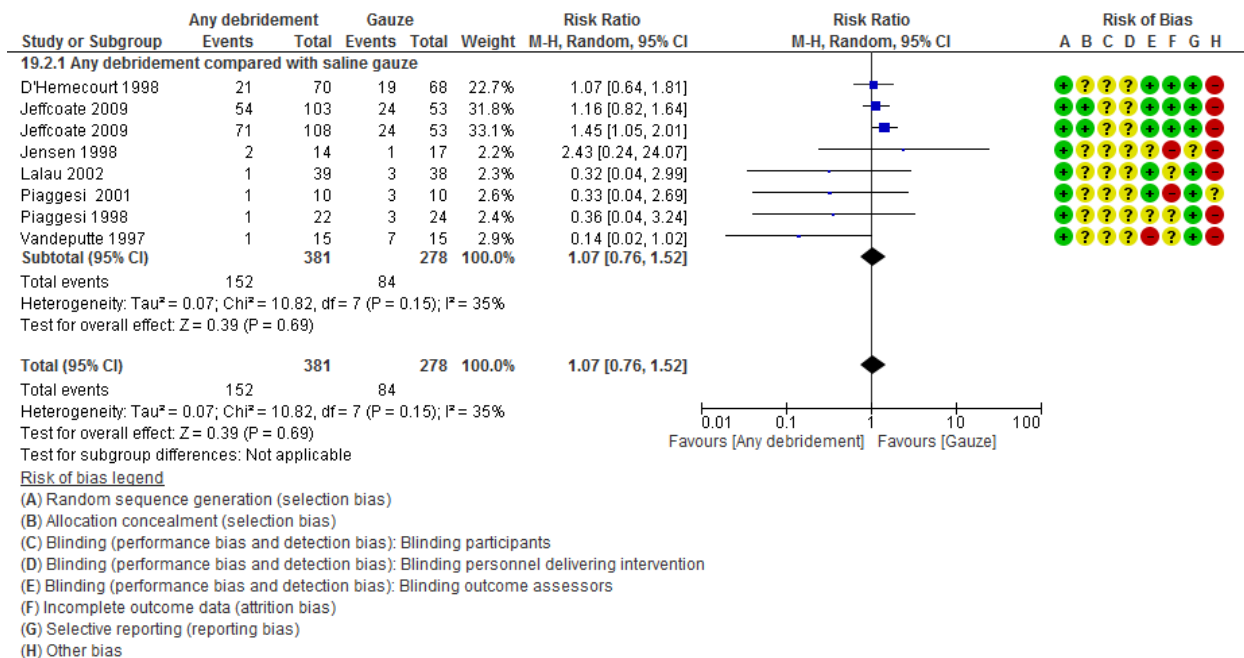
Forest plot of comparison: 13 Hydrofiber compared with gauze dressing, outcome: 13.5 Time to complete healing (days).

Figure 31 (Analysis 19.1)



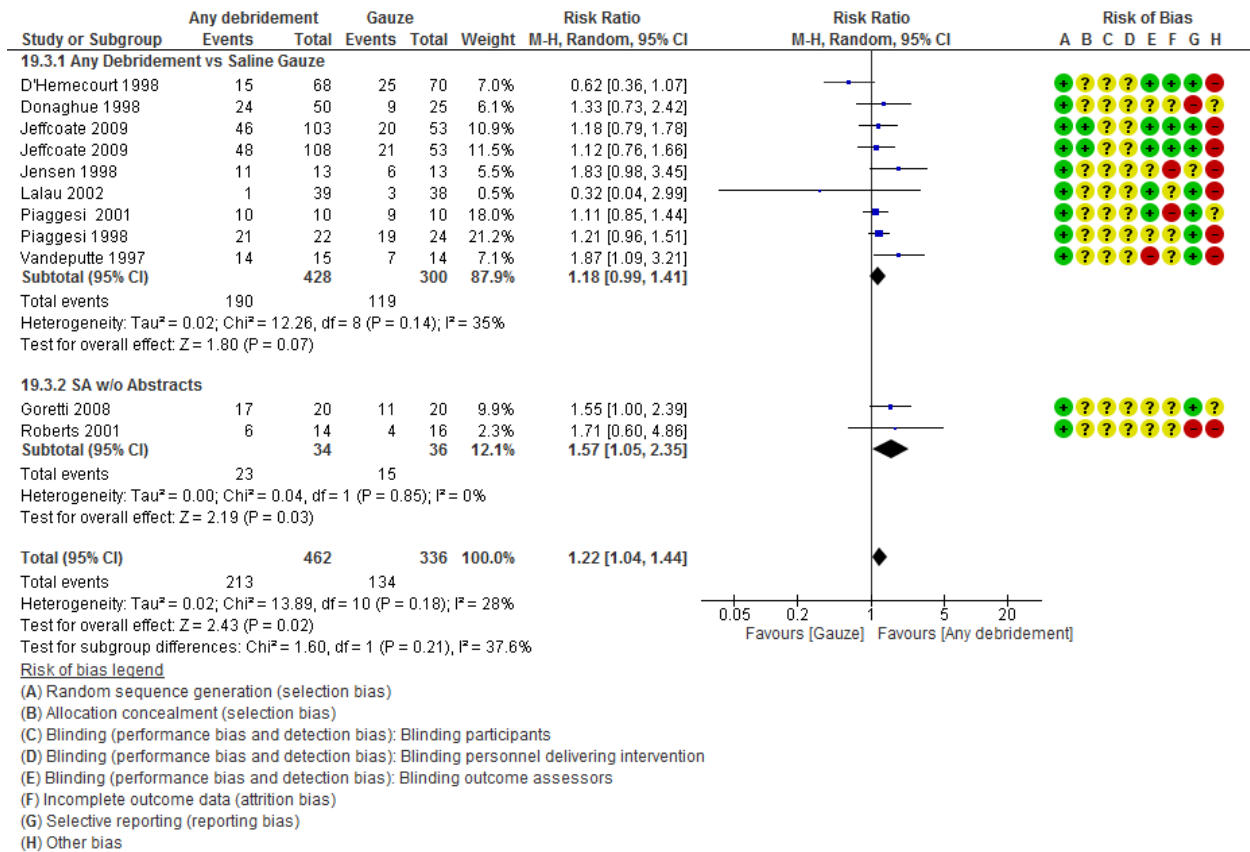
Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.1 Number of amputations reported.

Figure 32 (Analysis 19.2)



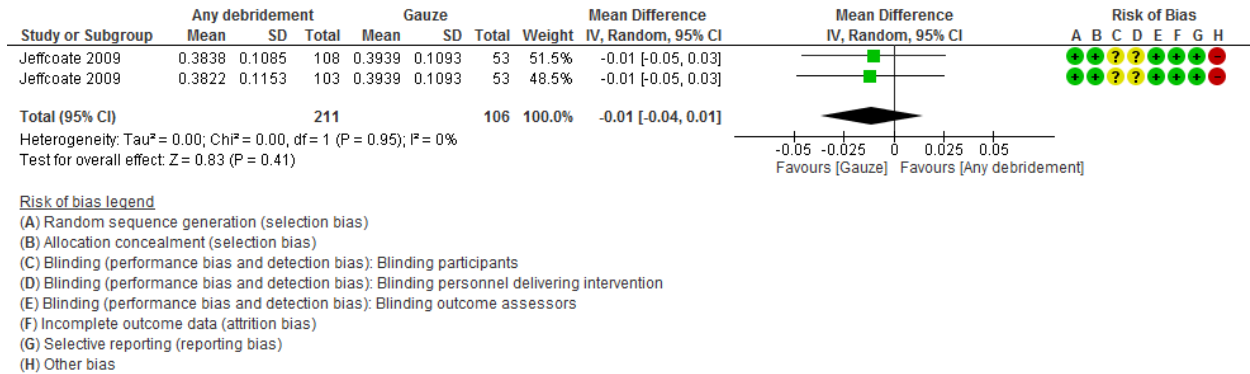
Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.2 Number of Infections reported.

Figure 33 (Analysis 19.3)



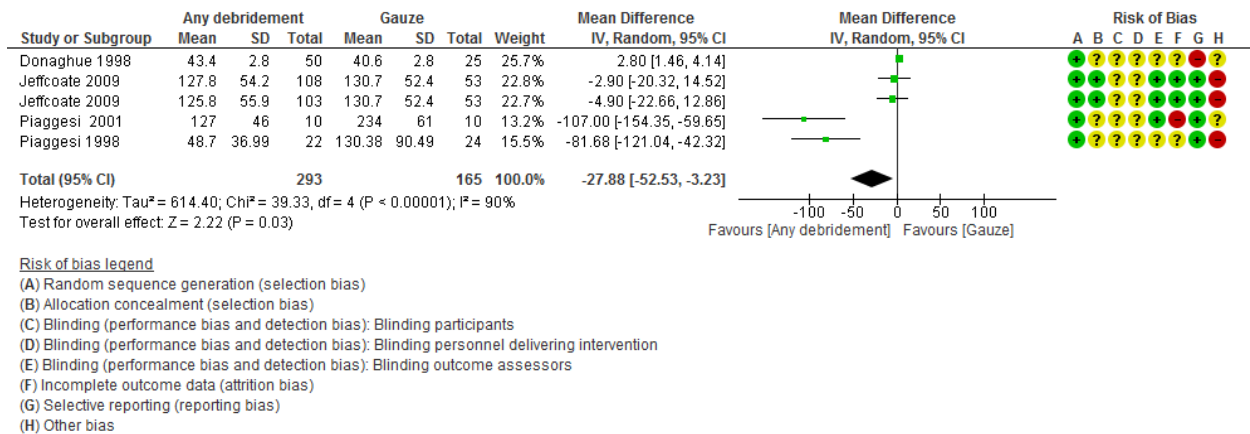
Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.3 Number of ulcers completely healed.

Figure 34 (Analysis 19.4)



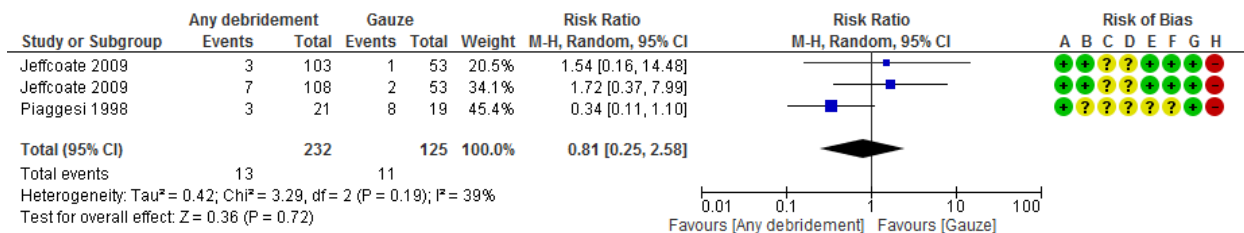
Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.4 Quality of life.

Figure 35 (Analysis 19.5)



Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.5 Time to complete healing (days).

Figure 36 (Analysis 19.6)

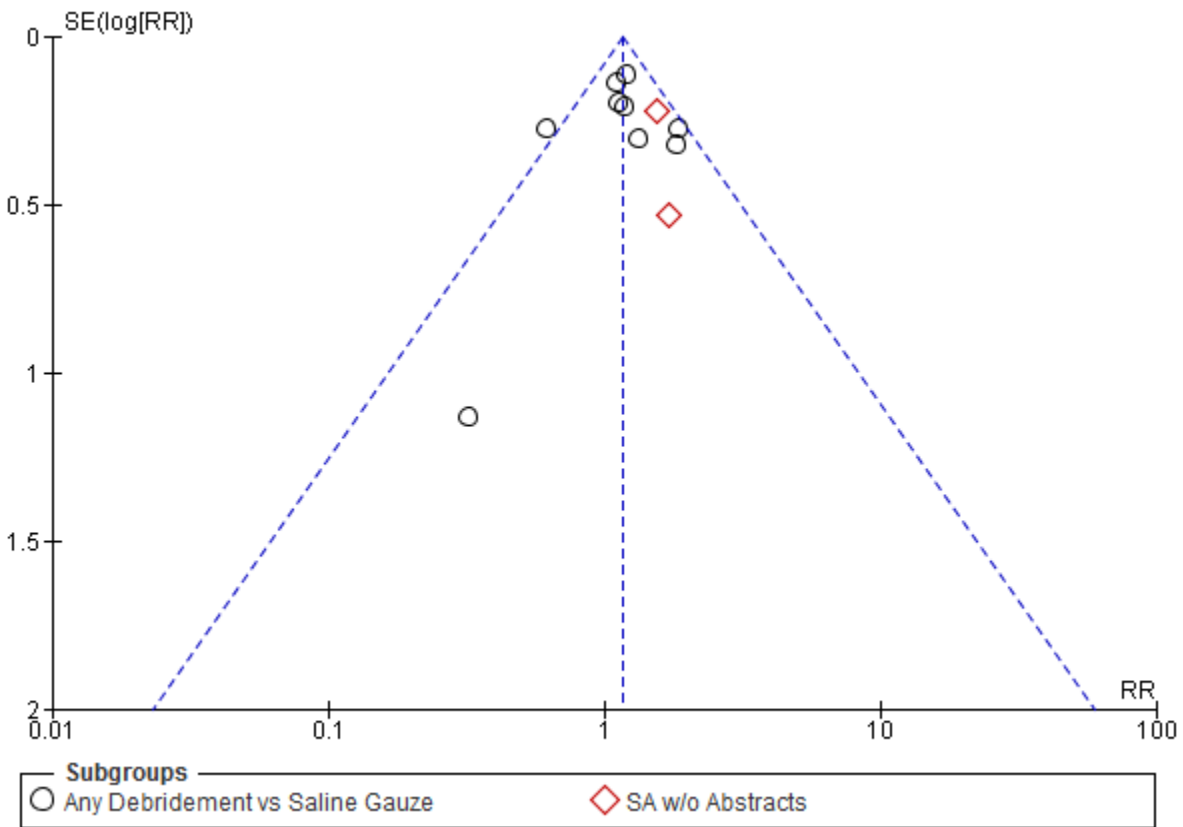


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias): Blinding participants
- (D) Blinding (performance bias and detection bias): Blinding personnel delivering intervention
- (E) Blinding (performance bias and detection bias): Blinding outcome assessors
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

Forest plot of comparison: 19 Any debridement compared with saline gauze control, outcome: 19.6 Recurrence rates.

Figure 37 (Analysis 19.3)



Funnel plot of comparison: 19 Any debridement compared with Saline Gauze, outcome: 19.3 Number of ulcers completely healed. Note: Funnel plot to assess for publication bias was performed on outcomes and interventions that included 10 or more studies. This included the outcome Number of ulcers healed for the intervention Any debridement vs. Saline gauze.

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Appendix – Search Strategies

1 Search strategy for the fourth update and expansion of the existing review 2014

There were three separate and independent searches conducted. The first search was carried out by the Cochrane Review Group - Wounds through the trials search coordinator. The second search was conducted as an institutional search by the authors independent of Cochrane Review Group - Wounds. The reason for this was that this systematic review was not strictly an update of an existing review but a significant expansion on the outcomes of interest in order to include additional public health related and clinical outcomes beyond the outcomes covered in the earlier reviews. This entailed expanding on the existing search provided through the trials search coordinator at CRG-wounds. It included new search terms with expanded dates and not restricted to the dates used by CRG-wounds. The search involved the same databases previously searched with the addition of the Web of Science database that is included. The third search was conducted by CRG-wounds to include any recent literature that might have been published since the last search provided by CRG-wounds through April 2015. All search strategies are described in detail below.

2 Ovid MEDLINE, PubMed search strategy

The trials search coordinator with the Cochrane Review Group - Wound searched the database Ovid Medline utilizing the following search strategy and dates:

Database: Ovid MEDLINE(R) without Revisions <1996 to March Week 4 2013>

Search Strategy:

-
- 1 exp Debridement/ (7831)
 - 2 (debrid\$ or slough\$ or deslough\$).ti,ab. (12051)
 - 3 exp Larva/ (24406)
 - 4 (larva\$ or maggot\$ or biosurgery or bio-surgery).ti,ab. (38005)
 - 5 (wound\$ adj (irrigat\$ or cleanse\$)).ti,ab. (161)
 - 6 whirlpool.ti,ab. (149)
 - 7 (collagenase\$ or fibrinolytic\$ or proteolytic\$ or trypsin or streptokinase or streptodornase or varidase).ti,ab. (58063)
 - 8 exp Papain/ (1033)
 - 9 papain.ti,ab. (2276)
 - 10 (hypochlorite or hydrogen peroxide).ti,ab. (25102)
 - 11 (malic acid or benzoid acid or salicylic acid or propylene glycol).ti,ab. (6877)
 - 12 dakin solution.ti,ab. (1)
 - 13 (dextranomer\$ or cadexomer or xerogel or eusol or debrisan).ti,ab. (451)
 - 14 (polysaccharide adj (bead\$ or paste\$)).ti,ab. (7)

15 (iodoflex or iodosorb).ti,ab. (8)
 16 (((gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber) adj dressing\$) or saline gauze or hydrocolloid\$ or granuflex or tegasorb or aquacel or hydrocoll or combiderm or duoderm).ti,ab. (1122)
 17 "wet-to-dry dressings".ti,ab. (18)
 18 exp Honey/ (1503)
 19 honey\$.ti,ab. (7264)
 20 exp Hydrogel/ (2336)
 21 (hydrogel\$ or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon).ti,ab. (9889)
 22 exp Zinc Oxide/ (2378)
 23 zinc oxide.ti,ab. (1273)
 24 or/1-23 (170471)
 25 exp Foot Ulcer/ (5689)
 26 exp Diabetic Foot/ (4929)
 27 (diabet\$ adj3 ulcer\$).ti,ab. (1975)
 28 (diabet\$ adj3 (foot or feet)).ti,ab. (3663)
 29 (diabet\$ adj3 wound\$).ti,ab. (1091)
 30 or/25-29 (7198)
 31 24 and 30 (800)
 32 randomized controlled trial.pt. (245491)
 33 controlled clinical trial.pt. (39951)
 34 randomized.ab. (200013)
 35 placebo.ab. (93002)
 36 clinical trials as topic.sh. (80489)
 37 randomly.ab. (137654)
 38 trial.ti. (74410)
 39 or/32-38 (554321)
 40 (animals not (humans and animals)).sh. (1639102)
 41 39 not 40 (504319)
 42 31 and 41 (111)
 43 (2009* or 2010* or 2011* or 2012* or 2013*).ed. (3070501)
 44 42 and 43 (50)

The authors conducted a search in conjunction with our library search coordinator at the University of Connecticut. The database Medline was searched utilizing the following search strategy and search dates:

PubMed

Dates Searched: 1940's to present

Results: 811

(diabetes OR diabetic* OR "Diabetes Mellitus"[Mesh]) AND (wound* OR ulcer* OR callus* OR "Diabetic Foot"[Mesh] OR "diabetic foot" OR "diabetic feet") AND ("Toes"[Mesh] OR toe OR toes OR phalange* OR "Lower Extremity"[Mesh] OR "Leg"[Mesh] OR leg OR legs OR extremity OR "Foot"[Mesh] OR foot OR feet) AND ("Debridement"[Mesh] OR debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR "bio-surgery" OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "dakins solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodisorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin) AND (("clinical"[tiab] AND "trial"[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh]) AND "humans"[mesh] NOT ("Cross-Sectional Studies"[MeSH Terms] OR "Case Reports"[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR "case control"[ti] OR "case report"[ti] OR "case study"[ti] OR "case series"[ti] OR "Case-Control Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "observational study"[ti] OR "prospective cohort"[ti] OR "cohort studies"[Mesh:NoExp] OR "cohort study"[ti] OR "Longitudinal Studies" [Mesh:NoExp] OR "Follow-Up Studies"[mesh] OR "Retrospective Studies"[mesh] OR "non-randomized"[ti] OR "follow up study"[ti] OR rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR dog[ti] OR dogs[ti] OR cats[ti])

PubMed Supplemental Search 1: systematic reviews & meta-analysis

Dates Searched: 1940's to present

Results: 237

(diabetes OR diabetic* OR "Diabetes Mellitus"[Mesh]) AND (wound* OR ulcer* OR callus* OR "Diabetic Foot"[Mesh] OR "diabetic foot" OR "diabetic feet") AND ("Toes"[Mesh] OR toe OR toes OR phalange* OR "Lower Extremity"[Mesh] OR "Leg"[Mesh] OR leg OR legs OR extremity OR "Foot"[Mesh] OR foot OR feet) AND ("Debridement"[Mesh] OR debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "daklin solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin) AND systematic [sb] NOT (rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR dog[ti] OR dogs[ti] OR cats[ti])

PubMed Supplemental Search 2: pre-indexed citations

Dates Searched: 2014 to present

Results: 89

(diabetes OR diabetic* OR "Diabetes Mellitus"[Mesh]) AND (wound* OR ulcer* OR callus* OR "Diabetic Foot"[Mesh] OR "diabetic foot" OR "diabetic feet") AND ("Toes"[Mesh] OR toe OR toes OR phalange* OR "Lower Extremity"[Mesh] OR "Leg"[Mesh] OR leg OR legs OR extremity OR "Foot"[Mesh] OR foot OR feet) AND ("Debridement"[Mesh] OR debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "daklin solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodisorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin) NOT ("Cross-Sectional Studies"[MeSH Terms] OR "Case Reports"[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR "case control"[ti] OR "case report"[ti] OR "case study"[ti] OR "case series"[ti] OR "Case-Control Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "observational study"[ti] OR "prospective cohort"[ti] OR "cohort studies" [Mesh:NoExp] OR "cohort study"[ti] OR "Longitudinal Studies" [Mesh:NoExp] OR "Follow-Up Studies"[mesh] OR "Retrospective Studies"[mesh] OR "non-randomized"[ti] OR "follow up study"[ti] OR rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR dog[ti] OR dogs[ti] OR cats[ti])

3 Ovid EMBASE, Embase via Scopus search strategy

The trials search coordinator with the Cochrane Review Group - Wound searched the database Embase utilizing the following search strategy and dates:

Database: Embase <1996 to 2013 Week 13>

Search Strategy:

1 exp Decubitus/ (9327)
2 (pressure adj (ulcer\$ or sore\$)).ti,ab. (5772)
3 (decubitus adj (ulcer\$ or sore\$)).ti,ab. (801)
4 (bedsore\$ or (bed adj sore\$)).ti,ab. (417)
5 or/1-4 (10522)
6 exp Nutrition/ (910056)
7 nutrition\$.ti,ab. (142489)
8 diet\$.ti,ab. (282256)
9 (tube adj (fed or feed or feeding)).ti,ab. (2344)
10 or/6-9 (1017934)
11 5 and 10 (1232)
12 exp Clinical trial/ (798274)
13 Randomized controlled trial/ (288746)
14 Randomization/ (50983)
15 Single blind procedure/ (15731)
16 Double blind procedure/ (86635)
17 Crossover procedure/ (32192)
18 Placebo/ (167856)
19 Randomi?ed controlled trial\$.tw. (81720)
20 RCT.tw. (10802)
21 Random allocation.tw. (919)
22 Randomly allocated.tw. (14440)
23 Allocated randomly.tw. (1221)
24 (allocated adj2 random).tw. (265)
25 Single blind\$.tw. (9774)
26 Double blind\$.tw. (91413)
27 ((treble or triple) adj blind\$).tw. (244)
28 Placebo\$.tw. (139064)
29 Prospective study/ (203909)
30 or/12-29 (1099022)
31 Case study/ (16391)
32 Case report.tw. (169255)
33 Abstract report/ or letter/ (515715)
34 or/31-33 (697032)
35 30 not 34 (1070653)

36 animal/ (727929)
37 human/ (8737685)
38 36 not 37 (486914)
39 35 not 38 (1048222)
40 11 and 39 (227)
41 (2011* or 2012* or 2013*).em. (2630697)
42 40 and 41 (47)

The authors conducted an independent search in conjunction with our library search coordinator at the University of Connecticut. The database EMBASE via Scopus was searched utilizing the following search strategy and search dates:

EMBASE via Scopus

Dates Searched: 1960 to present

Limiters: Exclude Publication Types: Review, Editorial, Letter

Results: 893

1 diabet*

2 (wound* OR ulcer* OR callus* OR "diabetic foot" OR "diabetic feet")

3 (toe OR toes OR phalange* OR "lower extremity" OR leg OR legs OR extremity OR foot OR feet)

4 (debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "dakín solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin)

5 (in article title) clinical OR trial

6 (in abstract) clinical OR trial

7 (in article title) random*

8 (in abstract) random*

9 "clinical trial"

10 #5 AND #6

11 #10 OR #7 OR #8 OR #9

12 #1 AND #2 AND #3 AND #4 AND #11

13 (in article title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review

14 #12 AND NOT #13

EMBASE Supplemental Search: systematic reviews & meta-analysis

Dates Searched: 1960 to present

Limiters: Exclude Publication Types: Editorial, Letter

Results: 189

1 diabet*

2 (wound* OR ulcer* OR callus* OR "diabetic foot" OR "diabetic feet")

3 (toe OR toes OR phalange* OR "lower extremity" OR leg OR legs OR extremity OR foot OR feet)

4 (debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "dakín solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin)

5 "systematic review" OR "systematic literature review" OR "meta-analysis" OR "meta-synthesis"

6 #1 AND #2 AND #3 AND #4 AND #5

7 (in article title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats

8 #6 AND NOT #7

4 EBSCO CINAHL search strategy

The trials search coordinator with the Cochrane Review Group - Wound searched the database EBSCO CINAHL utilizing the following search strategy and dates:

S30S23 and S29

S29S24 or S25 or S26 or S27 or S28

S28TI diabet* N3 wound* or AB diabet* N3 wound*

S27TI (diabet* N3 foot or diabet* N3 feet) or AB (diabet* N3 foot or diabet* N3 feet)

S26TI diabet* N3 ulcer* or AB diabet* N3 ulcer*

S25(MH "Foot Ulcer+")

S24(MH "Diabetic Foot")

S23S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22

S22TI zinc oxide or AB zinc oxide

S21(MH "Zinc Oxide")

S20TI (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon) or AB (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon)

S19(MH "Hydrogel Dressings")

S18TI honey or AB honey

S17(MH "Honey")

S16TI wet-to-dry dressings or AB wet-to-dry dressings

S15TI (dressing* or gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm) or AB (dressing* or gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm)

S14TI (iodoflex or iodisorb) or AB (iodoflex or iodisorb)

S13TI (polysaccharide bead* or polysaccharide paste) or AB (polysaccharide bead* or polysaccharide paste)

S12TI (dextranomer* or cadexomer or xerogel or eusol or debrisan) or AB (dextranomer* or cadexomer or xerogel or eusol or debrisan)

S11TI dakin solution or AB dakin solution

S10TI (malic acid or benzoid acid or salicylic acid or propylene glycol) or AB (malic acid or benzoid acid or salicylic acid or propylene glycol)

S9TI (hypochlorite or hydrogen peroxide) or AB (hypochlorite or hydrogen peroxide)

S8TI whirlpool or AB whirlpool

S7TI (wound irrigat* or wound cleans*) or AB (wound irrigat* or wound cleans*)

S6TI papain or AB papain

S5TI (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase) or AB (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase)

S4TI (larva* or maggot* or biosurgery or bio-surgery) or AB (larva* or maggot* or biosurgery or bio-surgery)

S3(MH "Larval Therapy")

S2TI (debrid* or slough* or deslough*) or AB (debrid* or slough* or deslough*)

S1(MH "Debridement")

The authors conducted an independent search in conjunction with our library search coordinator at the University of Connecticut. The database EBSCO CINAHL was searched utilizing the following search strategy and search dates:

CINAHL

Dates Searched: 1981 to present

Limiters: Exclude MEDLINE records; Human

Results: 57

S1 (MH "Diabetes Mellitus+")

S2 diabet*

S3 (MH "Diabetic Foot")

S4 wound* OR ulcer* OR callus* OR "diabetic feet" OR "diabetic foot"

S5 (MH "Toes")

S6 (MH "Lower Extremity+")

S7 (MH "Leg")

S8 (MH "Foot+")

S9 toe OR toes OR phalange* OR leg OR legs OR extremity OR foot OR feet

S10 (MH "Debridement+")

S11 debrid* or slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "dakins solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin

S12 TI (clinical OR trial) AND AB (clinical OR trial)

S13 (MH "Clinical Trials+")

S14 TI random* OR AB random*

S15 S1 OR S2

S16 S3 OR S4

S17 S5 OR S6 OR S7 OR S8 OR S9

S18 S10 OR S11

S19 S12 OR S13 OR S14

S20 S15 AND S16 AND S17 AND S18 AND S19

S21 (in title) rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review

S22 S20 NOT S21

CINAHL Supplemental Search: systematic reviews & meta-analysis

Dates Searched: 1981 to present

Limiters: Exclude MEDLINE records; Human; Publication Type: Meta Analysis, Meta Synthesis, Systematic Review

Results: 18

S1 (MH "Diabetes Mellitus+")

S2 diabet*

S3 (MH "Diabetic Foot")

S4 wound* OR ulcer* OR callus* OR "diabetic feet" OR "diabetic foot"

S5 (MH "Toes")

S6 (MH "Lower Extremity+")

S7 (MH "Leg")

S8 (MH "Foot+")

S9 toe OR toes OR phalange* OR leg OR legs OR extremity OR foot OR feet

S10 (MH "Debridement+")

S11 debrid* or slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR "hydrogen peroxide" OR acid OR acids OR "propylene glycol" OR "dakín solution" OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR "zinc oxide" OR phenytoin

S12 S1 OR S2

S13 S3 OR S4

S14 S5 OR S6 OR S7 OR S8 OR S9

S15 S10 OR S11

S16 S12 AND S13 AND S14 AND S15

5 Web of Science search strategy

The authors conducted an independent search in conjunction with our library search coordinator at the University of Connecticut. The database Web of Science was searched utilizing the following search strategy and search dates:

Web of Science

Dates Searched: 1974 to present

Results: 522

1 diabet*

2 (wound* OR ulcer* OR callus* OR “diabetic foot” OR “diabetic feet”)

3 (toe OR toes OR phalange* OR "lower extremity" OR leg OR legs OR extremity OR foot OR feet)

4 (debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR “hydrogen peroxide” OR acid OR acids OR “propylene glycol” OR “dakín solution” OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR “zinc oxide” OR phenytoin)

5 clinical AND trial

6 random*

8 #5 OR #6

11 #1 AND #2 AND #3 AND #4 AND #8

12 Title=(rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR “case report” OR comment OR editorial OR letter OR "case control" OR "case study" OR “case series” OR "follow-up study” OR “observational study” OR “prospective cohort” OR

“cohort study” OR “longitudinal study” OR “retrospective study” OR “non-randomized” OR review)

13 #11 NOT #12

Web of Science Supplemental Search: systematic reviews & meta-analysis

Dates Searched: 1974 to present

Results: 70

1 diabet*

2 (wound* OR ulcer* OR callus* OR “diabetic foot” OR “diabetic feet”)

3 (toe OR toes OR phalange* OR "lower extremity" OR leg OR legs OR extremity OR foot OR feet)

4 (debrid* OR slough* OR deslough* OR larva* OR maggot* OR MDT OR biosurgery OR bio-surgery OR surgery OR surgical OR scalpel* OR hydrogel* OR "moist wound healing" OR enzyme* OR mechanical OR autolytic OR ultrasound OR laser OR lasers OR sharp OR irrigate* OR irrigation OR cleanse* OR whirlpool* OR collagenase* OR fibrinolytic* OR proteolytic* OR trypsin OR streptokinase OR streptodornase OR varidase OR papain OR hypochlorite OR “hydrogen peroxide” OR acid OR acids OR “propylene glycol” OR “dakín solution” OR dextranomer* OR cadexomer* OR xerogel* OR eusol* OR debrisan* OR paste* OR iodoflex OR iodosorb OR gauze* OR tulle OR polysaccharide* OR bead OR alginate* OR foam* OR hydrofibre* OR hydrofiber* OR dressing* OR saline OR honey* OR gel OR gels OR hydrocolloid* OR granuflex OR tegasorb OR aquacel OR hydrocoll* OR combiderm OR duoderm OR sterigel* OR granugel* OR nugel OR purilon OR vigilon OR “zinc oxide” OR phenytoin)

5 ("systematic review" OR "systematic literature review" OR "meta-analysis" OR "meta-synthesis")

6 #1 AND #2 AND #3 AND #4 AND #5

7 Title=(rat OR rats OR mice OR mouse OR dog OR dogs OR cats)

8 #6 NOT #7

6 The Cochrane Library search strategy

The authors conducted an independent search in conjunction with our library search coordinator at the University of Connecticut. The database Web of Science was searched utilizing the following search strategy and search dates:

The Cochrane Library

Dates searched: 1898 to present

Results: 103 Central Register of Controlled Trials (CENTRAL)

3 Database of Abstracts of Reviews of Effect (DARE)

Title, Abstract, Keywords= debrid*

AND

Title, Abstract, Keywords= diabet*

NOT

Record Title=(rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized")

7 Cochrane Wounds Group Specialized Register (Searched 15/04/15)

Cochrane Wounds Group Specialized Register (Searched 15/04/15)

The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library 2015, Issue 3

Ovid MEDLINE & Ovid MEDLINE - In-Process & Other Non-Indexed Citations 2013 to April 14 2015

Ovid EMBASE - 2013 to April 14 2015

EBSCO CINAHL - 2013 to April 15 2015

Cinahl Search Strategy

S43 S30 and S42

S42 S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41

S41 MH "Quantitative Studies"

S40 TI placebo* or AB placebo*

S39 MH "Placebos"

S38 TI random* allocat* or AB random* allocat*

S37 MH "Random Assignment"

S36 TI randomi?ed control* trial* or AB randomi?ed control* trial*

S35 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)

S34 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)

S33 TI clinic* N1 trial* or AB clinic* N1 trial*

S32 PT Clinical trial

S31 MH "Clinical Trials+"

S30 S23 and S29

S29 S24 or S25 or S26 or S27 or S28

S28 TI diabet* N3 wound* or AB diabet* N3 wound*

S27 TI (diabet* N3 foot or diabet* N3 feet) or AB (diabet* N3 foot or diabet* N3 feet)

S26 TI diabet* N3 ulcer* or AB diabet* N3 ulcer*

S25 (MH "Foot Ulcer+")

S24 (MH "Diabetic Foot")

S23 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22

S22 TI zinc oxide or AB zinc oxide

S21 (MH "Zinc Oxide")

S20 TI (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon) or AB (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon)

S19 (MH "Hydrogel Dressings")

S18 TI honey or AB honey

S17 (MH "Honey")

S16 TI wet-to-dry dressings or AB wet-to-dry dressings

S15 TI (dressing* or gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm) or AB (dressing* or gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm)

S14 TI (iodoflex or iodisorb) or AB (iodoflex or iodisorb)

S13 TI (polysaccharide bead* or polysaccharide paste) or AB (polysaccharide bead* or polysaccharide paste)

S12 TI (dextranomer* or cadexomer or xerogel or eusol or debrisan) or AB (dextranomer* or cadexomer or xerogel or eusol or debrisan)

S11 TI dakin solution or AB dakin solution

S10 TI (malic acid or benzoid acid or salicylic acid or propylene glycol) or AB (malic acid or benzoid acid or salicylic acid or propylene glycol)

S9 TI (hypochlorite or hydrogen peroxide) or AB (hypochlorite or hydrogen peroxide)

S8 TI whirlpool or AB whirlpool

S7 TI (wound irrigat* or wound cleans*) or AB (wound irrigat* or wound cleans*)

S6 TI papain or AB papain

S5 TI (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase) or AB (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase)

S4 TI (larva* or maggot* or biosurgery or bio-surgery) or AB (larva* or maggot* or biosurgery or bio-surgery)

S3 (MH "Larval Therapy")

S2 TI (debrid* or slough* or deslough*) or AB (debrid* or slough* or deslough*)

S1 (MH "Debridement")

Search Name: 42 Smith Debridement for DFU_Issue 3 2015

Date Run: 17/06/15 08:33:47.466

Description: Re-ran searches over all issues (Issue 3 2015) [Revised SS Issue 2 2009]

ID Search Hits

#1 MeSH descriptor: [Debridement] explode all trees

#2 (debrid* or slough* or deslough*):ti,ab,kw

#3 MeSH descriptor: [Larva] explode all trees

#4 (larva* or maggot* or biosurgery or bio-surgery):ti,ab,kw

#5 (wound* next (irrigat* or cleanse*)):ti,ab,kw

#6 whirlpool:ti,ab,kw

#7 (collagenase* or fibrinolytic* or proteolytic* or trypsin or streptokinase or streptodornase or varidase):ti,ab,kw

#8 MeSH descriptor: [Papain] explode all trees

#9 papain:ti,ab,kw

#10 (hypochlorite or hydrogen peroxide):ti,ab,kw

#11 (malic acid or benzoic acid or salicylic acid or propylene glycol):ti,ab,kw

#12 "daklin solution":ti,ab,kw

#13 (dextranomer* or cadexomer or xerogel or eusol or debrisan):ti,ab,kw

#14 (polysaccharide next (bead* or paste*)):ti,ab,kw

#15 (iodoflex or iodosorb):ti,ab,kw

#16 (((gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber) next dressing*) or saline gauze or hydrocolloid* or granuflex or tegasorb or aquacel or hydrocoll* or combiderm or duoderm):ti,ab,kw

#17 "wet-to-dry dressings":ti,ab,kw

#18 MeSH descriptor: [Honey] explode all trees

#19 honey:ti,ab,kw 302

#20 MeSH descriptor: [Hydrogel] explode all trees

#21 (hydrogel* or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon):ti,ab,kw

#22 MeSH descriptor: [Zinc Oxide] explode all trees

#23 "zinc oxide":ti,ab,kw

#24 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23

#25 MeSH descriptor: [Foot Ulcer] explode all trees

#26 MeSH descriptor: [Diabetic Foot] explode all trees

#27 diabet* near/3 ulcer*:ti,ab,kw

#28 diabet* near/3 (foot or feet):ti,ab,kw

#29 diabet* near/3 wound*:ti,ab,kw

#30 #25 or #26 or #27 or #28 or #29

#31 #24 and #30

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp Debridement/
 - 2 (debrid\$ or slough\$ or deslough\$).ti,ab.
 - 3 exp Larva/
 - 4 (larva\$ or maggot\$ or biosurgery or bio-surgery).ti,ab.
 - 5 (wound\$ adj (irrigat\$ or cleanse\$)).ti,ab.
 - 6 whirlpool.ti,ab.
 - 7 (collagenase\$ or fibrinolytic\$ or proteolytic\$ or trypsin or streptokinase or streptodornase or varidase).ti,ab.
 - 8 exp Papain/
 - 9 papain.ti,ab.
 - 10 (hypochlorite or hydrogen peroxide).ti,ab.
 - 11 (malic acid or benzoid acid or salicylic acid or propylene glycol).ti,ab.
 - 12 dakin solution.ti,ab.
 - 13 (dextranomer\$ or cadexomer or xerogel or eusol or debrisan).ti,ab.
 - 14 (polysaccharide adj (bead\$ or paste\$)).ti,ab.
 - 15 (iodoflex or iodisorb).ti,ab.
 - 16 (((gauze or adherent or absorbent or tulle or polysaccharide or alginate or foam or hydrofibre or hydrofiber) adj dressing\$) or saline gauze or hydrocolloid\$ or granuflex or tegasorb or aquacel or hydrocoll or combiderm or duoderm).ti,ab.
 - 17 "wet-to-dry dressings".ti,ab.

18 exp Honey/

19 honey\$.ti,ab.

20 exp Hydrogel/

21 (hydrogel\$ or intrasite gel or intrasitgel or sterigel or granugel or nugel or purilon or vigilon).ti,ab.

22 exp Zinc Oxide/

23 zinc oxide.ti,ab.

24 or/1-23

25 exp Foot Ulcer/

26 exp Diabetic Foot/

27 (diabet\$ adj3 ulcer\$).ti,ab.

28 (diabet\$ adj3 (foot or feet)).ti,ab.

29 (diabet\$ adj3 wound\$).ti,ab.

30 or/25-29

31 24 and 30

32 randomized controlled trial.pt.

33 controlled clinical trial.pt.

34 randomized.ab.

35 placebo.ab.

36 clinical trials as topic.sh.

37 randomly.ab.

38 trial.ti.

39 or/32-38

40 (animals not (humans and animals)).sh.

41 39 not 40

42 31 and 41

Database: Embase <1974 to 2015 June 16>

Search Strategy:

1 exp Decubitus/

2 (pressure adj (ulcer\$ or sore\$)).ti,ab.

3 (decubitus adj (ulcer\$ or sore\$)).ti,ab.

4 (bedsore\$ or (bed adj sore\$)).ti,ab.

5 or/1-4

6 exp Nutrition/

7 nutrition\$.ti,ab.

8 diet\$.ti,ab.

9 (tube adj (fed or feed or feeding)).ti,ab.

10 or/6-9

11 5 and 10

12 exp Clinical trial/

13 Randomized controlled trial/

14 Randomization/

15 Single blind procedure/

16 Double blind procedure/

17 Crossover procedure/

18 Placebo/

19 Randomized controlled trial\$.tw.

20 RCT.tw.
21 Random allocation.tw.
22 Randomly allocated.tw.
23 Allocated randomly.tw.
24 (allocated adj2 random).tw.
25 Single blind\$.tw.
26 Double blind\$.tw.
27 ((treble or triple) adj blind\$).tw.
28 Placebo\$.tw.
29 Prospective study/
30 or/12-29
31 Case study/
32 Case report.tw.
33 Abstract report/ or letter/
34 or/31-33
35 30 not 34
36 animal/
37 human/
38 36 not 37
39 35 not 38
40 11 and 39

Appendix 2

DATA EXTRACTION CODING FORM DEBRIDEMENT OF DIABETIC FOOT ULCERS SYSTEMATIC REVIEW, META-ANALYSIS, AND META_REGRESSION

Developed July 2013

For any missing or unreported data, indicate with “blank”

Study Information

- (V1) **coder** _____ **Coder** (Dayya = 1, Huedo-Medina = 2, O'Neill = 3, Habib = 4, Other = 5)
- (V2) **study_id** _____ **Study ID #** Study Citation (e.g. 1stAuthorJournalYear, i.e. SmithJAMA2014):
- (V3) **pub_yr** _____ **Publication Year** (e.g. 2014) (*consider this missing if unpublished*)
- (V4) **data_yr** _____ **Estimated year of data collection** (e.g. 2014) (*earliest date for data collection or manuscript submission/publication; if unpublished and date unknown, use year manuscript was acquired; for dissertation or thesis, use year*)
- (V5) **lang** _____ **Language of publication**
0=English
1=Spanish
2=French
3=German
4=Other, specify: _____
- (V6) **source** _____:
0= journal
1= book
2= thesis/dissertation
3= conference proceedings
4= unpublished document/abstract
5= other, specify: _____
- (V7) **finance** _____ **Financial Support**
0= None
1= Public; agency: _____
2= Private; company: _____
3= Unclear
- (V8) **score** _____ **Impact Score of the Journal** (*use ISI Web of Knowledge journal citation reports*)
- (V9) **debride** _____ **Method of Debridement Intervention**
0= Autolytic
1= Sharp/Surgical Debridement
2= Biosurgery or Maggot debridement Therapy
3= Mechanical Debridement
4= Enzymatic Debridement

5= Ultrasound

6= Laser

Sample Characteristics (proportion: 0.0- 1.0)

(V7) eth	_____	Ethnicity reported? 0 = no; 1 = yes
(V8) prop_wh	_____	Proportion Caucasian (e.g. 0.50 for 50%); if whole number available: _____
(V9) prop_blk	_____	Proportion African American; if whole number: _____
(V10) prop_hisp	_____	Proportion Latino/Hispanic; if whole number: _____
(V11) prop_asian	_____	Proportion Asian; if whole number: _____
(V12) prop_min	_____	Proportion Minority/other; if whole number: _____
(V13) educ	_____	Education reported? 0 = no; 1 = yes
(V14) prop_hs	_____	Proportion high school; if whole number available: _____
(V15) prop_coll	_____	Proportion college; if whole number available: _____
(V16) prop_grad	_____	Proportion graduate school; if whole number available: _____
(V17) ses	_____	SES reported? 0 = no; 1 = yes
(V18) prop_low	_____	Proportion of low SES Low (< 25k)
(V19) prop_mid	_____	Proportion of Middle SES (25k-100k)
(V20) prop_high	_____	Proportion of high SES (>100k)
(V21) #female	_____	Number of Females in Sample as a whole number?
(V22) prop_fem	_____	Proportion of females in sample (e.g. 0.50 for 50%)
(V23) region	_____	of sample
		1=American city: _____
		2=Other U.S. general region (<i>city not specified</i>): _____
		3=Canada (city: _____)
		4=Europe (city: _____)
		5=South or Central America, Mexico, Caribbean (city: _____)
		6=Africa (city: _____)
		7=Asia (city: _____)
		8=Australia (city: _____)
(V24) us_zip	_____	Zip Code (US Only) _____
(V25) pop_type	_____	Population
		0= Not reported
		1= Outpatient Office
		2= Specialized Center source (e.g., wound clinic/center, hyperbaric center)

		3=Hospitalized; specify source (e.g. inpatient, hospital):

_____ **Notes on sample characteristics relevant to coding**

Risk Characteristics (if SEM, change to SD; $SD = SEM * \sqrt{n}$; use DSTAT to pool variances if applicable)

(V26)	age	_____	Mean age of total sample (years)
(V27)	age_sd	_____	SD for age (years)
(V28)	ht	_____	Mean height of total sample (cm)
(V29)	ht_sd	_____	SD of height (cm)
(V30)	wt	_____	Mean weight of total sample (kg)
(V31)	wt_sd	_____	SD of weight (kg)
(V32)	waist	_____	Mean waist circumference of total sample (cm)
(V33)	waist_sd	_____	SD of waist circumference (cm)
(V34)	w-h	_____	Mean Waist-to-Hip Ratio of total sample
(V35)	w-h_sd	_____	SD of Waist-to-Hip Ratio
(V36)	bmi	_____	Mean Body Mass Index of total sample (BMI, $\text{kg}\cdot\text{m}^{-2}$) (if calculating, use NHLBI equation)
(V37)	bmi_sd	_____	SD of mean BMI for total sample.
(V38)	bmi_norm	_____	Proportion normal weight (18.5-24.9)
(V39)	bmi_over	_____	Proportion overweight (25.0-29.9)
(V40)	bmi_obese1	_____	Proportion obese, Class I (30.0-34.9)
(V41)	bmi_obese2	_____	Proportion obese, Class II (35.0-39.9)
(V42)	bmi_obese3	_____	Proportion obese, Class III (≥ 40.0)
(V43)	bf%	_____	Mean value of body fat composition of total sample (Body Fat %)
(V44)	bf%_sd	_____	SD of Body Fat %
(V45)	bf%_assess	_____	Method of Body Fat % Assessment 1= Skinfold thickness 2= Hydrostatic weighing 3= Bioelectrical impedance, specify: _____ 4= Air displacement plethysmography, specify: _____ 5= Dual energy x-ray absorptiometry (DEXA), specify: _____ 6= Other, specify: _____
(V46)	prop_pad	_____	Proportion of total sample with peripheral arterial vascular disease; if whole number available__
(V47)	tcpo2	_____	Mean peri-wound tissue oxygenation levels (mmHg) for total sample.
(V48)	hgba1c	_____	Mean Hgba1c (% glycosylated Hgb) for total sample.
(V49)	prop_immune	_____	Proportion of total sample with immunosuppression including: HIV status, chemotherapy, steroids, immunosuppressants; If whole number available__
(V50)	prop_hd	_____	Proportion of total sample with history of coronary heart disease; if whole number available _____
(V51)	prop_htn	_____	Proportion of total sample with hypertension; if whole number available _____

- (V52) **prop_thyroid** _____ **Proportion of total sample with Thyroid disease; if whole number available _____**
(If mean TSH level available for total sample enter this value instead and Notate accordingly in coding form)
- (V53) **prop_neurop** _____ **Proportion of total sample with peripheral Neuropathy; if whole number available _____**
- (V54) **prop_venous** _____ **Proportion of total sample with Venous Insufficiency; if whole number available _____**
- (V55) **prop_rf** _____ **Proportion of total sample w/ Renal Failure/Dialysis; if whole number available _____**
(If mean creatinine level for total sample is available enter this value instead and notate accordingly in coding form)
- (V56) **prop_anemia** _____ **Proportion of total sample with Anemia; if whole number available _____**
(If mean hemoglobin level for total sample is available enter this value instead and notate accordingly in coding form)
- (V57) **prop_copd** _____ **Proportion of total sample with Chronic Obstructive Pulmonary Disease; if whole number available _____ OR if available report mean oxygen hemoglobin saturation for sample in mmHg. Notate accordingly here in coding form which is to be used.**
- (V58) **chf** _____ **Enter proportion of total sample with congestive heart failure**
- (V59) **heartfunc** _____ **If available enter the functional classification of CHF/Heart Disease for the sample according to New York Heart Association NYHA criteria.**
0= Not Reported
1= Class I, 2= Class II, 3= Class III, 4= Class IV
- (V60) **prop_sed** _____ **Proportion of sample that is sedentary (≤ 2 d/ wk of regular physical activity); if whole number available _____**
- (V61) **antithromb_med** _____ **Proportion of the patients on antithrombotic medications (includes anticoagulants, antiplatelet agents aspirin/Nsaids, etc.)**
- (V62) **prop_ocp_use** _____ **Proportion of total sample using oral contraceptives.**
- (V63) **caffeine_use** _____ **Mean number of days per week of caffeine consumption for total sample**
- (V64) **caffeine_day** _____ **Mean number of caffeinated beverages per day for total sample**
- (V65) **caffeine_wk** _____ **Mean number of caffeinated beverages per week for total sample**
- (V66) **prop_caffeine** _____ **Proportion of sample with regular caffeine consumption; if whole number available _____**
- (V67) **etoh_use** _____ **Mean number of days per week of alcohol consumption for total sample**
- (V68) **etoh_day** _____ **Mean number of alcoholic drinks per day for total sample**
- (V69) **etoh_wk** _____ **Mean number of alcoholic drinks per week for total sample**

- (V70) **prop_eto** _____ **Proportion of sample reporting regular alcohol consumptions. Those drinking at home and more often than restricting to social occasions; if whole number available _____**
- (V71) **smoking** _____ **Proportion of total sample currently smoking, or smoked within last 6 months.**
- (V72) **smoking_yrs** _____ **Mean number of years smoking for total sample**
- (V73) **smoke_pack** _____ **Mean number of packs per day for total sample**
- (V74) **smoke_pack_yrs** _____ **(Pack years calculated in pack/day*yrs for total sample)**
- (V75) **diabetes_duration** _____ **Enter the mean duration of diabetes in years for total sample.**

Notes on risk characteristics relevant to coding

Co-Interventions (Associated Standard of Care Measures in Diabetic Foot Ulcers)

- (V76) **offload** _____ 0= No, 1= Yes (includes orthotics, Inserts, crutches, wheelchairs, Partial weight-bearing, Non weight bearing etc.), 2= Unclear
- (V77) **pt** _____ 0= No, 1= Yes, 2= Unclear If so number of sessions _____
- (V78) **nutcons** _____ 0= No, 1= Yes, 2= Unclear If so number of sessions _____
- (V79) **vascsurg** _____ 0= No, 1= Yes (Includes percutaneous interventions such as angioplasty, stenting, or thrombectomy, bypass procedures), 2= Unclear If so number of procedures _____
- (V80) **hbot** _____ 0= No, 1= Yes, 2= Unclear If so number of sessions _____
- (V81) **antibiotic** _____ 0= No, 1= Yes (Includes topical or systemic treatment), 2= Unclear If so number of sessions _____

Methods & Design

DESIGN & MEASUREMENT

- (V82) **design_typ** _____Type of Design
1= Quasi-experimental
2= Matched with Randomization
3= Randomized controlled trial
4= Other:_____
- (V83) **unit_assign** _____Unit of Assignment
1= Community (e.g., city)
2= Group (hospital, clinic, etc.)
3= Individual
4= Other: _____
- (V84) **recruit_meth** _____Recruitment Method
1= Self-selected from community (e.g. via flyers, community centers, etc.)
2= Recruited on the internet
3= Recruited though chart review
4= Recruited through clinical contact (hospital, primary care, clinic, hyperbaric center, wound center,
other consultant etc)
5= Experimental credit or equivalent in class (i.e. subject pool)
6= Other, specify: _____
7= Unclear
- (V85) **accept_rate** _____Acceptance rate (if reported: percent successfully recruited = # who agreed to
participate / #
targeted)
- (V86) **incent** _____Specific incentives offered/facilitators:
1. Free Medical Care 5. Transportation provided
2. Monetary 6. No apparent
3. Food 7. Other, specify: _____
4. Childcare 8. Multiple, specify: _____
- (V87) **#f/u** _____Number of follow-ups: _____
(e.g 1= acute/post intervention only, 2= pre and postintervention, 3, 4, 5 follow ups)
- (V88) **f/u_int** _____Interval of follow-ups: _____
(0= acute, 1= every 3 days, 1= weekly, 2= biweekly, 3= monthly)
- (V89) **short_f/u** _____Short-term follow-up period for the entire study in weeks (if less than 1 year, specify
time(s):_____)
- (V90) **long_f/u** _____Long-term follow-up period for the entire study in years (if greater than 1 year or
more, specify
time(s):_____)

CONTROL/COMPARISON CONDITION:

**Label given by author and description of control condition (if more than one, use the control condition with the least

contact such as an assessment only condition):

-
- (V91) **cont** _____ Control condition:
0= No control/comparison group used.
1= Yes control/comparison group used.
2= Unclear
- (V92) **cont_grp** _____ Type of control group used
0= non-random assignment of individuals to conditions (i.e. intervention or control group)
1= random assignment of individuals to conditions (i.e. intervention or control group)
2= other, specify: _____
- (V93) **cont_comp** _____ Composition of comparison condition
0= Targeted to group, other specify:

1= Individual (e.g. targeted to one person)
2= Unclear
- (V94) **cont_meth** _____ Method of control/comparison delivery was followed according to generally accepted standards.
0= No
1= Yes
2= Unclear
- (V95) **#cont** _____ Total number of participants in control/comparison group (Men: _____; Women: _____)
- (V96) **#part_beg_cont** _____ Number of participants at study beginning in the control/comparison group.
- (V97) **#part_end_cont** _____ Number of participants at study completion in the control/comparison group.
- (V98) **#part_lost_cont** _____ Number of participants lost during study in the control/comparison group
- (V99) **%adhere_cont** _____ Percent Participant adherence in the control group (V97/V96) x 100 or
$$\left(\frac{\text{completed sessions}}{\text{total sessions}} \right) \times 100$$

EXPERIMENTAL/INTERVENTION CONDITION:

- (V100) **#exp_cond** _____ Number of experimental conditions for which effect sizes will be calculated (complete pages separately if needed, using variables for each experimental condition)
- (V101) **exp_cond** _____ **Specify intervention/experimental condition**
0= Autolytic
1= Sharp/Surgical Debridement
2= Biosurgery or Maggot debridement Therapy
3= Mechanical Debridement
4= Enzymatic Debridement
5= Ultrasound
6= Laser
- (V102) **del_meth** _____ Method of delivery:
0= Delivered by a primary care provider
1= Delivered by non-surgeon wound care physician
2= Delivered by a surgeon
3= Multiple/Other, specify:

4= Unclear
- (V103) **exp_meth** _____ Method of intervention delivery according to generally accepted standards.
0= No
1= Yes
2= Unclear
- (V104) **#part_beg_exp** _____ Number of participants at beginning of intervention in the experimental group
- (V105) **#part_end_exp** _____ Number of participants at study completion in the experimental group
- (V106) **#part_lost_exp** _____ Number of participants lost during study in the experimental group (V104-V105)
- (V107) **%adhere_exp** _____ Percent participant adherence in the experimental group (V105/V104) x 100
or $(\frac{\text{completed sessions}}{\text{total sessions}}) \times 100$
- (V108) **#sess_exp** _____ Number of sessions in experimental group
- (V109) **#fac/exp** _____ Number of facilitators/experimenters in the study. (blank if no contact/wait list)_____
- (V110) **rand_assign** _____ Random assignment
0= Violated randomization and/or nonequivalence of comparison group was not addressed
1= Quasi-experimental design; group assignment, arbitrary assignment; sequential; how:

2= Matching individuals on some variable or strata (e.g., SES, age), then random assignment
3= Random assignment of individuals

- (V111) **qual_cont** _____ Quality control
 0 = No standardization of treatment is specified
 1 = Treatment standardized by manual, specific training, content coding, sessions monitored for fidelity.
 2= Unclear
- (V112) **pretest_eval** _____ Pretest evaluation of intervention conducted. (0 = No, 1 = Yes, 2= Unclear)
- (V113) **f/u_rate** _____ Follow-up rate (i.e., largest follow-up rate at any delayed post-test)
 2 = 85-100% completed, 1 = 70 – 84% completed, 0 = <70% completed
- (V114) **f/u_length** _____ Follow-up length of the study. (i.e. final assessment interval) _____
 2 = 6 months or longer, 1 = 3 to 5 months, 0 = less than 3 months
- (V115) **obj_meas** _____ Used objective measures to define the intervention..
 0 = No objective measure used or unspecified
 1 = Objective measures (e.g., laboratory testing) used in more than 50% of the cases
 2= Unclear
- (V116) **with_drop** _____ Withdrawal/Drop-outs and/or attrition
 0 = Not reported or all non-completers were excluded from analyses
 1 = Enumerated
 2 = Compared with completed cases (e.g., intent-to-treat; baseline differences, imputing missing values)
- (V117) **%loss_f/u** _____ Loss to follow up?
 (e.g 10%, 20%, 50%) % Dropouts _____; If whole number available _____

_____ **Notes on methods & study design relevant to coding**

- (V118) **exper** _____ **Experimental condition(s)**

Independent (unrelated/unpaired) groups

- 1= autolytic debridement control/comparison + one experimental group
- 2= autolytic debridement control/ comparison + two experimental groups
- 3= autolytic debridement control/ comparison + three experimental groups
- 4= autolytic debridement control/ comparison + three experimental groups
- 5= autolytic debridement control/ comparison + four experimental groups
- 6= autolytic debridement control/ comparison + five experimental groups
- 7= autolytic debridement control/comparison + six experimental groups

Non-Independent (related/paired) groups

- 6= autolytic debridement control/comparison + one experimental group
- 7= autolytic debridement control/ comparison + two experimental groups
- 8= autolytic debridement control/ comparison + three experimental groups
- 9= autolytic debridement control/ comparison + three experimental groups
- 10= autolytic debridement control/ comparison + four experimental groups
- 11= autolytic debridement control/ comparison + five experimental groups
- 12= autolytic debridement control/comparison + six experimental groups

(V119) **exp_setting** _____ **Setting of Experiment/ Intervention**

1= private office

2= wound clinic/center

3= hospital setting

4= Other, specify: _____

5= multiple, specify: _____

(V120) **inter_lvl** _____ **Dose of level of intervention used in the study**

1= 1-3 debridement sessions required

2= 4-6 debridement sessions required

3= 7-9 debridement sessions required

4= 10-12 debridement sessions required

5= multiply, specify number of debridement sessions required: _____

(V121) **sub_group** (*i.e. female, male, hypertensive, normotensive, white, black, etc.*), specify: _____

(0= No, 1= Yes, 2=Unclear)

STUDY QUALITY

Cochrane Risk of Bias Table

(V122) **asg** _____ **Adequate sequence generation**

(0= No, 1=Yes, 2= Unclear)

(V123) **asc** _____ **Allocation sequence concealment**

(0= No, 1=Yes, 2= Unclear)

(V124) **blind** _____ **Blinding (single, double, triple)**

(0=No, 1= single, double, or triple blinding, 4= Unclear) Specify what level of blinding: _____

(V125) **inc_out_data** _____ **Incomplete outcome data addressed**

(0= No, 1= Yes 2= Unclear)

(If so how ITT, Bayesian methods, imputation, Last Observation Carried Forward

(LOCF), dropped

Missing data) _____

(V126) **fsr** _____ **Free of selective reporting**

(0= No, 1= Yes, 2= Unclear)

(V127) **fob** _____ **Free of other bias**

(0= No, 1= Yes, 2= Unclear)

(V128) **fs** _____ **Financial support**

(0= No, 1= Yes, 2= Unclear)

Other Study Quality Considerations

- (V129) **#hypothesis_test** _____ Number of hypothesis tests performed _____
- (V130) **alpha** _____ Alpha cutoff value used
- (V131) **typ1_error** _____ Type 1 error probability reported if positive study _____
- (V132) **power** _____ Power Reported
- (V133) **typ2_error** _____ Type 2 error probability reported if negative study
- (V134) **stat_anal** _____ Hypothesis test used for statistical Analyses
 0= No statistical analysis; inappropriate, or unspecified
 1= Appropriate statistical analyses of group differences (e.g., comparing two groups using at least more than one t or F test but did not control for baseline and/or other characteristics)
 2= Controlled for baseline and/or other characteristics in appropriate statistical analyses of group differences (e.g. compared two groups using at least a t or F test)
- (V135) **sampl_bal** _____ Samples Balanced for Confounders/Effect Modifiers between Sample and Control
 (0 = No, 1= Yes, 2= Unclear)
- (V136) **sampl_bias** _____ Sampling Bias Probable
 (0 = No, 1= Yes, 2= Unclear)
- (V137) **sel_bias** _____ Selection Bias Probable
 (0 = No, 1 = Yes, 2 = Unclear)
- (V138) **info_bias** _____ Information Bias Probable
 (0 = No, 1 = Yes, 2 = Unclear)

EFFECT SIZES

VARIABLE	Initial and Post Debridement Wound Assessments
(V139) total#part_beg # of participants at beginning of intervention	
(V140) total#part_end # of participants at study completion	
(V141) total#part_lost # of participants lost during study	
(V142) meanadherence Mean participant adherence $(\frac{\text{completed sessions}}{\text{total sessions}}) \times 100$	
(V143) wound_assess Wound Measurement Type 1= Length, width, depth 2= Surface area 3= Volume 4= multiple, specify #s_____	
(V144) wound_size_init_cont Initial Mean Wound Measurement control/comparison [size (cm), surface area (cm2)]	
(V145) wound_size_initial_cont_sd SD of Initial Mean Wound Size control/comparison	
(V146) wound_size_post_cont Post Intervention Mean Wound Measurement control/comparison. [size (cm), surface area (cm2)]	
(V147) wound_size_post_cont_sd SD of Post Intervention Mean Wound Size control/comparison (size, surface area)	
(V148) wound_size_init_exp Initial Mean Wound Measurement experimental group [size (cm), surface area (cm2)]	
(V149) wound_size_initial_exp_sd SD of Initial Mean Wound Size experimental group (size, surface area)	
(V150) wound_size_post_exp Post Intervention Mean Wound Measurement experimental group (size, surface area)	
(V151) wound_size_post_exp_sd SD of Post intervention Mean Wound Size	

experimental group (size, surface area?)	
(V152) wound_size_cont_absΔ Absolute change in mean wound size in control/comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V153) wound_size_cont_absΔ_sd SD of Absolute change in mean wound size in control group.	
(V154) wound_size_exp_absΔ Absolute change in mean wound size experimental group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V155) wound_size_exp_absΔ_sd SD of mean absolute change in wound size in experimental group.	
(V156) time_to_heal_cont Time to complete healing for control/comparison group.	
(V157) time_to_heal_cont_sd SD for time to complete healing for control/comparison group.	
(V158) time_to_heal_exp Time to complete healing for experimental group.	
(V159) time_to_heal_exp_sd SD for time to complete healing for experimental group.	
(V160) time_to_heal_cont_absΔ Absolute change in time to complete healing in control/comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V161) time_to_heal_cont_absΔ_sd SD of Absolute change time to complete healing in control/comparison group.	
(V162) time_to_heal_exp_absΔ Absolute change in time to complete healing in experimental group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	

(V163) time_to_heal_exp_absΔ_sd SD of Absolute change time to complete healing in experimental group.	
(V164) prop_indiv_heal_cont Proportion of individuals w/ complete healing control/comparison group.	
(V165) prop_indiv_heal_cont_sd SD for proportion of individuals w/ complete healing control/comparison group.	
(V166) prop_indiv_heal_exp Proportion of individuals w/ complete healing experimental group.	
(V167) prop_indiv_heal_exp_sd SD for proportion of individuals w/ complete healing in the experimental group.	
(V168) prop_indiv_heal_cont_absΔ Absolute change in proportion of individuals w/ complete healing in control/comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V169) prop_indiv_heal_cont_absΔ_sd SD of absolute change in proportion of individuals w/ complete healing in control/comparison group.	
(V170) prop_indiv_heal_exp_absΔ Absolute change in proportion of individuals w/ complete healing in experimental group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V171) prop_indiv_heal_exp_absΔ_sd SD of absolute change in proportion of individuals w/ complete healing in experimental group.	
(V172) prop_ulcers_recur_cont Proportion of individuals w/ ulcer recurrence in control/comparison group.	
(V173) prop_ulcers_recur_cont_sd SD for proportion of individuals w/ ulcer recurrence in control/comparison group.	
(V174) prop_ulcers_recur_exp	

Proportion of individuals w/ ulcer recurrence in experimental group.	
(V175) prop_ulcers_recur_exp_sd SD for Proportion of individuals w/ ulcer recurrence in experimental group.	
(V176) prop_ulcers_recur_cont_absΔ Absolute change in proportion of individuals w/ ulcer recurrence in control/comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V177) prop_ulcers_recur_cont_absΔ_sd SD of Absolute change in proportion of individuals w/ ulcer recurrence in control/comparison group.	
(V178) prop_ulcers_recur_exp_absΔ Absolute change in proportion of individuals w/ ulcer recurrence in experimental group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V179) prop_ulcers_recur_exp_absΔ_sd SD of Absolute change in proportion of individuals w/ ulcer recurrence in experimental group.	
(V180) amp_freq_cont or amp_prop_cont # of amputations/proportion of amputations in control/comparison group.	
(V181) amp_freq_cont_sd or amp_prop_cont_sd SD of # of amputations/proportion of amputations in control/comparison group	
(V182) amp_freq_exp or amp_prop_exp # of amputations/proportion of amputations in experimental group.	
(V183) amp_freq_exp_sd or amp_prop_exp_sd SD of # of Amputations/proportion of Amputations in experimental group.	
(V184) amp_freq_cont_absΔ or amp_prop_cont_absΔ Absolute change in amputation frequency or proportion of individuals requiring amputation in control/comparison condition	

<i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V185) amp_freq_cont_absΔ_sd or amp_prop_cont_absΔ_sd SD of Absolute change AMP_FREQ or PROP_AMP in control/comparison condition.	
(V186) amp_freq_exp_absΔ or amp_prop_exp_absΔ Absolute change in amputation frequency or proportion of individuals requiring amputation in experimental condition <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V187) amp_freq_exp_absΔ_sd or amp_prop_exp_absΔ_sd SD of Absolute change AMP_FREQ or PROP_AMP in experimental condition.	
(V188) inf_freq_cont or inf_prop_cont # of Infections/Proportion of Infections of control/comparison group	
(V189) inf_freq_cont_sd or inf_prop_cont_sd SD of # of Infections/Proportion of Infections of control/comparison group	
(V190) inf_freq_exp or inf_prop_exp # of Infections/Proportion of Infections in experimental group.	
(V191) inf_freq_exp_sd or inf_prop_exp_sd SD of # of Infections/proportion of amputations in experimental group.	
(V192) inf_freq_cont_absΔ or inf_prop_cont_absΔ Absolute change INF_FREQ or INF_PROP in control/comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V193) inf_freq_cont_absΔ_sd or inf_prop_cont_absΔ_sd SD of Absolute change INF_FREQ or	

INF_PROP in control/comparison condition.	
(V194) inf_freq_exp_absΔ or inf_prop_exp_absΔ Absolute change INF_FREQ or INF_PROP in experimental group. <i>If not calculated, leave blank (calculate in spreadsheet)</i>	
(V195) inf_freq_exp_absΔ_sd or inf_prop_exp_absΔ_sd SD of Absolute change INF_FREQ or INF_PROP in control/comparison condition.	
(V196) cost_cont Mean treatment cost for the control/comparison group.	
(V197) cost_cont_sd Standard Deviation for mean treatment cost for the control/comparison group.	
(V198) cost_exp Mean treatment cost for the experimental group.	
(V199) cost_exp_sd Standard Deviation for mean treatment cost for the experimental group.	
(V200) cost_cont_absΔ Absolute change mean COST in the control /comparison group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V201) cost_cont_absΔ_sd standard deviation of Absolute change in mean COST for the control/comparison group.	
(V202) cost_exp_absΔ Absolute change mean COST in the experimental group. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V203) cost_exp_absΔ_sd standard deviation of Absolute change in mean COST for the experimental group.	
(V204) qol_indices_cont Mean quality of life indices for the control/comparison group.	

(V205) qol_indices_cont_sd Standard Deviation for quality of life indices for the control/comparison group.	
(V206) qol_indices_exp Mean quality of life indices for the experimental group.	
(V207) qol_indices_exp_sd Standard Deviation for mean quality of life indices for the experimental group.	
(V208) qol_indices_cont_absΔ Absolute change QOL_INDICES for the control/comparison condition. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V209) qol_indices_cont_absΔ_sd SD of Absolute change QOL_INDICES for the control/comparison condition.	
(V210) qol_indices_exp_absΔ Absolute change QOL_INDICES for the experimental condition. <i>if not calculated, leave blank (calculate in spreadsheet)</i>	
(V211) qol_indices_exp_absΔ_sd SD of Absolute change QOL_INDICES for the experimental condition.	

_____ **Notes relevant to coding**

Statistical Analyses

<i>Statistical Variable</i>	<i>Control Autolytic</i>	<i>Sharp (specify :____)</i>	<i>Operative (specify: ____)</i>	<i>Biosurgery</i>	<i>Mechanical</i>	<i>Enzymatic</i>	<i>Ultrasound</i>	<i>Laser</i>
(V212) wound_size_pval P-Value (0= if not calculated)								
(V213) time_to_heal_pval P-Value (0= if not calculated)								
(V214) prop_indiv_heal_pval P-Value (0= if not calculated)								
(V215) prop_ulcers_recur_pval P-Value (0= if not calculated)								
(V216) amp_freq_pval l or amp_prop_pval P-Value (0= if not calculated)								
(V217) inf_freq_pval or inf_prop_pval P-Value (0= if not calculated)								
(V218) cost_pval P-Value (0= if not calculated)								
(V219) qol_indices_pval P-Value (0= if not calculated)								
(V220) wound_size_test_stat Test Statistic (0= if not calculated)								
(V221) time_to_heal_test_stat Test Statistic (0= if not calculated)								
(V222) prop_indiv_heal_test_stat Test Statistic (0= if not calculated)								

(V223) prop_ulcers_recur_test_stat Test Statistic (0= if not calculated)								
(V224) amp_freq_test_stat or amp_prop_test_stat Test Statistic (0= if not calculated)								
(V225) inf_freq_pval or inf_prop_test_stat Test Statistic (0= if not calculated)								
(V226) cost_test_stat Test Statistic (0= if not calculated)								
(V227) qol_indices_test_stat Test Statistic (0= if not calculated)								
(V228) wound_size_ci Confidence Interval (0= if not calculated)								
(V229) time_to_heal_ci Confidence Interval (0= if not calculated)								
(V230) prop_indiv_heal_ci Confidence Interval (0= if not calculated)								
(V231) prop_ulcers_recur_ci Confidence Interval (0= if not calculated)								
(V232) amp_freq_ci or amp_prop_ci Confidence Interval (0= if not calculated)								
(V233) inf_freq_pval or inf_prop_ci Confidence Interval (0= if not calculated)								
(V234) cost_ci Confidence Interval (0= if not calculated)								
(V235) qol_indices_ci Confidence Interval (0= if not calculated)								

_____ Notes on statistical analyses relevant to coding