Dressings and topical agents for treating venous leg ulcers

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[Intervention Review]

Dressings and topical agents for treating venous leg ulcers

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ABSTRACT

Background

Venous leg ulcers are open skin wounds on the lower leg which can be slow to heal, and are both painful and costly. The point prevalence of open venous leg ulcers in the UK is about 3 cases per 10,000 people, and many people experience recurrent episodes of prolonged ulceration. First-line treatment for venous leg ulcers is compression therapy, but a wide range of dressings and topical treatments are also used. This diversity of treatments makes evidence-based decision-making challenging, and a clear and current overview of all the evidence is required. This review is a network meta-analysis (NMA) which assesses the probability of complete ulcer healing associated with alternative dressings and topical agents.

Objectives

To assess the effects of (1) dressings and (2) topical agents for healing venous leg ulcers in any care setting and to rank treatments in order of effectiveness, with assessment of uncertainty and evidence quality.

Search methods

In March 2017 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid Embase and EBSCO CINAHL Plus. We also scanned reference lists of relevant included studies as well as reviews, meta-analyses, guidelines and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting. We updated this search in March 2018; as a result several studies are awaiting classification.

Selection criteria

We included published or unpublished randomised controlled trials (RCTs) that enrolled adults with venous leg ulcers and compared the effects of at least one of the following interventions with any other intervention in the treatment of venous leg ulcers: any dressing, or any topical agent applied directly to an open venous leg ulcer and left in situ. We excluded from this review dressings attached to external devices such as negative pressure wound therapies, skin grafts, growth factors and other biological agents, larval therapy and treatments such as laser, heat or ultrasound. Studies were required to report complete wound healing to be eligible.

Data collection and analysis

Two review authors independently performed study selection, 'Risk of bias' assessment and data extraction. We conducted this NMA using frequentist meta-regression methods for the efficacy outcome; the probability of complete healing. We assumed that treatment effects were similar within dressings classes (e.g. hydrocolloid, foam). We present estimates of effect with their 95% confidence intervals (CIs) for individual treatments focusing on comparisons with widely used dressing classes, and we report ranking probabilities for each intervention (probability of being the best, second best, etc treatment). We assessed the certainty (quality) of the body of evidence using GRADE for each network comparison and for the network as whole.

Main results

We included 78 RCTs (7014 participants) in this review. Of these, 59 studies (5156 participants, 25 different interventions) were included in the NMA; resulting in 40 direct contrasts which informed 300 mixed-treatment contrasts.

The evidence for the network as a whole was of low certainty. This judgement was based on the sparsity of the network leading to imprecision and the general high risk of bias in the included studies. Sensitivity analyses also demonstrated instability in key aspects of the network and results are reported for the extended sensitivity analysis. Evidence for individual contrasts was mainly judged to be low or very low certainty.

The uncertainty was perpetuated when the results were considered by ranking the treatments in terms of the probability that they were the most effective for ulcer healing, with many treatments having similar, low, probabilities of being the best treatment. The two most highly-ranked treatments both had more than 50% probability of being the best (sucralfate and silver dressings). However, the data for sucralfate was from one small study, which means that this finding should be interpreted with caution. When exploring the data for silver and sucralfate compared with widely-used dressing classes, there was some evidence that silver dressings may increase the probability of venous leg ulcer healing, compared with nonadherent dressings: RR 2.43, 95% CI 1.58 to 3.74 (moderate-certainty evidence in the context of a low-certainty network). For all other combinations of these five interventions it was unclear whether the intervention increased the probability of healing; in each case this was low- or very low-certainty evidence as a consequence of one or more of imprecision, risk of bias and inconsistency.

Authors' conclusions

More research is needed to determine whether particular dressings or topical agents improve the probability of healing of venous leg ulcers. However, the NMA is uninformative regarding which interventions might best be included in a large trial, largely because of the low certainty of the whole network and of individual comparisons.The results of this NMA focus exclusively on complete healing; whilst this is of key importance to people living with venous leg ulcers, clinicians may wish to take into account other patient-important outcomes and factors such as patient preference and cost.

PLAIN LANGUAGE SUMMARY

Dressings and topical agents (gels, ointments and creams) for treating venous leg ulcers

What is the aim of this review?

The aim of this review is to find out which dressings and topical agents (gels, ointments and creams) are most effective for treating a type of wound known as venous leg ulcers. These are long-term wounds in the lower leg caused by problems with blood flow back up the leg through the veins. Researchers from Cochrane found 78 relevant studies (randomised controlled trials) to answer this question. Randomised controlled trials are medical studies where patients are chosen at random to receive different treatments. This type of trial provides the most reliable evidence. We evaluated these studies using a method known as network meta-analysis (NMA), which allowed us to compare treatments across different studies and to rank them in terms of complete ulcer healing.

Key messages

We cannot be certain which dressings and topical agents are most effective for healing venous leg ulcers: over all studies there were not enough participants per treatment and there was high risk of bias; this means that many of the studies were conducted or reported in a way that means we cannot be sure if the results are accurate. The main treatment for venous leg ulcers is compression bandages or stockings and the choice of additional dressings or topical treatments should take into account the review findings and their uncertainty, alongside factors such as patient preference and cost.

What was studied in the review?

Venous leg ulcers are open wounds caused by poor blood flow through the veins of the lower leg. Increased pressure in the leg veins may cause damage to the skin and surrounding tissues, leading to an ulcer. Venous leg ulcers can be slow to heal and are painful and costly to treat. The main treatment is compression bandages or stockings but these are often combined with dressings (e.g. foam or nonadherent dressings) and topical creams, gels or ointments. We wished to know which of these additional treatments are most effective when it comes to ulcer healing.

What are the main results of the review?

We found 78 studies relevant to this question, dating from 1985 to 2016. The studies involved 7014 participants (a majority were women, and average age ranged from 46 to 81 where reported). Our NMA included 59 studies (5156 participants) and compared 25 different treatments such as hydrocolloid and silver-impregnated dressings and a variety of creams and gels.

Silver dressings may increase the probability of venous leg ulcer healing compared with nonadherent dressings. However, in the light of the rest of the NMA evidence, we cannot be very confident about any conclusion, and the network as a whole represents low-certainty evidence. This was due to the small numbers of people involved across all included studies, the small number of studies focusing on each treatment, and the high risk of bias. We cannot therefore be certain which are the most effective treatments for venous leg ulcers, or even which treatments it would be best to compare in future trials.

How up to date is this review?

We searched for studies published up to March 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

NMA evidence for base-case network: proportion with complete healing

Patient or population: people with venous leg ulcers
Intervention: dressing or topical agent
Comparator: alternative dressing or topical agent
Settings: hospital, community or care home, or combinations

Contrasts	Relative effect (95% CI)	Anticipated absolute effects* (95% CI) - from median of control groups in direct evidence		Certainty of the evidence (GRADE)	Comments
		Median CGR	With intervention		
Sucralfate versus nonadherent	RR 6.80 (2.24 to 20.7)	242 per 1000	1000 per 1000 (542 to 1000)	⊕⊕◯◯ Low[a,b]	Base-case: RR 17.2 (95% CI 1.52 to 193). Large differences between base-case and extended base-case The calculated absolute effect for the intervention is more than 1000 per 1000 for the point estimate and its upper confidence limit; and so the corresponding values for the absolute risk difference are also approximated by 1000 per 1000
		1000 more people healed per 1000 (300 to 1000 more)			
Sucralfate versus foam	RR 5.94 (1.96 to 18.0)	376 per 1000	1000 per 1000 (737 to 1000)	⊕⊕◯◯ Low[a,b]	Base-case: RR 14.8 (95% CI 1.30 to 169) Large differences between base-case and extended base-case. The calculated absolute effect for the intervention is

		1000 more people healed per 1000 (361 to 1000 more)			more than 1000 per 1000 for the point estimate and its upper confidence limit; and so the corresponding values for the absolute risk difference are also approximated by 1000 per 1000
Sucralfate versus hydrocolloid	RR 6.51 (2.17 to 19.6)	433 per 1000	1000 per 1000 (940 to 1000)	⊕⊕◯◯ Low[a,b]	Base-case: RR 16.24 (95% CI 1.43 to 185) Large differences between base-case and extended base-case The calculated absolute effect for the intervention is more than 1000 per 1000 for the point estimate and its upper confidence limit; and so the corresponding values for the absolute risk difference are also approximated by 1000 per 1000
		1000 more people healed per 1000 (507 to 1000 more)			
Silver versus nonadherent	RR 2.43 (1.58 to 3.74)	242 per 1000	588 per 1000 (382 to 905)	⊕⊕⊕◯ Moderate[a]	
		346 more people healed per 1000 (140 to 663 more)			
Silver versus foam	RR 2.12 (1.46 to 3.07)	376 per 1000	797 per 1000 (549 to 1000)	⊕⊕◯◯ Low[c]	Direct evidence: Analysis 1.24
		421 more people healed per 1000 (173 to 786 more)			
Silver versus hydrocolloid	RR 2.32 (1.58 to 3.41)	433 per 1000	1000 per 1000 (684 to 1000)	⊕⊕◯◯ Low[a,d]	

		567 more people healed per 1000 (251 to 1000 more)			
Sucralfate versus silver	RR 2.80 (0.88 to 8.97)	81 per 1000	225 per 1000 (71 to 722)	⊕◯◯◯ Very low[a,e]	Base-case: RR 6.99 (95% CI 0.60 to 82.0) Large differences between base-case and extended base-case
		145 more people healed per 1,000 (10 fewer to 642 more)			
Foam versus hydrocolloid	RR 1.10 (0.93 to 1.28)	433 per 1000	476 per 1000 (402 to 554)	⊕◯◯◯ Very low[f,g,h]	Direct evidence: Analysis 1.18
		43 more people healed per 1000 (from 31 fewer to 121 more)			
Foam versus nonadherent dressing	RR 1.15 (0.91 to 1.44)	242 per 1000	278 per 1000 (220 to 348)	⊕⊕◯◯ Low[a,h]	
		36 more people healed per 1000 (from 22 fewer to 106 more)			
Hydrocolloid versus nonadherent dressing	RR 1.04 (0.85 to 1.29)	242 per 1000	251 per 1000 (206 to 312)	⊕◯◯◯ Very low[a,h,i]	Direct evidence: Analysis 1.6
		9 more people healed per 1000 (from 36 fewer to 70 more)			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparator group and the **relative effect** of the intervention (and its 95% CI).

CGR: control group risk; **CI:** confidence interval; **NMA:** network meta-analysis; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty (quality): we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty (quality): we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty (quality): our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty (quality): we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a.] NMA risk of bias from contributions matrix and direct evidence risk of bias (downgrade once)
[b.] Imprecision - direct evidence involving sucralfate: 1 study 43/50 events (sucralfate); 5 events (hydrogel) (downgrade once)
[c.] Heterogeneity in point estimates for direct evidence; significant inconsistency in node splitting and in inconsistency factor (loop) (downgrade twice)
[d.] Significant inconsistency in node splitting and in inconsistency factor (loop) (downgrade once)
[e.] Imprecision - CI crosses one MID (1.25) and direct evidence involving sucralfate: 43/50 events (sucralfate) and 5 events (hydrogel) (downgrade twice)
[f.] NMA risk of bias from contributions matrix and direct evidence risk of bias (downgrade twice)
[g.] Slight heterogeneity in point estimates for direct evidence; significant inconsistency in node splitting and inconsistency factor (downgrade once)
[h.] Imprecision - CI crosses one MID (1.25) (downgrade once)
[i.] High heterogeneity in direct evidence (downgrade twice)

BACKGROUND

Description of the condition

Venous leg ulcers are common and recurring complex wounds that heal by secondary intention (that is by the growth of new tissue rather than by primary closure). Problems with the leg veins (such as damage to the valves, or blockages) reduce the efficient return of blood to the heart and increase the pressure in the veins (Ghauri 2010), which may result in venous leg ulcers. The precise chain of events that links high venous pressures (chronic venous hypertension) with skin breakdown and a chronic wound is not fully understood (Coleridge Smith 1988; Valencia 2001).

Venous leg ulcers commonly occur on the gaiter region of the lower leg (from just below the ankle up to mid-calf). A venous leg ulcer is defined as any break in the skin that has either been present for longer than six weeks or occurs in a person with a history of venous leg ulceration. Differential diagnosis of the type of leg ulcer (i.e. the underlying cause) is made by taking a clinical history, physical examination, laboratory tests and haemodynamic assessment (RCN 2013; SIGN 2010). True venous ulcers are moist, shallow and irregularly shaped and lie wholly or partly within the gaiter area of the leg. Leg ulcers can be associated with venous disease in combination with vascular disease, which impairs arterial blood supply; in these instances they are said to have a 'mixed' aetiology (to have more than one cause). Open skin ulceration due solely to limb ischaemia from vascular disease is less common.

Accurate, current estimates of leg ulcer prevalence are hard to identify because most surveys do not differentiate between causes of leg ulceration, or do so per limb but not per person (Moffatt 2004; Srinivasaiah 2007; Vowden 2009b). Estimates of the prevalence of open leg ulceration (any cause) range from 4 to 48 cases per 10,000 (Graham 2003; Johnson 1995; Walker 2002), with the point prevalence of venous leg ulceration in Australian and European studies being between 10 per 10,000 and 30 per 10,000 (Nelzen 2008). A recent estimate suggests that venous ulceration has a point prevalence of 2.9 cases per 10,000 in the United Kingdom (UK), whilst mixed arterial/venous leg ulceration has a point prevalence of 1.1 per 10,000 (Hall 2014).

Venous disease is a chronic condition which can be characterised by periods of ulceration (i.e. an open wound) followed by healing and then recurrence. An early cross-sectional survey reported that half of current or recent ulcers had been open for up to nine months and that 35% of people with leg ulcers had experienced four or more episodes (Callam 1987b). This picture was supported by a subsequent cross-sectional study (Nelzen 1994). More recent analysis of almost 1200 people with venous leg ulcers documented a 24-week healing rate of 76% and a recurrence at one year of 17% (Gohel 2005).

Venous ulcers are painful, can be malodorous and prone to infection, and may severely affect people's mobility and quality of life. The presence of leg ulceration has been associated with pain, restriction of work and leisure activities, impaired mobility, sleep disturbance, reduced psychological well-being and social isolation (Herber 2007; Maddox 2012; Persoon 2004). In severe cases, ulceration can lead to limb amputation, although this may be more common in people with comorbid arterial insufficiency (Dumville 2009; Nelzen 1997; Valencia 2001). Recent research suggests that people with complex wounds, including those with venous leg ulcers, commonly see complete wound healing as the most important outcome to them (Cullum 2016; Madden 2014).

The financial cost of treating an unhealed leg ulcer in the UK has most recently been estimated at around GBP 1700 per year (price year 2012) (Ashby 2014). An earlier evaluation estimated the average cost of treating a venous leg ulcer in the UK (based on costs for material for dressing changes) as between EUR 814 and EUR 1994 and, in Sweden as lying between EUR 1332 and EUR 2585 (price year 2002), with higher costs associated with larger and more chronic wounds (Ragnarson 2005). In Bradford, UK, GBP 1.69 million was spent on dressings and compression bandages, and GBP 3.08 million on nursing time (estimates derived from resource use data for all wound types) during the financial year 2006 to 2007 (Vowden 2009a). Data from a German study, which estimated total costs including those classified as indirect or intangible costs, estimated mean annual costs of leg ulcers as EUR 9060 per patient (price year 2006). This figure is higher than other estimates because it includes non-health service costs to the patient and to society (Augustin 2012). These data are all derived from high-income countries and thus may not be a true reflection of costs elsewhere, which may be higher or lower.

Description of the intervention

The review includes all dressings and topical agents applied directly onto or into wounds and left in situ. This contrasts with products used to irrigate, wash or cleanse wounds and that are only in contact with wounds for a short period. First-line treatment for venous leg ulcers is compression therapy in the form of bandages, stockings or mechanical devices (Nelson 2014; O'Meara 2012). This application of external pressure around the lower leg assists venous return and reduces venous reflux (Woo 2013). We therefore anticipated that wound dressings would commonly be used in combination with compression therapy.

Dressings are widely used in wound care with the aim of protecting the wound and promoting healing by influencing the local wound environment (Bradley 1999), typically by physical means, such as thermal insulation, absorption of exudate and physical protection. Dressings may also have pharmacological, immunological or metabolic actions. Topical agents include hydrogel gels, ointments and creams that are placed in contact with the wound and left in situ.

Dressings

The classification of dressings usually depends on the key material used in their construction, and whether additional substances are added to the dressing. Several attributes of an ideal wound dressing have been described (BNF 2016), including the ability of the dressing to:

- absorb and contain exudate without leakage or strike-through, in order to maintain a wound that is moist but not macerated;
- achieve freedom from particulate contaminants or toxic chemicals left in the wound;
- provide thermal insulation, in order to maintain the optimum temperature for healing;
- allow permeability to water, but not bacteria;
- optimise the pH of the wound;
- minimise wound infection and avoid excessive slough;
- avoid wound trauma on dressing removal;
- accommodate the need for frequent dressing changes;
- provide pain relief; and
- be comfortable.

There is a wide range of types of dressings available which may be used for treating wounds including venous leg ulcers; some of these and their properties are described below (BNF 2016). Impregnated dressings may have a range of bases, such as foams or alginates.

Absorbent dressings are applied directly to the wound and may be used as secondary absorbent layers in the management of heavily exuding wounds. Examples include Primapore (Smith & Nephew); this can be lifted off at dressing removal, or removed by irrigation. Bonding to a secondary viscose pad increases absorbency. Examples include: Curasorb (Covidien), SeaSorb (Coloplast) and Sorbsan (Unomedical).

Capillary-action dressings consist of an absorbent core of hydrophilic fibres held between two low-adherent contact layers. Examples include: Advadraw (Advancis) and Vacutex (Protex).

Permeable film and membrane dressings are permeable to water vapour and oxygen, but not to water or micro-organisms. Examples include Tegaderm (3M) transparent film and OpSite (Smith & Nephew).

Foam dressings contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface. There are a variety of versions and some include additional absorbent materials, such as viscose and acrylate fibres, or particles of superabsorbent polyacrylate, which are silicone-coated for non-traumatic removal. Examples include: Allevyn (Smith & Nephew), Biatain (Coloplast) and Tegaderm (3M) foam adhesive and non-adhesive dressings.

Honey-impregnated dressings contain medical-grade honey that is purported to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Examples include: Medihoney (Medihoney) and Activon Tulle (Advancis).

Hydrocolloid dressings are usually composed of an absorbent hydrocolloid matrix on a vapour-permeable film or foam backing. Examples include: Granuflex (ConvaTec) and NU DERM (Systagenix). Fibrous alternatives that resemble alginates and are not occlusive have also been developed: Aquacel (ConvaTec).

Iodine-impregnated dressings release free iodine, which is thought to act as a wound antiseptic when exposed to wound exudate. Examples include Iodoflex (Smith & Nephew) and Iodozyme (Insense).

Low-adherence dressings and **wound contact materials** usually consist of cotton pads that are placed directly in contact with the wound. They can be non-medicated (e.g. paraffin gauze dressing, saline gauze dressing) or medicated (e.g. containing povidone iodine or chlorhexidine). Examples include paraffin gauze dressing, BP 1993 and Xeroform (Covidien) dressing - a nonadherent petrolatum blend with 3% bismuth tribromophenate on fine mesh gauze.

Odour-absorbent dressings contain charcoal and are used to absorb wound odour. Often this type of wound dressing is used in conjunction with a secondary dressing to improve absorbency. An example is CarboFLEX (ConvaTec).

Other antimicrobial dressings are composed of a gauze or low-adherent dressing impregnated with an ointment thought to have antimicrobial properties (e.g. chlorhexidine gauze dressing (Smith & Nephew)). Alternatively, a dressing such as Cutimed Sorbact (BSN Medical) uses a hydrophobic layer to bind micro-organisms to the dressing surface, allowing them to be removed from the wound when the dressing is changed.

Protease-modulating matrix dressings alter the activity of proteolytic enzymes in chronic wounds. Examples include: Promogran (Systagenix).

Silver-impregnated dressings are used to treat infected wounds, as silver ions are thought to have antimicrobial properties. Silver versions of most dressing types are available, including silver impregnated dressings (e.g. silver hydrocolloid etc). Examples include: Acticoat (Smith & Nephew) and Urgosorb Silver (Urgo).

Soft polymer dressings are composed of a soft silicone polymer held in a nonadherent layer; these are moderately absorbent. Examples include: Mepitel (Mölnlycke) and Urgotul (Urgo).

Topical agents

The following types of topical agents are considered as interventions in this review.

Cadexomer-iodine paste consists of a water-soluble, modified starch polymer containing iodine. It releases free iodine when exposed to wound exudate. The free iodine acts as an antiseptic on the wound surface, and the cadexomer absorbs wound exudate and encourages de-sloughing. Examples include: Iodosorb (Smith & Nephew) ointment and powder.

Collagenase-containing ointment is an enzymatic debriding ointment. Collagenase is thought to digest collagen in necrotic tissue and to contribute to granulation and epithelialisation (the final stage of wound healing).

Hydrogels consist of a starch polymer and up to 96% water. They can absorb wound exudate or rehydrate a wound depending on the wound moisture levels. Hydrogels are often considered to be dressings, but are also topical in nature. They are supplied in either flat sheets, an amorphous hydrogel or as beads. Examples include: ActiformCool (Activa) and Aquaflo (Covidien).

Topical phenytoin is thought to promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition and antibacterial activity.

Silver sulfadiazine cream is a topical antimicrobial cream that is used to treat and prevent infection in wounds by damaging bacterial cell membranes. Examples include Flamazine (Smith & Nephew) and Silvadene (Pfizer).

We did not consider studies evaluating any products containing growth factors, platelet-rich plasma or other platelet-derived products and colony-stimulating factors.

How the intervention might work

Animal experiments conducted over 40 years ago suggested that acute wounds heal more quickly when their surfaces are kept moist rather than left to dry and scab (Winter 1962; Winter 1963a; Winter 1963b). A moist environment is thought to provide optimal conditions for the cells involved in the healing process with faster revascularisation (Dyson 1992), and development of granulation tissue (Svensjö 2000), as well as allowing autolytic debridement (removal of dead tissue by natural processes), which is thought to be an important part of the healing pathway (Cardinal 2009).

The desire to maintain a moist wound environment is a key driver for the use of wound dressings and related topical agents. Whilst a moist environment at the wound site has been shown to aid the rate of epithelialisation in superficial wounds, excess moisture at the wound site can cause maceration (breakdown) of the surrounding skin (Cutting 2002), and it has also been suggested that dressings that permit fluid to accumulate might predispose wounds to infection (Hutchinson 1991). Wound treatments vary in their level of absorbency, so that a very wet wound can be treated with an absorbent dressing (such as a foam dressing) to draw excess moisture away and avoid skin damage, whilst a drier wound can be treated with a more occlusive dressing or a hydrogel to maintain a moist environment.

Some dressings are now also formulated with an 'active' ingredient (e.g. silver, honey or protease modulators).

Why it is important to do this review

Venous leg ulcers are a relatively common type of complex wound that have a negative impact on people's lives and incur high costs for health services and society. Leg ulcers are painful, sometimes malodorous, prone to infection, and may severely affect people's mobility and quality of life, and in severe cases, there is a risk of limb amputation. There are a number of treatments for venous leg ulcers, but many ulcers prove hard to heal, although healing is a key outcome for patients.

We conducted an open consultation with consumers to ask them which treatments for treating venous leg ulcers they would like to see considered. Respondents self-selected through their response to a short questionnaire posted on the Cochrane Wounds website and Facebook page. Although some identified compression as the main consideration, others mentioned specific types of dressings. These included many of the dressing types listed in Description of the intervention, including charcoal-containing (odour-absorbing) dressings, dressings designed to reduce formation and presence of biofilms (bacteria which grow on a surface to form a film of cells) and dressings with antimicrobial properties and debriding actions. Also specifically identified as being of interest was Unna's boot; a specialised dressing which consists of gauze wraps impregnated with zinc oxide and calamine, sometimes in combination with other agents.

The diversity of dressings and related materials available to health professionals for treating venous leg ulcers makes evidence-based decision-making difficult when determining the optimum treatment regimen for a particular patient (NICE 2016a). With increasingly sophisticated technology being applied to wound care, practitioners need to know the relative effectiveness and cost-effectiveness of these sometimes expensive dressings. Even where cost is not an issue, the most effective treatment may not be available (e.g. in some developing countries) or may be difficult or to use, so that information on the second and third best treatments is important too (Salanti 2011).

There are a number of existing or ongoing evidence syntheses on venous leg ulcer treatments, including Cochrane reviews of different types of dressings or topical treatments (Briggs 2012; O'Meara 2013; O'Meara 2014; O'Meara 2015; Ribeiro 2013; Ribeiro 2014; Westby 2016). There are also wider reviews of particular types of treatment for all wound types which include data on venous leg ulcers for treatments such as honey, silver, aloe Vera, and phenytoin (Dat 2012; Jull 2015; Shaw 2007; Vermeulen 2007). Other reviews on non-healing or chronic ulcers have also included a substantial number of relevant trials (Greer 2013; AHRQ 2013), and there are also older general reviews (e.g. Bouza 2005; O'Donnell 2006).

Guidance drawing on reviews available at the time has also been published (Robson 2006; SIGN 2010). The SIGN 2010 guideline recommended that low-adherent dressings be used routinely but that alternative dressings (hydrocolloids, alginates or hydrogels) may be considered to assist with pain, exudate and slough respectively. Earlier guidance (Robson 2006), recommended that maintaining a moist wound environment be prioritised in dressing choice. Most recently the UK National Institute for Health and Care Excellence (NICE) issued advice on the use of advanced and

antimicrobial dressings for chronic wounds including venous leg ulcers (NICE 2016b). This updated the SIGN 2010 guidance to include the findings of the most recent systematic reviews.

However, despite the existence of high-quality recent systematic reviews, there is insufficient evidence to support the use of any particular type of advanced or antimicrobial dressing or treatment as the direct evidence is of low certainty and no network meta-analysis (NMA) has previously been undertaken in this area. Decision-makers currently have to consider the findings of a plethora of pairwise randomised controlled trials (RCTs) simultaneously and to make qualitative judgements across these in the face of uncertainty, when considering the evidence on dressing use.

NMA is the simultaneous comparison of linked, multiple, competing treatments in a single statistical regression model (Caldwell 2005; Lu 2004; Salanti 2008). NMA utilises evidence from both 'direct' (head-to-head or 'pairwise') comparisons (e.g. trials directly comparing treatments A and B) and 'indirect' comparisons (e.g. the combination of trials comparing A with C and trials comparing B with C). If both direct and indirect estimates are available, they can be meta-analysed, preserving within-trial randomisation (Grant 2013; Thorlund 2012; Tu 2012).

Where there are relevant common comparators, NMA produces a set of effect estimates for each treatment linked into the network, relative to every other, whether or not they have been compared in head-to-head trials: thus, NMA is a method of obtaining estimates for comparisons for which there is no (direct) trial evidence. Even when direct evidence is available there may not be much of it, so pooling it with data from indirect comparisons generally gives more robust evidence and reduces uncertainty in the estimates of effect (Higgins 1996; Thorlund 2012). It is also possible to calculate the probability of one treatment being the best for a specific outcome, reflecting the precision surrounding the estimates (Caldwell 2014; Salanti 2011).

A glossary of NMA terms is given in Appendix 1.

This review comprised a network meta-analysis (NMA) for the outcome of venous leg ulcer healing, for alternative dressings and topical agents for the treatment of venous leg ulcers. We drew on methods previously used in related work (Soares 2014; Westby 2017). The NMA was expected to enable us to determine which (if any) dressing or topical agent is the most effective for healing venous leg ulcers, taking into account direct and indirect evidence simultaneously. We also presented uncertainty around treatment estimates, and explored assumptions being made in the analysis.

OBJECTIVES

To assess the effects of (1) dressings and (2) topical agents for healing venous leg ulcers in any care setting and to rank treatments in order of effectiveness, with assessment of uncertainty and evidence quality.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials (RCTs), irrespective of language of report. We only included cross-over trials that reported outcome data at the end of the first treatment period and prior to cross-over. We excluded studies using quasi-random methods of allocation (such as alternation). We highlighted trials in which three or more interventions were randomised and included all relevant arms.

Types of participants

We included trials recruiting adults (aged at least 18 years) described as having venous leg ulcers, managed in any setting. We accepted study authors' definitions of venous leg ulcers. Where wounds were described only as "leg ulcers" without information as to aetiology, we assumed that they were venous in origin. Trials in which a minority of leg ulcers are described as having a mixed or arterial pathology were included provided that these were fewer than 25% of participants. Trials including other types of mixed wound populations were not included. We included participants at any stage of their treatment process - for example, participants with or without ulcers described as being hard to heal or clinically infected.

Types of interventions

The interventions evaluated are all those that can be directly applied as dressings or topical agents to open venous leg ulcers. We presented results for these interventions and included them in summary tables. In the context of a network of competing treatments, there are no 'comparators'. We used the term 'comparison' to mean two interventions compared in a single study and the term 'contrast' to mean two interventions compared across all studies with that comparison. A contrast may be represented by a single study, a simple direct meta-analysis or by the NMA.

We considered trials for which at least one of the interventions was (1) any dressing, including impregnated dressings or saline-moistened dressings or combination dressings*, or (2) any topical agent applied directly to an open venous leg ulcer and left in situ. The treatment of interest had to be the only systematic difference between treatment groups. We did not take into account secondary dressings. We also considered 'no dressing' as a valid intervention, where the wound is left open/covered only by compression bandaging.

* 'combination dressings' means two or more dressings applied sequentially over time (e.g. hydrocolloid for four weeks followed by alginate for four weeks), or a product containing two or more

types of dressing material (e.g. a multilayer product comprising silicone polymer and hydrocolloid).

Some of the interventions we considered are as follows; we used the categories listed below as the basis for grouping the treatments used in individual studies:

- basic wound contact dressings (includes low-adherence (including paraffin gauze) or absorbent dressings (of any absorbency));
- saline-moistened gauze (all degrees of moistness);
- hydrogel dressing (includes hydrogel sheet or hydrogel application (amorphous) or sodium hyaluronate);
- vapour-permeable films and membranes (includes adhesive film (semi-permeable) or adhesive film with absorbent pad);
- soft polymer dressings (with/without absorbent pad or cellulose);
- hydrocolloid dressing (with/without adhesive border or matrix hydrocolloid);
- fibrous (spun) hydrocolloid;
- foam dressings (all absorbencies);
- alginate dressings;
- capillary action dressings;
- alginate dressing with charcoal;
- other charcoal-containing dressing;
- honey sheet dressing or topical honey;
- cadexomer Iodine ointments;
- iodine-containing dressings;
- soft polymer dressing (with silver);
- hydrocolloid (with silver);
- foam dressings (with silver);
- alginate dressings (with silver);
- silver sulfadiazine (SSD) cream;
- protease-modulating matrix (PMM) dressings;
- collagenase-containing ointment;
- topical phenytoin;
- topical zinc oxide;
- no dressing (wound left exposed); and
- other treatments considered by the review team (with additional clinical advice where required) to be dressings or topical agents applied directly to the wound and left in situ.

The following interventions were excluded from evaluation: treatments in which dressings were attached to external devices such as negative pressure wound therapies, skin grafts, growth factor treatments, platelet gels and larval therapy. We also excluded interventions which, although topical, are not delivered as a physical presence (liquid or solid) on the wound surface such as oxygen, ultrasound, laser or radiant heat therapies. These treatments were considered to be outside the scope of a review focused on dressings and topical treatments used in place of dressings. Where studies compared an eligible with an ineligible intervention we included them if they usefully linked the network of studies evaluating two eligible treatments. Data from these linking studies were fully extracted and they were assessed for risk of bias. Studies which evaluated only one eligible intervention and did not perform this linking function were treated as excluded studies and are clearly identified in the list of excluded studies (Characteristics of excluded studies). Where studies used a placebo comparator for an eligible intervention, we included them and treated the placebo as being the vehicle used to deliver it; for example as an emollient cream, an inactive powder or a hydrogel. For example, a comparison of a cream containing an antibiotic with a placebo would be treated as a comparison of topical antibiotic with an emollient cream.

We grouped together dressings in the same class, for example, all hydrocolloid dressings were grouped together regardless of whether they were adhesive or non-adhesive (BNF 2016). This grouping was regardless of a particular brand's stated absorbency, size, concentration of active component or degree of moistness. Thus, where studies only compared two dressings from the same class (for example, two alginates or two foam dressings), we excluded them from the review as they contributed no information about the effectiveness of the class. We considered an impregnated dressing to be in a different class from a non-impregnated dressing. Judgements about whether particular dressings belonged to the same class were made on the basis of British National Formulary (BNF) classifications (BNF 2016), and clinical expert advice where there was remaining uncertainty. Evidence from comparisons between dressings of the same class can be found in the individual Cochrane reviews of particular types of dressings. Trials of this type are also identified as such in the list of excluded studies.

We anticipated that the great majority of participants would be treated with concurrent compression therapy and noted the type of compression therapy used. We also included any RCT in which other concurrent therapies were given (e.g. antibiotics, debridement), provided that these treatments were delivered in a standardised way across the trial arms of the individual trial (such that the treatment of interest is the only systematic difference). We did not treat separately comparisons with and without concurrent therapies, that is, we considered intervention 1 + concurrent therapy versus intervention 2 + concurrent therapy to be the same as intervention 1 versus intervention 2.

We assumed that the interventions are exchangeable, that is, participants in the network could, in principle, be randomised to any of the treatments being compared. For example, that a person with a venous leg ulcer could be equally likely to be randomised to a silver dressing, a polyurethane foam dressing, honey or saline gauze. Depending on the wound requirements for the dressing (e.g. highly absorbent), this may not always be a good assumption for individual wounds, but may be reasonable across the population in the trials.

Types of outcome measures

We reported outcome measures at the last time point available (assumed to be at the end of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this was different from latest time point available). Initially,

we noted when studies reported results at other time points, or whether they included Kaplan-Meier plots, or both.

Primary outcomes

The primary outcome for this review is complete wound healing. We regarded the following as providing the most relevant measures of outcome for the analyses:

- the proportion of wounds healed (frequency of complete healing: arm-level data);
- time to complete healing (survival data: study-level data reported as a hazard ratio (HR) with standard error (SE)).

We accepted the authors' definitions of what constitutes a healed wound.

Secondary outcomes

We did not consider any secondary outcomes here, however they are considered in other relevant reviews (Briggs 2012; O'Meara 2013; O'Meara 2014; O'Meara 2015; Westby 2016) and ongoing reviews (Ribeiro 2013; Ribeiro 2014).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify reports of relevant randomised clinical trials:

- Cochrane Wounds Specialised Register (searched 29 March 2017);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) (searched 29 March 2017);
- Ovid MEDLINE (1946 to 29 March 2017);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, to 29 March 2017);
- Ovid Embase (1974 to 29 March 2017);
- EBSCO CINAHL Plus (1937 to 29 March 2017).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 2. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2018). There were no restrictions with respect to language, date of publication or study setting.

An updated search was conducted on 16 March 2018; these results have been added to Studies awaiting classification and Ongoing studies, and will be incorporated into the review at the next update.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included studies as well as relevant systematic reviews, meta-analyses, guidelines and health technology assessment reports. We used any additional unpublished data for included studies obtained by previous reviews, contacting review authors where appropriate, and undertook cross-checking to ensure that all relevant studies with evaluable outcome data were included.

Data collection and analysis

Data collection and analysis were carried out according to methods stated in the published protocol (Norman 2017), which were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection of studies

Two review authors independently assessed the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we obtained full-text copies of all studies considered to be potentially relevant. Two review authors independently checked the full papers for eligibility; disagreements were resolved by discussion and, where required, the input of a third review author. Where required and possible, we attempted to contact study authors where the eligibility of a study was unclear. We recorded all reasons for exclusion of studies for which we had obtained full-text copies. We completed a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies were reported in multiple publications/reports we sought to obtain all publications. Whilst the study was included only once in the review, we extracted data from all reports to ensure maximal relevant data were obtained.

Data extraction and management

We extracted the following information from each included study:

- interventions being compared, including any ineligible interventions randomised to additional trial groups;
- duration of the intervention;
- details of any co-interventions;
- unit of randomisation (e.g. participant or ulcer);
- number of ulcers per person;
- unit of analysis (including any selection methods for people with multiple ulcers);
- number of participants in each arm;

- hazard ratio (HR) and its 95% confidence interval (CI) (or any data that will allow its calculation (Parmar 1998; Tierney 2007)) for comparisons between arms);
- number of participants who healed in each arm, both at the latest time point and (if different) at another time specified as of primary interest in the study's methods section;
- all other follow-up times reported;
- if a Kaplan Meier plot is displayed;
- missing data rates per arm, and reasons for 'missingness', including the number of people dying.

Data on potential effect modifiers

We are not aware of any population-specific effect modifiers for this research question: there is no existing evidence to suggest that one type of dressing works better than another for certain subgroups, such as different baseline ulcer characteristics (e.g. size and duration of ulcer), although it may be the case that some dressings are evaluated only in particular groups (e.g. those classed as having 'hard-to-heal' ulcers).
However, we extracted from each included study data that may act as effect modifiers (in this context):
- type of funding (e.g. industry, academic, government); this was grouped into not-for-profit and other where reported;
- risk of bias; this was classed as low or unclear, high or very high.

We did not give more weight to any individual domains of the 'Risk of bias' assessment.

Other data

We also extracted the following baseline and study data, reporting separately for each intervention arm if possible:
- care setting;
- age of participants;
- duration of leg ulcer(s);
- size of venous leg ulcer(s) (area/volume);
- wound status (e.g. sloughy, necrotic, infected, 'hard-to-heal').

Assessment of risk of bias in included studies

We assessed risk of bias for each included study, and calculated separately the overall risk of bias for each direct pairwise meta-analysis for the complete healing data. Two review authors independently assessed included studies using the Cochrane tool for assessing risk of bias (Higgins 2011b); a third review author was consulted where consensus could not be reached. The Cochrane risk of bias tool addresses six specific domains: sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other issues (Appendix 3). We then summarised data for the key biases reflected by these domains: selection bias, detection bias, attrition bias, reporting bias and other bias. We also noted the comparability of participant characteristics at baseline across the two groups, including whether an adjusted analysis was conducted. We used these data to help inform decisions on the risk of selection bias. For the category of "other bias" we paid particular attention to unit of analysis errors since they are highly prevalent in wounds research. We recorded all problems of unit of analysis, for example, where participants with multiple wounds were randomised and each of their wounds contributed outcome data.
We interpreted the overall risk of bias for each contrast of the network meta-analysis, drawing on both indirect and direct data (see the section on Quality Assessment of Evidence (GRADE 2013), below).

Overall risk of bias and linking to GRADE assessment

In order to link these Cochrane risk of bias ratings to the GRADE assessment for study limitations (downgrading 0, 1 or 2 times), we used a two-stage process. Firstly, we obtained an all-domain (overall) risk of bias classification for each study and then we used this to produce an overall risk of bias for each contrast.

All-domain risk of bias for each study

We summarised data for each of the key domains of selection bias, detection bias, attrition bias, reporting bias and other bias, assigning one of four ratings: low, unclear, high and very high. For example, selection bias was informed by sequence generation, allocation concealment and comparability of baseline characteristics. In an adaption of the GRADE approach (Guyatt 2011), we produced an all-domain risk of bias, with four ratings defined as:
- 'very high' - two or more key domains with a high risk of bias or a single domain with very high levels of uncertainty (e.g. very high degree of differential missing data);
- 'high' - high risk of bias for any one domain or 'almost high' risk of bias across more than one domain;
- 'low' - low risk of bias for each of the key domains;
- 'unclear' - insufficient information for at least one key domain (with the other domains being at low risk of bias).

We included this all-domain risk of bias in the summary 'Risk of bias' figure, by adding additional columns to the 'Risk of bias' figure for each study. For the purposes of the GRADE assessment, we then grouped together studies with low and unclear all-domain risks of bias.

Overall risk of bias for a direct comparison (the comparison of two intervention in one or more trials)

Where a single study contributed to a comparison, the overall risk of bias was that of the all-domain risk of bias assigned to that study. Where more than one study contributed to a comparison, we assigned an overall comparison risk of bias by calculating a weighted average based on the inverse variance-derived weights from the

meta-analysis, and using this in conjunction with the overall risk of bias (where numerical values were assigned to the all-domain ratings for each study: low/unclear (1), high (2) and very high (3)). We aligned comparison 'Risk of bias' assessment with the GRADE categories of no limitations (not downgraded for risk of bias), serious limitations (downgraded once), and very serious limitations (downgraded twice) (Guyatt 2011; Salanti 2014). We presented the overall risk of bias associated with each direct estimate in a network diagram using colours to represent different ratings.

Overall risk of bias in the network

Each direct contrast in the network contributed differently to the estimation of each NMA summary effect (each NMA comparison). The contribution of each piece of indirect evidence to a mixed treatment contrast depends on its point estimate, precision and relative location within the network, and on that of any direct evidence or other indirect evidence (Chaimani 2013; Salanti 2014). A recently published tool, Krahn 2013, allows the contribution of each direct estimate to be determined for each contrast in the network informed by mixed evidence (direct and indirect), or when multiple loops of indirect evidence inform the same link. We used the CINeMA web tool (CINeMA 2017) to calculate the percentage contribution of each direct contrast to each network estimate. The overall risk of bias for each NMA comparison estimate is a composite measure of the risks of bias for all the direct contrasts contributing to that NMA comparison and was determined by calculating a weighted average risk of bias using the percentage contributions and the all-domain risks of bias for all the direct contrasts. We acknowledge that this approach returns approximate weights.

Measures of treatment effect

Relative treatment effects

We were not able to calculate the hazard ratio (HR) for the majority of studies, and therefore presented the risk ratio (RR) (95% CI) for the proportion of people healed. In order to conduct these analyses (see Data synthesis), we used outcome data reported in individual studies, as raw data at the latest time point, unless otherwise stated. If there had been sufficient data, we had planned to calculate the HR with 95% CI and to model time-to-event data.

Unit of analysis issues

We expected the main unit of analysis issues to occur when participants had more than one wound per person. We treated the participant as the unit of analysis when the number of wounds assessed appeared equal to the number of participants (e.g. one wound per person). This included studies in which participants were randomised to treatments and there was more than one wound per person, but results were reported for one selected wound; we considered whether there was risk of bias in the selection process.

Where studies randomised at the participant level, we used the allocated treatment on multiple wounds per participant, and measured and analysed outcomes at the wound level, (e.g. wound healing), there were unit of analysis issues if the data were not correctly analysed. In these cases, we assessed whether it was possible and appropriate to approximate the correct analyses in accordance with Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using information adapted from Higgins 2011c. Where this was not possible, we made a decision about inclusion of data in the analysis, and recorded these studies as being at high risk of bias if the number of participants and the mean number of wounds per person were judged to warrant this.

If cluster-randomised trials had been identified, we would have decided the analytical approach based on the type and volume of cluster data. We accounted for the correlation between the effect sizes from multi-arm studies in the analysis.

Dealing with missing data

It is common to have data missing from trial reports. Excluding participants post-randomisation, or ignoring those participants who withdraw from the trial or are lost to follow-up, compromises the randomisation and potentially introduces bias into the trial. Where there were missing data for the primary outcome of proportion of ulcers healed, we assumed participants did not have the outcome (i.e. they will be considered in the denominator but not the numerator). We considered examining this assumption in a sensitivity analysis but decided this was not necessary given the small numbers of trials with differences in attrition between treatment groups.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We assessed the presence of clinical heterogeneity within each pairwise comparison (i.e. the degree to which studies vary in terms of participant, intervention and outcome characteristics) by comparing data extracted for included studies. We focused on key variables that are potential effect modifiers, such as whether studies were at high risk of bias in key domains and the source of funding for the study. We also considered the generalisability of our findings with reference to participant characteristics such as ulcer size and duration.

Assessment of transitivity across treatment comparisons

'Transitivity' refers to the situation in which an intervention effect measured using an indirect comparison is valid and equivalent to the intervention effect measured using a direct comparison. Thus,

where there are differences in effect modifiers across comparisons, the transitivity assumption may not be met and there will be inconsistency in the network (Grant 2013; Jansen 2013). We did not identify any potential effect modifiers from the literature, and therefore had to assume that there is transitivity with respect to known effect modifiers across the pairwise comparisons. There are also limited underlying theoretical reasons to consider effect modification for these treatments - however, in preparing the network we explored the effect of differences in risk of bias as possible effect modifiers across the network. We investigated inconsistency in the network (see Data synthesis).

We had also planned to investigate the effect of funding source as a potential effect modifier. However although many studies reported funding by a manufacturer of one of the assessed interventions, a substantial number of studies did not report the funding source. Only a minority of trials clearly reported a third sector or public funding source; a much smaller number reported non-industry funding or a mixture of industry and non-industry sources. In view of this imbalance and the high level of uncertainty around trials which did not report funding sources we did not attempt this analysis.

Assessment of reporting biases

We assessed the presence of reporting bias using a contour-enhanced funnel plot, (Peters 2008; Salanti 2014).

Data synthesis

General methods

We performed pairwise meta-analyses in a frequentist framework using the statistical software STATA 13 (STATA 2011; Salanti 2014). Experience (Westby 2017) suggested that there were likely to be insufficient data for us to model the impact of follow-up duration on estimates of effect. We therefore conducted analyses based on binary data, analysed using risk ratios (RRs). We had planned to extract or calculate HRs where possible using established methods (Parmar 1998; Tierney 2007), and would have considered modelling the hazard function (Dias 2014; Soares 2014) using WINBUGS (WinBUGS 2016). However, there were insufficient HR data.

We used STATA 13 (STATA 2011) to calculate the contributions matrix for the network and used the results of this together with the evaluation of risk of bias (see Assessment of risk of bias in included studies) to inform a GRADE evaluation for the entire network (Salanti 2014). We summarised the findings according to GRADE principles (GRADE 2013; Schünemann 2011a; Schünemann 2011b). Where there were zero events in any trial arm, we followed the general approach taken by STATA and added 0.5 to the numerator and 1 to the denominator for each arm in the trial.

Methods for standard meta-analysis

We performed pairwise meta-analyses in a frequentist framework using Review Manager 5 (RevMan 2014) or STATA 13 (STATA 2011) as appropriate, using inverse variance weighting and a random-effects model, and only analysing trials reporting that pairwise comparison. We also presented the data for these direct comparisons from the network in forest plots (Schünemann 2011a); for reasons of space we did not present all possible comparisons. While we report treatment effects for all data (see appendices), we focus on discussing selected comparisons chosen for their clinical relevance.

Methods for network meta-analysis

We used STATA 13 to produce a network diagram based on all included studies in order to inform the analysis plan (Chaimani 2013). We excluded from the analysis two-arm studies in which one of the interventions could be described as 'standard care' or 'mixed care'. These are treatment arms where the 'intervention' involves the choice of more than one treatment: they are unlikely to be consistently applied. We had anticipated that such interventions might have been acceptable for a grouped sensitivity analysis (see section on Sensitivity analysis), but experience (Westby 2017) led us to conclude that this was unlikely to be informative; such studies are therefore summarised in Appendix 4, but not considered further. We also excluded from the main analysis studies that had one intervention of direct interest (e.g. hydrocolloid) compared with one ineligible intervention (e.g. ultrasound), unless we found, after examining the network diagram, that the ineligible intervention linked two or more interventions of direct interest; such interventions were included in a sensitivity analysis looking at an expanded base-case.

We performed multivariable network meta-analysis using STATA 13. We used the 'mvmeta' command and adopted a random-effects approach and a consistency model. We used per-arm data (see Data extraction and management) throughout. The STATA routine took into account correlations between the effect sizes from multi-arm studies. The NMA results were reported for all 'mixed treatment contrasts', which means the meta-analysis involved both direct evidence and indirect evidence from across the whole network. The output was reported as pooled RRs, with their 95% CIs. If there were sufficient data we had also planned to perform an analysis of time-to-event data using the log HR with its standard error (SE).

We carried out analyses for network comparisons (where indirect evidence alone, or both direct and indirect evidence contributes) in a frequentist framework as above. Where required, we accounted for correlations induced by multi-arm studies. We also presented the data in forest plots.

We obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti 2011) for each treatment. Both these measures are based on an assess-

ment of the probability of each treatment being best, second best, etc. in terms of being the most likely to heal venous leg ulcers (when compared with all other evaluated treatments). We used the STATA methods described by Chaimani 2013.

We had planned to present two different networks: one for individual treatments and a sensitivity analysis in which interventions were grouped in broader clinically relevant categories. In practice, there were many different dressings and a wide range of topical agents too, and we decided, post-hoc, to restrict the main analysis to treatments that were considered most important and widely used. Selection of treatments for analysis was decided by two review authors working independently, with guidance from a clinical review author who had not seen the data.This set of interventions was termed the 'base-case network'.

Interventions which were considered in the base-case were: alginate, cadexomer iodine, film, foam, gentian violet, hyaluronic acid, hyaluronic-acid with povidone iodine, hydrocolloid, hydrofibre, hydrogel, ibuprofen-releasing foam, nonadherent, octenidine, paste bandage, saline gauze, phenytoin, povidone iodine, protease-modulating matrix (PMM), PMM silver, silver sulfadiazine (SSD), sucralfate, silver and zinc oxide. Only one of these - phenytoin - could not subsequently be joined into the network. Sensitivity analyses explored the impact of extending the number of treatments included or further restricting it (see Sensitivity analysis).

Comparisons of two eligible interventions not joined into the network remained in the review and we reported the direct evidence.These included comparisons between a specified intervention such as cadexomer iodine, silver or honey and "standard care" as well as comparisons between two individual interventions where one or both were only partly relevant to the network or could not be joined to the network.

There was a very large number of contrasts in the NMA and we decided to focus our reporting of the analysis firstly on results for the network as a whole, and then in the 'Summary of findings' table to report the treatment effect data for some specific treatment comparisons. This was done in order to maximise the clinical utility of the NMA and the accessibility of the review. We decided, post-hoc to focus on the two treatments with the highest probabilities for being one of the best treatments and to examine in detail the results of their comparisons with three of the most common and widely used treatments (foam, hydrocolloid and nonadherent dressings). The results for all contrasts are also shown in forest plots.

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

We assessed the presence of heterogeneity within each pairwise comparison using the I^2 statistic that measures the percentage of variability that cannot be attributed to random error (Higgins 2003). We also took into account the overlap of confidence intervals and the variability in the point estimates. We regarded effect estimates where an I^2 was less than 50% as having low levels of heterogeneity, given the potential for wide confidence intervals in pairwise comparisons within a network, which we had anticipated may be sparse.

Assessment of statistical inconsistency

We assessed inconsistency in two main ways: determining local inconsistencies (around particular contrasts in the network) and assessing inconsistency for the network as a whole. These tests are often underpowered so we carried out the assessment using the 90% significance level.

Local approaches to evaluating inconsistency

To evaluate the presence of inconsistency locally we used two main approaches. Firstly, we considered a loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor, IF). Then, the magnitude of the inconsistency factors and their 90% CIs can be used to make inferences about the presence of inconsistency in each loop. We assumed a common heterogeneity estimate within each loop.

Secondly, we considered a 'node splitting' approach (Dias 2010; Salanti 2014). This method was applied, singly, to each direct contrast (called a 'node' by Dias 2010). A STATA routine was used to calculate an indirect estimate using the rest of the network, by running the NMA after excluding the direct evidence for that contrast. The indirect estimates were then compared with the respective direct estimates.

For both approaches a ratio of risk ratios (RoRR) with its 90% CI was calculated for each contrast. If the CI excluded 1, there is statistically significant inconsistency. We also considered whether the CI included 2 or more (or 0.5 or less). This would mean that the direct estimate could be twice as large (or half as big) as the indirect estimate, which is an indication of potential inconsistency (Chaimani 2013).

Where we detected serious inconsistency, either in the direct evidence or between the direct and indirect evidence for a contrast, we downgraded the evidence for that contrast.

Global approaches to evaluating inconsistency

We evaluated consistency in the entire network simultaneously, by extending the analysis to include an inconsistency model that omits consistency equations (Dias 2013). This used a design-by-treatment interaction model, which allows for different trial designs (Higgins 2012; White 2012). This approach produced a set of inconsistency parameters. After fitting the inconsistency model we tested the null hypothesis of consistency by globally testing the

set of inconsistency parameters using a global Wald test. This test may lack power and we considered a significance level of P < 0.1. Inconsistency in the entire network was considered a reason for downgrading the certainty of the evidence which the network, as a whole, represented.

Investigation of heterogeneity and inconsistency

Where sufficient studies were available, we planned to perform network meta-regression (data permitting) or subgroup analyses using funding source and risk of bias as possible sources of inconsistency or heterogeneity, or both. In the event we were able to perform an analysis using risk of bias as a possible source of heterogeneity.

Sensitivity analysis

We re-analysed the network with studies removed if they were considered to be at high risk of bias for any one or more of selection, attrition or detection bias (Appendix 3).

We considered a sensitivity analysis to assess the possible impact of missing outcome data on the network estimates, via assessment of risk of attrition bias (as defined in Appendix 3), testing the assumption of imputation of no event for missing data.

Where one or more studies were clearly outliers (i.e. in terms of direction or size of relative treatment effect, or both, or as flagged in inconsistency testing), we had planned to conduct a sensitivity analysis where the study was removed from the network, as long as the network was still analysable; in the event we did not need to do this.

We had planned to conduct a sensitivity analysis, in which dressings interventions were grouped in broader categories, with clinical guidance, but this was not conducted. Instead, we conducted two post-hoc sensitivity analyses for the base-case network: one restricted the dataset to a narrower set of clinically appropriate interventions; the other included additional treatments outside the base-case, which reinforced the network with more links. The reduced network excluded the following interventions which were included in the base-case: gentian violet, hyaluronic-acid with povidone iodine, ibuprofen-releasing foam, octenidine, phenytoin and sucralfate. The expanded base-case added nine trials and the following supplementary interventions to the base-case decision set: blood product (non-eligible intervention); emollient cream; and growth factor (non-eligible intervention). We conducted this sensitivity analysis to investigate the impact of strengthening the network through indirect evidence provided by comparisons of key decision set interventions such as saline gauze and hydrogel with these supplementary interventions.

Quality assessment of evidence (GRADE) generated from the network meta-analysis (NMA)

We summarised the findings according to GRADE principles (Schünemann 2011a; Schünemann 2011b). The quality and certainty of the data included in any synthesis model are key to determining the validity of the results and of inferences made. We explored the application of GRADE methodology to NMA, focusing on the approach of Salanti 2014. We assessed evidence quality in two main ways, for each contrast and separately, for the network as a whole, in order to assess the quality of the ranking order. We assessed individual GRADE factors as follows.

- Risk of bias: contributions for each particular contrast were considered, and used to assess the overall risk of bias for that contrast. We assessed overall risk of bias per contrast and also for the network as a whole (see Assessment of risk of bias in included studies).
- Indirectness: this was assessed as without limitations because we did not identify any effect modifiers.
- Inconsistency: at the level of the contrast, we considered both heterogeneity in the direct evidence for that comparison and inconsistency related to different routes of analysis for the comparison (e.g. direct versus indirect evidence). We noted that inconsistency can only be assessed where there is both direct and indirect evidence. GRADE inconsistency was assessed as a serious limitation if there was heterogeneity in the direct estimate or inconsistency in the network with respect to that comparison. Very serious limitations were attributed to the comparison if there was severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency. At the level of the network, we considered the global Wald test for inconsistency (see Data synthesis; Assessment of heterogeneity). Tests of this nature are typically underpowered, so a P value less than 0.1 was considered significant. Additionally, if several contrasts showed direct and indirect results that would have led to different clinical decisions, we considered inconsistency to be present.
- Imprecision: at the level of the contrast, we assessed imprecision for each pairwise comparison using the GRADE default minimally important difference (MID) values of 1.25 and 0.75 for the RR. For contrasts that were not part of the 'core' of the network, we also took into account the number of events informing the direct evidence and considered it in relation to the optimal information size. At the level of the network, we assessed the overlap of the rankograms and the magnitude of the SUCRA estimates.
- Publication bias: was assessed for each pairwise comparison using standard GRADE (where there were 10 or more studies); we used contour-enhanced funnel plots where appropriate to examine publication bias in the network as a whole.

'Summary of Findings' tables

We presented the main results of the review in a 'Summary of findings' table, reporting the results for a representative set of contrasts, with one row for each contrast. We focused on interven-

tions which the SUCRA suggested were likely to be high ranked and the comparisons between these and commonly-used types of intervention. This table presents key information concerning the certainty of the evidence, the magnitude of the effects for the contrasts examined, and the sum of the available data (Schnemann 2011a). The 'Summary of findings' table also includes an overall grading of the evidence using the GRADE approach.

For calculating absolute risk differences for the probability of healing we used a 'control group risk', calculated as the median of the risks for the comparator across all direct evidence studies with these comparators.

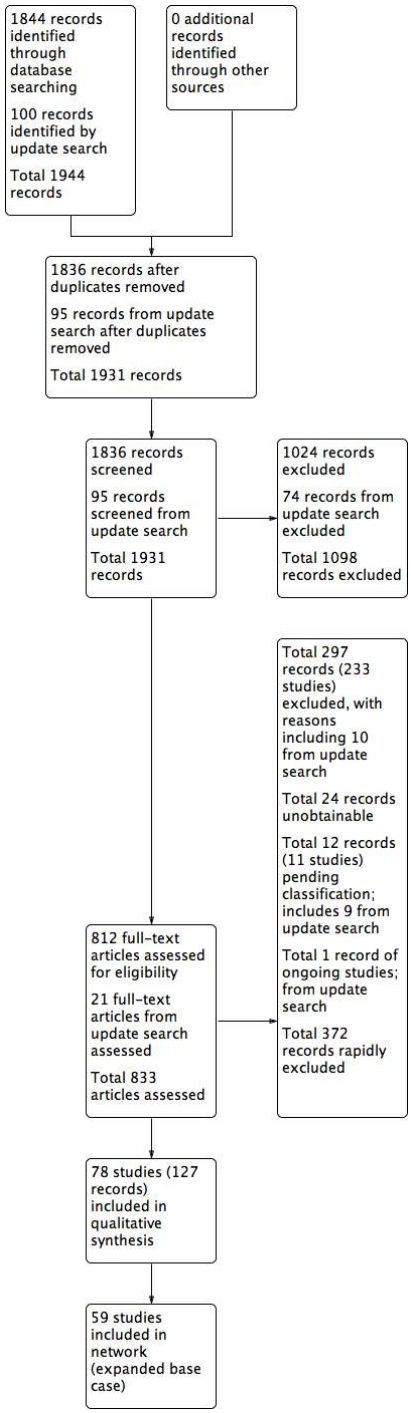
RESULTS

Description of studies

Results of the search

Electronic searches identified 1836 records after deduplication. Of these, we excluded 1024 after initial screening of title and abstract. Full-text screening of 812 records led to the identification of 127 relevant reports of 78 studies (see Figure 1).

Figure 1. Study flow diagram.



We included studies that compared two eligible interventions (see criteria for inclusion - interventions (Types of interventions). We also included studies that assessed only one eligible intervention, but which provided linking for the network of eligible studies. Therefore there were three types of included study:

- studies which compared two eligible interventions and which were included in the NMA;
- studies which compared two eligible interventions but which could not be joined into the NMA;
- studies which compared an eligible intervention with one or more ineligible interventions but which strengthened the network by linking other two or more eligible interventions.

A total of 78 studies with 7014 randomised participants was included in one or more of these categories.

An updated search in March 2018 retrieved 100 additional records. Of these 23 required consideration in detail. Two records were added as additional publications to studies already identified as excluded studies in the review. Ten studies (11 records) could be clearly excluded (see excluded studies) and nine studies were added to Studies awaiting classification. One study was added to ongoing studies (see Characteristics of ongoing studies).

Included studies

There were 47 studies that we joined into the network with two relevant interventions as outlined in Data synthesis: (Armstrong 1997; Backhouse 1987; Banerjee 1997; Blair 1988a; Blair 1988b; Bowszyc 1995; Brandrup 1990; Callam 1992; Casoni 2002; Charles 2002; Dimakakos 2009; Fogh 2012; Gottrup 2008; Hanft 2006; Hansson 1998; Harding 2001; Humbert 2013; Ivins 2006; Jørgensen 2005; Kelechi 2012; Kucharzewski 2013; Lanzara 2008; Leaper 1991; Meaume 2012; Meredith 1988; Moffatt 1992a; Moffatt 1992b; Nelson 2007; Norkus 2005; Ohlsson 1994; Ormiston 1985; Petkov 1997; Romanelli 2015a; Rubin 1990; Schulze 2001; Scurr 1994; Senet 2014; Smith 1992; Smith 1994; Sopata 2016; Stacey 2000; Taddeucci 2004; Thomas 1997; Tumino 2008; Vanscheidt 2012; Vin 2002; Zuccarelli 1992).

A further 13 studies (Alvarez 2012; Beckert 2006; Bishop 1992; Caprio 1992; De Araujo 2016; Dereure 2012a; Greguric 1994; Luiza 2015; Kalis 1993; Moss 1987; Romero-Cerecero 2012; Solovastru 2015; Tarvainen 1988), all assessed comparisons between two eligible treatments, which could be linked to the network but where one or both interventions was considered to be only partly relevant and therefore only the direct evidence was considered, or the trial was included only in a sensitivity analysis. These interventions included dextranomer, *A. Pinchinsensis* extract, ozonated oil, shale oil, papain, magnesium sulphate and cellulose. Summaries of these comparisons are provided in Appendix 4.

There were a number of studies that evaluated relevant interventions but which could we could not connect into the network. This included the following studies that compared a particular treatment with 'standard care' (which was either not specified or included a range of different dressings or topical treatments): Arnold 1994; Brown 2014; Jull 2008; Harcup 1986; Lindsay 1986; Michaels 2009; Steele 1986. Other studies not joined into the network were Hokkam 2011, which compared two interventions which did not otherwise link to the network: phenytoin with no treatment and Salim 1992, which compared sulphadryl powders to inactive powder. Summaries of these comparisons are also provided in Appendix 4.

We included nine studies that had only one relevant intervention in an expanded base-case to strengthen the network (Arenbergerova 2013; Biland 1985; Rasmussen 1991; Robson 1995; Robson 2001; Robson 2004; Senet 2003; Senet 2011; Stacey 1997). These were all two-arm trials with one relevant intervention from the base-case or partly relevant interventions such as emollient cream or an ineligible intervention.

Summary details of all trials in the review are shown in Table 1; a summary of the status of individual studies within the review and the networks is shown in Table 2, which clearly denotes which trials are included in the base-case and the sensitivity analyses and which are included only in the review and not in the network.

Interventions

Included studies evaluated a wide range of dressings and topical treatments. A total of 20 different types of dressings were evaluated; this included dressings which were impregnated with agents such as ibuprofen, silver, povidone iodine or zinc oxide. Sixteen different topical treatments were included. Although the majority of trials compared two dressings or two topical treatments (and most of these compared two dressings), some compared a dressing with a topical treatment (e.g. a hydrocolloid dressing compared with silver sulfadiazine (SSD)). A minority of trials compared arms which included more than one treatment option and these included both dressings and topical treatments.

The number and types of Interventions are fully detailed in the effects of interventions section (Effects of interventions) and in supplementary tables (Table 2; Table 3; Table 4), which also show the status of each trial in the review and network analyses.

Characteristics of participants in included studies

See Characteristics of included studies for full details

Most studies included only people with venous leg ulcers; six studies also included some participants with mixed aetiology or arterial ulcers (although we excluded those with more than 25% of such

participants); in 10 studies it was not clear whether a minority of people with non-venous ulcers were included. The mean or median age range reported for participants ranged between 46 and 81 years. Almost all studies enrolled a majority of women; there were no single sex studies. The mean sizes of ulcers at baseline varied by up to a factor of 10 but were typically between 5 cm^2 and 10 cm^2. The mean duration of ulceration at enrolment ranged between one month and 75 months. Many studies excluded participants with either any type of infection or with a specified severity of infection (typically requiring systemic antibiotics); only one study specified that the participant must have an infected ulcer at baseline (Dimakakos 2009). Reporting of other types of ulcer characteristics such as level of slough or exudate was limited. All studies reported some use of compression although the methods and the specificity of the reporting of this varied.

Characteristics of studies

Where funding was reported, it was often industry funding by a manufacturer of one of the assessed interventions (30 studies). However, a substantial number of studies reported no funding or did not report the funding source. A minority of trials reported a third sector or public funding source. Most studies used participants as the unit of both randomisation and analysis, only two reported data at the ulcer or leg level Caprio 1992; Stacey 1997), while a small number appeared to randomise at the level of the person but analyse at the level of the ulcer; in each case these were dealt with in the "Risk of bias' assessment. Follow-up ranged between four weeks and 12 months but most trials had follow-up of three months or less.
For more details on study characteristics see Table 1.

Excluded studies

A large number of records were rapidly excluded after reading the full-text. A list of these studies is available on request from the authors (see Figure 1). Some studies were excluded after more detailed consideration. These studies are listed with reasons for their exclusion in Characteristics of excluded studies. An additional ten studies were excluded from records retrieved by an update search in March 2018.
Two studies are awaiting classification (Belcaro 2011; Polignano 2010) from the original search. A further nine studies are awaiting classification following an update search in March 2018 (Alvarez 2017; Cavalcanti 2017; Colenci 2016; Cullen 2017; Glukhov 2017; Moreno-Eutimio 2017; Oliveira 2017; Robinson 1988; Somani 2017). One ongoing study was identified in the update search (Jull 2018).

Risk of bias in included studies

Allocation

Risk of selection bias is assessed based on generation of randomisation sequence and allocation concealment. Many studies were at unclear risk of bias for one or both of these, most commonly for allocation concealment. High risk of bias for randomisation was documented for only one study where errors were noted to have compromised the process. However only a minority (20 studies) were considered to have a low risk of bias. The remainder did not report the processes used clearly enough for us to determine the risk of bias. The number of studies considered to be at low risk for allocation concealment was even lower, with only 12 considered to be clearly at low risk of bias.

Blinding

Many studies were at high or unclear risk of performance bias. Although only a minority (18 studies) were clearly at high risk, many more had an unclear risk. Only 10 studies were considered to be at low risk. For detection bias, we observed a similar pattern although more studies clearly had outcomes determined by blinded observers; 20 were considered to be at low risk of detection bias.

Incomplete outcome data

Twenty-six studies were considered to be at high risk of attrition bias. However, a larger number had a low risk of bias and only ten were considered to be at unclear risk.

Selective reporting

Only four studies were at high risk of selective reporting bias; a further 16 had an unclear risk in this domain; the remainder were considered to be at low risk of bias.

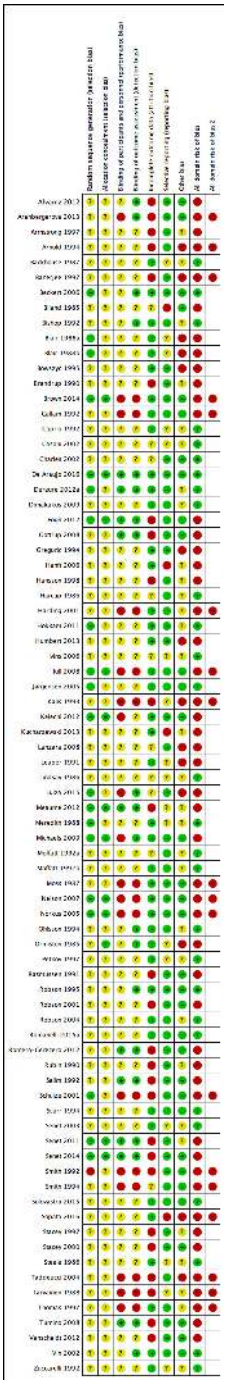
Other potential sources of bias

Thirteen studies were considered to be at high risk from other forms of bias, mostly due to issues with the analysis. A further 27 had an unclear risk of bias, again primarily related to the reporting of the analysis.

All-domain risk of bias

All-domain (overall) risk of bias was assessed for each study. In total 51 studies were considered to have a high or very high all-domain risk of bias (Figure 2) and 27 studies were considered to be at unclear or low overall risk of bias (these were grouped together for analysis purposes). No study was at low overall risk of bias since all studies had an unclear rating for one or more domains.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** NMA evidence: proportion with complete healing

Interventions and comparisons: base-case network and sensitivity analyses

The base-case network comprised 47 studies assessing 22 interventions: 12 eligible dressings (foam, hydrocolloid, hydrofibre, alginate, ibuprofen-releasing foam, nonadherent, paste bandage, protease-modulating (PMM), PMM-silver, silver-containing, film, saline gauze); and 10 topical agents (hydrogel, cadexomer iodine, gentian violet, hyaluronic acid, hyaluronic-acid with povidone iodine, octenidine, povidone iodine, silver sulfadiazine (SSD), sucralfate and zinc oxide). One study was a three-arm trial (Hansson 1998; hydrocolloid, nonadherent and cadexomer iodine). The total number of comparisons was 49, encompassing a total of 4026 participants, who experienced a total of 1479 events (complete healing).

The sensitivity analysis using an extended base case contained 59 studies assessing 25 interventions in 5156 participants with 1925 events; added interventions were blood product, emollient cream and growth factor. This explored the impact of strengthening the network with more links by including trials which contained an eligible intervention compared to one of three ineligible interventions.

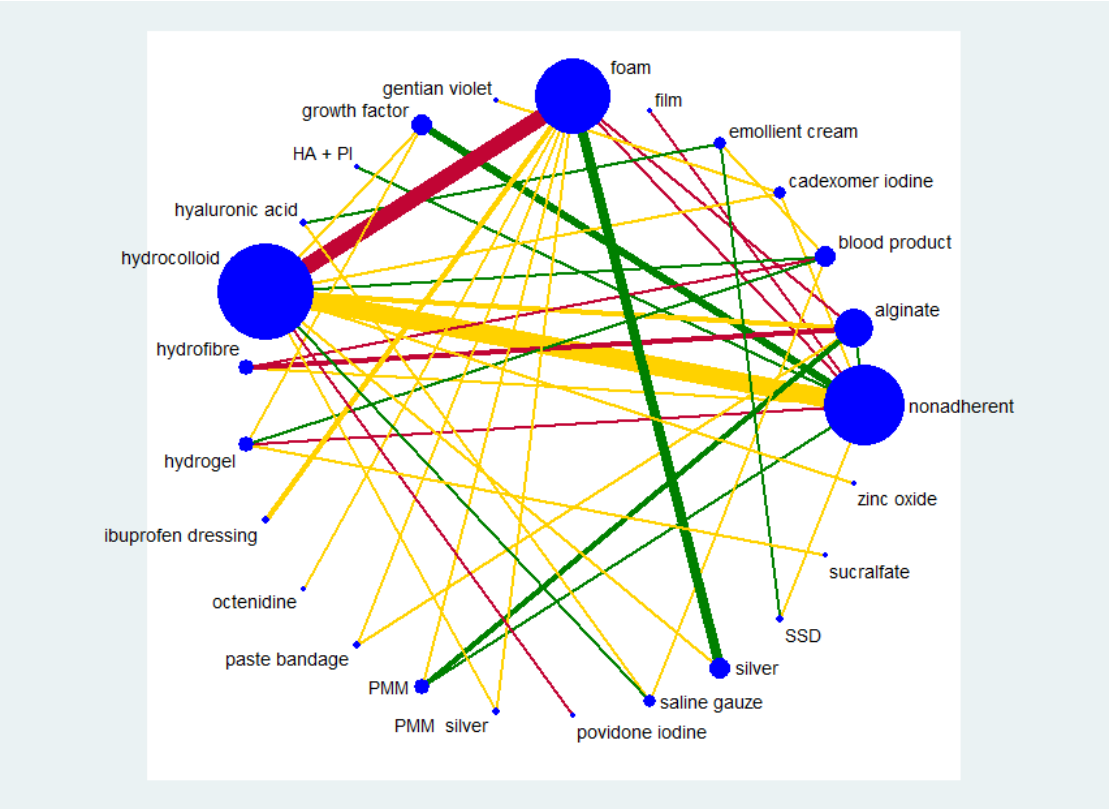
An additional sensitivity analysis looked at a narrower set of 17 interventions assessed in 41 studies that included 3435 participants with 1331 events; removed interventions were ibuprofen-releasing foam, gentian violet, hyaluronic-acid with povidone iodine, octenidine and sucralfate. This explored the impact of restricting the network to a narrower set of interventions which excluded interventions that are not widely used in clinical practice.

In the base-case network, there were 31 different direct contrasts and 12 triangular loops; the extended base-case sensitivity analysis had 40 direct contrasts, 15 triangular loops and six quadratic loops; and the narrower network had 26 direct contrasts and 12 triangular loops.

We carried out network meta-analysis for the base-case and the two sensitivity analyses (Appendix 5). The extended base-case sensitivity analysis identified instability in the base-case results for contrasts of some treatments and in the rank order of treatments. Additionally, in the extended base-case, the point estimates and confidence intervals (CIs) for contrasts with sucralfate were often considerably reduced compared with the base-case; and the direction of effect was reversed for most contrasts with hydrogel. This instability for some treatments is likely to occur because, in the base-case, the direct evidence (from single small studies) had an important contribution. As a consequence, we placed more reliance on the extended base-case sensitivity analysis and therefore report the results for this sensitivity analysis in the rest of the results section. Full details and results for the base-case and both sensitivity analyses are given in Appendix 5.

The network diagram for the extended base-case is shown in Figure 3. We weighted node (circle) size by the number of studies reporting each intervention and weighted the thickness of the edge lines according to the inverse variance of the treatment effect estimates for the direct evidence contrast (Chaimani 2013).

Figure 3. Network diagram - extended network, by risk of bias (3 categories)Key: green = low/unclear; yellow = high; red = very high overall risk of bias for the contrast. The number of studies for each contrast is given in .



Most treatments in the extended base-case were part of at least one loop ('core interventions') and eight interventions were 'hanging' treatments (film, gentian violet, hyaluronic acid plus povidone iodine, ibuprofen dressing, octenidine, povidone iodine, sucralfate and zinc oxide).

Risk of bias for the extended base-case network

We report risk of bias in three ways (see Methods: Assessment of risk of bias in included studies):

- for each study, as the all-domain risk of bias - taking into account selection bias, detection bias, attrition bias, reporting bias and other bias;
- for each direct comparison of two interventions, as an overall risk of bias - taking into account the all-domain risk of bias for the studies (1 above) and the weighting in the meta-analysis for that comparison;
- for each contrast in the network (any pair of interventions in the network) as the overall risk of bias - taking into account the risk of bias for each direct comparison (2 above) and their percentage contributions to the network estimate. We also calculated the overall risk of bias in the network as a whole.

All-domain risk of bias for each study is shown in Figure 2. For the extended base-case network , we judged no included studies to be at low risk of bias and 21 at unclear risk of bias (Backhouse 1987; Bishop 1992; Casoni 2002; Charles 2002; De Araujo 2016; Dereure 2012a; Dimakakos 2009; Ivins 2006; Jørgensen 2005; Meredith 1988; Moffatt 1992a; Moffatt 1992b; Ohlsson 1994; Petkov 1997; Robson 1995; Robson 2004; Romanelli 2015a; Scurr 1994; Senet 2003; Vin 2002; Zuccarelli 1992). Twelve were at very high risk of bias (Arenbergerova 2013; Banerjee 1997; Callam 1992; Harding 2001; Nelson 2007; Norkus 2005; Schulze 2001; Smith 1992; Smith 1994; Sopata 2016; Taddeucci 2004; Thomas 1997), and the rest we assessed to be at high risk of bias. We grouped the low and unclear categories together.

We have indicated the overall risk of bias for each direct comparison in the network diagram in Figure 3, using colour for three risk of bias ratings: low/unclear (green), high (yellow), very high

(red). There is a substantial amount of direct evidence at high or very high risk of bias. For selected contrasts in the network, we calculated the overall risk of bias as described in Appendix 6.

Network meta-analysis results

We examined the results in two ways: as risk ratios (RRs) with their 95% CIs for each intervention compared with every other intervention in the network (NMA effect estimates); and for the network as a whole, giving the rank order for the interventions in the network and the probability that a particular intervention is the best, second best, etc treatment.

There are 300 mixed treatment contrasts in the extended network, so we report results for the rank order first, and then, for the NMA effect estimates, we focus on contrasts involving the top two treatments and three common and widely used treatments. In Appendix 5, we report results for all contrasts in the extended network, and give the full rank orders for the base-case and the two sensitivity analyses.

Extended base-case network

The NMA generated results for 300 mixed treatment contrasts (i.e. all possible pairwise combinations of the interventions). There were 40 direct contrasts, of which 32 were informed by only one study and the average number of events per mixed treatment contrast was around six (1925/300). The data were sparse and there was uncertainty around the estimates.

As a consequence of the sparseness in the network, only 55 of 300 contrasts had precise estimates. The majority of CIs were wide or very wide, crossing at least one default minimally important difference (MID); i.e. the value of 0.75 or 1.25 was included in the CI (see Sensitivity analysis, GRADE assessment). Fifty-four contrasts with precise estimates had the whole of the CI above the default MID (i.e. the whole confidence interval lay above 1.25), but 21 of these involved treatments for which the direct evidence comprised one study and had small numbers of events in at least one arm ('fragility'): this applied to contrasts with sucralfate. Overall, 89% of the contrasts were considered to have imprecise results: the exceptions (ignoring contrasts with ineligible interventions) were silver versus each of the following: nonadherent, alginate, foam, hydrocolloid, hydrogel, povidone iodine, saline gauze, SSD; hydrocolloid versus foam; and saline gauze versus alginate,foam, hydrofibre, hyaluronic acid/povidone iodine, paste bandage, PMM and PMM silver.

Ranking of treatments

The NMA produced a large number of estimates. An alternative way of presenting and interpreting data from the whole NMA was to summarise using rankograms: data for each intervention were shown as the probability that each intervention is the best, second best, third best treatment, etc. These probabilities are based on uncertainty, reflecting the effectiveness from the network contrasts and the precision around the estimates. The closer the probability of a rank to 100% (or 0%) and the narrower the distribution across different ranks, the greater the confidence in the ranking. Results are given in Figure 4, Figure 5 and Appendix 5 and summarised here, but must be interpreted in the light of the uncertainty and sparseness in the network.

Figure 4. Rankograms for the extended base-case showing the probability that each intervention is the best, second best, third best treatment, etc.

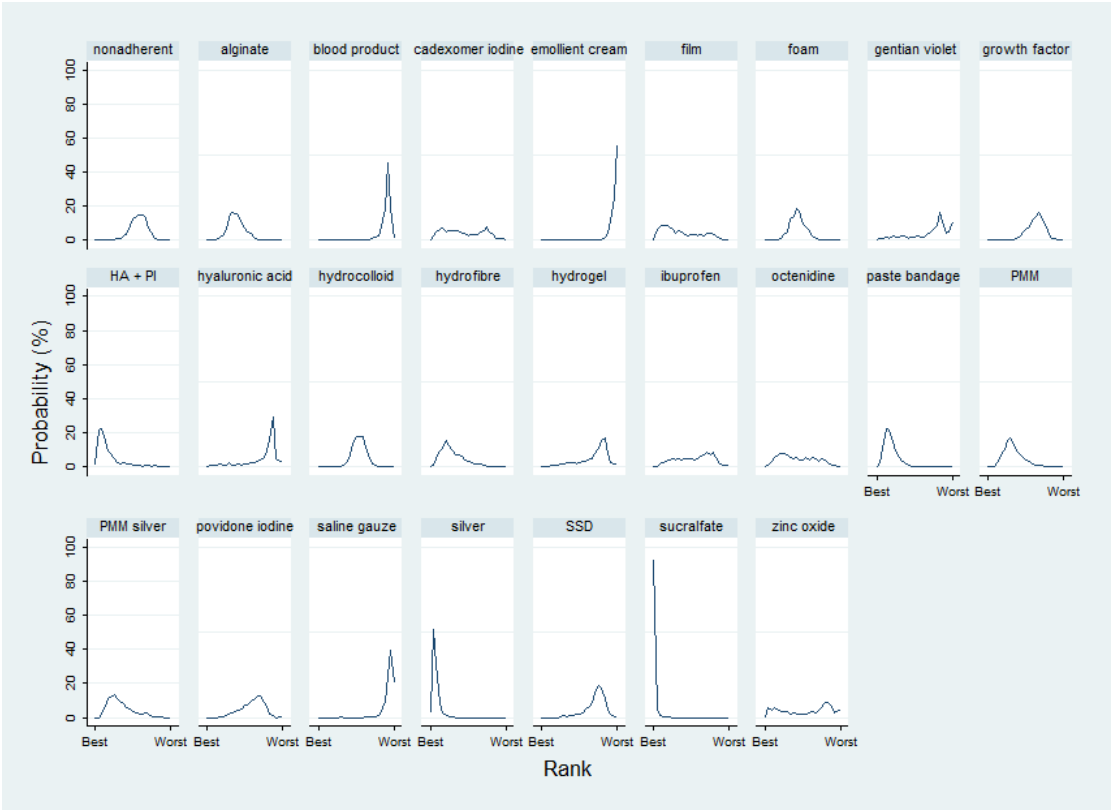
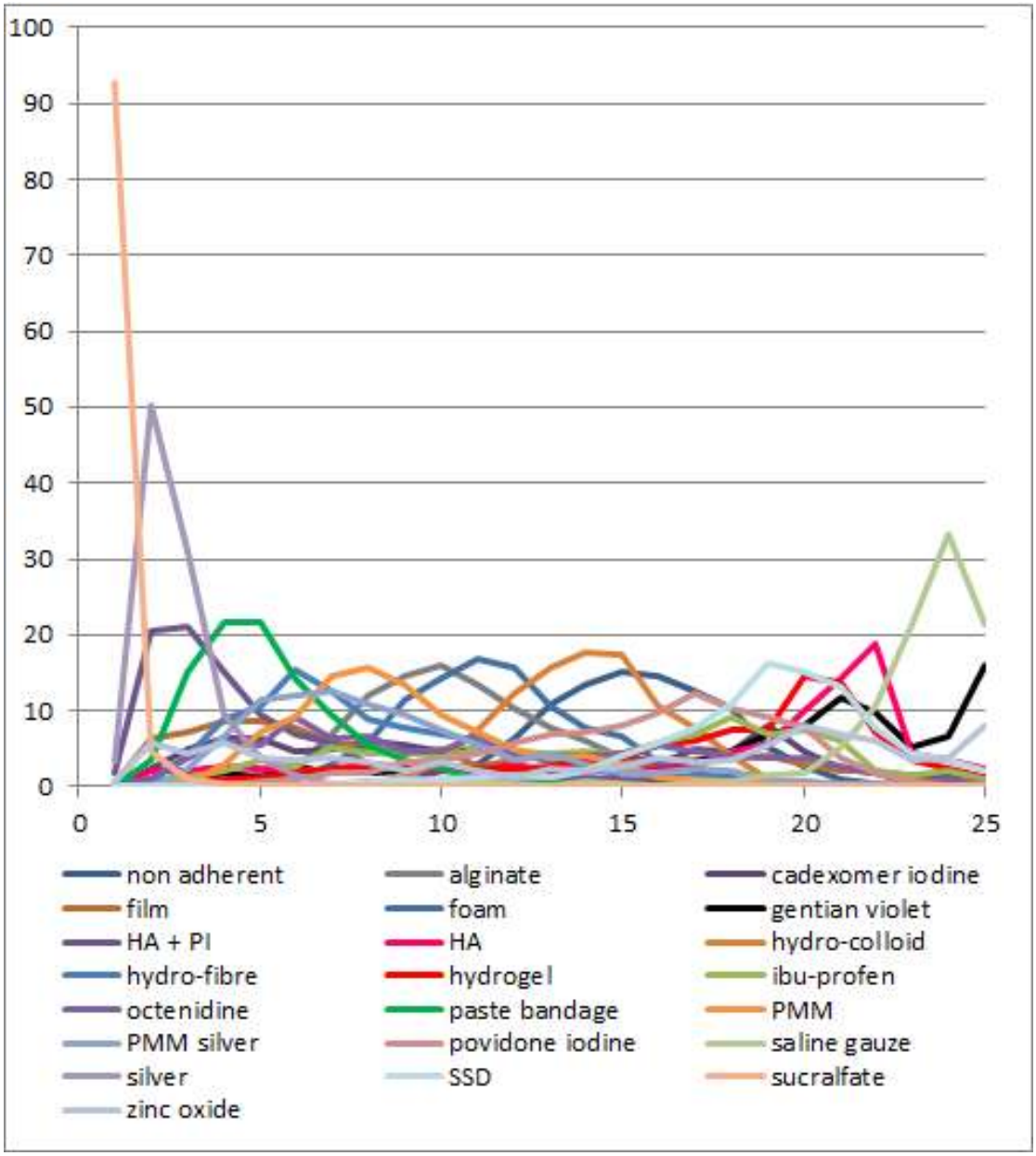


Figure 5. Rankograms for all treatments in the extended base-case network showing the probability that each intervention is the best, second best, third best treatment, etc.



Numerically, sucralfate had by far the highest probability of being the best treatment (93%), and saline gauze was most likely to be the worst treatment (33%). However, the sucralfate ranking is likely to be artificially high: sucralfate is connected to the core of the network via hydrogel and the direct evidence for sucralfate versus hydrogel involves one study with 43 (of 50) healing events for sucralfate and five healing events for hydrogel. The NMA results for all comparisons with sucralfate have very wide CIs and large point estimates. Consequently, sucralfate (versus other interventions) has a high probability of having a very large effect estimate (at the upper confidence limit), in turn leading to an artificially high probability of being the best treatment. Silver also had a high probability of being among the most effective treatments (50% at rank 2). Surface under the cumulative ranking curve (SUCRA) values were generally between 0.3 and 0.8, but one treatment had a SUCRA value of 1 or 0 (sucralfate was 1), with another two treatments having values of 0.9 or 0.1 (silver 0.9 and saline gauze 0.1).

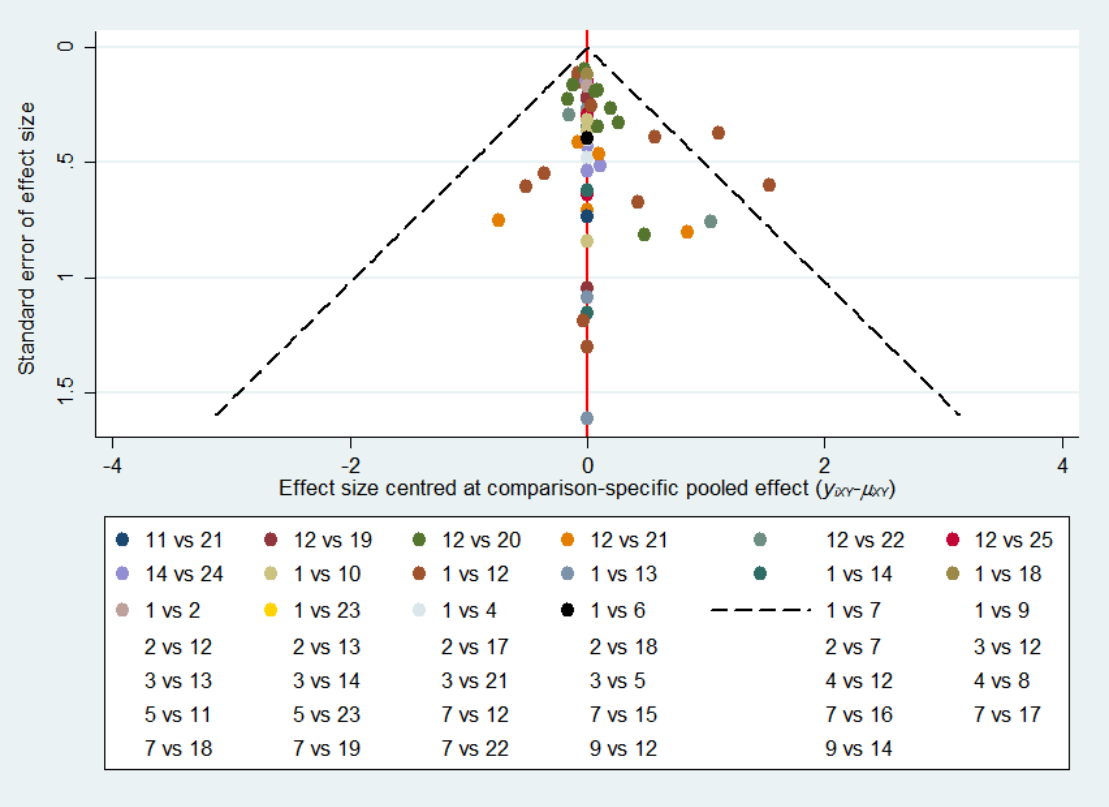
The rankograms for many treatments are broad and uninformative (Figure 4, Figure 5). Of the eligible interventions in the extended network, only five had a maximum probability above 20%. The mean ranks for these treatments were: sucralfate 1.1, silver 2.7, hyaluronic acid plus povidone iodine 5.3, paste bandage 5.4 and saline gauze 23.0.

Certainty/quality assessment of the evidence across the whole network

Further details of information used for GRADE assessment can be found in Appendix 5, Appendix 6 and Appendix 7.

The risk of bias across the extended base-case network was estimated to be high (Appendix 6). There appeared to be little inconsistency in the network (Appendix 7) and there were relatively few contrasts with conflicting results for direct and indirect or NMA estimates, so across the network we did not downgrade for inconsistency. We downgraded the evidence once for imprecision: in addition to the sparseness (and probably as a consequence of it), there is some overlap of the individual rankograms (see Appendix 5). A contour-enhanced funnel plot is shown in Figure 6. There does not appear to be a small-studies effect. Overall, we classed the evidence for the whole network as being of low certainty (downgraded once for risk of bias and once for imprecision).

Figure 6. Contour-enhanced funnel plot for the extended base-case network showing comparison-specific pooled effect sizes1=non-adherent, 2=alginate, 3=blood product, 4=cadexomer iodine, 5=emollient cream, 6=film, 7=foam, 8=gentian violet, 9=growth factor,10=hyaluronic acid + povidone iodine, 11=hyaluronic acid, 12=hydrocolloid, 13=hydrofibre, 14=hydrogel, 15=ibuprofen, 16=octenidine,17=paste bandage, 18=PMM, 19=PMM silver, 20=povidone iodine, 21=saline gauze, 22=silver, 23=SSD, 24=sucralfate, 25=zinc oxide



Results and quality assessment for selected individual comparisons

Here we focus on the treatment effect data for some specific treatment combinations to provide further insights into the results of the NMA. We considered comparisons of sucralfate, silver, foam, hydrocolloid and nonadherent dressings. These represent the two with the highest probabilities for ranks 1 to 3 in Figure 4. (sucralfate and silver) and three common and widely used treatments (foam, hydrocolloid and nonadherent dressings). These widely used treatments were selected by authors who did not have knowledge of the precise results of the network. The results for the extended base-case are shown in Table 5. We calculated absolute risk differences using the median risk for the comparator, which was obtained from the risks for that comparator in all direct evidence studies. For all four comparators, the risk varied widely across studies. We report GRADE assessment of selected contrasts in Summary of findings for the main comparison. Most of the evidence for these individual contrasts was of low or very low certainty.

For the contrast of the two interventions with the highest mean ranks - sucralfate and silver dressing - it is unclear whether there is a difference in the probability of venous leg ulcer healing (RR 2.80, 95% CI 0.88 to 8.97; very low-certainty evidence, downgraded once for risk of bias and twice for imprecision).

Silver dressings may increase the probability of venous leg ulcer healing, compared with nonadherent dressings (RR 2.43, 95% CI 1.58 to 3.74; moderate-certainty evidence, downgraded for risk of bias). This corresponds to an absolute risk difference of 346 more people healed per 1000 (95% CI 140 to 663 more), for a nonadherent median probability of healing of 242 per 1000. Although this contrast was assessed as itself representing moderate-certainty evidence, it sits in the context of a network which was, overall, judged to represent low-certainty evidence, and should

therefore be considered with appropriate caution. We also note that many of the trials which contributed to the contrast (and the direct comparison) were at an unclear risk of bias. Therefore, although there is no clear high risk of bias, there is also a lack of clarity about the true risk of bias.

For each of six contrasts the low certainty of the evidence means it is unclear whether the intervention increases the probability of healing; for two more the certainty of the evidence was very low:

- sucralfate versus foam dressing (RR 5.94, 95% CI 1.96 to 18.0);
- sucralfate versus hydrocolloid dressing (RR 6.51; 95% CI 2.17 to 19.6);
- sucralfate versus nonadherent dressing (RR 6.80, 95% CI 2.24 to 20.7);
- silver dressing versus foam dressing (RR 2.12; 95% CI 1.46 to 3.07);
- silver dressing versus hydrocolloid dressing (RR 2.32; 95% CI 1.58 to 3.41);
- foam dressing versus nonadherent dressing (RR 1.15; 95% CI 0.91 to 1.44);
- foam dressing versus hydrocolloid dressing (RR 1.10; 95% CI 0.93 to 1.28);
- hydrocolloid dressing versus nonadherent dressing (RR 1.04; 95% CI 0.85 to 1.29).

In each of these six contrasts, the evidence was graded as low certainty; downgraded either once for imprecision and once for risk of bias (sucralfate versus foam; sucralfate versus hydrocolloid; sucralfate versus nonadherent dressing; foam versus nonadherent) or twice for inconsistency (silver versus foam); or once for risk of bias and once for inconsistency (silver versus hydrocolloid).

It is unclear whether there is a difference in the probability of healing for the remaining two contrasts because the evidence is of very low certainty (downgraded for risk of bias (twice) and imprecision (once) or for risk of bias, imprecision and inconsistency): foam versus hydrocolloid; and hydrocolloid versus nonadherent dressing. The contrasts with sucralfate were informed by one study with 100 participants in the direct evidence, with 43/50 events for sucralfate and five events for hydrogel; we therefore downgraded further for imprecision to allow for the fragility this invoked.

Comparison of results from the NMA with the direct evidence

Of the eight contrasts with more than one study, five had an I^2 of 0%; the remaining three were downgraded for inconsistency; one was downgraded twice for inconsistency. Details are given in Table 3.

DISCUSSION

Summary of main results

We conducted a network meta-analysis (NMA) of dressings and topical agents for healing venous leg ulcers. The network included 59 studies with 5156 participants. The systematic review that underpins the NMA includes 78 RCTs involving a total of 7014 participants, comparing different dressings or topical agents or combinations of treatments for the healing of venous leg ulcers. This included a range of treatments from the most widely-used categories of dressings to experimental treatments assessed by a single research study.

We treated each topical agent as a separate intervention, but grouped dressings by class as described in the BNF 2016 (e.g. alginates, hydrocolloids). There were many interventions, often involving small single studies with atypical or experimental treatments. In order to simplify and rationalise the NMA, we produced a list of important and more widely-used treatments with clinical direction and input from review authors who had not seen the results. This led to the 'base-case' NMA, which we extended following sensitivity analysis, adding three linking 'ineligible' interventions to obtain greater robustness.

Alongside the analysis, we have applied a new method of GRADE assessment (Salanti 2014), which allows us to view the results in the light of the certainty of their findings. Using this approach, we found the evidence for the network as a whole was of low certainty (downgraded for risk of bias and imprecision). The network presents results derived from 59 studies of 25 interventions evaluating 40 direct comparisons: we highlight the results from contrasts involving the two treatments with the highest mean ranks (sucralfate and silver): the majority of the evidence for individual contrasts was of low or very low certainty, and was mainly downgraded for risk of bias and imprecision; there was a limited degree of inconsistency for some contrasts (see Quality of the evidence).

In summary:

- overall findings reflect the uncertainty of the component evidence and the sparseness of the network. For the network as a whole, the evidence was of low certainty. With so many interventions that appeared to have similar efficacies, there was considerable uncertainty in the middle ranks, but numerically two treatments had more than 50% probability of being the best (sucralfate and silver dressings); - see also Quality of the evidence.
- for the head-to-head comparison of these two treatments with the highest mean ranks, it is very uncertain whether there is a difference between sucralfate and silver dressing in the probability of venous leg ulcer healing (very low-certainty evidence);
- silver dressings may increase the probability of venous leg ulcer healing, compared with nonadherent dressings: RR 2.43, 95% CI 1.58 to 3.74 (moderate-certainty evidence in the context of a low-certainty network);
- in the other contrasts between these treatments with the highest probability of being best and the most widely-used dressing classes, it was unclear whether the intervention increased

the probability of healing; in each case this was low- or very low-certainty evidence characterised by wide confidence intervals;

- one of the sensitivity analyses highlighted some instability in key aspects of the network; this instability is likely to be due to sparseness. As a consequence, we reported the results of the extended sensitivity analysis.

Overall completeness and applicability of evidence

The studies included in the review do not represent all the studies which have been conducted on relevant interventions; substantial numbers of studies were excluded because they did not report the outcome of complete wound healing. However, this was an issue across treatments and did not appear to impact disproportionately on any particular treatment or comparison. As discussed below we believe that this approach was the appropriate one for the purpose of the review.

The populations represented in the included studies appear representative of the people who present with venous leg ulcers in clinical practice in terms of age, gender and ulcer characteristics at enrolment. However, although many studies specified characteristics such as ulcer dimensions, duration and infection in inclusion criteria or reported these in participant details, they were much less likely to specify or describe wound characteristics such as levels of slough, exudate or necrosis.

We identified a wide range of eligible interventions, and included both dressings and topical treatments; specific dressing types such as impregnated dressings and modern 'advanced' dressings were well represented. We conducted sensitivity analyses in order to assess the stability of the network and the impact of decreasing the number of included interventions to a smaller clinically-defined set, or expanding it in order to increase the amount of evidence available for key interventions which were particularly poorly linked into the network.

The review included a substantial number of studies not included in the network; in particular, studies which compared specific interventions such as honey with standard care or choices of multiple treatments. The inclusion of these studies in the review means that they are easily identifiable for researchers who may wish to conduct alternative analyses using this type of data. We believe that the choices we have made concerning data to include in the network meta-analysis are likely to maximise its relevance to clinical decision-making, but acknowledge that this is balanced against the availability of only direct evidence for some comparisons.

Quality of the evidence

A high proportion of the included studies were considered to be at high risk of bias for one or more domains and a substantial number were at very high risk of overall bias. The principal reasons for a study to be considered at high risk of bias were lack of blinding of one or more groups of participants, professionals and outcome assessors, and attrition bias. However, many studies which were not considered to be at high risk of bias had unclear risks of bias for several or even all domains. Therefore, even when a contrast has not been downgraded due to high risk of bias in the contributions matrix, this does not mean that we are confident that there is a low risk of bias pertaining to the contrast, but merely that there is no known high or very high risk of bias.

Many comparisons (the majority) were informed by a single trial, and most trials were small and underpowered. Only a few comparisons - between some of the most widely-used dressing types - were represented by multiple trials and substantial numbers of participants and events. This is reflected in the wide confidence intervals and therefore the imprecision of most contrasts in the NMA. Some contrasts were also judged to be affected by inconsistency. These factors, together with high risks of bias, meant that many key contrasts were judged to be low or very low certainty while the network as a whole was judged to represent low-certainty evidence.

The inclusion criteria and the nature of the evidence included meant that we did not downgrade for indirectness and we also found no evidence of publication bias.

Potential biases in the review process

Although all the included studies were reported in English, we ordered a number of full-texts in languages other than English; including Polish, German, Portuguese, Dutch, Norwegian, Chinese, Italian and Spanish. These were ultimately excluded as they did not meet the inclusion criteria, but would clearly have been included if they had proved eligible.

We searched a number of databases and checked the references of reviews and included studies; time constraints meant that the planned searches of trials registers were not conducted. We found no evidence of publication bias, and our focus on the single outcome of healing means that trials identified from registers were unlikely to have data which would have led to their inclusion in the network. We found a relatively small number of unobtainable records; close examination of the records for these led us to conclude that the studies they represented were unlikely to have been included in the review.

This NMA and review focused on the outcome of complete healing. The impact of including only studies reporting healing in this way was considerable; lack of these data was the single most common substantive reason for excluding a study. Complete healing is the outcome which is most important to people living with venous leg ulcers and therefore we believe that the decision to focus the network on this outcome was the right one. Other reviews include studies that focused on other outcomes considered important to people with lived experience of the condition; this review stands alongside those syntheses and does not seek to replicate them.

There is potential for bias in our choice of base-case and sensitivity analysis and also our choice of studies with only one eligible intervention for the expanded base-case sensitivity analysis. We made a post-hoc decision to focus on a base-case of interventions which were likely to be used in clinical practice. Clearly post-hoc decisions of this nature could be a source of bias in their impact on which interventions were included. However, no interventions were excluded from the review on the basis of this decision: comparisons including interventions judged to be partly relevant are included in the review and the direct evidence is available to the reader. The decisions on which interventions should be included in the base-case and the narrow sensitivity analysis were made on clinical grounds rather than on the basis of known results; they were made independently by two authors, one of whom had no access to the extracted data at that point, and who were in almost complete agreement when the decisions were compared; where there was a disagreement a more inclusive approach was adopted. The effect of the approach adopted was to remove some of the noise in what was a sparsely-populated network and to increase our ability to examine the relative effectiveness of treatments relevant to clinical practice.

Our updated search in March 2018 identified nine studies, which may be eligible for inclusion but which have not yet been incorporated into the review. None of these was large in absolute terms but the results of these studies may nevertheless have some impact on our sparse network.

Agreements and disagreements with other studies or reviews

We have been unable to identify any other NMAs examining dressings and topical agents for healing venous leg ulcers. The high level of uncertainty around contrasts between most dressings reflects that in the most recent NICE guidance (NICE 2016a) and the most recent report by the AHRQ (AHRQ 2013); these reflect in part the findings of a number of Cochrane reviews of individual types of dressing (see Why it is important to do this review). The 2010 guidance by SIGN (SIGN 2010) recommended the use of nonadherent dressings with possible alternatives being hydrocolloids, alginates or hydrogels. The results of the NMA do not conflict with this advice, suggesting broadly comparable efficacy for complete healing in these dressing categories.

The finding that silver dressings may increase the number of ulcers healed does not take account of the largest trial available for silver (Michaels 2009). This is because both arms of this trial contained more than one treatment class (specifically, silver-containing dressings and silver sulfadiazine (SSD)), and hence could not be integrated into the NMA. Michaels 2009 found no difference in overall healing between the silver and non-silver arms of this study (an RR of 1.00, 95% CI 0.95 to 1.06 at one year's follow-up), but we note that the 'silver' arm included 39% of participants receiving SSD, which may have substantially changed the effect in this study. Nevertheless, the data from this trial should be borne in mind when considering the results and when planning any further research on these treatments.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this network meta-analysis (NMA) are mostly findings of low-certainty evidence for key comparisons. Although there was some evidence that silver dressings may increase the probability of venous leg ulcer healing, compared with nonadherent dressings, this needs to be seen in the context of the low certainty of the network as a whole. We do not therefore believe that this evidence is a sufficient basis for treatment decisions. It is possible that the results may be affected by the studies which are awaiting classification and have not yet been incorporated into the review. The results of this NMA focus exclusively on complete healing; whilst this is of key importance to people living with venous leg ulcers, clinicians may wish to take into account other patient-important outcomes reported in other reviews on this subject, whilst cost considerations will also be a factor for decision makers.

Implications for research

There is a lack of high-quality research evidence relating to whether particular wound dressings or topical treatments have a beneficial impact on healing of venous leg ulcers. This is despite the existence of a large number of trials relating to a range of treatments. The poor or uncertain quality of the evidence is problematic given the impact on the lives of individuals of living with chronic wounds and the substantive healthcare implications of caring for them. The NMA's findings of low-certainty evidence make clear the generally poor quality of randomised controlled trials (RCTs) of venous leg ulcer treatments, suggesting a need for radical improvements in the planning, conduct and reporting of trials in this field.

There was uncertainty surrounding most of the interventions evaluated when we look at the rankings of their relative effectiveness. Therefore, any future evaluations of interventions should focus - as this NMA does - on those most widely used in clinical practice; they may wish to look in particular at silver-containing dressings. Where trials are conducted, they should be adequately powered to assess differences in complete wound healing, which should ideally be reported as time-to-event data. Choice of secondary outcomes should be informed by consultation with people with lived experience of leg ulcers. Trials should adhere to international guidance on design, conduct and reporting of randomised trials. In particular, they should undertake and report adequate randomisation and allocation procedures and blinded outcome assessments, while losses to follow-up should be fully accounted for.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alvarez 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: confirmed non-healing (no progress after 4 weeks of compression and standard care) VLU of minimum 2 months duration and requiring autolytic debridement (> 50% ulcer bed covered with non-viable yellow tissue). If participants had multiple VLU, the ulcer of longest duration was used for the study, or if duration equal, the one with largest surface area Exclusion criteria: clinical signs of infection, cellulitis, osteomyelitis, inadequate nutrition, uncontrolled diabetes, any other clinically-significant conditions that would impair wound healing. Use of corticosteroids, immunosuppressants, radiation or chemotherapy within 1 month prior to study entry Number participants: 48 Participant characteristics Age: 69.0 (8.3) vs 63.0 (10.3) years (range 55 to 72 vs 58 to 70) N male: 12 (48) vs 11 (48) Ulcer details Size: 743.9 (103.8) vs 629.0 (106.9) mm² (median 785 vs 627 mm²) Duration: 10.9 (2.2) vs 8.9 (1.2) months (range 8 to 14 vs 4 to 12)
Interventions	Intervention 1 class: biosynthetic (bio-cellulose) Intervention 1 details (name and details of application): Suprasorb X (Lohmann & Rauscher) changed weekly Intervention 2 class: nonadherent Intervention 2 details (name and details of application): Adaptic (Systagenix) changed weekly Compression: modified Unna's boot or a 4-layer bandage system (Viscopaste, Profore; Smith & Nephew Inc, Coban LF; 3M Inc) Other co-interventions: wound cleansing with saline, without forceful irrigation
Outcomes	Intervention 1: 7/25 Intervention 2: 7/23
Notes	Funding type: industry Funding details Xylos corporation

Risk of bias

Bias	Authors' judgement	Support for judgement

Alvarez 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients were allocated ... according to a block randomisation schedule" Comment: method of generating the sequence was not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomisation was done using sealed envelopes, which were opened after pre-test measurements were taken" Comment: unclear if the envelopes were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "digital photographs were assessed by a clinician who was blinded as to the treatment allocation" Comment: blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 28% and 35% of participants were excluded from the analysis - variety of reasons and it is not clear if these were reasonable
Selective reporting (reporting bias)	Low risk	Comment: all outcomes appear to have been reported
Other bias	Low risk	No evidence of other bias
All domain risk of bias	High risk	

Arenbergerova 2013

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 13 weeks
Participants	Inclusion criteria: VLU minimum 1.6 cm in all directions, maximum area 50 cm^2, > 8 weeks duration, ABI > 0.8 Exclusion criteria: vasculitis, non-venous leg ulcer, treatment with systemic antibiotics, corticosteroids or oral immunosuppressants, pregnancy Participant characteristics Number participants: 72 Age: 65 vs 59 years

	N (%) male: 11 (30.6) vs 15 (41.7) Ulcer details Size: mean (SD) 18.7 (9.9) cm² vs 17.5 (9.3) cm² Duration: mean (range) 2 years (3 months to 6 years) vs 2 years (3 months to 6 years)
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): haemoglobin spray (10% purified porcine haemoglobin in aqueous solution) + Nanotextile (Elmarco), fixed with gauze. Daily dressing change. Treated in hospital for 2 weeks, then at home Intervention 2 class: placebo Intervention 2 details (name and details of application): placebo spray (0.9% saline) + Nanotextile (Elmarco) fixed with gauze Compression: compression therapy used in all according to current guidelines in Czech Republic based on clinical experience, initiated 2 weeks prior to study inclusion. All used Ideal/Hartmann bandages Other co-interventions: meticulous wound cleaning and disinfection prior to dressing
Outcomes	Intervention 1: 1/36 Intervention 2: 0/36
Notes	Funding type and details: non-industry Funding details: Czech Ministry of Health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: study described as randomised but no methods reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the nurses involved in treatment and wound care were not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the attending doctor whom evaluated the wound surface area and assessed the condition of the wound were blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2/36 vs 5/36 dropped out of study, reasons reported but disparity and higher than healing rate
Selective reporting (reporting bias)	Low risk	Comment: all outcomes appear to be reported
Other bias	Low risk	Comment: no evidence of other bias

All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Armstrong 1997

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: ulcer 7.5 cm or larger in diameter producing moderate to heavy amounts of exudate Exclusion criteria: not reported Participant characteristics Number participants: 44 Age: 71 (10) vs 65 (11) years N (%) male: 10 (48) vs 13 (57) Ulcer details Non VLU: < 25% mixed/arterial); 3 (14%) vs 3 (13%) mixed aetiology, 1 (5%) vs 1 (4%) other Size: median (range) 491 (64 to 2081) mm^2 vs 611 (60 to 1830) mm^2 Duration: median (range) 9 (1 to 47) months vs 12 (1 to 120) months
Interventions	Intervention 1 class: hydrofibre Intervention 1 details (name and details of application): Aquacel; dressing changed every 7 days (or sooner if leakage, infection suspected or pain) Intervention 2 class: alginate Intervention 2 details (name and details of application): Kaltostat; dressing changed every 7 days (or sooner if leakage, infection suspected or pain) Compression: class 3c compression bandage (Tensopress) Other co-interventions: secondary dressing, occlusive hydrocolloid (DuoDerm Extra Thin) and, if indicated, orthopaedic padding
Outcomes	Intervention 1: 6/21 Intervention 2: 2/23
Notes	Funding type: industry Funding details: ConvTec Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were then randomised to the primary dressings under investigation

		by the use of sealed envelopes opened in numerical order" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "subjects were then randomised to the primary dressings under investigation by the use of sealed envelopes opened in numerical order" Comment: not clear whether the envelopes used were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high levels of withdrawals (24% vs 30%) all but one due to adverse events
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	Unclear risk	Comment: no evidence of other bias but secondary dressing appears to have been a problem; cause of the high adverse events
All domain risk of bias	High risk	

Arnold 1994

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 10 weeks
Participants	Inclusion criteria: non-infected lower leg ulceration secondary to venous stasis Exclusion criteria: ulcers resulting from arterial insufficiency, vasculitis, rheumatoid arthritis, sickle cell anaemia, tumours, other dermatological conditions. Evidence of peri-wound erythema, cellulitis, oedema. Deep dermal involvement and exposure of muscle, tendon or bone Participant characteristics Number participants: 70 Age: 65 (SE 3.3) vs 60 (SE 2.9) years

Arnold 1994 (*Continued*)

	% male 36 or 37(calculating from %) (52) Ulcer details Size: 2100 mm² (SE 685) vs 1983 mm² (SE 659) Duration: 47.8 weeks vs 46.2 weeks
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): DuoDERM CGF (ConvaTec); dressing changed every 7 days Intervention 2 class: nonadherent Intervention 2 details (name and details of application): gauze (paraffin-impregnated in US study centres, saline/betadine-impregnated in UK); US centres: Telfa (Kendall Healthcare Products); dressing changed every 7 days Compression: zinc oxide paste bandage (Unna's boot) and gradient compression bandage (worn during working hours) Other co-interventions: not reported
Outcomes	Intervention 1: 11/35 Intervention 2: 14/35
Notes	Funding type: not reported Funding details: 2 of the authors are from Bristol-Myers Squibb Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "following the initial assessment, patients were randomly assigned to the study or control treatment" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "following the initial assessment, patients were randomly assigned to the study or control treatment" Comment: unclear whether allocation was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 20% vs 26% withdrawal for various reasons but ITT analysis

Arnold 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	High risk	Comment: authors highlight differences between outcomes in different study centres
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Backhouse 1987

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: Doppler-assessed venous or gravitational ulcers Exclusion criteria: ulcers > 10 cm^2 in area Participant characteristics Number participants: 56 Age: 69.9 vs 67.5 years % male: 23 (41) Ulcer details Non VLU: comment: ulcers were "gravitational or venous" Size: 3.4 (0.4) cm^2 vs 3.1 (0.4) cm^2 Duration: 22 vs 21 months (median)
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application) Granuflex (Squibb Surgicare), no further details Intervention 2 class: nonadherent Intervention 2 details (name and details of application): NR (Johnson & Johnson), no further details Compression: below-knee graduated compression bandage; layer crepe bandage, layer Elset bandage (Seton Products Ltd); layer Coban cohesive bandage (3M Health Care Ltd) Other co-interventions: saline wash, removal of slough, absorbent velband (Johnson & Johnson) over dressing
Outcomes	Intervention 1: 21/28 Intervention 2: 22/28
Notes	Funding type: industry Funding details: Johnson & Johnson Ltd, 3M Health Care, Sigvaris (Camp Ltd), Zyma UK Ltd, Squibb Surgicare

Backhouse 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "fifty-six patients referred to a venous ulcer clinic were randomized" Comment: no detail on how randomisation sequence generated
Allocation concealment (selection bias)	Unclear risk	Quote: "fifty-six patients referred to a venous ulcer clinic were randomized" Comment: no information on whether allocation was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information was reported on blinding participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information on who performed the assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Comment: planned outcomes were not clearly reported so difficult to be sure whether they were fully reported
Other bias	Unclear risk	Comment: no evidence of other bias but reporting insufficient to be certain
All domain risk of bias	Low risk	unclear/low

Banerjee 1997

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 17 weeks
Participants	Inclusion criteria: in-patient or attendee day hospital for elderly with varicose leg ulcer Exclusion criteria: significant peripheral vascular disease (Doppler assessed) Participant characteristics Number participants: 71 Age: 75.9 (7.7) vs 81.2 (7.3) years % male: 7 (19) vs 7 (20)

Banerjee 1997 (*Continued*)

	Ulcer details Size: median (range) 12.2 cm² (1.1 to 138.0) vs 11.4 cm² (1.3 to 134.0) Duration: '"approximately 2 years in each group"
Interventions	Intervention 1 class: film Intervention 1 details (name and details of application): polyurethane 'synthetic skin'; Synthaderm (Arrow Pharmaceuticals) Intervention 2 class: nonadherent Intervention 2 details (name and details of application): paratulle (no further details) Other co-interventions: warm saline poured over ulcer to clean. Primary dressing was backed by a pad and a support bandage applied using a K-bnd Parema conforming bandage from toes to just below the knee
Outcomes	Intervention 1: 11/36 Intervention 2: 8/35
Notes	Funding type and details: not reported Notes: a high proportion of ulcers were infected 29 (81%) vs 21 (60%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "treatment allocation was random" Comment: unclear how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "treatment allocation was random" Comment: unclear whether allocation was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal was 3% vs 23% giving a large imbalance between the arms
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	High risk	Comment: differences in nursing time/visits noted by authors
All domain risk of bias	High risk	

Banerjee 1997 (*Continued*)

All domain risk of bias 2	High risk	

Beckert 2006

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 20 weeks
Participants	Inclusion criteria: leg ulcer due to CVI > or = 3 cm², ABI > 0.8 Exclusion criteria: ulceration not due to CVI, severe cardiac, respiratory, gastrointestinal, live or renal disease, malignancy, signs of wound infection. Pregnant or nursing mothers Participant characteristics Number participants: 119 Age: 66.8 (13.7) vs 70.6 (11.1) years % male: 20 (32.3) vs 19 (33.3) Ulcer details Size: mean (SD) 26.2 (49.0) cm² vs 17.2 (21.0) cm² Duration: mean (SD) 24.9 (51.2) months vs 17.8 (18.4) months
Interventions	Intervention 1 class: pale sulphonated shale oil (PSSO) gel Intervention 1 details (name and details of application) 10% Leukichtan (Ichthyol-Gesellschaft); gel applied to wound daily as 2 mm to 2.5 mm thick layer Intervention 2 class: vehicle (gel) Intervention 2 details (name and details of application): gel applied to wound daily as 2 mm to 2.5 mm thick layer Compression: short stretch elastic bandages (Putter-Bandages, Hartmann) Other co-interventions: Jelonet (Smith & Nephew) nonadherent gauze dressing applied over the gel
Outcomes	Intervention 1: 21/62 Intervention 2: 13/57
Notes	Funding type and details: industry Funding details: Ichthyol-Gesellschaft Cordes, Hermanni & Co (GmbH & Co)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to one of the treatment groups by using a centralized computer system with block randomization (1:1) (Randcode, IDV, Gauting, Germany)" Comment: appropriate method of sequence generation

Beckert 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "investigators were blinded to the randomization process to eliminate bias" Comment: unclear how allocation was concealed and hence whether the process was adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"[ulcer] area was calculated in a blinded manner using a standardized computer system" Comment: it appears that blinded outcome assessment was conducted for healing
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "ultimately, 119 patients were enrolled in the study; 62 were randomized to PSSO 10% and 57 to vehicle treatment. Eighteen (15%) of the 119 patients-nine each in the in the PSSO 10% and vehicle groups- did not complete the study for other reasons than ulcer healing. These patients were included in data analysis with their assigned group" Comment: ITT analysis
Selective reporting (reporting bias)	Low risk	All specified outcomes were fully reported
Other bias	Low risk	No evidence of other bias and reporting sufficient
All domain risk of bias	Low risk	low/unclear

Biland 1985

Methods	RCT Arms: 4 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: venous or mixed arteriovenous ulcers, minimum diameter 1.5 cm, without claudication Exclusion criteria: purely arterial ulcers, neuropathy, treatment with vaso-active drugs, antibiotics or steroids Participant characteristics Number participants: 197

Biland 1985 (*Continued*)

	Age: 61 (15) vs 60 (12) vs 60 (12) vs 61 (12) years N (%) male: 15 (34) vs 13 (23) vs 17 (33) vs 10 (22) Ulcer details Non VLU: < 25% mixed/arterial Size: range 2 cm² to 321 cm², median 32 cm² Duration: < 12 weeks 26 (59%) vs 30 (54%) vs 31 (60%) vs 27 (60%), 12-24 weeks 6 (14%) vs 11 (20%) vs 6 (12%) vs 3 (7%), > 24 weeks 12 (27%) vs 15 (27%) vs 15 (29%) vs 15 (33%)
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): haemodialysate ointment (dialysate of calf blood: Solcoseryl (Solco Basle Ltd)) plus placebo IV Intervention 2 class: placebo Intervention 2 details (name and details of application): placebo ointment plus placebo IV Intervention 3 class: blood product Intervention 3 details (name and details of application): haemodialysate ointment + haemodialysate IV Intervention 4 class: placebo Intervention 4 details (name and details of application): placebo ointment + haemodialysate IV Compression: all received continuous compression with foam-rubber padded bandage Other co-interventions: twice daily application of compress with isotonic saline. 3 x weekly painting of skin around ulcer with 4% methylrosaniline chloride
Outcomes	Intervention 1: 21/44 Intervention 2: 18/56 Intervention 3: 25/52 Intervetnion 4: 19/45
Notes	Funding type: not reported Funding details: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: described as randomised and mention of stratification but no method details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: described as "double blind" but no method detail

Biland 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as "double blind" but no method detail
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 13/210 dropped out of study, reasons given; unclear which arms these were from
Selective reporting (reporting bias)	High risk	Comment: no evidence of selective reporting but withdrawals not clearly reported
Other bias	Low risk	Comment: no evidence of other bias
All domain risk of bias	High risk	

Bishop 1992

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks
Participants	Inclusion criteria: age 21-90, venous stasis ulcer of at least 3 months duration, surface area 3 cm^2 to 50 cm^2, for relevant participants negative pregnancy test and use of adequate contraception Exclusion criteria: hypersensitivity to test medication, > 10^5 bacteria/g of tissue in ulcer, systemic sepsis or bone infection arm/ankle arterial perfusion index < 0.5, hypercupraemia, systemic immunosuppressive or cytotoxic therapy, insulin-dependent diabetes Participant characteristics Number participants: 93 randomised (86 analysed) Age: 58.2 (14.5) vs 58.2 (17.3) vs 51.6 (14.6) years % male: 14 (48) vs 9 (32) vs 20 (69) Ulcer details Size: mean (SD) 9.9 (8.5) cm^2 vs 11.9 (11.2) vs 9.6 (8.1) cm^2 median 6.5 vs 6.9 cm^2 vs 6.2 cm^2 Duration: mean (SD) 57.1 (94.9) vs 44.1 (58.0) vs 38.0 (88.7) months, median 11.0 vs 19.0 vs 12.0 months
Interventions	Intervention 1 class: copper tripeptide Intervention 1 details (name and details of application): copper tripeptide complex cream; GHK: Cu; participant applied cream and covered with nonadherent dressing Intervention 2 class: SSD Intervention 2 details (name and details of application): 1% silver sulfadiazine cream; Silvadene (Marion Laboratories); participant applied cream and covered with nonadherent dressing Intervention 3 class: vehicle (cream)

Bishop 1992 (*Continued*)

	Intervention 3 details (name and details of application): Unibase (Parke-Davis); participant applied cream and covered with non adherent dressing Compression: "elastic wrap" Other co-interventions: saline used to clean wound at dressing change
Outcomes	Intervention 1: 0/29 Intervention 2: 6/28 Intervention 3: 1/29
Notes	Funding type: industry Funding details: Schering-Plough Research Notes: 1-year follow-up found 5/6 healed participants in silver sulfadiazine group still healed, as well as the healed placebo-treated participant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "this study reports a prospective randomized evaluator-blinded trial comparing ..." Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "this study reports a prospective randomized evaluator-blinded trial comparing ..." Comment: no information on whether allocation was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is no information on this but the fact that study medication was removed before a blinded assessor saw the wound means that there may be an inherent lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "before evaluation, all study medication was removed and the ulcer cleansed to keep the evaluator blinded" Comment: assessors were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all the participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: all planned outcomes were reported
Other bias	Unclear risk	Comment: no evidence of other bias but reporting insufficient to be certain

Bishop 1992 (*Continued*)

All domain risk of bias	Low risk	low/unclear

Blair 1988a

Methods	RCT Arms: 2 [see notes] Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous ulcers < 10 cm² Exclusion criteria: ABPI < 0.8 on Doppler (arterial insufficiency) Participant characteristics Number participants: 120 Age: 69.9 (range 34 to 92) vs 67.5 (30 to 90) years % male: not reported Ulcer details Size: 3.4 (SEM 0.4) vs 3.1 (SEM 0.4) cm² Duration: 22 (SEM 1.9) vs 21 (SEM 2.7) months
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex (Squibb Surgicare); no further details Intervention 2 class: nonadherent Intervention 2 details (name and details of application): manufactured by Johnson & Johnson; no further details Compression: standard high-pressure graduated compression bandage 4 layers: Velband (Johnson & Johnson) + crepe bandage + Elset (Seton Products) + Coban (3M Health Care) Other co-interventions: ulcers cleaned with saline prior to dressing
Outcomes	Intervention 1: 22/30 Intervention 2: 23/30
Notes	Funding type and details: not reported Notes: study was in 2 parts which actually form 2 different randomised trials

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the ulcers were cleaned with saline and the dressing applied according to randomisation using a sequential system of sealed envelopes with treatment allocation by random number table" Comment: an appropriate method for deriving the randomisation sequence was re-

Blair 1988a (*Continued*)

		ported
Allocation concealment (selection bias)	Unclear risk	Quote: "the ulcers were cleaned with saline and the dressing applied according to randomisation using a sequential system of sealed envelopes with treatment allocation by random number table" Comment: unclear if the envelopes used were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Comment: there was no evidence of selective reporting
Other bias	High risk	Comment: it is unclear how the randomisation was managed across the two trials reported together
All domain risk of bias	High risk	

Blair 1988b

Methods	RCT Arms: 2 (see notes) Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous ulcers < 10 cm^2 Exclusion criteria: ABPI < 0.8 on Doppler (arterial insufficiency) Participant characteristics Number participants: 120 Age: 70.1 (42 to 90) vs 67.3 (36 to 86) years % male: not reported Ulcer details Size: 3.8 (SEM 0.6) cm^2 vs 3.4 (SEM 0.5) cm^2 Duration 27.8 (SEM 3.4) months vs 33.4 (SEM 4.1)

Blair 1988b (*Continued*)

Interventions	Intervention 1 class: nonadherent Intervention 1 details (name and details of application): manufactured by Johnson & Johnson; no further details Intervention 2 class: SSD Intervention 2 details (name and details of application): Flamazine (Smith & Nephew); no further details Compression: standard high-pressure graduated compression bandage 4 layers: Velband (Johnson & Johnson) + crepe bandage + Elset (Seton Products) + Coban (3M Health Care) Other co-interventions: ulcers cleaned with saline prior to dressing
Outcomes	Intervention 1: 24/30 Intervention 3: 19/30
Notes	Funding type and details: not reported Notes: Study was in 2 parts which actually form 2 different randomised trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the ulcers were cleaned with saline and the dressing applied according to randomisation using a sequential system of sealed envelopes with treatment allocation by random number table" Comment: an appropriate method for deriving the randomisation sequence was reported
Allocation concealment (selection bias)	Unclear risk	Quote: "the ulcers were cleaned with saline and the dressing applied according to randomisation using a sequential system of sealed envelopes with treatment allocation by random number table" Comment: unclear if the envelopes used were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included in the analysis

Blair 1988b (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: there was no evidence of selective reporting
Other bias	High risk	Comment: it is unclear how the randomisation was managed across the two trials reported together
All domain risk of bias	High risk	

Bowszyc 1995

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: leg Follow-up: 16 weeks
Participants	Inclusion criteria: chronic venous ulcer Exclusion criteria: API < 0.8 (arterial insufficiency), diabetes, heavily exuding wounds, necrotic tissue in ulcer, clinically infected wound, general poor state of health, immunosuppressed, receiving corticosteroid treatment Participant characteristics Number participants: 80 Age: 64.2 (14.4) vs 55.5 (14.7) years % male: 12 (29) vs 15 (37) Ulcer details Size: 3.95 (6.89) cm^2 vs 3.47 (7.76) cm^2 (total ulcer area) Duration: 26.2 (37.6) vs 36.1 (70.9) weeks
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Lyofoam; changed weekly or when exudate leaked visibly through bandage Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): Granuflex; changed weekly or when exudate leaked visibly through bandage Compression: high compression bandage (Setopress) Other co-interventions: sloughy wounds treated with sodium chloride solution (Chlorasol) before entry to the study
Outcomes	Intervention 1: 24/41 Intervention 2: 24/41
Notes	Funding type: industry Funding details: Seton Healthcare Group Notes: 2 participants had ulcers on both legs and analysis was by leg giving n = 82
Risk of bias	

Bowszyc 1995 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were allocated to treatment groups according to a pre-prepared randomisation listing" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were allocated to treatment groups according to a pre-prepared randomisation listing" Comment: unclear how allocation concealment was undertaken
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 withdrew in each group for various reasons
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	High risk	There is uncertainty over the unit of analysis as participants/legs/ulcers referred to in different places, see notes
All domain risk of bias	High risk	

Brandrup 1990

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 8 weeks
Participants	Inclusion criteria: ulcers with area between 1 cm^2 to 100 cm^2, with lowest edge in lower two-thirds of the lower leg and upper edge above the malleoli. Negative patch tests to the dressings Exclusion criteria: not reported Participant characteristics Number participants: 43 Age: 73 (14) vs 77 (9) years

Brandrup 1990 (*Continued*)

	% male: 5 (31)vs 2 (13) Ulcer details Non VLU: < 25% mixed/arterial - 7 (16%) arterial Size: 13.7 cm² (15.9) vs 11.1 cm² (9.1) Duration: median (range) 8 months (2 to 24) vs 5 months (1 to 68)
Interventions	Intervention 1 class: nonadherent Intervention 1 details (name and details of application): occlusive zinc-oxide medicated dressing; Mezinc (Mölnlycke); applied to ulcer and 0.5 cm surrounding skin. Changed daily for first 14 days, then every third day Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): Duoderm; applied to ulcer and 0.5 cm surrounding skin. Changed daily for first 14 days, then every third day Compression: compression bandage Dauerbinde (Lohmann) used on venous ulcers Other co-interventions: loosely attached necrotic material removed and ulcers cleaned with 0.9% NaCl at each dressing change. Absorbent material used on top of dressings for heavily discharging ulcers
Outcomes	Intervention 1: 4/22 Intervention 2: 4/21
Notes	Funding type and details: not reported Notes: baseline stats were given for completers (n = 16 vs n = 15). For participants with multiple ulcers, all were treated but only largest was monitored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were consecutively matched in pairs within these two groups [venous and arterial]" "from sealed envelopes, each member of the pair was randomly allocated." Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were consecutively matched in pairs within these two groups [venous and arterial]" "from sealed envelopes, each member of the pair was randomly allocated." Comment: no information on how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Brandrup 1990 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Data are only presented for completers (withdrawal 27% vs 29% for various reasons)
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Unclear risk	Protocol was incorrectly followed in one participant. No other evidence of other sources of bias but reporting insufficient to be certain
All domain risk of bias	High risk	

Brown 2014

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks (24 weeks but optional cross-over at 12)
Participants	Inclusion criteria: chronic venous ulcer (confirmed with duplex or Doppler sonography and ankle/brachial arterial Doppler pressure index between 0.8 and 1.3), duration between 3 months and 5 years, size 5 cm^2 to 40 cm^2, viable wound bed with granulation tissue and no exposed muscle, tendon or bone Exclusion criteria: ulcers of non-venous aetiology, signs of ulcer infection, medications and therapies inhibiting wound healing, uncontrolled diabetes, uncontrolled organ failure, active malignancies, pregnant or nursing women Participant characteristics Number participants: 121 Age: 65.5 (13.3) vs 70.1 (13.8) years % male: 28 (46.7) vs 30 (50.0) Ulcer details Size: mean (SD) 13.7 (8.2) cm^2 vs 13.4 (9.0) cm^2 Duration: mean (SD) 18.9 months (16.0) vs 18.1 (15.3) months
Interventions	Intervention 1 class: silica gel fibre Intervention 1 details (name and details of application): dressing 0.2 cm thick, cut to exact size and applied at baseline visit. Re-application only took place if it was completely absorbed Intervention 2 class: mixed standard comparators Intervention 2 details (name and details of application): Mepilex for exudative wounds or Mepitel for non-exudative (Molnlycke Healthcare); dressing changed at least twice

	weekly, debridement or cleansing with isotonic sodium chloride solution was performed as necessary Compression: 4-layer bandaging system (Profore, Smith & Nephew) from toe to knee Other co-interventions: complete sharp or ultrasonic debridement of all non-viable tissue prior to initial dressing
Outcomes	Intervention 1: 10/60 Intervention 2: 16/60
Notes	Funding type: industry Funding details: Bayer Innovation GmbH Note: authors were contacted to confirm that compression treatment was applied equally to both groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomization list was generated by the Biometrical Department of Winicker Norimed GmbH" Comment: appears to be appropriate computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "randomization numbers were assigned to eligible subjects in ascending order at each centre. Enrolment of subjects was competitive across all participating centres" Comment: appears that central allocation will have ensured adequate concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was described as "open"
Incomplete outcome data (attrition bias) All outcomes	Low risk	127 entered study; 121 participants "randomised and treated at least once"; 120 analysed
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of other bias
All domain risk of bias	High risk	

Brown 2014 (*Continued*)

All domain risk of bias 2	High risk	

Callam 1992

Methods	RCT Arms: 4 (factorial design; participants also randomised to different types of bandaging) Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: patients attending leg ulcer clinics with a VLU of at least 4 weeks duration Exclusion criteria: Doppler ultrasound ABPI < 0.8; unable to walk; on waiting list for inpatient treatment; rheumatoid arthritis or diabetes; taking medication for venous disorders, e.g. Paroven, Trental, stanozolol Participant characteristics Number participants: 132 Age: 63 vs 64 years % male: 30 (45) vs 29 (44) Ulcer details Size: 8.35 cm^2 vs 10.87 cm^2 Duration: 11.2 vs 11.7 months
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Allevyn (Smith and Nephew) Intervention 2 class: nonadherent Intervention 2 details (name and details of application): knitted viscose dressing (Tricotex) Compression: factorial design - half participants randomised to elastic bandaging and half to non-elastic bandaging Other co-interventions: cleansed with water and if necessary loose debris and slough removed physically. If appropriate surrounding skin treated for dry eczema (Betnovate RD cream) or weeping eczema (2% aqueous eosin)
Outcomes	Intervention 1:31/66 Intervention 2: 23/66
Notes	Funding type: industry Funding details: Smith and Nephew

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study described as randomised - currently no additional information

Callam 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Study described as randomised - currently no additional information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study described as "open"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of other bias
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Caprio 1992

Methods	RCT Arms: 2 Unit of randomisation: ulcer Unit of analysis: ulcer Follow-up: 8 weeks
Participants	Inclusion criteria: clean leg ulcers of venous origin Exclusion criteria: not reported Participant characteristics Number participants: 93 with 98 ulcers Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Duoderm E covered by gauze and cotton bandage Intervention 2 class: collagen Intervention 2 details (name and details of application): lyophilised collagen tablets covered by gauze and cotton bandage Compression: not reported Other co-interventions: not reported

Caprio 1992 (*Continued*)

Outcomes	Intervention 1: 25/47 Intervention 2: 20/49
Notes	Funding type and details: not reported Abstract only so information incomplete and numbers unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "ulcers were randomised" Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote "ulcers were randomised" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a clinical examination was made" Comment: no information on who made the assessment and whether they were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All ulcers were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to be certain whether this was an issue
Other bias	Unclear risk	Insufficient reporting to be certain whether this was an issue
All domain risk of bias	Low risk	low/unclear

Casoni 2002

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 3 months
Participants	Inclusion criteria: non-healing vascular leg ulcers (failed to reduce by 10% after 4 weeks conventional treatment)

Casoni 2002 (*Continued*)

	Exclusion criteria: diabetes, severe peripheral atherosclerotic disease with ABPI < 0.6, severe chronic cardiac or hepatic failure, nephrotic syndrome Participant characteristics Number participants: 65 Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: hyaluronic acid plus povidone iodine Intervention 1 details (name and details of application): occlusive dressing with hyaluronic acid and povidone iodine Intervention 2 class: nonadherent Intervention 2 details (name and details of application): no details Compression: Unna bandage changed weekly Other co-interventions: not reported
Outcomes	Intervention 1: 15/32 Intervention 2: 8/33
Notes	Funding type and details: not reported Abstract only so information incomplete

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "65 homogeneous [sic] cases with non-healing vascular leg ulcers were randomized 4 weeks after conventional treatment" Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "65 homogeneous [sic] cases with non-healing vascular leg ulcers were randomized 4 weeks after conventional treatment" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was reported on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The main end point for this trial was the time to complete healing, anyway a comparison of images and of life tables up

Casoni 2002 (*Continued*)

		to 3 months of treatment was done." Comment: no information on who performed the outcome assessment or whether they were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Results: At the end of the study 48% of patients treated with occlusive dressing and 24% to an NA pancement [sic] had completely healed Comment: Reporting was insufficient to be sure whether all participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Reporting was insufficient to know whether this was an issue
Other bias	Unclear risk	Reporting was insufficient to know whether there were additional sources of potential bias
All domain risk of bias	Low risk	Low/unclear

Charles 2002

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: ambulatory participants with venous leg ulcer 2 cm to 12 cm at widest perpendicular diameter, ABPI > or = 0.8 Exclusion criteria: corticosteroid treatment within last 2 months, insulin-dependent diabetics, allergy to test product, history of radiation or cytotoxic treatment near ulcer site, primary arterial occlusive disease, HIV+, registered alcoholic, unlikely to comply with treatment/follow-up Participant characteristics Number participants: 91 Age: mean (range) 71 (53-84) vs 72 (53-91) vs 72 (56-85) years N (%) male: 15 (48) vs 12 (39) vs 13 (45) Ulcer details Size: mean (range) 881 (271 to 3182) mm^2 vs 930 (234 to 3642) mm^2 vs 1035 (205 to 3795) mm^2 Duration: mean (range) 137 (4 to 1560) vs 95 (1 to 1560) vs 104 (3 to 1040) weeks
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Cutinova; applied according to manufacturer's instructions and changed as frequently as necessary Intervention 2 class: hydrocolloid

	Intervention 2 details (name and details of application): Granuflex new formulation; applied according to manufacturer's instructions and changed as frequently as necessary Intervention 3 class: hydrocolloid Intervention 3 details (name and details of application): Comfeel; applied according to manufacturer's instructions and changed as frequently as necessary Compression: short-stretch compression bandaging Comprilan (Beiersdorf UK) Other co-interventions: secondary dressing of padding on bony prominences
Outcomes	Intervention 1: 18/31 Intervention 2: 17/31 Intervention 3: 17/29
Notes	Funding type: industry Funding details: Biersdorf UK (BSN Medical)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated ... using a minimisation method derived from that of Pocock and Simon (1976)" Comment: insufficient information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocate ... using a minimisation method derived from that of Pocock and Simon (1976)" Comment: insufficient information on how allocation concealment was achieved
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was reported on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was reported on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 7% withdrawal but all included in analysis; some slight imbalance between groups but unclear whether this was sufficient to impact analysis
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting

Charles 2002 (*Continued*)

Other bias	Low risk	Comment: no evidence of other sources of bias; extensive reporting
All domain risk of bias	Low risk	Low/unclear

De Araujo 2016

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: ulcer Follow-up: 60 days
Participants	Inclusion criteria: chronic venous ulcer > 5 cm^2, wound bed with devitalised tissues, no use of venonic drugs or active topical agents for prior 2 weeks Exclusion criteria: severely infected ulcer (criteria given) arterial or mixed aetiology, ABI < 0.9 or chronic ulcer of other aetiology, pregnancy or breastfeeding Participant characteristics Number participants: 55 with 63 ulcers Age: median (range) 62 (28 to 85) for all participants years % male: 12 (57) vs 8 (42) vs 11 (48) Ulcer details Size: data presented on a graph only Duration: mean (SD) 62.9 (2.9) vs 57.9 (3.4) vs 63.9 (3.5) months
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): fibrin gel; gel prepared from pool of 5 cryoprecipitate units, 100 I/mL purified human thrombin cryoprecipitate, 6% vitamin A and E, 5% calcium gluconate in carbopol gel; participants received pack and instructions and followed up every 15 days Intervention 2 class: papain Intervention 2 details (name and details of application): papain gel; 8% papain in carbopol gel; participants received pack and instructions and followed up every 15 days Intervention 3 class: placebo Intervention 3 details (name and details of application): carbopol gel (carrier vehicle used for the other interventions); participants received pack and instructions and followed up every 15 days Compression: Compressive elastic bandage (Surepress) Other co-interventions: wound bed flushed with warm 0.9% saline at dressing changes
Outcomes	Intervention 1: 3/21 Intervention 2: 4/19 Intervention 3: 7/23
Notes	Funding type: non-industry Funding details: funded by Botucatu Medical School, and Boston Medical Device donated high compression bandages

De Araujo 2016 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "randomization protocol was based on numbers randomly generated by software" Comment: appropriate method of randomisation sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "the pharmacist ... prepared all the products which were numbered and similar in appearance and presentation. The pharmacist kept the envelopes and the randomization list. The investigators were unblinded only by the end of the study" Comment: appears that allocation concealment was adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the pharmacist ... prepared all the products which were numbered and similar in appearance and presentation. The pharmacist kept the envelopes and the randomization list. The investigators were unblinded only by the end of the study" Comment: appears that both personnel and participants were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the investigators were unblinded only by the end of the study" Comment: presume this means they were blinded for duration of study including for outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no dropouts, data presented for all"
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	Low risk	Comment: no evidence of other bias; adequate reporting
All domain risk of bias	Low risk	

Dereure 2012a

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 60 days
Participants	Inclusion criteria: in- or outpatient with at least one leg ulcer of venous or mixed aetiology of 2 months to 4 years duration, surface area 5 cm² to 40 cm² with no necrotic tissue, suitability to and use of compression therapy, ABPI > 0.8, albuminaemia > 25 g/L, history of DVT or clinical evidence of post-thrombotic syndrome or Doppler evidence of residual thrombosis or a reflux on the venous system. If more than one ulcer, target ulcer selected as best meeting inclusion criteria Exclusion criteria: ulcer of non-vascular origin or due to general cause, significant arterial insufficiency (ABPI < 0.8), clinical suspicion of infection, hepatic or renal failure, venous thrombosis within previous 3 months, diabetes, allergy to local anaesthetic or study treatment, treatment that delays healing process Participant characteristics Number participants: 101 (multiple ulcers, one selected per participant) Age: 68.6 (12.4) vs 69.7 (14.7) years N (%) male: 23 (46) vs 22 (43) Ulcer details Non VLU: not clearly reported how many had mixed aetiology Size: median (range) 11.1 (2.8 to 39.3) cm² vs 11.7 (3.67 to 41.1) cm² Duration: median (range) 7.5 (1 to 48) months vs 9.0 (2 to 42) months
Interventions	Intervention 1 class: hyaluronic acid Intervention 1 details (name and details of application): Ialuset cream (Laboratoires Genevrier); applied daily, in a 2 mm to 3 mm-thick layer, then covered with a bandage (grade 2 or 3) in accordance with standard care Intervention 2 class: placebo Intervention 2 details (name and details of application): same formulation as Ialuset cream without hyaluronic acid (Laboratoires Genevrier); applied daily, in a 2 mm to 3 mm-thick layer, then covered with a bandage (grade 2 or 3) in accordance with standard care Compression: type 2 long-stretch elastic (90% participants) or multilayer bandages Other co-interventions: systemic antibiotics could be used if clinically relevant infection
Outcomes	Intervention 1: 3/50 Intervention 2: 4/51
Notes	Funding type: industry Funding details: Laboratoires Genevrier

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation list was generated by a computer and prepared by

		the data management and statistics unit of IBSA using validated software“ Comment: an appropriate method was used to generate the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: ”the randomisation list was generated by a computer and prepared by the data management and statistics unit of IBSA using validated software“ Comment: not clear how allocation concealment was ensured although remote management of randomisation suggests it may have been adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ”both treatments were supplied in the same form, external packaging, shape, odour and texture, in order to maintain the double blinding“ Comment: effective double-blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ”treatment allocation and evaluation were assessed by a blinded physician“
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: ”The primary analysis was conducted on an intention-to-treat (ITT) basis on all randomised patients who received, at least once, the allocated treatments Comment: ITT analysis - 0 patients received no treatments
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	Quote: “in patients with multiple ulcers, only one ulcer was selected by the investigator (on the basis that it complied best with the inclusion criteria)” Comment: if allocation concealment/ blinding was effective this would not present a risk, allocation concealment has an unclear risk of bias, however
All domain risk of bias	Low risk	Low/unclear

Dimakakos 2009

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 9 weeks
Participants	Inclusion criteria: infected venous leg ulcer(s) with clinical signs of inflammation Exclusion criteria: pregnancy, psychiatric disorders, diabetes, collagen disease, steroid use, history of allergies, ABPI < 1 Participant characteristics Number participants: 42 Age; 61.2 vs 58.7 years N (%) male: 9 (43) vs 7 (33) Ulcer details Size: diameter = 2.37 cm vs 2.23 cm Duration: not reported
Interventions	Intervention 1 class: silver Intervention 1 details (name and details of application): Contreet Ag (Coloplast); dressing size 10 cm x 10 cm or 15 cm x 15 cm depending on ulcer size. Changed twice a week Intervention 2 class: foam Intervention 2 details (name and details of application): Biatain (Coloplast); dressing size 10 cm x 10 cm or 15 cm x 15 cm depending on ulcer size. Changed twice a week Compression: short-stretch bandage Other co-interventions: wounds cleansed with sterile water and 10% povidone iodine solution (Betadine, Lavipharm Hellas) prior to initial dressing
Outcomes	Intervention 1: 17/21 Intervention 2: 10/21
Notes	Funding type and details: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "forty-two patients were included in the study and were randomized into two groups." Comment: unclear whether an appropriate method was used to generate the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "forty-two patients were included in the study and were randomized into two groups." Comment: unclear whether an appropriate method was used to ensure allocation concealment

Dimakakos 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis
Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting was not sufficient to be certain
All domain risk of bias	Low risk	Low/unclear

Fogh 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: moderately to highly exuding, painful (at least 4 on 11 point scale) VLU on lower limb. Duration > 8 weeks, ABI > 0.8, size 1.6 cm to 11 cm in any direction. Treated with moist wound-healing dressings and compression for 2 weeks prior Exclusion criteria: use of per need medication in 3 days prior, painful ulcer resistant to analgesics for 6 months, hypersensitivity to study products, infection, vasculitis, erysipelas, cellulitis, contraindication to analgesics, diabetes, use of systemic antibiotics corticosteroids, immunosuppressants cancer chemotherapy, pregnancy or lactation Participant characteristics Number participants: 120 Age: 71.6 (12.8) vs 69.5 (12.5) years % male: 18 (30) vs 20 (33) Ulcer details Size: mean (SD) 9.1 (10.9) cm^2 vs 12.2 (9.4) cm^2, median (range) 4.82 (1.09 to 57.6) cm^2 vs 8.18 (0.93 to 40.1) cm^2 Duration: mean (SD) 1.5 (3.0) vs 11.5 (2.5) years
Interventions	Intervention 1 class: ibuprofen-releasing foam Intervention 1 details (name and details of application): Biatain Ibu Non-Adhesive (Coloplast) [foam] Intervention 2 class: foam

	Intervention 2 details (name and details of application); Biatain Non-Adhesive (Coloplast) Compression: use of compression mandatory, appropriate compression selected by investigator. No change in compression type during first 5 days of study. Actual compression used included short stretch (48% vs 50%), long stretch (32% vs 42%), 4 layer (5% vs 0%), other mainly compression stockings (15% vs 8%) Other co-interventions: not reported
Outcomes	Intervention 1: 9/60 Intervention 2: 11/60
Notes	Funding type: industry Funding details: Coloplast

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "by using the IVRS, the subjects were centrally randomized and allocated to one of the two treatment groups." Comment: external company randomised participants centrally using interactive voice response system. Stratification by pain intensity
Allocation concealment (selection bias)	Low risk	Quote: "by using the IVRS, the subjects were centrally randomized and allocated to one of the two treatment groups." Comment: appropriate methods to ensure allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "therefore, allocation of treatment to each patient was blinded to the clinicians, the patient, and the sponsor." Comment: blinding of relevant groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ulcer margins were traced on wound tracing sheets and ulcer area and perimeter were calculated at Coloplast A/S"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 12/60 vs 15/60 withdrawals, reasons given but a high number
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting

Fogh 2012 (*Continued*)

Other bias	Low risk	Comment: no evidence of other sources of bias and reporting sufficient to be reasonably confident
All domain risk of bias	High risk	

Gottrup 2008

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 42 days
Participants	Inclusion criteria: painful chronic venous leg ulcer > 8 weeks duration, diagnosis based on ABPI > 0.8, duplex scan/phlebography, clinical diagnosis, toe pressure and palpable foot pulse. Minimum length 1.6 cm, maximum area 50 cm². Minimum moderate pain score on 5-point verbal rating scale Exclusion criteria: painful ulcers resistant to analgesic treatment for 6+ months, pregnant or lactating women, clinical infection, local infection or bacterial imbalance, vasculitis, allergy to ibuprofen or related analgesics, history of asthma, rhinitis or urticaria, diabetes, use of various medications Participant characteristics Number participants:122 Age: 66.0 (14.8) vs 70.0 (11.7) years % male: 19 (31) vs 23 (38) Ulcer details Size: mean (SD) 11.0 (9.6) cm² vs 7.3 (5.7) cm² Duration: mean (SD) 23.1 (42.9) months vs 19.8 (41.8) months
Interventions	Intervention 1 class: ibuprofen Intervention 1 details (name and details of application): Biatain-Ibu Non-Adhesive foam dressing (Coloplast A/S); dressing changed every 48 hours Intervention 2 class: foam Intervention 2 details (name and details of application): Biatain Non-Adhesive (Coloplast A/S); dressing changed every 48 hours Compression: compression use required for 2 weeks prior to inclusion and throughout study period. Same compression to be used throughout and to keep a constant circumference at the ankle Other co-interventions: not reported
Outcomes	Intervention 1: 8/62 Intervention 2: 8/60
Notes	Funding type: industry Funding details: Coloplast A/S

Risk of bias

Gottrup 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization in closed envelopes took place after inclusion and before study initiation. The patients were randomized 1:1 either to the ibuprofen-foam group or to the comparator group. Block randomization was applied in blocks of 4." Comment: unclear how the blocked randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomization in closed envelopes took place after inclusion and before study initiation ... The randomization was carried out before packaging of the products, which were packed and labelled specifically for each patient due to the blinding." Comment: not completely clear how allocation concealment was achieved
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "study personnel and patients were blind to treatment" "both dressings were specially designed for this double-blind study to be anonymous with the use of topfilms without any print" Comment: blinding of these groups recorded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ulcer area was assessed with wound tracings of the ulcer margins at baseline, at days 15, 29, and at day 42. Wound healing was also tested using a linear healing parameter" Comment: it was not clear who performed the outcome assessment but since personnel were blinded it was likely to have been a blinded assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "there were 29 dropouts: 16 in the ibuprofen-foam group and 13 in the comparator group"; at 42 day crossover point these numbers were 15 vs 11 Comment: there were a substantial number of dropouts who were not included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: there was no evidence of selective reporting of outcomes

Gottrup 2008 (*Continued*)

Other bias	Low risk	Comment: there was no evidence of other bias and reporting was sufficient to be reasonably confident
All domain risk of bias	High risk	

Greguric 1994

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: until healing or 10 dressings used but dressing changes were at different frequencies in the two groups (2.10 days vs 1.01 days)
Participants	Inclusion criteria: venous ulcer 2.5 cm to 5 cm diameter. Diagnosis based on medical history and ABPI > or = 0.9 Exclusion criteria: ulcer due to arterial insufficiency, rheumatoid arthritis, sickle cell disease, known sensitivity to treatment materials, malignant ulcers, malignant disease including use of antineoplastic agents, corticosteroid treatment > 5mg prednisolone daily, immune deficiency, use of immune suppressive drugs, pregnancy, conditions causing abnormal wound healing, those better treated by alternative regimen Participant characteristics Number participants: 110 Age: 61 (15) vs 61 (13) years % male: 21 (38) vs 24 (44) Ulcer details Size: not reported Duration: median (95% central range) 1737 (15902) days vs 1987 (12218) days
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Varihesive E; 10cm x 10cm dressing. Held in place with tubular gauze over lower leg. Changed before the softened area reached the edge of the dressing or when leakage occurred Intervention 2 class: magnesium sulphate paste Intervention 2 details (name and details of application): approximately 15 g magnesium sulphate paste spread into ulcer, Vaseline type ointment rubbed gently onto surrounding skin, then ulcer covered with approximately 6 pieces of sterile gauze Compression: two tubular bandages used to create toe-to-knee compression Other co-interventions: ulcer cleansed with mixture of normal saline and hydrogen peroxide solution and dried with sterile gauze
Outcomes	Intervention 1: 3/55 Intervention 2: 0/55
Notes	Funding type and details: not reported

Greguric 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: study described as randomised but no details given on how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "a sealed envelope with the next consecutive patient number was then opened to determine which dressing the patient had been randomized to receive" Comment: unclear whether envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears that all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: there was no evidence of selective reporting
Other bias	High risk	Comment: duration of study was 10 dressing changes and frequency of dressing change was different in the two groups
All domain risk of bias	High risk	

Hanft 2006

Methods	RCT Arms: 2 Unit of randomisation: unclear Unit of analysis: unclear Follow-up: 12 weeks
Participants	Inclusion criteria: ≥18 years; VLU ulcer area > 3 cm^2 but < 25 cm^2; ulcer open for > 1 month but < 18 months; ABI > 0.8, HbA1c < 10; free of clinical signs of infection Exclusion criteria: prior treatment with becaplermin or other topical recombinant therapy within 30 days; prior treatment with skin substitute or growth factor; significant acute or chronic disease; enzymatic debridement in previous 7 days

	Participant characteristics Number participants: 49 Age: not reported % male: not reported Ulcer details Size: mean 6.9 cm^2 vs 5.6 cm^2 Duration: mean 4.3 months vs 5.1 months
Interventions	Intervention 1 class: PMM silver Intervention 1 details (name and details of application): protease-modulating matrix + silver dressing + hydrocolloid dressing: collagen, silver & oxidised regenerated cellulose matrix dressing + hydrocolloid (Collagen/ORC + silver + Adaptic®) Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application); hydrocolloid dressing: non-adherent petrolatum impregnated dressing (Adaptic® (Johnson & Johnson)); (n = 27; duration 12 weeks) Compression: standardised compression therapy Other co-interventions: prior treatment: 1 week run in with standardised leg compression; debridement
Outcomes	Intervention 1: 14/22 Intervention 2: 16/27
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomized, prospective, open-label, multicenter, comparative trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized, prospective, open-label, multicenter, comparative trial" Comment: outcome assessors likely to be unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote from author communication: "intervention group 9% (2/22) did not complete the study, 1 was lost to follow up and 1 chose to withdraw. In the control group 11% (3/27) did not complete, 2 subjects died from severe AEs (unrelated to the

Hanft 2006 (*Continued*)

		study interventions) and one chose to withdraw." Healing risks were 64% and 59%
Selective reporting (reporting bias)	High risk	Limited reporting of results - some obtained from the author, but some protocol outcomes not reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists
All domain risk of bias	High risk	

Hansson 1998

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: exudating or sloughy venous leg ulcer 1 cm^2 to 100 cm^2 on lower leg Exclusion criteria: systolic ankle pressure < 80 mmHg or systolic ankle/arm index < 0.8, clinical infection in or around ulcer with redness and pain, diabetes, known sensitivity to study products, treatment with systemic antimicrobials or study product in week before trial, systemic corticosteroids or cytostatic drugs in 4 weeks before trial, disease that could affect ulcer healing, undergoing investigation of thyroid gland Participant characteristics Number participants: 153 Age: 74 vs 74 vs 72 years N (%) male: 48 (31) Ulcer details Size: 8.8 (11.9) cm^2 vs 10.7 (20.6) cm^2 vs 7.1 (7.1) cm^2 Duration: not reported
Interventions	Intervention 1 class: cadexomer iodine Intervention 1 details (name and details of application): cadexomer iodine paste Iodosorb (Perstorp AB); changed when moisture saturated Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): Duoderm E (ConvaTec); changed when leaking or saturated with fluid Intervention 3 class: nonadherent Intervention 3 details (name and details of application) paraffin gauze; Jelonet (Smith & Nephew); changed when leaking or saturated with fluid Compression: short stretch bandage; Comprilan (Beiersdorf AG) Other co-interventions: not reported
Outcomes	Intervention 1: 8/56 Intervention 2: 5/48

Hansson 1998 (*Continued*)

	Intervention 3: 7/49	
Notes	Funding type: industry Funding details: Perstorp Pharma	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to receive one of three treatments" Comment: no detail of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomized to receive one of three treatments" Comment: no information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants withdrawn due to reasons unrelated to efficacy were excluded from analysis (18%) but those who withdrew for reasons related to efficacy (11%) were included
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Unclear risk	There was no evidence of other sources but reporting was limited
All domain risk of bias	High risk	

Harcup 1986

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks (8 weeks, cross-over at 4 weeks)
Participants	Inclusion criteria: aged over 30, exuding chronic venous ulcers of lower limbs, not responding favourably to existing treatments Exclusion criteria: concomitant serious or life-threatening disease, suspected malignant change in ulcer, insulin-dependent diabetes, pregnancy, iodine-sensitivity, psychiatric disease, very low intelligence, dementia or other condition affecting patient compliance Participant characteristics Number participants: 72 Age: mean (range) 67.8 (40 to 85) years N (%) male: 22 (31) Ulcer details Size: 7.74 (1.04) cm^2 vs 9.08 (1.37) cm^2 Duration: mean (range) 16.9 (1 to 256) months
Interventions	Intervention 1 class: cadexomer iodine (CI) Intervention 1 details (name and details of application): cadexomer iodine microbeads; Iodosorb (Stuart Pharmaceuticals and Perstorp AB) applied to the whole ulcer area - at least 3 mm depth and covered with dry sterile dressing. CI replaced daily, ulcer cleaned using sterile wet swab, stream of water or saline and/or soaking Intervention 2 class: standard dressing (various) Intervention 2 details (name and details of application): "Dry dressing" or elastocrepe bandaging, Sofra-Tulle, Melolin, Polyfax ointment, Betadine ointment, Dermicel tape, Aserbine cream, Gamgee tissue, Flamazine cream, Tubigrip, bactigras. Generally a dry dressing plus support bandaging. Use of a topical antibacterial cleanser (e.g. Eusol) permitted Compression: support bandaging or stocking Other co-interventions: not reported
Outcomes	Intervention 1: 13/41 Intervention 2: 1/31
Notes	Funding type and details: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised to receive either standard dressing or CI" Comment: sequence generation methods were not reported.

Harcup 1986 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomised to receive either standard dressing or CI" Comment: allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: it appears that all participants were included in the 4 week analysis although two participants assigned to standard treatment received CI so were included in that group instead
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting of outcomes
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting insufficient to be sure
All domain risk of bias	Low risk	Low/unclear

Harding 2001

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: not reported in available copy Exclusion criteria: not reported in available copy Participant characteristics Number participants: 131 Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: hydrofibre Intervention 1 details (name and details of application): Aquacel (ConvaTec) frequency of dressing change according to clinical need, could be left up to 7 days

Harding 2001 (*Continued*)

	Intervention 2 class: alginate Intervention 2 details (name and details of application): Sorbsan (Maersk) frequency of dressing change according to clinical need, could be left up to 7 days Compression: Class 3c bandage (SurePress, ConvaTec Ltd) over orthopaedic padding Other co-interventions: if wound became infected, systemic antibiotic prescribed and, if in alginate group, dressing changed daily
Outcomes	Intervention 1: 17/66 Intervention 2: 17/65
Notes	Funding type and details: industry Funding details: Convatec Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "an open, prospective, randomized, controlled, multicenter evaluation" Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "an open, prospective, randomized, controlled, multicenter evaluation" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "an open, prospective, randomized, controlled, multicenter evaluation" Comment: The trial had an open design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "an open, prospective, randomized, controlled, multicenter evaluation" Comment: the trial had an open design
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appeared that all participants were included in the ITT analysis
Selective reporting (reporting bias)	Low risk	Comment: there was no evidence of selective outcome reporting
Other bias	Unclear risk	Comment: there was no evidence of other sources of bias but the reporting was insufficient to be sure
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Hokkam 2011

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 8 weeks
Participants	Inclusion criteria: single chronic venous leg ulcer (clean and with healthy granulation tissue) Exclusion criteria: allergy to phenytoin, Marjolin's ulcers, ulcers with infected gangrene, multiple ulcers, surgery within previous 6 months Participant characteristics Number participants: 104 Age: 47.3 (6.4) vs 45.9 (3.8) years N (%) male: 21 (38.9) vs 21 (42) Ulcer details Size: 5.7 (2.8) cm^2 vs 6.1 (3.1) cm^2 Duration: 3.1 (1.3) weeks vs 3.9 (1.0) weeks
Interventions	Intervention 1 class: phenytoin Intervention 1 details (name and details of application): phenytoin lotion; thin layer of phenytoin applied then covered with gauze. Daily dressing Intervention 2 class: placebo Intervention 2 details (name and details of application) placebo unclear, saline stated, possibly covered with gauze Compression: compression bandage Other co-interventions: oral phlebotrophic drug (Diosmin). Washed with normal saline
Outcomes	Intervention 1: 35/54 Intervention 2: 26/50
Notes	Funding type and details: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the study was carried out as randomized controlled trial." "they were divided into study group and control group using coin flipping technique" Comment: Coin toss represents an adequate method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "the study was carried out as randomized controlled trial." Comment: no information on how allocation was concealed

Hokkam 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was no information on this
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the ulcer status was assessed every week and at the end of the eight weeks the ulcer's condition was evaluated as complete healing, partial healing, no improvement and worsening" Comment: no information on who performed the evaluation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were evaluated
Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting.
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting insufficient to be certain
All domain risk of bias	Low risk	Low/unclear

Humbert 2013

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 60 days
Participants	Inclusion criteria: venous or mixed leg ulcers, present for 2 months to 4 years, 5 cm^2 to 40 cm^2, no necrotic tissue, history/evidence of DVT or post-thrombotic syndrome, post-phlebitic sequels, reflux on venous system, ABPI 0.8+. No use of HA in previous 3 months. Use of compression device. If several, target ulcer selected Exclusion criteria: ulcer of non-vascular or general cause, diabetes, arterial insufficiency (ABPI < 0.8), hepatic or renal failure, recent history of venous thrombosis (< 3 months) , pregnancy or breastfeeding, allergy to local anaesthetic or study materials, treatment delaying healing process Participant characteristics Number participants: 89 Age: mean (SEM) 59.4 (2.5) vs 64.1 (2.7) years N (%) male: 25 (55.6) vs 20 (45.5) Ulcer details Non VLU - not clear Size: Mean (SEM) 13.8 (1.3) cm^2 vs 12.9 (1.3) cm^2 Duration: Mean (SD) 12.4 (12.3) vs 12.8 (12.2) months

Humbert 2013 (*Continued*)

Interventions	Intervention 1 class: hyaluronic acid (HA) Intervention 1 details (name and details of application): 0.05% hyaluronic acid impregnated cotton gauze pad, Ialuset (Laboratoires Genevrier), pad applied then covered with sterile gauze and appropriate bandage. Changed daily Intervention 2 class: placebo Intervention 2 details (name and details of application): neutral vehicle pad; Ialuset without HA (Laboratoires Genevrier); pad applied then covered with sterile gauze and appropriate bandage. Changed daily Compression: type 2 compression with long stretching elastic bandage (> 96% participants) Other co-interventions: surgical wound excision procedures, systemic analgesia, systemic antibiotics used if necessary
Outcomes	Intervention 1: 17/45 Intervention 2: 7/43
Notes	Funding type and details: industry Funding details: Laboratoires Genevrier

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "for each patient included in the study, a target ulcer was selected by the investigator and randomly assigned to be locally treated" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "for each patient included in the study, a target ulcer was selected by the investigator and randomly assigned to be locally treated Comment: unclear how the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind clinical trial" Comment: it was not clear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind clinical trial" Comment: it was not clear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All except one participant, who died, were included in the analysis

Humbert 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	High risk	Unclear how the investigator selected the target ulcer; potential for bias here given the lack of clarity over risk of selection bias
All domain risk of bias	High risk	

Ivins 2006

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks
Participants	Inclusion criteria: chronic venous or mixed venous/arterial e.g. ulcers with delayed healing Exclusion criteria: not reported Participant characteristics Number participants: 45 Age: not reported % male: not reported Ulcer details Non VLU - unclear how many mixed venous/arterial ulcers Size: not reported Duration: not reported
Interventions	Intervention 1 class: silver Intervention 1 details (name and details of application): not reported Intervention 2 class: foam Intervention 2 details (name and details of application): not reported Compression: not reported Other co-interventions: not reported
Outcomes	Intervention 1: 2/25 Intervention 2: 1/20
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "[the patients] were re-randomised to receive treatment with either the silver foam or the non-silver foam"

Ivins 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	Abstract only so limited reporting
Other bias	Unclear risk	Not enough information to judge
All domain risk of bias	Low risk	Unclear

Jull 2008

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous ulcer (ankle brachial pressure index > 0.8) or mixed venous/arterial ulcer (ankle brachial pressure index > 0.7), can tolerate compression Exclusion criteria: history of diabetes, rheumatoid arthritis or peripheral arterial disease, allergy to calcium alginate or Manuka honey, already using honey treatment Participant characteristics Number participants: 368 Age: 66.9 (17.5) vs 68.3 (17.1) years N (%) male: 91 (48) vs 89 (49) Ulcer details Non VLU: 2 (1%) vs 5 (3%) mixed Size: median (range) 2.7 (0.1 to 193) cm^2 vs 2.6 (0.2 to 81) cm^2 Duration: median (range) 20 (3 to 688) weeks vs 16 (2 to 999) weeks
Interventions	Intervention 1 class: honey Intervention 1 details (name and details of application): Manuka-honey-impregnated calcium alginate; Apinate UMF 12+ (Comvita New Zealand); changed at frequency determined by clinical need Intervention 2 class: standard care Intervention 2 details (name and details of application): usual care; various dressings (alginate, hydrofibre, hydrocolloid, foam, hydrogel, nonadherent, iodine, silver); dressing dependent on local availability and as deemed appropriate by district nurse

	Compression: all received compression bandaging varying according to range available at study centres and nurse/patient choice Other co-interventions: not reported
Outcomes	Intervention 1: 104/187 Intervention 2: 90/181
Notes	Funding type: Mixed Funding details: Funding both non-industry (Health Research Council of New Zealand) and industry (Comvita New Zealand, USL Medical)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomly assigned to one of two groups by an independent central telephone service; The allocation sequence was stratified by study centre and the Margolis index using minimization." Comment: appears that an appropriate method was used to generate the randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "participants were randomly assigned to one of two groups by an independent central telephone service" Comment: appears that appropriate methods were used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "this open-label, multicentre randomized controlled trial" Comment: the trial was open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the primary outcome measure was….Determined by the research nurse. The research nurse was not blind to allocation" Comment: unblinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the ITT analysis
Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting
Other bias	Low risk	There was no evidence of other potential sources of bias

Jull 2008 (*Continued*)

All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Jørgensen 2005

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks
Participants	Inclusion criteria: moderately or highly exuding, chronic venous or mixed venous/arterial leg ulcer with delayed healing (0.5 cm^2 or less area reduction) and at least one sign of critical colonisation (increased exudate, increased pain, discolouration of granulation tissue, foul odour) in past 4 weeks, ABI > 0.65, compression therapy for past 4 weeks, ulcer dimension > 2 cm^2 and fitting within 10x10cm dressing with 1.5 cm edge Exclusion criteria: clinical infection including erysipelas and cellulitis of peri-ulcer skin, treatment with antiseptics or antibiotics from 1 week prior to inclusion, uncontrolled diabetes, treatment with systemic corticosteroids > 10 mg/day, immunosuppressants from 4 weeks prior to inclusion, diseases that may interfere with ulcer healing Participant characteristics Number participants: 129 Age: median (range) 72.0 (40 to 99) vs 75.5 (42 to 90) years N (%) male: 21(32) vs 26 (41) Ulcer details Non VLU - not clear Size: median (range) 6.1 (1.1 to 53.4) cm^2 vs 6.7 (1.3 to 50.6) cm^2 Duration: median (range) 1.1 (0.1 to 32.0) years vs 1.0 (0.1 to 10.0) years
Interventions	Intervention 1 class: silver Intervention 1 details (name and details of application): silver foam; Contreet (Coloplast) ; dressing changes left as long as clinically possible - max 7 days Intervention 2 class: foam Intervention 2 details (name and details of application): Allevyn (Smith & Nephew) Compression: mandatory compression (according to clinical practice of treatment centre) Other co-interventions: wound cleansed with sterile saline or tap water at dressing changes. When necessary, peri-ulcer area treated with mild zinc cream (Conveen) or topical steroid ointment
Outcomes	Intervention 1: 5/65 Intervention 2: 5/64
Notes	Funding type and details: industry Funding details: Coloplast A/S

Risk of bias

Jørgensen 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised ... by computer-generated randomisation" Comment: appropriate method of randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomised ... by computer-generated randomisation" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants included in ITT analysis, PP analysis also performed excluding participants withdrawn for protocol violation
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Low risk	There was no evidence of other forms of bias
All domain risk of bias	Low risk	Low/unclear

Kalis 1993

Methods	RCT Arms: 2 Unit of randomisation: unclear Unit of analysis: ulcer Follow-up: 56 days
Participants	Inclusion criteria: leg ulcer of venous or mixed origin Exclusion criteria: not reported Participant characteristics Number participants: 89 participants with 109 ulcers Age: not reported % male: not reported Ulcer details Non VLU - some unknown

Kalis 1993 (*Continued*)

	Size: not reported Duration: not reported
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex Intervention 2 class: dextranomer Intervention 2 details (name and details of application): paste covered by dressing and cotton band Compression: not reported Other co-interventions: not reported
Outcomes	Intervention 1: 13/54 Intervention 2: 10/54
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "we carried out an open, comparative and randomised good clinical practice (GCP) trial" Comment: no information on how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "we carried out an open, comparative and randomised good clinical practice (GCP) trial" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we carried out an open, comparative and randomised good clinical practice (GCP) trial" Comment: open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "we carried out an open, comparative and randomised good clinical practice (GCP) trial" Comment: open trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "drop-outs were more frequent in the dextranomer group (10 cases), due to deterioration (2 patients), clinical infection (3), cutaneous reaction (4), or pain (1); in the Granuflex group (2 cases): 0, 0, 2 and 0 patients, respectively"

Kalis 1993 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine
Other bias	High risk	Unclear if there is a difference between the unit of randomisation and the unit of analysis; potential for unit of analysis issues very unclear
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Kelechi 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 20 weeks
Participants	Inclusion criteria: people aged 21+ with partial-thickness venous ulcer, diagnosed in previous 4 weeks, size 2 cm^2 to 20 cm^2, no recent skin grafts or use of growth factors, viable clean wound bed 90% free of necrotic debris Exclusion criteria: full thickness ulcers extending beyond dermis, infection, ABI < 0.8 or > 1.3, duration > 6 months, history of collagen vascular disease, severe arterial disease, organ transplant, Charcot disease, sickle cell disease, radiation therapy, haemodialysis, pregnant Participant characteristics Number participants: 82 Age: 59 (13.5) vs 63.2 (14.8) vs 60.8 (12.2) vs 63.0 (15.3) years N (%) male: 5 (25) vs 13 (59.1) vs 13 (65) vs 10 (50) Ulcer details Size: mean (SD) 12.1 (11.3) cm^2 vs 9.8 (7.3) cm^2 vs 10.5 (10.3) cm^2 vs 12.8 (12.0) cm^2 Duration: mean (SD) 3.4 (1.5) months vs 3.6 (1.8) months vs 2.7 (2.1) months vs 2.7 (1.6) months
Interventions	Intervention 1 class: nanofibre matrix Intervention 1 details (name and details of application): pG1cNAc nanofibre matrix (Talymed, Marine Polymer Technologies) applied once + nonadherent dressing (Mepilex, Molnlycke HealthCare) Intervention 2 class: nanofibre matrix Intervention 2 details (name and details of application): pG1cNAc nanofibre matrix (Talymed, Marine Polymer Technologies) applied every other week + nonadherent dressing (Mepilex, Molnlycke HealthCare) Intervention 3 class: nanofibre matrix Intervention 3 details (name and details of application): pG1cNAc nanofibre matrix (Talymed, Marine Polymer Technologies) applied every third week + nonadherent dressing (Mepilex, Molnlycke HealthCare) Intervention 4 class: nonadherent

	Intervention 4 details (name and details of application): Mepilex (Molnlycke Health Care) Compression: zinc oxide impregnated bandage (Viscopaste PB7, Smith & Nephew), cotton padding wrap, self-adherent elastic wrap (Coban, 3M) Other co-interventions: wound cleaned with saline, patted dry with gauze, moisture barrier applied
Outcomes	Intervention 1: 9/20 Intervention 2: 19/22 Intervention 3: 13/20 Intervention 4: 9/20
Notes	Funding type: industry Funding details: supported by Marine Polymer Technologies Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization to treatment groups after informed consent, eligible patients were randomly assigned to 1 of 4 study arms using computer-generated, stratified, permuted block randomization" Comment: appropriate generation of randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "randomization was stratified by site to ensure equal subject allocation across the 4 treatment arms. Block size was randomly varied to minimize the likelihood that study nurses could guess the next allocation on the basis of previous allocations" Comment: appears that central allocation took appropriate steps to ensure concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "patients and certified wound care nurses, who provided wound treatment and applied the wound-healing product, were not blinded to subject group assignment" Comment: neither participants nor personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quotes: "randomized, investigator-blinded, parallel group, controlled trial" "study nurses measured wound length and width at each visit"

Kelechi 2012 (*Continued*)

		Comment: it is not clear whether the unblinded study nurses or the blinded investigators determined outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "82 subjects were randomly assigned to one of the 4 study groups, and 71 completed the study. Seven subjects were lost to follow-up and 4 subjects who developed systemic infections were withdrawn" Comment: an ITT analysis was performed with clear procedures for dealing with data from participants lost to follow-up
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	

Kucharzewski 2013

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 16 weeks (data extracted at 7 weeks)
Participants	Inclusion criteria: chronic venous ulcer due to primary varicosis Exclusion criteria: not reported Participant characteristics Number participants: 58 Age: 65.3 (9.1) vs 66.9 (6.4) years N (%) male: 11 (37) vs 10 (36) Ulcer details Size: mean (range) 8.52 (7.02-9.89) cm^2 vs 8.29 (7.02-10.1) cm^2 Duration: mean (range) 2.5 (1.2-3.4) years vs 2.4 (1.1- 3.6) years
Interventions	Intervention 1 class: silver Intervention 1 details (name and details of application): silver membrane plus gauze; Texts Bioactiv (Biocell); ulcer washed with Ringer's solution before application of silver membrane, then gauze pads and elastic bandage. Dressing rinsed several times daily with Ringers. External dressing changed daily, membrane every 7 days Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): hydrocolloid with Unna's boot, applied after saline rinse, changed every 7 days Compression: all received compression therapy Other co-interventions: wounds were bathed in detergent (pH 5.5), washed with saline and rinsed with Octenisept, surgically cleaned, washed with saline and covered with an

Kucharzewski 2013 (*Continued*)

	Octenisept compress
Outcomes	Intervention 1: 30/30 Intervention 2: 6/28
Notes	Funding type and details: not reported Notes: Data reported for healing curve; time point selected

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were divided randomly .. ." Comment: no information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were divided randomly .. ." Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed until healing
Selective reporting (reporting bias)	High risk	There was no defined endpoint
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting was insufficient to be confident
All domain risk of bias	High risk	

Lanzara 2008

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous leg ulcers Exclusion criteria: not reported Participant characteristics Number participants: 30 Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: PMM silver Intervention 1 details (name and details of application): PMM + silver dressing + foam dressing - collagen, silver & oxidised regenerated cellulose matrix dressing + hydropolymer foam (Collagen/ORC + silver (Systagenix) + Tielle Family® (Systagenix) + Tielle Family® (Systagenix)): dressing changes every week; (n = 15; duration 12 weeks) Intervention 2 class: foam Intervention 2 details (name and details of application): foam dressing (Tielle Family® (Systagenix)); (n = 15; duration 12 weeks) Compression: short stretch multilayer compression for all Other co-interventions: not reported
Outcomes	Intervention 1: 11/15 Intervention 2: 7/15
Notes	Funding type: industry Funding details: appears to be Systagenix Notes: poster presentation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients... were randomized" Comment: no information on how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients... were randomized" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: dressings were sufficiently different for participants and personnel to be unblinded - two dressings versus one dress-

Lanzara 2008 (*Continued*)

		ing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "study duration was 12 weeks, with dressing changes every week as well as measurements on wound size and assessment of wound appearance" Comment: implication that outcome assessors were also responsible for dressing changes, who were not blinded as above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Apparently no missing data, but no details
Selective reporting (reporting bias)	Low risk	Unclear reporting. Some results (healing) only reported on the Systagenix website
Other bias	High risk	Baseline differences in ulcer size: 6 cm^2 versus 9 cm^2
All domain risk of bias	High risk	

Leaper 1991

Methods	RCT Arms: 2 Unit of randomisation: unclear Unit of analysis: ulcer Follow-up: 12 weeks; cross-over of some participants at 6 weeks
Participants	Inclusion criteria: leg ulcers, community or hospital based Exclusion criteria: critically Ischaemic vascular disease (Doppler index < 0.5), insulin-dependent diabetes, terminal illness Participant characteristics Number participants: 76 participants with 94 ulcers Age: 75.0 (10.4) vs 73.8 (9.8) years % male: 17 (45) vs 11 (29) Ulcer details Non VLU: unclear - "the majority of leg ulcers were of venous origin" Size: 15.9 (38.3) cm^2 vs 19.4 (31.4) cm^2 Duration: range 2 weeks to 43 years "the durations of the ulcer existence were similar in the two dressing groups"
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Comfeel Ulcer Dressing (Coloplast); dressing covered minimum 2 cm rim of skin around ulcer. Changed every 2-3 days during debridement stage, 3 to 4 days during healthy granulation, 5 to 7 days during epithelialisation and contraction Intervention 2 class: nonadherent

	Intervention 2 details (name and details of application): gauze (paraffin-impregnated); Jelonet (Smith & Nephew); dressing covered minimum 2cm rim of skin around ulcer. Changed every 2 to 3 days during debridement stage, 3 to 4 days during healthy granulation, 5 to 7 days during epithelialisation and contraction Compression: venous leg ulcers (Doppler index > 0.7) used Venosan bandages Other co-interventions: irrigation and wash with sterile saline solution and cotton wool soaks before dressing. Some ulcers required surgical debridement
Outcomes	Intervention 1: 14/46 Intervention 2: 3/48
Notes	Funding type: industry Funding details: Coloplast

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "a clinical assessment was made for each patient ... prior to randomization to a treatment group, with stratification" Comment: no details of sequence generation method
Allocation concealment (selection bias)	Unclear risk	Quote: "a clinical assessment was made for each patient ... prior to randomization to a treatment group, with stratification" Comment: no details of allocation concealment given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information reported for all participants/ulcers
Selective reporting (reporting bias)	Unclear risk	There is no evidence of selective reporting but it is not clearly reported enough to be sure
Other bias	High risk	There is strong potential for a unit of analysis issue as it appears that randomisation was at the participant level but that analysis was at the level of the ulcer

Leaper 1991 (*Continued*)

		There was cross-over at 6 weeks for some but not all participants; they were analysed in the groups to which they were randomised however
All domain risk of bias	High risk	

Lindsay 1986

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks - but see notes
Participants	Inclusion criteria: female, over 30, chronic exuding venous ulcer(s) of lower limbs, not responding favourable to existing treatments Exclusion criteria: concomitant serious or life-threatening disease, suspected malignant change in ulcer, insulin-dependent diabetes, pregnancy, iodine sensitivity, psychiatric disease, very low intelligence, dementia or other condition affecting patient compliance Participant characteristics Number participants: 28 Age: mean (range) 66.7 (52 to 90) years % male: 0 Ulcer details Size: not reported Duration: mean 20.1 months
Interventions	Intervention 1 class: cadexomer iodine (CI) Intervention 1 details (name and details of application): Iodosorb (Stuart Pharmaceuticals and Perstorp AB); cadexomer iodine applied to whole ulcer surface to depth of at least 3mm and wound covered with dry sterile dressing. Changed on alternate days. CI removed using sterile wet swab or stream of water or saline or soaking Intervention 2 class: standard care Intervention 2 details (name and details of application): various, generally sterile non-adherent dressing including Terra-Sortril, povidone iodine, Savlon, Bactigras, Melolin, Sofra Tulle, crepe bandage, elastocrepe bandage; changed on alternate days Compression: see other co-interventions Other co-interventions: "dressing secured with support bandaging or stocking as required" (cadexomer iodine and most of the standard treatment)
Outcomes	Intervention 1: 4/14 Intervention 2: 1/14
Notes	Funding type and details: industry Funding details: Stuart Pharmaceutical Notes: 10 week trial but optional cross-over at 4 weeks so main analysis applied at this point (with numbers N = 12 vs N = 13). 1 participant was removed from demographic data - her ulcer duration was "60+". It is not clear whether the healing data refer to the

Lindsay 1986 (*Continued*)

	4 weeks time point	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised to receive either standard dressing or CI" Comment: no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomised to receive either standard dressing or CI" Comment: no details of allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many participants had dropped out and for what reason - 4 weeks analysis appears to include 25/28 participants
Selective reporting (reporting bias)	Unclear risk	Unclear whether outcomes were pre-specified
Other bias	Unclear risk	No evidence of other bias but reporting insufficient to be confident
All domain risk of bias	Low risk	Low/unclear

Luiza 2015

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: ulcer Follow-up: 12 weeks
Participants	Inclusion criteria: leg ulcer(s) of at least 6 weeks duration Exclusion criteria: infected ulcer, erysipelas, cellulitis, lymphangitis, devitalized tissue covering wound bed, circular limb lesions, non-palpable distal pulse, alcoholism or psychiatric disease, liver or kidney problems, allergy to study materials or latex

	Participant characteristics Number participants: 21 participants (data reported for 18 completers and 28 ulcers) Age: all: 61.94 (12.5) range 45 to 85; grouped: < 60 years 40% vs 50%, > 60 years 60% vs 50% % male: 4 (40) vs 5 (62.5) Ulcer details Non VLU: unclear Size: not reported Duration: not reported by group > 10 years 53.6%, 7 to 10 years 3.6%, 4 to 6 years 32.1%, < 3 years 10.7%
Interventions	Intervention 1 class: papain Intervention 1 details (name and details of application): 2% papain gel developed at university pharmacy Intervention 2 class: placebo Intervention 2 details (name and details of application): 2% carboxymethyl cellulose gel developed at university pharmacy Compression: not reported Other co-interventions: dressing kit contained gauze, bandage, 0.9% saline solution, soothing solution for the skin surrounding the lesion
Outcomes	Intervention 1: 2/16 Intervention 2: 0/12
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "for the sake of randomization a research collaborator used a table with random numbers" Comment: appropriate method of allocation concealment
Allocation concealment (selection bias)	Unclear risk	Quote: "the study participants were only informed about which group the patient would be allocated to at the moment of each volunteer's first consultation" Comment: it was unclear whether allocation was also concealed from personnel
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the blinding of the participants and researchers was compromised due to the product characteristics" Comment: appears that unblinding occurred

Luiza 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the evaluators of the result, who carried out the statistical analysis of the data, were blinded" Comment: appears that outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three participants (unknown number of ulcers) did not complete; 1 in the intervention group and 2 in the control group. Because the number of ulcers is unknown the impact on the estimate is unclear
Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting
Other bias	High risk	There is a probable unit of analysis issue because randomisation took place at the level of the participant while analysis took place at the level of the ulcer
All domain risk of bias	High risk	

Meaume 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 8 weeks
Participants	Inclusion criteria: venous leg ulcer, 5 cm^2 to-50 cm^2, 6 to 36 month duration, ABPI 0.8-1.3, at least 50% wound bed covered with granulation tissue without any black necrotic tissue. If multiple ulcers, the one best meeting selection criteria was selected (had to be at least 3 cm from other wounds) Exclusion criteria: infection requiring systemic antibiotics, known sensitivity to carboxymethylcellulose, venous surgery in previous 2 months, DVT in previous 3 months, concomitant severe comorbid disease or poor health status, malignant wound degeneration, treatment with immunosuppressive agents or high-dose corticosteroids Participant characteristics Number participants: 187 Age: 72.6 (13.0) vs 74.4 (12.1) years % male: 31 (33.3) vs 34 (36.2) Ulcer details Size: mean (SD) 17.0 (15.6) cm^2 vs 16.6 (15.8) cm^2, median (range) 12.9 (2.3 to 86.9) cm^2 vs 10.5 (2.7 to 85.3) cm^2 Duration: mean (SD) 15.6 (9.1) vs 15.1 (8.7) months, median (range) 12 (3 to 35) vs 12 (6 to 36) months

Meaume 2012 (*Continued*)

Interventions	Intervention 1 class: PMM Intervention 1 details (name and details of application): Urgostart (Laboratoires Urgo) Intervention 2 class: foam Intervention 2 details (name and details of application): Urgotul Absorb (Laboratoires Urgo) Compression: "an appropriate compression therapy system, according to patient and ulcer status, was selected and applied by the investigating physician" Other co-interventions: not reported
Outcomes	Intervention 1: 6/93 Intervention 2: 7/94
Notes	Funding type: industry Funding details: Laboratoires URGO

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomization code was generated in blocks of two using a computer program and was stratified by center" Comment: computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "Individual sterile dressings were packed in boxes of 35 dressings per participant. Each box and dressing was identified by a center identification number and participant number corresponding to the chronological participant inclusion number... the procedure to break the randomization code was not provided to the participating centers" Comment: probably sufficient for low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both dressings were identical in appearance, shape, color and packaging ... they could be used in a double-blind trial" "the procedure to break the randomization code was not provided to the participating centers" Comment: appears personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the VLU was evaluated by the investigating physician ... at each visit, the

Meaume 2012 (*Continued*)

		wound evaluations were repeated (clinical assessment, acetate tracing, and wound photo)" Comment: double-blind trial and outcome assessors were the investigators
Incomplete outcome data (attrition bias) All outcomes	High risk	4/93 (4%) and 6/94 (6%) withdrew and were lost to follow-up. An additional 11/93 (12%) and 11/94 (12%) switched to "another" dressing, but were followed up in the groups to which they were randomised. Number missing comparable with number of events for healing (6 and 7)
Selective reporting (reporting bias)	Unclear risk	High risk for outcomes other than healing; unclear whether there may be issues with the healing reporting
Other bias	Unclear risk	Potential for baseline differences between groups but unclear what the impact of these would be
All domain risk of bias	High risk	

Meredith 1988

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: leg ulcer diagnosed clinically as due to venous insufficiency. All clinic attendees eligible, including diabetics Exclusion criteria: treatment with Jelonet or Granuflex in previous 2 weeks, treatment with systemic corticosteroids exceeding 0.5 mg/day, malignant ulcer, obvious peripheral arterial ischaemia Participant characteristics Number participants: 50 (49 reported on) Age: mean (range) 70.4 (32 to 92) years % male: 15 (30) Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex; applied to extend at least 3cm beyond ulcer margin. Changed weekly, or sooner if exudate leaked

Meredith 1988 (*Continued*)

	Intervention 2 class: nonadherent Intervention 2 details (name and details of application): paraffin gauze; Jelonet; applied to cover the ulcer then cotton dressing gauze pad placed over and secured with micropore tape. Changed when exudate penetrated to outer layers of dressings Compression: support bandaging with elastocrepe or non-shaped Tubigrip Other co-interventions: ulcers cleaned with saline and/or povidone iodine
Outcomes	Intervention 1: 19/25 Intervention 2: 6/25
Notes	Funding type: not reported Funding details: not reported but Squibb Surgicare employees listed in acknowledgements

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "they were randomised to either of the two treatments according to a table of random numbers held by ourselves" Comment: appropriate method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "they were randomised to either of the two treatments according to a table of random numbers held by ourselves" Comment: unclear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrew and was excluded from results but this is unlikely to have impacted the estimate of effect
Selective reporting (reporting bias)	Unclear risk	Not clear which outcomes were pre-specified
Other bias	Unclear risk	No evidence of other bias but reporting insufficient to be certain
All domain risk of bias	Low risk	Low/unclear

Michaels 2009

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: leg (1 limb/participant designated as index) Follow-up: 12 weeks
Participants	Inclusion criteria: ulceration of lower leg present for > 6 weeks. If ulceration on both legs, that with greater ulcer area was index limb Exclusion criteria: insulin-controlled diabetes, pregnancy, sensitivity to silver, ABPI < 0. 8, ulcer with maximum diameter < 1 cm, atypical ulcers, oral or parenteral antibiotics Participant characteristics Number participants: 213 (107 vs 106), 208 included in results Age: 68.8 (16.7) vs 72.4 (13.7) years % male: 54 (50) vs 44 (42) Ulcer details: Size: > 3 cm: 30 (28%) vs 30 (28%), < 3 cm 77 (72%) vs 76 (72%) Duration: not reported
Interventions	Intervention 1 class: silver Intervention 1 details (name and details of application): choice of Aquacel Ag (ConvaTec), Acticoat, Acticoat 7, Acticoat Absorbent (all Smith & Nephew), Contreet Foam (Coloplast), Urgotul SSD (Urgo); dressings changed on weekly basis (or sooner if judged necessary) Intervention 2 class: nonadherent Intervention 2 details (name and details of application): Urgotul, Biatain (Coloplast) , Atrauman (Paul Hartmann Ltd), Allevyn (Smith & Nephew); dressings changed on weekly basis (or sooner if judged necessary) Compression: multilayer compression bandaging Other co-interventions: debridement if clinically appropriate
Outcomes	Intervention 1: 62/104 Intervention 2: 59/104
Notes	Funding type and details: non-industry Funding details: HTA (NIHR)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "treatment allocation ... was carried out using a computer program to generate stratified block randomisation with variable block size" Comment: appropriate methods of sequence generation

Michaels 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "trial numbers and randomisation were allocated through a telephone-based service" Comment: appropriate method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "it was not possible to blind either the patients or the nurses applying the dressings" Comment: neither participants nor personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the staff measuring ulcers sizes based upon tracings ... were all blinded to the treatment allocation of the patient" Comment: blinded outcome assessment reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the analysis. This is unlikely to have affected the treatment effect
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	

Moffatt 1992a

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous ulcer that had failed to heal within 24 weeks of high compression therapy or had failed to reduce in size by more than 20% within 12 weeks Exclusion criteria: arterial disease (ABI < 0.8), known allergy to study products Participant characteristics Number participants: 60 Age: median (range) 74 (50 to 89) vs 71 (26 to 87) years % male: 15 (50) vs 12 (40) Ulcer details Size: median (range) 7.3 (1.3 to 66.3) cm² vs 6.7 (2.6 to 14.9) cm^2 Duration: not reported

Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Comfeel (Coloplast) Intervention 2 class: nonadherent Intervention 2 details (name and details of application): not reported Compression: 4 layer bandage technique Other co-interventions: not reported
Outcomes	Intervention 1: 13/30 Intervention 2: 7/30
Notes	Funding type and details: industry Funding details: Comfeel Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization took place by assigning sequential numbers to each patient as they entered the trial, and relating this number to a randomization group" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomization took place by assigning sequential numbers to each patient as they entered the trial, and relating this number to a randomization group" Comment: unclear how allocation concealment was carried out
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "patients were followed up to 12 weeks with the exception of four patients, two of whom refused to continue with the treatment, and two patients who died within the 12-week period" Comment: it was not clear to which group participants who were not followed up were assigned

Moffatt 1992a (*Continued*)

Selective reporting (reporting bias)	Low risk	The main endpoint was specified and reported
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting was insufficient to be confident of this
All domain risk of bias	Low risk	Low/unclear

Moffatt 1992b

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: Venous leg ulcer with surface area < 10 cm² Exclusion criteria: ABPI < 0.8 (arterial component to ulcer) Participant characteristics Number participants: 60 Age: median (range) 78 (44 to 88) vs 70 (38 to 88) years % male: 10 (33) vs 13 (44) Ulcer details Size: median (range) 3.6 (0.9 to 9.8) cm² vs 6.4 (1.1 to 9.9) cm² Duration: median (range) 2.0 (1 to 192) vs 3 (1 to 20) (units not reported - months?)
Interventions	Intervention 1 class: alginate Intervention 1 details (name and details of application) Tegagel (3M); Dressing changed weekly unless excessive exudate or infection Intervention 2 class: nonadherent Intervention 2 details (name and details of application): NA (Johnson & Johnson); Dressing changed weekly unless excessive exudate or infection Compression: Graduated compression bandage system- 40 mmHg2 at ankle Other co-interventions: not reported
Outcomes	Intervention 1: 26/30 Intervention 2: 24/30
Notes	Funding type: industry Funding details: 3M Health Care Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Moffatt 1992b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "patients were entered into the trial and randomised to either of the two dressing types" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were entered into the trial and randomised to either of the two dressing types" Comment: unclear how the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not reported on
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not reported on
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appeared to be included in the analysis.
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting; reporting was limited but the trial appeared designed to measure the outcome reported
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting was insufficient to be certain
All domain risk of bias	Low risk	Low/unclear

Moss 1987

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks (26 week trial with optional cross-over at 6 weeks)
Participants	Inclusion criteria: unresponsive leg ulcer of > 3 months duration which did not improve after 6 weeks observation on a variety of treatments. Venous insufficiency diagnosed by history of DVT or signs e.g. swelling, dermatosclerosis, pigmentation, atrophie blanche Exclusion criteria: not reported Participant characteristics Number participants: 42 (43 randomised, one dropped out and not included in analysis)

Moss 1987 (*Continued*)

	Age: median (SD) 70 (8) vs 68 (11) years % male: 6 (29) vs 3 (14) Ulcer details Size: median (SD) 19.7 (19.8) cm² vs 25.5 (29.5) cm² Duration: median (SD) 75 (127) months vs 61 (68) months
Interventions	Intervention 1 class: cadexomer iodine (CI) Intervention 1 details (name and details of application): Iodosorb; ulcer cleaned with saline, then filled with powder and covered with non-adhesive pad. Changed daily Intervention 2 class: dextranomer Intervention 2 details (name and details of application): Debrisan; ulcer cleaned with saline, then filled with powder and covered with non-adhesive pad. Changed daily Compression: see other co-interventions Other co-interventions: saline wash; treatment powder dressing covered with non adhesive pad, cotton-wool wadding, stockingnette and firm elastic bandage
Outcomes	Intervention 1: 0/21 at 6-week cross-over Intervention 2: 0/21 at 6-week cross-over
Notes	Funding type: industry Funding details: TIL (Medical) Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "those still not improving (n = 42) were randomly allocated to treatment with either dextranomer or CI" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "those still not improving (n = 42) were randomly allocated to treatment with either dextranomer or CI" Comment: unclear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "although the trial was not blind because the treatments can easily be distinguished by colour" Comment: trial not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "assessments [...] could not be blind because, even after the dressings were removed, difference in colour were still apparent"

Moss 1987 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant was not included in the analysis
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting of outcomes
Other bias	Low risk	There was no evidence of other sources of bias; it was not clear whether the cross-over was planned but this does not impact on the data before the cross-over point
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Nelson 2007

Methods	RCT Arms: 2 relevant groups (a 2 x 2 x 2 factorial design for compression and pentoxifylline also) Unit of randomisation: participant Unit of analysis: participant Follow-up: 24 weeks
Participants	Inclusion criteria: clinically diagnosed (clinical signs and Doppler confirmation of venous pathology) venous leg ulcer at least 1 cm length and 8 weeks duration Exclusion criteria: significant arterial disease (ABPI < 0.8), diabetes mellitus, pregnant or lactating women, known concurrent severe illness, sensitivity to methylxanthines or caffeine, using warfarin, steroids, oxpentifylline, oxerutins, Naftidrofuryl, life expectancy < 6 months, grossly infected or gangrenous ulcer, immobile, immunosuppression Participant characteristics Number participants: 245 Age: 70.3 (12.0) vs 69.7 (10.6) years % male: 43 (34) vs 37 (31) Ulcer details Size: mean (SD) 794 (1210) mm^2 vs 910 (2600) mm^2, median (range) 404 (50 to 10118) mm^2 vs 359 (63 to 26311) mm^2 Duration: mean (SD) 11.3 (25.0) months vs 14.8 (29.8) months, median (range) 4.0 (2 to 204) months vs 6.5 (2 to 240) months
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex E (ConvaTec), also known as Duoderm CGF; dressing changed weekly or more frequently if required Intervention 2 class: nonadherent Intervention 2 details (name and details of application): NA (Johnson & Johnson); dressing changed weekly or more frequently if required Compression: participants were randomised to either 4-layer bandage applied using Charing Cross technique or single layer hydrocolloid-lined, woven, elastomeric, adhesive

	bandage applied in figure-8 technique Other co-interventions: ulcers cleansed with tap water and skin moisturised with arachis or olive oil. Within factorial design participants were also randomised to receive pentoxifylline or placebo
Outcomes	Intervention 1: 72/127 Intervention 2: 69/118
Notes	Funding type and details: industry/mixed Funding details: "supported by Hoechst Roussel Ltd, ConvaTec UK Ltd and Chief Scientist Office, Scotland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was stratified by clinical center and simple/non simple venous disease using permuted blocks of length 8" Comment: likely that appropriate method used to generate sequence
Allocation concealment (selection bias)	Low risk	Quote: "sealed, sequentially numbered opaque envelopes were use to allocate participants" Comment: appropriate method used to ensure adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "both patients and nurses were aware of the allocated bandage and dressing after assignment" Comment: neither participants nor personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "nurses completed a dressing log at each leg ulcer dressing visit, which recorded whether or not an ulcer was healed" Comment: outcome assessed by unblinded nurses
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting and reporting was clear
Other bias	Low risk	There was no evidence of other sources of bias

Nelson 2007 (*Continued*)

All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Norkus 2005

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: up to 12 months
Participants	Inclusion criteria: highly exuding leg ulcer present for at least 4 weeks, maximum ulcer size 8 cm x 8 cm, ABPI $\geq$ 0.8. Largest ulcer used if more than one cm Exclusion criteria: clinical signs of wound infection, severe eczema, lymphatic or malignant ulcers, systemic treatment with corticosteroids other immunosuppressants during study or in 3 months prior Participant characteristics Number participants: 97 Age: median (range) 70 (33 to 89) vs 70 (29 to 97) years % male: 21 (43) vs 23 (48) Ulcer details Non VLU: 89.6% vs 93.5% venous, protocol violation meant some mixed (10.4% vs 4.4%) and arterial (0% vs 2.1%) were included Size: median (range) 9.3 cm^2 (0.9 to 38.1) cm^2 vs 6.4 cm^2 (0.5 to 51.4) cm^2 Duration: median (range) 1.0 (0.1 to 19.0) years vs 0.7 (0.1 to 27.0) years
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Alione (Coloplast A/S); Dressing changed when necessary (maximum 7 days) Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): Tielle and Tielle plus (Johnson & Johnson); Tielle Plus used at start of study, changing to Tielle when dressing changes required less than once per day. Dressing changed when necessary (maximum 7 days) Compression: those treated with compression at the start continued using it throughout study (36 (75%) vs 32 (68%) participants used it) Other co-interventions: ulcers cleaned and debrided if necessary according to normal practice at centre
Outcomes	Intervention 1: 25/49 Intervention 2: 19/48
Notes	Funding type and details: industry Funding details: Coloplast A/S

Risk of bias

Norkus 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the study used an open comparative block randomised multicentre design" Comment: appears very likely that appropriate sequence generation methods were used
Allocation concealment (selection bias)	Low risk	Quote: "the study used an open comparative block randomised multicentre design" Comment: appears that centralised allocation will have ensured concealed allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study used an open comparative block randomised multicentre design" Comment: an open design was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "after cleansing with water or isotonic saline, the ulcer was traced using planimetry, photographed and redressed" Comment: it was not clear who assessed healing but the open design means there is a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the statistical analysis was carried out as intention to treat (ITT) with last observation carried forward (LOCF)" Comment: ITT analysis
Selective reporting (reporting bias)	Low risk	All the specified outcomes were fully reported
Other bias	Low risk	There was no apparent risk of other bias and reporting was sufficient to be reasonably confident of this
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Ohlsson 1994

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: leg ulcer of venous or mixed aetiology Exclusion criteria: not reported Participant characteristics Number participants: 30 (28 analysed) Age: median (range) 76 (49 to 89) years % male: 4 (13) Ulcer details Non VLU: 4/14 (29%) vs 2/14 (14%) mixed venous/arterial (21% overall) Size: mean 1387 mm^2 vs 857 mm^2 Duration: not reported
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): changed once a week or more frequently if needed Intervention 2 class: saline gauze Intervention 2 details (name and details of application): changed once a week or more frequently if needed Compression: low-stretch compression bandage Other co-interventions: ulcers cleaned with soap and water
Outcomes	Intervention 1: 7/14 Intervention 2: 2/14
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomly allocated ..." Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "the patients were randomly allocated ..." Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Ohlsson 1994 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "changes in ulcer area/healing were blindly measured by two independent investigators" Comment: blinded outcome evaluation
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out of the study one in each group, reasons were given
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting of outcomes
Other bias	Unclear risk	There was no evidence of other sources of bias but reporting was insufficient to be certain
All domain risk of bias	Low risk	Low/unclear

Ormiston 1985

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 24 weeks (optional cross-over at 12 weeks)
Participants	Inclusion criteria: chronic venous ulcer > 3 months Exclusion criteria: clinical or laboratory evidence ulcer was of non-venous aetiology, ABPI < 0.7, expected poor compliance Participant characteristics Number participants: 61 (60 analysed) Age: 67.3 (9.7) vs 70.3 (13.3) years % male: 13 (43%) vs 8 (27%) Ulcer details Size: mean (SD) 12.1 (13.9) cm^2 vs 10.2 (8.7) cm^2 Duration: mean (SD) 45.9 (105.9 months) vs 15.9 (19.5) months, median (range) 8.5 (3 to 517) vs 6 (3 to 96) months
Interventions	Intervention 1 class: cadexomer iodine Intervention 1 details (name and details of application): ulcer cleaned with saline; sprinkled in layer 0.3 cm to 0.5 cm deep, covered with gauze pad Intervention 2 class: gentian violet Intervention 2 details (name and details of application): gentian violet and polyfax (polymyxin and bacitracin) ointment; gentian violet painted on, polyfax applied over in generous layer, covered with nonadherent (Melolin) pad Compression: crepe bandage followed by cotton crepe compression bandage Other co-interventions: ulcer cleaned with saline

Outcomes	Intervention 1: 12/30 Intervention 2: 7/30	
Notes	Funding type and details: not reported; Perstorp AB provided cadexomer iodine	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "for each number there was a double sealed envelope that contained a paper stating which treatment the patient should receive. The sequence [...] Was randomised and the code of randomisation was not available to the investigators" Comment: generation of randomisation sequence was unclear
Allocation concealment (selection bias)	Low risk	Quote: "for each number there was a double sealed envelope that contained a paper stating which treatment the patient should receive. The sequence .. Was randomised and the code of randomisation was not available to the investigators" Comment: appropriate concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Almost all participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	There is no obvious selective reporting but outcomes are not clearly specified
Other bias	High risk	Quote: "ulcers in the group receiving cadexomer iodine had not healed for a mean of 46 months, compared with 16 months for the standard group" Comment: impact of this baseline imbalance was unclear but it is substantial enough to constitute a risk of bias

Ormiston 1985 (*Continued*)

All domain risk of bias	High risk	

Petkov 1997

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 months
Participants	Inclusion criteria: exuding venous ulcers, < 100 cm², not infected, ABPI > 0.7 Exclusion criteria: current treatment with topical medications, ulcer covered with dry necrotic tissue, undergoing therapy which may retard wound healing, pregnant or lactating, silver sulphadiazine used in previous 7 days, in another research study in previous 3 months Participant characteristics Number participants: 100 Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: PMM Intervention 1 details (name and details of application): Fibracol (Johnson & Johnson) Intervention 2 class: alginate Intervention 2 details (name and details of application): Kaltostat (ConvaTec) Compression: "standardized compression bandaging" Other co-interventions: not reported
Outcomes	Intervention 1: 34/50 Intervention 2: 32/50 (author information - public data says 31/50)
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "100 patients ... were randomised" Comment: no details on method
Allocation concealment (selection bias)	Unclear risk	Quote: "100 patients ... were randomised" Comment: no details on method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Petkov 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to determine if reporting bias
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists
All domain risk of bias	Low risk	Low/unclear

Rasmussen 1991

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: chronic leg ulceration Exclusion criteria: diabetes mellitus, malignant or rheumatic disease, allergy to dressings, peripheral arterial disease, cellulitis, anaemia, sever maceration of surrounding skin Participant characteristics Number participants: 37 randomised, 29 included in analysis (18 vs 11) Age: 80.7 (6.7) vs 78.1 (11.8) years % male: 5 (28) vs 4 (36) Ulcer details Non VLU: 2 (11%) vs 1 (9%) mixed Size: mean (SD) 10.7 (2.0) cm^2 vs 8.15 (2.5) cm^2 Duration: not reported (minimum 3 weeks)
Interventions	Intervention 1 class: human growth hormone Intervention 1 details (name and details of application): Norditropin (Novo-Nordisk) + Comfeel (Coloplast); biosynthetic human growth hormone + hydrocolloid; Norditropin dissolved in water administered 5 days per week through connecting piece in the dressing. Treatment for at least 2 weeks Intervention 2 class: placebo + hydrocolloid Intervention 2 details (name and details of application): Comfeel (Coloplast); placebo administered 5 days per week through connecting piece in the dressing. Treatment for at least 2 weeks Compression: Compression bandages worn by all (Comprilan, Beirsdorf) Other co-interventions: not reported

Rasmussen 1991 (*Continued*)

Outcomes	Intervention 1: 3/18 Intervention 2: 1/11
Notes	Funding type and details: Coloplast and Beiresdorf provided study materials, but study funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: stratification before randomisation explained but randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Comment: not reported how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	18/37 withdrawals which were not included in analysis. Reasons provided
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Low risk	There was no evidence of other sources of bias
All domain risk of bias	High risk	

Robson 1995

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: chronic venous ulcers 1 cm^2 to 25 cm^2, > 3 months duration, or proximal to malleolus and distal to tibial tuberosity, no clinical signs of infection, aged 18 to 90, > 45 kg, ABI > 0.5, if female, postmenopausal or surgically sterile Exclusion criteria: bleeding disorder, severe dermatosclerosis, organised oedema, local

Robson 1995 (*Continued*)

	or systemic infection, disease or medication interfering with healing, hypersensitivity to bovine collagen Participant characteristics Number participants: 36 Age: 48.4 (17.6) vs 56.3 (8.0) vs 54.2 (11.4) years % male: 4 (33) vs 7 (58) vs 5 (42) Ulcer details Size: mean (SD) 3.9 (3.20) cm^2 vs 5.9 (5.6) cm^2 vs 7.1 (5.6) cm^2 Duration: mean (SD) 22 (40 vs 14 (13) vs 20 (16) months
Interventions	Intervention 1 class: human growth hormone + collagen Intervention 1 details (name and details of application): bTGF-B2 in collagen matrix (Celtrix Pharmaceutical); matrix cut to fit ulcer, hydrated with sterile saline if necessary, covered with non-absorbant dressing and layer of gauze sponge Intervention 2 class: placebo + collagen Intervention 2 details (name and details of application): placebo collagen matrix (Celtrix Pharmaceutical); matrix cut to fit ulcer, hydrated with sterile saline if necessary, covered with non-absorbant dressing and layer of gauze sponge Intervention 3 class: nonadherent Intervention 3 details: gauze dressing; Xeroform (Sparta Surgical Corp), 3 x per week Compression: ace elastic compression bandage (Becton-Dickenson) consisting of 2 layers in opposing figure of eight configuration Other co-interventions: sterile saline used to cleanse ulcer at weekly clinic visits
Outcomes	Intervention 1: 3/12 Intervention 2: 3/12 Intervention 3: 2/12
Notes	Funding type and details: Celtrix Pharmaceuticals produced clinical study material, some authors work for them

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients [...] were randomized to one of the treatment groups. Randomization was balanced for gender and age and for ulcer area and duration" Comment: no method detail for sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients [...] were randomized to one of the treatment groups. Randomization was balanced for gender and age and for ulcer area and duration" Comment: no information on how allocation was concealed

Robson 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all assessments were performed by an observer blinded to the ulcer treatment" Comment: blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants withdrew (3 from bTGF-B2 group, 1 from standard dressing), decision to exclude from analysis made before unblinding. (randomised numbers extracted here, however)
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Low risk	There was no evidence of other sources of bias
All domain risk of bias	Low risk	Low/unclear

Robson 2001

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous insufficiency with ulcer 3 cm^2 to 30 cm^2 and 3 to 36 months duration Exclusion criteria: significant arterial insufficiency, increased bacterial burden, active vasculitis, cellulitis or collagen vascular disease, active skin disease, malignant neoplasm, significant acute or chronic systemic disease, significant clinical laboratory abnormalities, known allergies to study materials, treatment with investigational agents, pentoxifylline, immunosuppressive or cytotoxic agent, pregnancy, use of topical antibiotics in 7 days prior or during treatment Participant characteristics Number participants: 94 Age: 61 (13) vs 59 (14) vs 59 (13) years % male: 71(22) vs 66 (21) vs 58 (18) Ulcer details Size: mean (SD) 8.7 (6.2) cm^2 vs 8.4 (.5) vs 8.1 (6.7) cm^2 Duration: mean (SD) 11 (8) vs 14 (10) vs 11 (7) months
Interventions	Intervention 1 class: human growth hormone Intervention 1 details (name and details of application): Repifermin spray (20 µg/cm^2)

Robson 2001 (*Continued*)

	+ nonadherent dressing Intervention 2 class: human growth hormone Intervention 2 details (name and details of application): Repifermin spray (60 µg/cm²) + nonadherent dressing Intervention 3 class: nonadherent (placebo spray) Intervention 3 (name and details of application): placebo + nonadherent dressing Compression: self-adherent elastic wrap Other co-interventions: not reported
Outcomes	Intervention 1: 10/31 Intervention 2: 12/32 Intervention 3: 9/31
Notes	Funding type and details: industry Funding details: Human Genome Sciences Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients with venous insufficiency (aged 18 years or older) were randomized as follows" Comment: described as randomised but no methods given
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients with venous insufficiency (aged 18 years or older) were randomized as follows" Comment: described as randomised but no methods given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind, placebo-controlled but no details given so not clear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind, placebo-controlled but no details given so not clear who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	5 withdrawals (9.7% vs 3.1% vs 3.2%), ITT
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	

Robson 2004

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 20 weeks
Participants	Inclusion criteria: venous ulcer 3 cm² to 25 cm² and 3 to 36 months duration, venous insufficiency (venous duplex scanning or impedance plethysmography), prescribed compression for 7 to 28 days prior to trial Exclusion criteria: participated in a clinical trial of an investigational agent within the last 30 days, been treated with repifermin (KGF-2) have the designated ulcer below the malleolus, on the foot, or above the base of the knee, have had the study ulcer treated with Regranex (PDGF-BB) within the last 30 days or treated at any time with a skin substitute or an autologous growth factor, had a surgical procedure to treat venous or arterial disease within the last 90 days, evidence of significant arterial insufficiency (an ankle brachial index of 1.2 must have a toe brachial index of > 0.6 or a supine transcutaneous oxygen measurement (TcPO2) > 30 mmHg, clinical evidence of active infection at the ulcer site, a granulation tissue colony count ≥ 106/g of tissue or beta-haemolytic streptococci at any level, evidence of active vasculitis, cellulitis, or collagen vascular disease, a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin or uterine cervix, significant acute or chronic diseases (i.e. cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological, or infectious diseases), which are not adequately controlled by medical treatment as determined by the investigator's judgment, diabetes mellitus with a haemoglobin A1c ≥8%, active skin disease, such as psoriasis, which could impair the ability to assess the wound, an allergy to the dressings used in the study,require treatment to the study ulcer with any topical agent other than normal saline within 7 days of the first repifermin/placebo treatment or with topical lidocaine for anaesthesia prior to study ulcer debridement after the first repifermin/placebo treatment, or concomitant use of pentoxifylline or clopidogrel bisulphate during the study, undergone enzymatic debridement at any time during the screening period, known history of allergies to *Escherichia coli*-derived or paraben-containing products, any requirement for the use of systemic steroids or immunosuppressive or cytotoxic compounds during the period of the study,expected to undergo hyperbaric oxygen therapy at any time during treatment or through the 4-week follow-up visit, pregnant female or nursing mother (all females with an intact uterus, regardless of age must have a negative serum pregnancy test result at screening and use contraception during the study), during the first 20 weeks of the study be expected to miss 3 or more consecutive visits or be expected to miss 2 consecutive visits more than once Participant characteristics Number participants: 352 Age: 61.8 (15.6) vs 60.9 (13.7) vs 61.0 (15.4) years % male: 59 (52.7) vs 76 (61.8) vs 81 (69.2) Ulcer details Size: mean (SD) 8.7 (5.3) cm² vs 9.4 (5.4) cm² vs 9.9 (6.2) cm², median (range) 7.1 (2.4 to 22.9) cm² vs 8.4 (3.0 to 25.0) cm² vs 7.4 (3.0 to 24.3) cm² Duration: mean (SD) 8.7 (5.3) months vs 12.3 (9.2) vs 11.8 (9.3) months, median (range) 6.0 (3.0 to 36.0) months vs 9.0 (3.0 to 36.0) months vs 7.0 (3.0 to 35.0) months

Interventions	Intervention 1 class: human growth hormone Intervention 1 details (name and details of application): growth factor-repifermin (KGF-2) higher dose (120 µg/cm²) + petrolatum gauze; Gauze dressing = ADAPTIC (Johnson & Johnson); 2 x per week spray application of drug, then covered with dressing Intervention 2 class: human growth hormone Intervention 2 details (name and details of application): growth factor-repifermin (KGF-2) lower dose (60 µg/cm²) + petrolatum gauze; Gauze dressing = ADAPTIC (Johnson & Johnson); 2 x per week spray application of drug, then covered with dressing Intervention 3 class: nonadherent (placebo spray) placebo + petrolatum gauze: gauze dressing= ADAPTIC (Johnson & Johnson) Intervention 3 details (name and details of application): not reported Compression: multi-layer sustained graduated compression bandage system (DYNAFLEX, Johnson & Johnson) Other co-interventions: pre-study screening period involved debridement and biopsy to check infection
Outcomes	Intervention 1: 58/112 Intervention 2: 72/123 Intervention 3: 72/117
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized, double-blinded" Comment: described as randomised but no details of methods for sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized, double-blinded" Comment: described as randomised but no details of methods for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomized, double-blinded" Comment: no information on who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized, double-blinded" Comment: no information on who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 18% vs 15% vs 13% dropout, reasons given, ITT analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Unclear risk	No evidence of other sources of bias

Robson 2004 (*Continued*)

All domain risk of bias	Low risk	Low/unclear

Romanelli 2015a

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous leg ulcer, venous insufficiency established by colour Doppler test, no measurable improvement over 6 weeks standard treatment Exclusion criteria: diabetes, autoimmune disease, peripheral arterial disease ABPI < 0.8, smokers, ulcer with signs of infection Participant characteristics Number participants: 40 Age: 68 (5) vs 65 (2) years % male: 7(35) vs 5(25) Ulcer details Size: mean (SD) 26 (4) vs 24 (5) cm^2 Duration: mean (SD) 24 (6) vs 20 (4) weeks
Interventions	Intervention 1 class: PMM Intervention 1 details (name and details of application): collagen membrane + non adherent + alginate; ProHeal (MedSkin Solutions) + Adaptic (Systa Genix) + Curasorb (Kendal); dressing changed twice a week Intervention 2 class: alginate Intervention 2 details (name and details of application): Curasorb (Kendal); dressing changed twice a week Compression: short stretch bandaging (Rosidal K, Lohmann and Rauscher) Other co-interventions: saline used to cleanse wounds
Outcomes	Intervention 1: 6/20 Intervention 2: 5/20
Notes	Funding type: industry Funding details: MedSkin Solutions

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was established by a random permuted block of five patients, prepared in advance" Comment: not specified how the sequence was generated

Romanelli 2015a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "randomisation was established by a random permuted block of five patients, prepared in advance" Comment: allocation concealment method was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of additional sources of bias
All domain risk of bias	Low risk	Low/unclear

Romero-Cerecero 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 10 months
Participants	Inclusion criteria: people aged 18 to 70 with clinical diagnosis of chronic venous leg ulcer 2 cm to 15 cm in diameter, < 10 years duration, no infection or severe oedema, no previous topical treatment in previous month Exclusion criteria: pregnancy or breastfeeding, sensitivity to topical treatments, oedema in legs, diabetes Participant characteristics Number participants: 34 Age: 60.5 (17) vs 61.5 (20) years % male: 7/17 (41) vs 3/17 (18) Ulcer details Size: mean (SD) 1894.8 (51.3) vs 2068.6 (52.9) (unit of size unclear) Duration: < 1 year 32.2% vs 47.0%, 1 to 5 years 41.4% vs 32.2%, 6 to 10 years 23.4% vs 17.6%
Interventions	Intervention 1 class: A.pichinchensis extract Intervention 1 details (name and details of application): administered weekly Intervention 2 class: alginate

	Intervention 2 details (name and details of application): 7% propylene glycol alginate (control) administered weekly Compression: not reported Other co-interventions: "strict wound hygiene, plus debridement and the placement of dressings"	
Outcomes	Intervention 1: 15/17 Intervention 2: 9/17	
Notes	Funding type and details: mixed Funding details: CONACYT and Mexican Institute of Social Security	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quotes: "two treatment groups were randomly organized" "treatments were randomly assigned" Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quotes: "two treatment groups were randomly organized" "treatments were randomly assigned" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "in order to blind the experimental procedure, both treatments were formulated and packed in identical collapsible tubes" "neither the patient nor the physician knew the identity of the treatments" Comment: both participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "in order to blind the experimental procedure, both treatments were formulated and packed in identical collapsible tubes" "neither the patient nor the physician knew the identity of the treatments" Comment: it appears that outcome assessment was performed by personnel who were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	6/17 vs 2/17 withdrawals; however there was an ITT analysis, the impact of the withdrawals is unclear but unbalanced

Selective reporting (reporting bias)	Low risk	There was no evidence of selective outcome reporting
Other bias	Low risk	There was no evidence of any other source of bias
All domain risk of bias	High risk	

Rubin 1990

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 months
Participants	Inclusion criteria: ambulatory with lower-extremity chronic venous stasis ulceration Exclusion criteria: history of non-compliance, significant arterial insufficiency (Doppler ankle brachial pressure index < 0.8), history of significant associated medical risk factors e. g. collagen vascular disease, uncontrolled diabetes, ongoing dermatologic disease, chronic corticosteroid therapy Participant characteristics Number participants: 36 Age: not reported % male: not reported Ulcer details Size: mean (range) 32.2 cm² (6.0 to 270) vs 76.0 cm² (0.02 to 600) Duration: not reported
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): PFD (Synthaderm Armour Pharmaceutical); dressing changed on weekly and/or biweekly schedule Intervention 2 class: paste bandage Intervention 2 details (name and details of application): gauze bandage impregnated with glycerin, zinc oxide and calamine lotion; dressing changed on weekly and/or biweekly schedule Compression: all participants had elastic bandages applied from toes to knees Other co-interventions: wounds were cleansed routinely with 20% Poloxamer cleansing solution Shur-Cleans (Merck & Co)
Outcomes	Intervention 1: 7/17 Intervention 2: 18/19
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rubin 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "each patient was randomized by the study co-ordinator" Comment: unclear how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "the study co-ordinator did not see the randomization card and was therefore blinded as to the treatment cohort" Comment: blinding but unclear allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the study co-ordinator did not see the randomization card and was therefore blinded as to the treatment cohort" Comment: not clear whether other personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the study co-ordinator did not see the randomization card and was therefore blinded as to the treatment cohort" Comment: not clear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	9 (52.9%) of Group 1 withdrew due to wound odour whereas 100% of group 2 completed the study
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Unclear risk	No evidence of other sources of bias but insufficient evidence to be certain
All domain risk of bias	High risk	

Salim 1992

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous ulceration (diagnosed from history, examination and Doppler assessment of arterial pressure at ankles) of one leg, on medial side, < 10 cm^2, occurring for the first time, not yet treated in any way, not infected or associated with gross leg oedema Exclusion criteria: surgery or injection sclerotherapy for varicose veins, alcoholism, preg-

	nancy, diabetes, hypertension, steroid or NSAIDSs in previous year, on regular medication, hepatic or renal disorder, serious underlying disease, rheumatoid arthritis, collagen disease Participant characteristics Number participants: 168 randomised; 137 analysed Age: mean (range) 56 (31 to 68) vs 57 (29 to 71) vs 58 (28 to 71) years % male: 23 (50) vs 21 (47) vs 21 (46) Ulcer details Size: mean (SD) 5.3 (0.3) cm^2 vs 5.5 (0.1) vs 4.6 (0.2) cm^2 Duration: mean 20 months vs 24 vs 22 months
Interventions	Intervention 1 class: sulphadryl Intervention 1 details (name and details of application): DL-cysteine powder + Terylene and cotton gauze; powder manufactured by Sigma, Terylene dressing NADD (Johnson & Johnson); powder liberally sprayed on ulcer, covered with dressings. Repeated every day for 7 days, then weekly Intervention 2 class: sulphadryl Intervention 2 details (name and details of application): DL-methionine-methyl sulphonium chloride powder + Terylene and cotton gauze; powder manufactured by Sigma, Terylene dressing NADD (Johnson & Johnson); powder liberally sprayed on ulcer, covered with dressings. Repeated every day for 7 days, then weekly Intervention 3 class: inactive powder (placebo) Intervention 3 details (name and details of application): placebo powder + Terylene and cotton gauze; powder manufactured by Sigma, Terylene dressing NADD (Johnson & Johnson); powder liberally sprayed on ulcer, covered with dressings. Repeated every day for 7 days, then weekly Compression: below knee graduated compression bandage (layer of crepe bandage, layer of Elset (Seton Ltd) and layer of Coban cohesive bandage (3M Health Care Ltd)) Other co-interventions: ulcer cleaned with olive oil and washed with saline. Skin surrounding ulcer and of leg oiled with propylene glycol monostearate (BP)
Outcomes	Intervention 1: 43/46 Intervention 2: 42/45 Intervention 3: 32/46
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was carried out by drawing sealed envelopes" Comment: unclear how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomization was carried out by drawing sealed envelopes" Comment: unclear how allocation was con-

Salim 1992 (*Continued*)

		cealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the treatment code was only broken 3 months after treatment had started (end point of the study)" Comment: described as double-blind and uses placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the treatment code was only broken 3 months after treatment had started (end point of the study)" Comment: described as double-blind; appears that blinded outcome assessment was used
Incomplete outcome data (attrition bias) All outcomes	High risk	9/55 vs 11/57 vs 11/56 excluded from analysis- reasons given
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	

Schulze 2001

Methods	RCT Arms: 3 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 weeks
Participants	Inclusion criteria: moderate to heavily exuding leg ulcers of venous origin (ABPI > or = 0.8 measured by Doppler ultrasound or colour Duplex sonography), < 1 cm deep, < 11cm wide Exclusion criteria: wounds with hard black necrotic tissue, wounds with clinical signs of infection, known hypersensitivity to study dressings, treatment in another research study within previous 30 days Participant characteristics Number participants: 113 Age: 73.6 (13.9) vs 72.4 (13.5) vs 72.7 (14.5) years % male: 16 (30) vs 10 (45) vs 12 (32) Ulcer details Size: mean (SD) 13.7 (12.2) cm^2 vs 18.5 (18.5) cm^2 vs 11.2 (13.2) cm^2, median (range) 8.8 (0.7 to 48.8) cm^2 vs 12.9 (0.3 to 75.2) cm^2 vs 7.5 (0.6 to 68.3) cm^2 Duration: mean (SD) 49.5 (131.5) months vs 45.6 (97.2) months vs 35.0 (74.1) months, range 0.5 to 744 vs 0.5 to 396 vs 0.2 to 360 months

Schulze 2001 (*Continued*)

Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Tielle plus hydropolymer adhesive dressing (Johnson & Johnson Medical); changed when clinically required, maximum 7 days; secondary dressing of film (Opsite flexigrid, Smith & Nephew). Changed when clinically required, maximum 7 days Intervention 2 class: alginate Intervention 2 details (name and details of application): Kaltostat wound dressing (ConvaTec) Intervention 3 class: alginate Intervention 3 details (name and details of application): Kaltostat wound dressing (ConvaTec); secondary dressing switched later in the study to sterile swabs (Topper-8, Johnson & Johnson) due to side effects. Changed when clinically required, maximum 7 days Compression: all participants had short-stretch compression bandaging Other co-interventions: not reported
Outcomes	Intervention 1: 2/54 Intervention 2: 3/22 Intervention 3: 1/37
Notes	Funding type and details: industry Funding details: Johnson & Johnson Medical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "assignment to treatment group was by random allocation according to a predetermined, computer-generated, randomisation schedule" Comment: appropriate sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "the dressing details for each patient number were provided inside individually sealed envelopes, which the investigators opened on each new patient's recruitment" Comment: unclear if envelopes were opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: trial described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: trial described as "open"

Schulze 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	All participants accounted for, but high number of withdrawals for adverse events especially in alginate + film group 10/22
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Scurr 1994

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: venous ulcer (assessed with photoplethysmography, Doppler, ankle-brachial pressure indices and duplex imaging) Exclusion criteria: undergone chemotherapy or radiation treatment, on or recently received steroid medication, diabetes, peripheral arterial disease Participant characteristics Number participants: 40 Age: 62 mean (years) % male: 22 (55) Ulcer details Size: mean (SD) 2.28 (1.49) cm^2 vs 5.31 (5.46) cm^2 Duration: not reported
Interventions	Intervention 1 class: alginate Intervention 1 details (name and details of application): Sorbsan (Steriseal); dressing applied and covered with 2 layers of gauze and 1 layer surgical pad dressing. held in place with tape. Dressing change frequency determined by wound discharge (range daily to weekly) Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): DuoDerm (Convatec, US) also known as Granuflex (UK); dressing applied and secured with tape. Changed every 2-7 days Compression: class III graduated elastic compression stocking Other co-interventions: before applying dressings, wounds were adequately debrided and slough removed. Saline irrigation used to clean wounds at dressing changes
Outcomes	Intervention 1: 6/20 Intervention 2: 2/20

Scurr 1994 (*Continued*)

Notes	Funding type and details: industry Funding details: Grants from Steriseal Ltd and Dow B Hickam

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients ... were randomly allocated either to the calcium alginate or the hydrocolloid group" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "patients ... were randomly allocated either to the calcium alginate or the hydrocolloid group" Comment: method of allocation concealment unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Authors noted difference in size between groups due to one participant and performed analyses both with and without them
All domain risk of bias	Low risk	Low/unclear

Senet 2003

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks

Senet 2003 (*Continued*)

Participants	Inclusion criteria: at least one venous ulcer, duration at least 2 months, 3 cm² to 50 cm², no tendency for healing in past 2 months, venous disease confirmed by venous duplex ultrasound scan and clinical symptoms, absence of arterial insufficiency ABI > 0.8 Exlcusion criteria: pregnancy, allergy to hydrocolloid dressings, uncontrolled or evolving systemic disease, serum creatinine > 180 umol/L, systemic corticosteroids or cytotoxic drugs, limited physical capacity or immobility, ulcer with exposed tendon/bone, infected ulcer requiring systemic antibiotics, uncontrolled diabetes, various serological findings (details in paper) Participant characteristics Number participants: 15 randomised (data analysed for 13) Age:mean (range) 72.3 (45 to 88) vs 72.3 (50 to 83) years % male: 4 (57) vs 3 (50) Ulcer details Size: mean (range) 13.7 (4.8 to 27.25) cm² vs 10.85 (3.7 to 26.5) cm² Duration: mean (range) 50.6 (4 to 240) vs 70 (24 to 120) months
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): frozen autologous platelets (FAP) (suspension in saline) + hydrocolloid; Comfeel Plus Opaque (Coloplast); FAP suspension applied to wound surface with syringe. Dressings changed 3 x per week Intervention 2 class: saline/hydrocolloid (placebo) Intervention 2 details (name and details of application): placebo (saline) + hydrocolloid; placebo applied to wound surface with syringe. Dressings changed 3 x per week Compression: standard graded compression with cotton bandages (Nylex, Laboratoires URGO) and elastic bandages (Biflex Plus Forte, Laboratoires Thuasne) Other co-interventions: not reported
Outcomes	Intervention 1: 1/7 Intervention 2: 1/6
Notes	Funding type and details: mixed Funding details: grants from Institut national de la santé et de la recherche médicale and Coloplast Note: participants randomised immediately after collection of platelets

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients who complied with entry and exclusion criteria were randomised to one of two treatment groups" Comment: method of sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Quote: "patients who complied with entry and exclusion criteria were randomised to one of two treatment groups" Comment: method of allocation conceal-

Senet 2003 (*Continued*)

		ment unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: described as double-blind but no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double-blind but no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/8 vs 1/7 withdrawals, included in analysis as failure to heal
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting but reporting insufficient
Other bias	Unclear risk	No evidence of other sources of bias but reporting insufficient
All domain risk of bias	Low risk	Low/unclear

Senet 2011

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: people with one or more hypertensive leg ulcers (defined by clinical criteria) 1 cm^2 to 30 cm^2, with hypertension and/or diabetes without clinical signs of severe CVI and without significant peripheral arterial occlusive disease (presence of peripheral pulses or ABI > 0.8); if several ulcers, most recent chosen Exclusion criteria: cutaneous vasculitis, systemic disease associated with pyoderma gangrenosum or necrotising vasculitis (e.g. rheumatoid arthritis), autoimmune disease, cryobulinemia, allergy to study materials, cancer, evolving systemic disease, creatinemia, uncontrolled diabetes, exposed bone or joint, corticosteroids, immunosuppressive or cytotoxic drugs, iloprost in prior 3 months Participant characteristics Number participants: 64 randomised, data from 59 Age: 73.7 (8.3) vs 75.3 (9.7) years % male: 12 (43) vs 11 (35) Ulcer details Size: mean (SD) 19.6 (20.1) cm^2 vs 24.4 (24.6) cm^2 Duration: mean (SD) 11.8 (8.6) vs 10.5 (9.7)
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): Becaplermin (human platelet derived growth factor) 0.1% in hydrogel + gauze; Regranex gel (Ethicon division of

	Johnson & Johnson Wound Management); continuous thin layer of gel applied, covered with moist saline gauze and bandage. Treatment for 8 weeks Intervention 2 class: hydrogel (placebo gel) Intervention 2 details (name and details of application): DuoDerm Hydrogel (ConvaTec) + gauze; continuous thin layer of gel applied, covered with moist saline gauze and bandage. Treatment for 8 weeks Compression: not reported; unclear if bandage applied compression Other co-interventions: wound irrigation with saline. Moist saline gauze and bandage
Outcomes	Intervention 1: 10/28 Intervention 2: 8/31
Notes	Funding type and details: mixed Funding details: study supported by AP-HP (Assistance publique - Hôpitaux de Paris) , the French Society of Dermatology, and the AFSSAPS (Agence nationale de sécurité du médicament et des produits de santé); Johnson & Johnson provided study materials (Regranex)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "eligible participants were randomly assigned by facsimile through a central automated system designed by the Clinical Research Regional Department (AP-HP)" "a computer engineer not responsible for data acquisition prepared the assignments" Comment: appropriate sequence generation method appears to have been used
Allocation concealment (selection bias)	Low risk	Quote: "a central automated system ... a computer engineer not responsible for data acquisition prepared the assignments" Comment: appears to be appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all participants and investigators were blinded to assigned treatment" "masked 15g tubes ... identical in color, shape and size, were provided in blister packs by the AP-HP central pharmacy" Comment: blinding of both groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all participants and investigators were blinded to assigned treatment" "masked 15g tubes ... identical in color, shape and size, were provided in blister

Senet 2011 (*Continued*)

		packs by the AP-HP central pharmacy" Comment: appears that assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	7/28 vs 13/31 did not receive treatment or complete follow-up - ITTanalysis performed but this is a very high rate of loss with disparity between arms
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other source of bias
All domain risk of bias	High risk	

Senet 2014

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: venous or predominantly venous leg ulcer (ABI > 0.8) between 2cm and 13 cm in all directions, moderately or severely exudating in the phase of debridement or formation of granulation tissue, size reduction < 20% in 4-week pre-study treatment phase Exclusion criteria: clinically infected ulcer requiring systemic antibiotics, surgery on saphenous trunk within 2 months prior, systemic antibiotics 2 weeks prior, systemic corticoids or cytostatics within 3 months prior, unbalanced diabetes, known allergy to study dressings, pregnant or breastfeeding, taking part in another study Participant characteristics Number participants: 182 (1 erroneously enrolled and subsequently excluded) Age: 72.1 (12.4) vs 75.1 (11.8) years % male: 50 (53) vs 34 (39) Ulcer details Size: mean (SD) 15.4 (14.1) cm^2 vs 14.5 (13.4) cm^2 Duration: mean (SD) 2.8 (4.2) years vs 2.9 (5.1) years
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Biatain (Coloplast A/S) Intervention 2 class: silver (foam) Intervention 2 details (name and details of application): Biatain-Ag (Coloplast A/S) Compression: compression therapy was mandatory for all according to clinical practice of the centre Other co-interventions: not reported

Senet 2014 (*Continued*)

Outcomes	Intervention 1: 3/94 Intervention 2: 7/87
Notes	Funding type: industry Funding details: Coloplast

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "centrally randomised (by computer system)" Comment: appropriate method of sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "allocated ... using Interactive Voice Response Service (IVRS)" Comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study was designed as double-blinded. All products were ... packed in identical packing and blinded by an external company ... No dressings could be compared by the subject or investigator in the knowledge that they were different products" Comment: effective blinding described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the planimetry records were read blind by a person who was not aware of the nature of the treatment" Comment: blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	11 vs 18 withdrawals - reasons given and ITT analysis performed but still a high level of withdrawal and an imbalance between the groups
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other sources of bias
All domain risk of bias	High risk	

Smith 1992

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 4 months
Participants	Inclusion criteria: venous leg ulceration assessed by continuous wave ultrasound and photoplethysmography Exclusion criteria: brachial ankle systolic pressure < 0.75, diabetes, rheumatoid arthritis, infected ulcers requiring treatment , known intolerance to iodine, neurological disease causing trophic impairment Participant characteristics Number participants: 200 Age: 74 (12) vs 72 (13) vs 76 (8) vs 73 (11) years % male: not reported Ulcer details Size: median (IQR) 3.1 (2 to 5) cm² vs 2.6 (2 to 4) cm² vs 13.3 (9 to 27) cm² vs 17.6 (9 to 38) cm² Duration: median (IQR) 5 (3 to 9) vs 3 (2 to 10) vs 14 (2 to 45) vs 17 (6 to 58) months
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Biofilm (Clinimed); ulcer filled with biofilm powder until level with margins, then biofilm dressing applied with 2cm overlap Intervention 2 class: povidone iodine Intervention 2 details (name and details of application): standard Jelonet/Betadine dressing; Betadine + Jelonet (Smith & Nephew); Dressing cut to exactly fit ulcer and absorbant pad placed over Compression: 2 layers of shaped Tubigrip or a Venosan 2002 stocking for all participants Other co-interventions: ulcers cleansed with sterile isotonic saline
Outcomes	Intervention 1: 38 + 12/64 + 35 Intervention 2: 43 + 4/62 + 39
Notes	Funding type: industry Funding details: Clinimed Ltd provided financial support to one study nurse co-ordinator

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "patients ... were randomly allocated to each treatment group" Comment: stratification and block size mentioned but not method of sequence generation; 'Clerical errors' with treatment allocation - randomisation compromised

Smith 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as "not a blind study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as "not a blind study"
Incomplete outcome data (attrition bias) All outcomes	High risk	60 (30%) dropped out, reasons given. 5 received incorrect treatment due to 'clerical error', included as PP
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No additional risks - see random sequence generation
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Smith 1994

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: venous leg ulcer > 2.5 cm diameter Exclusion criteria: condition which might affect wound healing (infection, immune deficiency, steroid treatment, malignant disease), if ulcer not clearly venous, fibrinolytic or anticoagulant therapy Participant characteristics Number participants: 40 Age: not reported % male: not reported Ulcer details Size: mean 12.74 cm^2 vs 22.17 cm^2 Duration: not reported
Interventions	Intervention 1 class: alginate Intervention 1 details (name and details of application): gauze used as secondary dressing Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): improved formulation Granuflex

	Compression: compression bandaging used for all participants Other co-interventions: wounds cleaned with saline
Outcomes	Intervention 1: 2/18 Intervention 2: 4/22
Notes	Funding type: industry Funding details: Convatec

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients were allocated randomly" Comment: no information on how randomisation sequence generated
Allocation concealment (selection bias)	Unclear risk	Quote: "eligible patients were allocated randomly" Comment: no information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/18 vs 6/22 withdrawals, reasons given
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of this
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Solovastru 2015

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 30 days
Participants	Inclusion criteria: chronic VLUs < 2 years duration Exclusion criteria: confined to bed 24 hours, ulcers covered by necrosis or fibrin, infected ulcers, multiresistant germs in wound, poorly controlled diabetes, those on dialysis, advanced peripheral arterial occlusive disease (ABPI < 0.80 and presence of distal pulse) , immunodeficiency, lymphopenia, hepatic insufficiency, renal insufficiency, anaemia, autoimmune disease, BMI > 30, hypersensitivity to study materials, low white blood cells or thrombocytes Participant characteristics Number participants: 29 Age: 58.0 vs 59.0 years % male: 9 (60) vs 10 (71) Ulcer details Size: mean (SD) 4.36 (5.61) cm^2 vs 4.59 (3.46) cm^2 Duration: mean 13 months vs 16 months
Interventions	Intervention 1 class: ozonated oil Intervention 1 details (name and details of application): ozonated oil and alpha-bisabolol spray + gauze; sunflower oil with O^3 (Neozone, Neovalis) and Azexin (Alfa Wassermann) ; administered daily for 30 days Intervention 2 class: emollient cream Intervention 2 details (name and details of application): epithelialization cream (vitamins A & E, talc, zinc oxide, Vaseline) + gauze; administered daily for 30 days Compression: none Other co-interventions: mechanical debridement at days 0, 7, 14
Outcomes	Intervention 1: 5/15 Intervention 2: 0/14
Notes	Funding type and details: not reported but authors employed by pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly divided into 2 groups" Comment: no information on how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly divided into 2 groups" Comment: no information on how alloca-

Solovastru 2015 (*Continued*)

		tion was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of this
All domain risk of bias	Low risk	Low/unclear

Sopata 2016

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: until participants healed (maximum 40 weeks) or died
Participants	Inclusion criteria: people with VLU confirmed by ultrasound Doppler and ABPI, no clinical signs of infection, no intolerance or allergy to octenidine dihydrochloride Exclusion criteria: not reported Participant characteristics Number participants: 50 Age (years): female 39 to 91, 68.9 ± 12.2, mean = 70.5; male 24 to 93,65.7 ± 20.2, mean = 70 % male: 15 (30) Ulcer details Size: female: 3.0 to 156.5 cm^2, 28.8 ± 28.5, mean = 24.2; male 2.8-75.2 cm^2, 20.4 ± 27.1, mean = 12.2 Duration: not reported
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex (ConvaTec); dressing changed every 2-4 days Intervention 2 class: foam Intervention 2 details (name and details of application): Biatain (Coloplast); dressing changed every 2-4 days Compression: short stretch bandages used for all participants, with a spiral two layer bandaging technique Other co-interventions: for 4 weeks prior to randomisation all participants were treated

	with nonadherent silicone N-A dressing (Systagenix) and Sterilux EX (Hartmann) gauze bandages soaked in octenidine dihydrochloride antiseptic (Octenisept) and covered with absorbent Zetuvit (Hartmann) dressing	
Outcomes	Intervention 1: 17/25 Intervention 2: 21/25	
Notes	Funding type: non-industry Funding details: Grant from University of Medical Science, Poznan Notes: Demographic data not presented by treatment group	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "in the second period the patients were randomly allocated to two groups" Comment: no information on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "in the second period the patients were randomly allocated to two groups" Comment: no information on how the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis (those that did not have final assessment explained in text)
Selective reporting (reporting bias)	High risk	Study design does not have defined time end point
Other bias	High risk	No baseline information for study groups, just split male vs female
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Stacey 1997

Methods	RCT Arms: 3 Unit of randomisation: leg Unit of analysis: leg Follow-up: 9 months
Participants	Inclusion criteria: proven venous ulcers 0.5 cm to 10 cm diameter Exclusion criteria: diabetes, rheumatoid arthritis, arterial diease, cellulitis Participant characteristics Number participants: 133 legs (113 participants) Age: median (range) 73 (33 to 89) vs 76 (31 to 89) vs 70.5 (36 to 92) years % male: 17 (41) vs 16 (39) vs 22 (48) Ulcer details Size: mean 10.11 cm^2 vs 9.14 vs 11.02 cm^2, median (range) 3.60 (0.15 to 57.46) cm^2 vs 2.94 cm^2 (0.24 to 75.37) cm^2 vs 4.57 cm^2 (0.36 to 61.32) cm^2 Duration: median (range) 6.00 (0.25 to 192) vs 6.00 (0.25 to 5.04) vs 4.00 (0.25 to 2.64) months
Interventions	Intervention 1 class: paste bandage Intervention 1 details (name and details of application): zinc oxide paste bandage; Viscopaste (Smith & Nephew); applied in spiral fashion from base of toes to just below the knee. Changed weekly or sooner if excessive exudate Intervention 2 class: paste bandage Intervention 2 details (name and details of application): zinc oxide stockingette; Acoband (Auspharm); applied from base of toes to just below knee. Changed weekly or sooner if excessive exudate Intervention 3 class: alginate Intervention 3 details (name and details of application): Kaltostat (Faulding Pharmaceuticals); moistened with saline and applied over ulcer. Changed weekly or sooner if excessive exudate Compression: over dressings 2 elastocrepe bandages (Smith & Nephew) applied from toe to knee and Tubigrip stockingette (Seton) over them Other co-interventions: leg and foot washed in soap-water bath and ulcer debrided
Outcomes	Intervention 1: 34/43 Intervention 2: 26/44 Intervention 3: 26/46
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no methods given
Allocation concealment (selection bias)	Unclear risk	No information provided

Stacey 1997 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	5/43 vs 6/44 vs 10/46 withdrawals, reasons given. Imbalance between groups
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Unclear risk	Unclear if the analysis adjusted for some clustering of data
All domain risk of bias	High risk	

Stacey 2000

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 9 months
Participants	Inclusion criteria: venous ulcer (established with photoplethysmography - venous refilling time < 25s) Exclusion criteria: arterial disease (ABPI < 0.9) Participant characteristics Number participants: 66 Age: Median (range) 72 (35 to 90) vs 70 (26 to 92) years % male: 15 (36) vs 21 (48) Ulcer details Size: mean (SD) 5.06 (8.70) cm^2 vs 4.79 (8.24) cm^2, median (range) 1.79 (0.23 to 50.76) cm^2 vs 2.09 (0.15 to 47.8) cm^2 Duration: median (range) 3.0 (1 to 244) months vs 3.0 (0.75 to 360) months
Interventions	Intervention 1 class: blood product Intervention 1 details (name and details of application): platelet lysate-soaked gauze; dressing changed twice weekly Intervention 2 class: saline gauze (placebo/vehicle liquid) Intervention 2 details (name and details of application): placebo (buffer solution) soaked gauze; dressing changed twice weekly Compression: dressings covered with Viscopaste bandage (Smith & Nephew) followed by 2 Comprilan bandages (Beiersdorf) and Tubigrip stockingette (Seton) Other co-interventions: see above

Stacey 2000 (*Continued*)

Outcomes	Intervention 1: 34/42 Intervention 2: 33/44
Notes	Funding type: mixed Funding details: Medical Research Fund of Western Australia and Beiersdorf AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was by a sealed envelope system" Comment: no information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomisation was by a sealed envelope system" Comment: no information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: described as "double blind" but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as "double blind" but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	5/42 vs 6/44 withdrawals, reasons given, over 10% lost
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of this
All domain risk of bias	High risk	

Steele 1986

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 6 weeks
Participants	Inclusion criteria: venous leg ulcers present for 3 months and > 2 cm^2 Exclusion criteria: arterial disease (palpable dorsalis pedis and posterior tibial pulses and absence of ischaemic skin signs), diabetes, rheumatoid arthritis, neurological disease,

Steele 1986 (*Continued*)

	connective tissue disease Participant characteristics Number participants: 60 Age: mean (SE) 69.5 (2.4) vs 73.4 (1.6) years % male: 8 (29) vs 8 (28) Ulcer details Size: mean (SE) 1264 (291) mm^2 vs 1759 (397) mm^2 Duration: mean (SE) 16.6 (2.7) months vs 16.3 (2.5) months
Interventions	Intervention 1 class: cadexomer iodine Intervention 1 details (name and details of application) powder sprinkled onto ulcer and covered with gauze. Changed 3 times per week Intervention 2 class: standard treatment Intervention 2 details (name and details of application): various including topical antibiotics, antiseptics, hydrophilic agents, bland agents, steroids, dry dressings; dressing applied and covered with gauze. Changed 3 times per week Compression: all participants wore crepe compression bandages Other co-interventions: ulcers cleansed with saline
Outcomes	Intervention 1: 3/28 Intervention 2: 1/29
Notes	Funding type and details: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "the patients were divided into two groups using random numbers" Comment: unclear how the random number sequence was obtained
Allocation concealment (selection bias)	Unclear risk	Quote "the patients were divided into two groups using random numbers" Comment: unclear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	57/60 completed and reasons for withdrawal given

Steele 1986 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	No evidence of this
All domain risk of bias	Low risk	Low/unclear

Taddeucci 2004

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis:ulcer Follow-up: 8 weeks
Participants	Inclusion criteria: venous ulceration present for > 3 months Exclusion criteria: arterial, metabolic or traumatic ulcers, infected ulcers with cellulitis, immunosuppressive, corticosteroid or cytostatic therapy in previous 4 weeks, insulin-dependent diabetes, concomitant diseases, pregnancy Participant characteristics Number participants: 17 participants (24 ulcers) Age: not reported % male: not reported Ulcer details Size: not reported Duration: not reported
Interventions	Intervention 1 class: hydrogel Intervention 1 details (name and details of application): Hyalofill-F (Fidia Advanced Biopolymers); dressing applied and covered with sterile gauze. Changed every 2-3 days initially then less frequently depending on wound condition Intervention 2 class: nonadherent Intervention 2 details (name and details of application): paraffin gauze; dressing applied and covered with sterile gauze. Changed every 2-3 days initially then less frequently depending on wound condition Compression: compression bandage Pehacrepp E (Paul Hartmann) Other co-interventions: initial debridement if necessary, then cleansing with saline at every dressing change
Outcomes	Intervention 1: 2/12 Intervention 2: 1/12
Notes	Funding type and details: funding not reported but some authors work for Fidia Advanced Biopolymers

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Taddeucci 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised study "subjects ... were ... assigned sequentially to one of two treatments" Comment: unclear how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Described as randomised study "subjects ... were ... assigned sequentially to one of two treatments" Comment: unclear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as "open"
Incomplete outcome data (attrition bias) All outcomes	High risk	1/12 vs 5/12 ulcers withdrawn, reasons given; imbalance and larger numbers than those healed
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	High risk	Unit of analysis issue. Unclear if clustering of some data adjusted for
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Tarvainen 1988

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 8 weeks
Participants	Inclusion criteria: chronic exuding leg ulcer Exclusion criteria: insulin-dependent diabetes, rheumatoid arthritis, connective tissue disease, goitre, known allergy to iodine Participant characteristics Number participants: 27 randomised; 21 analysed Age: 67.7 (13.3) vs 68.8 (14.6), range 39 to 86 vs 38 to 87 years % male: 4 (29) vs 3 (23)

	Ulcer details Non VLU: "[ulcers] were clinically judged to be mainly of venous origin" Size: not reported Duration: mean (SD) 54.8 (108.7) months vs 12.2 (23.0) months, range 1 to 360 months vs 1 to 72 months
Interventions	Intervention 1 class: cadexomer iodine Intervention 1 details (name and details of application): cadexomer iodine powder; applied in 3mm layer, then "covered with protective clean compress". Changed daily Intervention 2 class: dextranomer Intervention 2 details (name and details of application): dextranomer powder; applied in 3mm layer, then "covered with protective clean compress". Changed daily Compression: "a normal compression bandage was applied" Other co-interventions: ulcers washed with water or saline solution
Outcomes	Intervention 1: 7/11 Intervention 2: 5/10
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "random allocation to treatment" Comment: no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "each patient was allocated to the treatment by using a sealed enclosure envelope containing the treatment code of the individual patient"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as "open"
Incomplete outcome data (attrition bias) All outcomes	High risk	3/14 vs 5/13 appear to have dropped out for reasons other than healing - reasons given but numbers do not tally with text
Selective reporting (reporting bias)	Unclear risk	Results section confusing - data don't match

Tarvainen 1988 (*Continued*)

Other bias	Unclear risk	Reporting somewhat unclear; risks of bias uncertain
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Thomas 1997

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 13 weeks
Participants	Inclusion criteria: over 16 years. Venous leg ulcer maximum dimension 8 cm confirmed by medical history, clinical examination and ABPI > 0.8 Exclusion criteria: history of poor compliance, insulin-dependent diabetes, unlikely to survive study period, previous adverse reaction to study materials, clinically infected wounds Participant characteristics Number participants: 100 Age: 75.3 (14.4) vs 73.4 (13.2) years % male: 16 (32) vs 13 (26) Ulcer details Non VLU: (pressure ulcers included in separate stratified analysis) Size: mean (range) 335 (10 to 2758) mm^2 vs 431 (16 to 1876) mm^2 Duration: no summary statistic, grouped data < 1 month (3 vs 2) 1 to 3 months (13 vs 9) > 3 months (34 vs 39)
Interventions	Intervention 1 class: hydrocolloid Intervention 1 details (name and details of application): Granuflex Intervention 2 class: foam Intervention 2 details (name and details of application): Tielle Compression: type 3c compression bandage (Tensopress) applied over layer of orthopaedic wadding (Velband) Other co-interventions: Wounds cleansed with 0.9% NaCl (saline) solution as necessary
Outcomes	Intervention 1: 19/50 Intervention 2: 17/50
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Thomas 1997 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "patients ... were allocated to the two treatment groups on a randomised basis, using a system of sealed envelopes" Comment: unclear how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients ... were allocated to the two treatment groups on a randomised basis, using a system of sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as "open"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Unclear risk	No evidence of this but reporting insufficient
All domain risk of bias	High risk	
All domain risk of bias 2	High risk	

Tumino 2008

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 90 days
Participants	Inclusion criteria: non-infected venous stasis or post-phlebitis ulcers Exclusion criteria: hypersensitivity to study drug, pregnancy, neoplastic or other concomitant disease, previous use of local treatment for ulcer Participant characteristics Number participants: 100 Age: 64.9 (12.1) vs 67.7 (6.5) years % male: 23 (46) vs 26 (52) Ulcer details Size: 6.6 (8.9) vs 4.7 (9.1) (unit of size unclear) Duration: not reported

Interventions	Intervention 1 class: sucralfate Intervention 1 details (name and details of application): SUC-LIS 95 (Lisapharma); sucralfate hydrophilic gel; applied once daily for 30 to 90 days, covered with dry gauze Intervention 2 class: hydrogel (placebo gel) Intervention 2 details (name and details of application): manufactured by Lisapharma; applied once daily for 30 to 90 days, covered with dry gauze Compression: a few cases were covered with elastic bandage (no further details) Other co-interventions: cleaning with saline and iodine solution following surgical removal of debris
Outcomes	Intervention 1: 43/50 Intervention 2: 5/50
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information on how sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind and uses placebo manufactured externally
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind and uses placebo manufactured externally
Incomplete outcome data (attrition bias) All outcomes	High risk	5/50 vs 4/50 dropouts or deviations from protocol; not a high rate but close to the event rate in the placebo arm
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of this
All domain risk of bias	High risk	

Vanscheidt 2012

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: locally infected chronic venous leg ulcer below knee joint (CVI grade C6 according to CEAP classification), confirmed diagnosis of CVI, ulcer duration 4 weeks to 2 years, 2 cm^2 to 20 cm^2, presence of at least 2/9 infection criteria Exclusion criteria: contraindication with local wound therapy and compression therapy with bandages, hypersensitivity to study materials, previous or concomitant therapy with non permitted local or systemic drug therapy Participant characteristics Number participants: 126 (demographics for 124) Age: 66.9 (10.6) vs 68.7 (13.0) years % male: 30 (51) vs 23 (35) Ulcer details Size: mean (SD) 6.68 (4.76) cm^2 vs 6.98 (5.51) cm^2 Duration: not reported
Interventions	Intervention 1 class: octenidine Intervention 1 details (name and details of application): octenidine solution spray (+ non adhesive foam dressing); Ulcer completely moistened with spray at each dressing change (at least once a week, maximum 3 x per week) Intervention 2 class: foam (placebo (Ringer solution) spray) Intervention 2 details (name and details of application): Ringer solution spray (+ non adhesive foam dressing); ulcer completely moistened with spray at each dressing change (at least once a week, maximum 3 x per week) Compression: elastic bandages Other co-interventions: non-adhesive foam dressing used for all
Outcomes	Intervention 1: 15/60 Intervention 2: 16/66
Notes	Funding type and details: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no methods given
Allocation concealment (selection bias)	Unclear risk	Described as randomised but no methods given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind. Methods not clear about who was blinded

Vanscheidt 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind. Methods not clear about who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for dropouts explained - some were lost from analysis due to wound healing which is our outcome of interest
Selective reporting (reporting bias)	Low risk	No evidence of this
Other bias	Low risk	No evidence of this
All domain risk of bias	High risk	

Vin 2002

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: venous leg ulcer > 30 days duration, not infected, venous aetiology confirmed by Doppler ultrasound and ABPI > or =0.8, between 2 cm and 10 cm in any dimension. If multiple ulcers, largest selected (had to be 3 cm away from other ulcers) Exclusion criteria: unwilling to wear compression bandages, immobile, concomitant wound healing condition e.g. carcinoma, vasculitis, connective tissue disease, immune system disorder, used corticosteroids, immunosuppressive agents, radiation therapy or chemotherapy within 30 days prior Participant characteristics Number participants: 73 Age: 74.1 (12.1) vs 71.7 (11.4), range 33 to 87 vs 37 to 88 years % male: 15 (40.5) vs 11 (30.6) Ulcer details Size: mean (SD) 7.0 (6.8) cm^2 vs 9.5 (9.5) cm^2, range 1.6 to 35.5 vs 1.2 to 34.5 cm^2 Duration: mean (SD) 8.5 (11) vs 9.9 (20.2) months
Interventions	Intervention 1 class: PMM Intervention 1 details (name and details of application): Promogran (Johnson & Johnson) (+ Adaptic); Promogran cut to fit ulcer, Adaptic placed over the top. Dressing changed at least twice weekly Intervention 2 class: nonadherent Intervention 2 details (name and details of application): Adaptic (Johnson and Johnson Medical) Compression: compression bandages Biflex 16+ graduated version with tension indicator (Thuasne) worn continuously by all between dressing changes Other co-interventions: wound cleaned with warm sterile saline before dressing. Gauze pad (Topper, Johnson & Johnson) applied as secondary dressing to all

Vin 2002 (*Continued*)

Outcomes	Intervention 1: 18/37 Intervention 2: 12/63
Notes	Funding type and details: industry Funding details: Johnson & Johnson Wound Management, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised study. No details reported
Allocation concealment (selection bias)	Unclear risk	Described as randomised study. No details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all measures were performed by an investigator blinded to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all participants, ITT and PP analyses
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence
All domain risk of bias	Low risk	low/unclear

Zuccarelli 1992

Methods	RCT Arms: 2 Unit of randomisation: participant Unit of analysis: participant Follow-up: 12 weeks
Participants	Inclusion criteria: leg ulcer clinic outpatients Exclusion criteria: not reported Participant characteristics Number participants: 38 Age: not reported % male: not reported Ulcer details

Zuccarelli 1992 (*Continued*)

	Non VLU: not reported Size: not reported Duration: not reported
Interventions	Intervention 1 class: foam Intervention 1 details (name and details of application): Allevyn Intervention 2 class: hydrocolloid Intervention 2 details (name and details of application): not reported Compression: "elastic compression bandaging was standardised" Other co-interventions: not reported
Outcomes	Intervention 1: 9/19 Intervention 2: 9/19
Notes	Funding type: industry (unclear) Funding details: Smith and Nephew (unclear)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were recruited and randomised.." Comment: no information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were recruited and randomised.." Comment: No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included
Selective reporting (reporting bias)	Unclear risk	Limited information reported
Other bias	Unclear risk	Too little information to be confident
All domain risk of bias	Low risk	Low/unclear

Abbreviations::**ABI:** ankle brachial index; **ABPI:** ankle brachial pressure index; **BMI:** body mass index; **CEAP:** Comprehensive Classification System for Chronic Venous Disorders; **CVI** : chronic venous insufficiency; **DVT:** deep vein thrombosis; **HbA1c:** glycated; haemoglobin (average plasma glucose concentration (blood sugar levels)); **HTA:** health technology assessment; **IQR:** interquartile range; **ITT:** intention-to-treat (an ITT analysis is a comparison of the treatment groups that includes all patients as originally allocated after randomisation); **IV:** intravascular; **LOCF:** LAST IBSERVATION CARRIED FORWARD; **NaCL:** sodium chloride; **NIHR:** National Institute for Health Research; **PMM:** protease-modulating-matrix; **PP:** per-protocol (a PP analysis is a comparison of treatment groups that includes only those patients who completed treatment); **RCT:** randomised controlled trial; **SD:** standard deviation; **SE:** standard error; **SEM:** standard error of the mean; **SSD:** silver sulfadiazine; **VLU:** venous leg ulcer; **vs** versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acosta 1992	Did not report wound healing
Alvarez 2004	Did not report analysable healing data
Andersen 2002	Compares dressings of the same type
Andreev 2010	Did not report analysable healing data
Andriessen 2009	Did not report wound healing
Asselman 1995	Did not report analysable healing data
Bale 2004	Did not report wound healing
Bartoletti 1997	Dressing is not the only difference between groups
Bartoszewicz 2013	Did not report wound healing
Bastami 2012	Did not report wound healing
Beitner 1985	Did not report analysable healing data
Belcaro 2007	Did not report analysable healing data
Bianchi 2018	Only one eligible intervention, does not link network
Binic 2010	Did not report analysable healing data
Bruckner 2009	Did not report analysable healing data
Bull 1995a	Compares dressings of the same type
Burgess 1993	Compares dressings of the same type

(*Continued*)

Burgos 1989	Did not report wound healing
Cabete 2004	Did not report wound healing
Caetano 2009	Only one eligible intervention, does not link network
Callam 1987a	Only one eligible intervention, does not link network
Cardinal 2009a	Did not report analysable healing data
Cardinal 2009b	Did not report analysable healing data
Carville 2008	Did not report wound healing
Casoni 2006	Only one eligible intervention, does not link network
Cervadoro 2003	Dressing is not the only difference between groups
Chaloner 1992	Did not report analysable healing data
Chaloner 2004a	Compares dressings of the same type
Charles 2002a	Did not report wound healing
Cherry 1992	Did not report wound healing
Cherry 1998	Did not report analysable healing data
Chiummariello 2009	Did not report analysable healing data
Choucair 1998	Dressing is not the only difference between groups
Collier 1992	Did not report analysable healing data
Cordts 1992	Dressing is not the only difference between groups
Cullen 2012	Did not report analysable healing data
D'Alicandro 2003	Did not report wound healing
Daltrey 1981	Did not report wound healing
Davis 1992	Did not report analysable healing data
De Caridi 2016	Did not report analysable healing data

(*Continued*)

De la Brassinne 2006	Compares dressings of the same type
Dereure 2012b	More than 25% non-venous ulcers
Dini 2010	Did not report wound healing
Dini 2013	Did not report analysable healing data
Dmochowska 1999	Did not report analysable healing data
Duhra 1992	Only one eligible intervention, does not link network
Egan 1983	Did not report wound healing
El Heneidy 2016	Only one eligible intervention, does not link network
Eriksson 1984a	Dressing is not the only difference between groups
Eriksson 1984b	Did not report analysable healing data
Eriksson 1984c	Did not report analysable healing data
Eriksson 1991	Only one eligible intervention, does not link network
Falabella 1998	Did not report analysable healing data
Falanga 1996	Did not report wound healing
Falanga 1998	Only one eligible intervention, does not link network
Falanga 1999	Only one eligible intervention, does not link network
Falanga 2000	Only one eligible intervention, does not link network
Falanga 2001	Only one eligible intervention, does not link network
Farina 1997	Did not report analysable healing data
Fernández-Gines 2017	Ineligible population (includes participants with pressure ulcers)
Fischer 1984	Did not report wound healing
Floden 1978	Did not report analysable healing data
Frade 2012	Did not report analysable healing data

(*Continued*)

Franek 2002	Did not report analysable healing data
Franks 2007	Compares dressings of the same type
Freak 1992a	Did not report analysable healing data
Freak 1994	Did not report analysable healing data
Fumal 2002	Did not report analysable healing data
Galiano 2017	Only one eligible intervention, does not link network
Garcia 1984	Did not report analysable healing data
Garkaz 2014	Did not report analysable healing data
Gatti 2011	Did not report wound healing
Gethin 2008	Retracted study
Ghatnekar 2015	Compares dressings of the same type
Gibbons 2015	Only one eligible intervention, does not link network
Gibson 1995	Compares dressings of the same type
Gilligan 2014	More than 25% non-venous ulcers
Gravante 2013	Did not report analysable healing data
Groenewald 1980	Did not report analysable healing data
Groenewald 1981	Did not report analysable healing data
Gronberg 2014	Ineligible interventions
Grotewohl 1994	Did not report analysable healing data
Guarnera 2010	Only one eligible intervention, does not link network
Handfield-Jones 1988	Did not report analysable healing data
Harding 2005	Only one eligible intervention, does not link network
Harding 2012	Compares dressings of the same type

(*Continued*)

Harding 2013	Did not report wound healing
Harvey 1985	Did not report analysable healing data
He 2008	Did not report analysable healing data
Hellgren 1983	Did not report analysable healing data
Hill 2004	Did not report analysable healing data
Hillstrom 1988	Did not report analysable healing data
Holloway 1989	Did not report analysable healing data
Hornemann 1987	Did not report analysable healing data
Humbert 2014	Did not report analysable healing data
Hutchinson 1994	Did not report wound healing
Jasiel 1997a	Did not report wound healing
Jasiel 1997b	Did not report wound healing
Jones 2003	Compares dressings of the same type
Judy 2010	Did not report analysable healing data
Jørgensen 2006	Not an RCT
Jørgensen 2008	Did not report wound healing
Jørgensen 2009	Did not report analysable healing data
Kerihuel 2010	Did not report analysable healing data
Kikta 1988	Dressing is not the only difference between groups
Kirsner 2012	Only one eligible intervention, does not link network
Kirsner 2016a	Only one eligible intervention, does not link network
Kirsner 2016b	Only one eligible intervention, does not link network
Klemp 1986	Did not report wound healing

(*Continued*)

Klostermann 1974	Did not report analysable healing data
Koksal 2003	Dressing is not the only difference between groups
Kopera 2005	Did not report analysable healing data
Krasowski 2015	Did not report analysable healing data
Kucharzewski 2012	Did not report wound healing
König 2005	Did not report analysable healing data
La Marca 1999	Compares dressings of the same type
Lammoglia-Ordiales 2012	Compares dressings of the same type
Larsen 1995	Did not report analysable healing data
Larsen 1997	Did not report analysable healing data
Larsen 2005	Compares dressings of the same type
Laudanska 1988	Did not report analysable healing data
Lazareth 2008	Did not report analysable healing data
Limová 1996	Compares dressings of the same type
Limová 2002	Compares dressings of the same type
Limová 2003	Compares dressings of the same type
Lindgren 1998	Only one eligible intervention, does not link network
Lindholm 1995	Did not report wound healing
Ljungberg 1998	Compares dressings of the same type
Lofferer 1982	Did not report analysable healing data
Lopez 1998	Did not report analysable healing data
Lundeberg 1990	Only one eligible intervention, does not link network
Lundeberg 1991	Only one eligible intervention, does not link network

(*Continued*)

Maggio 2007	Did not report wound healing
Maggio 2012	Only one eligible intervention, does not link network
Mansson 1997	Did not report analysable healing data
Meaume 2005a	Did not report analysable healing data
Meaume 2005c	Did not report analysable healing data
Meaume 2008	Did not report analysable healing data
Meaume 2014	Did not report analysable healing data
Mehtar 1988	Did not report analysable healing data
Miller 2010	More than 25% non-venous ulcers
Milward 1991	Did not report analysable healing data
Moffatt 2014	More than 25% non-venous ulcers
Morimoto 2015	Not an RCT
Mosti 2010	Did not report analysable healing data
Mosti 2015	Did not report wound healing
Mostow 2005	Only one eligible intervention, does not link network
Mudge 2014	Did not report wound healing
Mulder 1995	Did not report analysable healing data
Mulligan 1988	Did not report analysable healing data
Nagl 2003	Did not report wound healing
Navratilova 2004	Only one eligible intervention, does not link network
Neander 2003	Did not report wound healing
Nelson 2011	Only one eligible intervention, does not link network
Nieves 2015	Only one eligible intervention, does not link network
Nowak 1996	Did not report analysable healing data

(*Continued*)

Nyfors 1982	Did not report analysable healing data
Olyaie 2013	Only one eligible intervention, does not link network
Omar 2004	Only one eligible intervention, does not link network
Ortonne 1996	Did not report analysable healing data
Osman 2014	Only one eligible intervention, does not link network
Pardes 1993	Did not report wound healing
Passarini 1982	Did not report analysable healing data
Peschen 1997	Only one eligible intervention, does not link network
Pessenhofer 1989	Did not report analysable healing data
Pessenhofer 1992	Did not report analysable healing data
Petres 1994	Did not report analysable healing data
Planinsek 2007a	Did not report analysable healing data
Planinsek 2007b	Did not report analysable healing data
Polignano 2001	Did not report wound healing
Poskitt 1987	Only one eligible intervention, does not link network
Price 2004	Did not report wound healing
Prins 2000	Did not report analysable healing data
Purcell 2017	Ineligible population < 75% with venous aetiology
Rainey 1993	Did not report wound healing
Rainey 1996	Compares dressings of the same type
Raposio 2018	Quasi-RCT
Rivera-Arce 2007	Did not report analysable healing data
Robinson 1993	Compares dressings of the same type

(*Continued*)

Robinson 1998	Did not report analysable healing data
Roldan 2009	Did not report analysable healing data
Romanelli 2006	Did not report analysable healing data
Romanelli 2008	Did not report analysable healing data
Romanelli 2009	Did not report wound healing
Romanelli 2011	Did not report analysable healing data
Romanelli 2015	Compares dressings of the same type
Rucigaj 2007	Did not report analysable healing data
Rundle 1981	Only one eligible intervention, does not link network
Sabolinski 1996	Dressing is not the only difference between groups
Santamato 2012	Did not report analysable healing data
Scalise 2017	Did not report wound healing
Schmutz 1997	Did not report wound healing
Schmutz 2008	Did not report analysable healing data
Serena 2011	Only one eligible intervention, does not link network
Serena 2014	Only one eligible intervention, does not link network
Serra 2010	Did not report analysable healing data
Sibbald 2005	Did not report analysable healing data
Sibbald 2007	Did not report analysable healing data
Sibbald 2011	Did not report analysable healing data
Siqueira 2014	Only one eligible intervention, does not link network
Skog 1983	Did not report analysable healing data
Smeets 2008	Did not report analysable healing data

(*Continued*)

Smith-Strom 2006	Did not report analysable healing data
Soares 2009	Only one eligible intervention, does not link network
Sparholt 2002	Compares dressings of the same type
Sridhar 2017	Ineligible population
Sriram 2014	Ineligible population
Sriram 2015	Did not report analysable healing data
Stiller 1992	Only one eligible intervention, does not link network
Stone 2016a	Did not report wound healing
Stone 2016b	Only one eligible intervention, does not link network
Sánchez-Vázquez 2008	Did not report analysable healing data
Taradaj 2008	Only one eligible intervention, does not link network
Teepe 1993	Only one eligible intervention, does not link network
Texier 1980	Did not report analysable healing data
Thomas 1997a	Compares dressings of the same type
Vanscheidt 2004	Compares dressings of the same type
Vanscheidt 2007	Only one eligible intervention, does not link network
Vas 2008	Only one eligible intervention, does not link network
Veraart 1994a	Did not report wound healing
Vitse 2017	Only one eligible intervention, does not link network
Vowden 2007	Only one eligible intervention, does not link network
Vuerstaek 2006	Compares dressings of the same type
Wayman 2000	Only one eligible intervention, does not link network
Weiss 1996	Compares dressings of the same type

(*Continued*)

Werner-Schlenzka 1994	Compares dressings of the same type
Westh 1998	Did not report wound healing
Wieman 2003	Compares dressings of the same type
Wild 2010	Did not report analysable healing data
Wong 2006	Did not assess eligible interventions
Woo 2009	Compares dressings of the same type
Woo 2010	Did not report analysable healing data
Wunderlich 1991	Did not report analysable healing data

Abbreviations:**RCT:** randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Alvarez 2017

Methods	RCT; 2 arms
Participants	16 participants with venous leg ulcers with at least 6 months duration
Interventions	Hyaluronic extracellular matrix Nonadherent silicone foam dressing
Outcomes	Complete wound healing at 16 weeks
Notes	Identified in updated search March 2018 Interim analysis

Belcaro 2011

Methods	RCT; 2 arms
Participants	People with “difficult” venous leg ulceration
Interventions	Four weeks treatment with silver oxide ointment or “best management”
Outcomes	Healing rate

Belcaro 2011 (*Continued*)

Notes	Abstracts only, unable to obtain full paper despite ILL

Cavalcanti 2017

Methods	RCT; 2 arms
Participants	25 participants with chronic venous leg ulcers
Interventions	Bacterial cellulose membrane Triglyceride oil
Outcomes	Complete wound healing at 120 days
Notes	Identified in updated search March 2018

Colenci 2016

Methods	RCT; 2 arms
Participants	29 participants with venous ulcers
Interventions	Hemicellulose biomembrane Collagenase
Outcomes	Complete wound healing at 90 days
Notes	Identified in updated search March 2018 Conference abstract only

Cullen 2017

Methods	RCT; 2 arms
Participants	49 participants with venous leg ulcers
Interventions	Collagen, oxidised regenerated cellulose and silver dressing Nonadherent dressing
Outcomes	Wound healing at 12 weeks
Notes	Identified in updated search March 2018

Glukhov 2017

Methods	RCT; 4 arms
Participants	85 participants with venous leg ulcers (stage II)
Interventions	Collagen and platelet-rich plasma Foam, hydrogel, alginate or hydrocolloid dressings Collagen only Platelet rich plasma only
Outcomes	Complete wound healing
Notes	Identified in update search March 2018

Moreno-Eutimio 2017

Methods	RCT; 2 arms
Participants	40 participants with venous leg ulcers
Interventions	Polysacharide with zinc oxide “Simple dressings”
Outcomes	Complete wound healing may be reported
Notes	Identified in update search March 2018 Spanish language - will require translation to confirm eligibility

Oliveira 2017

Methods	RCT; 2 arms
Participants	16 participants with 21 venous leg ulcers
Interventions	Hydrocolloid dressing Homologous platelet gel
Outcomes	Complete wound healing
Notes	Identified in updated search March 2018

Polignano 2010

Methods	RCT; 2 arms
Participants	29 participants with venous leg ulcers present for at least 6 months
Interventions	Purified omental lipids (POL) cream zinc oxide Three months treatment/follow-up Unclear if there is an additional difference between arms and ulcer aetiologies also unclear from Italian text
Outcomes	Healing
Notes	Paper in Italian, eligibility unclear without author contact and further translator assistance if eligible

Robinson 1988

Methods	Unclear, potential RCT
Participants	Potentially people with venous leg ulcers
Interventions	Duoderm Viscopaste PB7 bandage
Outcomes	Not known
Notes	Identified in updated search March 2018 Title record only

Somani 2017

Methods	RCT; 2 arms
Participants	15 participants with venous leg ulcers of at least 6 months duration
Interventions	Saline dressing Blood-based topical treatment
Outcomes	Complete closure reported for 5 participants in blood group versus 0 in saline group
Notes	Identified in updated search March 2018 Would potentially contribute to extended base-case network

Abbreviations: **ILL:** inter-library loan; **RCT:** randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Jull 2018

Trial name or title	Keratin4VLU
Methods	2-arm RCT
Participants	People with a venous leg ulcer present for more than 26 weeks or an ulcer > 5 cm^2
Interventions	Keramatrix - keratin-based dressing Usual care non-medicated dressing selected from the formulary of dressings available at each study centre. These dressings will include hydrogel, alginate, hydrofibre, polyurethane foam and silicon-impregnated dressings Compression therapy in both arms; secondary dressings as appropriate
Outcomes	Primary outcome - complete healing at 24 weeks
Starting date	Recruitment began March 2017
Contact information	a.jull@auckland.ac.nz
Notes	NCT02896725

Abbreviation: **RCT:** randomised controlled trial

DATA AND ANALYSES

Comparison 1. Direct evidence - included in base-case network

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alginate vs nonadherent	1	60	Risk Ratio (IV, Random, 95% CI)	1.08 [0.86, 1.36]
2 Cadexomer iodine vs nonadherent	1	105	Risk Ratio (IV, Random, 95% CI)	1.0 [0.39, 2.56]
3 Film vs nonadherent	1	71	Risk Ratio (IV, Random, 95% CI)	1.34 [0.61, 2.92]
4 Foam vs nonadherent	1	132	Risk Ratio (IV, Random, 95% CI)	1.35 [0.89, 2.05]
5 Hyaluronic plus povidone vs nonadherent	1	65	Risk Ratio (IV, Random, 95% CI)	1.93 [0.95, 3.92]
6 Hydrocolloid vs non-adherent	7	662	Risk Ratio (IV, Random, 95% CI)	1.26 [0.92, 1.72]
7 Hydrofibre vs nonadherent	1	82	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.88, 2.46]
8 Hydrogel vs nonadherent	1	24	Risk Ratio (IV, Random, 95% CI)	2.0 [0.21, 19.23]
9 PMM vs nonadherent	1	74	Risk Ratio (IV, Random, 95% CI)	1.42 [0.80, 2.51]
10 SSD vs nonadherent	1	60	Risk Ratio (IV, Random, 95% CI)	0.79 [0.57, 1.10]
11 Foam vs alginate	1	113	Risk Ratio (IV, Random, 95% CI)	0.55 [0.10, 2.86]
12 Hydrocolloid vs alginate	2	80	Risk Ratio (IV, Random, 95% CI)	0.72 [0.15, 3.42]
13 Hydrofibre vs alginate	2	175	Risk Ratio (IV, Random, 95% CI)	1.47 [0.48, 4.47]
14 Paste bandage vs alginate	1	133	Risk Ratio (IV, Fixed, 95% CI)	1.22 [0.91, 1.63]
15 PMM vs alginate	2	140	Risk Ratio (IV, Random, 95% CI)	1.10 [0.84, 1.46]
16 Gentian violet vs cadexomer iodine	1	60	Risk Ratio (IV, Random, 95% CI)	0.58 [0.27, 1.28]
17 Hydrocolloid vs cadexomer iodine	1	104	Risk Ratio (IV, Random, 95% CI)	0.73 [0.26, 2.08]
18 Hydrocolloid vs foam	6	458	Risk Ratio (IV, Random, 95% CI)	0.92 [0.77, 1.08]
19 Ibuprofen foam vs foam	2	242	Risk Ratio (IV, Random, 95% CI)	0.88 [0.48, 1.61]
20 Octenidine vs foam	1	126	Risk Ratio (IV, Random, 95% CI)	1.03 [0.56, 1.90]
21 Paste bandage vs foam	1	36	Risk Ratio (IV, Random, 95% CI)	2.30 [1.29, 4.10]
22 PMM vs foam	1	187	Risk Ratio (IV, Random, 95% CI)	0.87 [0.30, 2.48]
23 PMM silver vs foam	1	30	Risk Ratio (IV, Random, 95% CI)	1.57 [0.84, 2.92]
24 Silver vs foam	4	397	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.08, 2.52]
25 Saline gauze vs hyaluronic acid	1	88	Risk Ratio (IV, Random, 95% CI)	0.52 [0.23, 1.17]
26 PMM silver vs hydrocolloid	1	49	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.69, 1.67]
27 Povidone iodine vs hydrocolloid	1	200	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
28 Saline gauze vs hydrocolloid	1	28	Risk Ratio (IV, Fixed, 95% CI)	0.29 [0.07, 1.14]
29 Silver vs hydrocolloid	1	58	Risk Ratio (M-H, Random, 95% CI)	4.39 [2.23, 8.65]
30 Zinc oxide vs hydrocolloid	1	43	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.27, 3.33]
31 Sucralfate vs hydrogel	1	100	Risk Ratio (IV, Random, 95% CI)	8.60 [3.72, 19.90]

Comparison 2. Direct evidence - not in base case network, in expanded base case

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood product vs emollient	1	197	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.94, 1.82]
2 Blood product vs hydrocolloid	1	13	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.07, 10.96]
3 Blood product vs hydrogel	1	44	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.14, 1.58]
4 Blood product vs saline gauze	1	86	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.35]
5 Hyaluronic vs emollient cream	1	101	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.18, 3.25]
6 Growth factor vs hydrocolloid	1	29	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.22, 15.51]
7 Growth factor vs hydrogel	1	59	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.64, 3.01]
8 Growth factor vs nonadherent	3	460	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.14]
9 SSD vs emollient	1	57	Risk Ratio (M-H, Random, 95% CI)	6.21 [0.80, 48.38]

Comparison 3. Direct evidence - not in network

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *A. Pichinchensis* vs alginate	1	34	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.03, 2.70]
2 Non-adherent vs cellulose	1	48	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.38, 2.22]
3 Phenytoin vs no treatment	1	104	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.90, 1.74]
4 Cadexomer iodine vs standard treatment	3	157	Risk Ratio (M-H, Random, 95% CI)	5.16 [1.56, 17.10]
5 Honey vs standard treatment	1	368	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.36]
6 Papain vs hydrogel	2	70	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.25, 3.49]
7 Shale oil vs hydrogel	1	119	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.82, 2.68]
8 Tripeptide copper vs hydrogel	1	57	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.26]
9 Hydrocolloid vs collagen	1	96	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.50, 1.18]
10 Hydrocolloid vs dextranomer	1	108	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.37, 1.60]
11 Hydrocolloid vs magnesium sulphate	1	110	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.37, 132.40]
12 Hydrocolloid vs nonadherent or iodine	1	70	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.48]
13 Ozonated oil vs zinc oxide	1	29	Risk Ratio (M-H, Random, 95% CI)	10.31 [0.62, 170.96]
14 Cadexomer iodine vs dextranomer	2	63	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.64, 2.75]
15 Silica gel fibre vs standard care	1	120	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.31, 1.26]
16 Silver vs non-silver	1	213	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.16]
17 Sulphadryl vs inactive powder	1	168	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.10, 1.56]
18 Tripeptide copper vs emollient cream	1	58	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.86]
19 Tripeptide copper vs SSD	1	57	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.26]

ADDITIONAL TABLES

Table 1. Summary characteristics of individual studies

Study characteristic	Details of studies
Publication	Abstract or poster only: Caprio 1992; Casoni 2002; Hanft 2006; Ivins 2006; Kalis 1993; Lanzara 2008; Petkov 1997; Zuccarelli 1992. All other studies had a full publication
Multiple interventions	Three arms: Bishop 1992; De Araujo 2016; Hansson 1998; Robson 1995. All other studies had two arms
Unit of randomisation	Ulcer: Caprio 1992 Leg: Stacey 1997 Unclear: Hanft 2006; Kalis 1993; Leaper 1991 All other studies used participants as the unit of randomisation
Funding	Industry: Armstrong 1997; Backhouse 1987; Beckert 2006; Bishop 1992; Bowszyc 1995; Charles 2002; Dereure 2012a; Fogh 2012; Gottrup 2008; Hansson 1998;Humbert 2013; Jørgensen 2005; Kelechi 2012; Lanzara 2008; Leaper 1991; Meaume 2012; Moffatt 1992a; Moffatt 1992b; Moss 1987; Nelson 2007; Norkus 2005; Robson 1995; Scurr 1994; Senet 2003; Senet 2014; Smith 1992; Smith 1994; Stacey 2000; Vin 2002; Zuccarelli 1992. Others did not report funding source or reported no funding or a non-industry source
Follow-up time	4 weeks: Bishop 1992; Ivins 2006; Jørgensen 2005; Schulze 2001; 30 days: Solovastru 2015; 6 weeks: Armstrong 1997; Biland 1985;Fogh 2012; Gottrup 2008; Leaper 1991; Meredith 1988; Ohlsson 1994; Robson 1995; Scurr 1994; Senet 2014; Smith 1994;Steele 1986; 8 weeks: Brandrup 1990; Caprio 1992; Meaume 2012; Taddeucci 2004; Tarvainen 1988; 60 days: De Araujo 2016; Dereure 2012a; Humbert 2013; 9 weeks: Dimakakos 2009; Kalis 1993 10 weeks: Arnold 1994;12 weeks: Backhouse 1987; Blair 1988a; Blair 1988b; Callam 1992; Charles 2002; Hanft 2006; Hansson 1998; Harding 2001;Lanzara 2008; Luiza 2015; Moffatt 1992a; Moffatt 1992b; Ormiston 1985; Rasmussen 1991; Robson 2001; Romanelli 2015a; Salim 1992; Senet 2003; Senet 2011; Vanscheidt 2012; Vin 2002; Zuccarelli 1992; 3 months: Casoni 2002; 90 days: Tumino 2008; 13 weeks:Arenbergerova 2013; Thomas 1997; 4 months: Smith 1992; 20 weeks: Beckert 2006; Kelechi 2012; Robson 2004; 24 weeks: Nelson 2007;26 weeks: Moss 1987; Petkov 1997; 9 months: Stacey 1997; Stacey 2000; 10 months: Romero-Cerecero 2012; 12 months; Norkus 2005; Rubin 1990; Unclear/ till healing: Greguric 1994; Sopata 2016 (max 40 weeks) Kucharzewski 2013 (max 16 weeks)
Included < 25% non venous leg ulcers	Included non-venous leg ulcers: Armstrong 1997; Biland 1985; Brandrup 1990; Norkus 2005; Ohlsson 1994; Rasmussen 1991 Unclear: Backhouse 1987; Humbert 2013; Ivins 2006; Jørgensen 2005; Leaper 1991; Luiza 2015; Romero-Cerecero 2012; Senet 2011; Tarvainen 1988; Zuccarelli 1992. All others enrolled only participants with VLU

VLU: venous leg ulcers

Table 2. Studies: status in network/review

Study	Interventions	No eligible interventions	Expanded base-case	Base-case	Sensitivity analysis	Risk of bias
Alvarez 2012[c]	Cellulose Nonadherent	2	X	X	X	High
Arenbergerova 2013[b]	Hydrofibre Blood product	1	√	X	X	Very high
Armstrong 1997[a]	Alginate Hydrofibre	2	√	√	√	High
Arnold 1994[c]	Hydrocolloid Iodine OR non-adherent	2	X	X	X	Very high
Backhouse 1987[a]	Nonadherent Hydrocolloid	2	√	√	√	Low/Unclear
Banerjee 1997[a]	Nonadherent Film	2	√	√	√	Very high
Beckert 2006[c]	Shale oil Hydrogel	2	X	X	X	Low/unclear
Biland 1985[b]	Blood product Emollient cream	1	√	X	X	High
Bishop 1992[b]	Tripeptide copper Emollient cream SSD	3	√	X	X	Low/unclear
Blair 1988a[a]	Nonadherent Hydrocolloid	2	√	√	√	High
Blair 1988b[a]	Nonadherent SSD	2	√	√	√	High
Bowszyc 1995[a]	Foam Hydrocolloid	2	√	√	√	High
Brandrup 1990[a]	Hydrocolloid Zinc oxide	2	√	√	√	High
Brown 2014[c]	Silica gel Alternative traditional dressings	2	X	X	X	Very high

Table 2. Studies: status in network/review (*Continued*)

Callam 1992[a]	Nonadherent Foam		√	√	√	Very high
Caprio 1992[c]	Hydrocolloid Collagen	2	X	X	X	Low/unclear
Casoni 2002[a]	Nonadherent Hyaluronic+Povid	2	√	√	X	Low/unclear
Charles 2002[a]	Foam Hydrocolloid	2	√	√	√	Low/unclear
De Araujo 2016[b]	Blood product Hydrogel Papain	3 (2 in network)	√	X	X	Low/unclear
Dereure 2012a[b]	Hyaluronic acid Emollient cream	2	√	X	X	Low/unclear
Dimakakos 2009[a]	Foam Silver	2	√	√	√	Low/unclear
Fogh 2012[a]	Foam Silver	2	√	√	√	High
Gottrup 2008[a]	Foam Silver	2	√	√	√	High
Greguric 1994[c]	Magnesium sulphate Hydrocolloid	2	X	X	X	High
Hanft 2006[a]	PMM silver Hydrocolloid	2	√	√	√	High
Hansson 1998[a]	Nonadherent Cadexomer iodine Hydrocolloid	3	√	√	√	High
Harcup 1986[c]	Standard care Cadexomer iodine	2	X	X	X	Low/unclear
Harding 2001[a]	Alginate Hydrofibre	2	√	√	√	Very high

Table 2. Studies: status in network/review (*Continued*)

Hokkam 2011[c]	Phenytoin No treatment	2	X	X	X	Low/unclear
Humbert 2013[a]	Hyaluronic acid Saline gauze	2	√	√	√	High
Ivins 2006[a]	Foam Silver	2	√	√	√	Low/unclear
Jørgensen 2005[a]	Foam Silver	2	√	√	√	Low/unclear
Jull 2008[c]	Honey Standard care	2	X	X	X	Very high
Kalis 1993[c]	Hydrocolloid Dextranomer	2	X	X	X	Very high
Kelechi 2012[a]	Nonadherent Hydrofibre	2	√	√	√	High
Kucharzewski 2013[a]	Hydrocolloid Silver	2	√	√	√	High
Lanzara 2008[a]	PMM silver Foam	2	√	√	√	High
Leaper 1991[a]	Nonadherent Hydrocolloid	2	√	√	√	High
Lindsay 1986[c]	Standard care Cadexomer iodine	2	X	X	X	Low/unclear
Luiza 2015[c]	Papain Hydrogel	2	X	X	X	High
Meaume 2012[a]	PMM Foam	2	√	√	√	High
Meredith 1988[a]	Nonadherent Hydrocolloid	2	√	√	√	Low/unclear
Michaels 2009[c]	Silver non-silver	2	X	X	X	High
Moffatt 1992a[a]	Nonadherent Hydrocolloid	2	√	√	√	Low/unclear

Table 2. Studies: status in network/review (*Continued*)

Moffatt 1992b[a]	Alginate Nonadeherent	2	√	√	√	Low/unclear
Moss 1987[c]	Cadexomer iodine Dextranomer	2	X	X	X	Very high
Nelson 2007[a]	Nonadherent Hydrocolloid	2	√	√	√	Very high
Norkus 2005[a]	Foam Hydrocolloid	2	√	√	√	Very high
Ohlsson 1994[a]	Hydrocolloid Saline gauze	2	√	√	√	Low/unclear
Ormiston 1985[b]	Cadexomer iodine gentian violet	2	√	√	X	High
Petkov 1997[a]	PMM Alginate	2	√	√	√	Low/unclear
Rasmussen 1991[b]	Growth factor Hydrocolloid	1	X	X	√	High
Robson 1995[b]	Growth factor Nonadherent	1	X	X	√	Low/unclear
Robson 2001[b]	Growth factor Nonadherent	1	X	X	√	High
Robson 2004[b]	Growth factor Nonadherent	1	X	X	√	Low/unclear
Romanelli 2015a[a]	PMM Alginate	2	√	√	√	Low/unclear
Romero-Cerecero 2012[c]	*A. Pichinchensis* Alginate	2	X	X	X	High
Rubin 1990[a]	Foam paste bandage	2	√	√	√	High
Salim 1992[c]	Sulphadryl Inactive powder	2	X	X	X	High

Table 2. Studies: status in network/review (*Continued*)

Schulze 2001[a]	Foam alginate	2	√	√	√	Very high
Scurr 1994[a]	Hydrocolloid Alginate	2	√	√	√	Low/unclear
Senet 2003[b]	Blood product Hydrocolloid	1	X	X	√	Low/unclear
Senet 2011[b]	Growth factor Hydrogel	1	X	X	√	High
Senet 2014[a]	silver foam	2	√	√	√	High
Smith 1992[a]	Hydrocolloid Povidone iodine	2	√	√	√	Very high
Smith 1994[a]	Hydrocolloid alginate	2	√	√	√	Very high
Solovastru 2015[c]	Ozonated oil Emollient cream	2	X	X	X	Low/unclear
Sopata 2016[a]	hydrocolloid foam	2	√	√	√	Very high
Stacey 1997[a]	Paste bandage alginate	2	√	√	√	High
Stacey 2000[b]	Blood product Saline gauze	1	X	X	√	High
Steele 1986[c]	Standard care Cadexomer iodine	2	X	X	X	Low/unclear
Taddeucci 2004[a]	Nonadherent Hydrogel	2	√	√	√	Very high
Tarvainen 1988[c]	Cadexomer iodine Dextranomer	2	X	X	X	Very high
Thomas 1997[a]	Foam Hydrocolloid	2	√	√	√	Very high

Table 2. Studies: status in network/review (*Continued*)

Tumino 2008[a]	Sucralfate Hydrogel	2	√	√	√	High
Vanscheidt 2012[a]	Octenidine Foam	2	√	√	X	High
Vin 2002[a]	PMM nonadherent	2	√	√	√	Low/unclear
Zuccarelli 1992[a]	Foam Hydrocolloid	2	√	√	√	Low/unclear

Abbreviations: **PMM:** protease modulating matrix; **SSD:** silver sulphadiazine
[a] Study in original base-case
[b] Study only included in sensitivity analysis
[c] Study included in review but not in network

Table 3. Direct comparisons for individual interventions compared with NMA results

Contrast/comparison	Number of studies (participants)	Studies	RR (95% CI) direct evidence. Random effects (inverse variance) Heterogeneity statistics	NMA results (extended base-case; consistency assumption): RR (95% CI)
Comparisons with ***nonadherent: RR*** *> 1 indicates greater proportion healing with specified alternative treatment*				
Alginate	1 (113)	Moffatt 1992b	1.08 (0.86 to 1.36)	1.21 (0.92 to 1.60)
Cadexomer iodine	1 (105)	Hansson 1998	1.00 (0.39 to 2.56)	1.16 (0.50 to 2.69)
Film	1 (71)	Banerjee 1997	1.34 (0.61 to 2.92)	1.34 (0.61 to 2.95)
Foam	1 (124)	Callam 1992	1.35 (0.89 to 2.05)	1.15 (0.91 to 1.44)
Hyaluronic acid plus povidone iodine	1 (55)	Casoni 2002	1.93 (0.95 to 3.92)	1.93 (0.94 to 3.96)
Hydrocolloid	7 (662)	Backhouse 1987; Blair 1988a; Hansson 1998; Leaper 1991; Meredith 1988; Moffatt 1992a; Nelson 2007	1.26 (0.92 to 1.72) I^2 = 69%; P = 0.004	1.04 (0.85 to 1.29)
Hydrofibre	1 (82)	Kelechi 2012	1.47 (0.88 to 2.46)	1.39 (0.93 to 2.08)
Hydrogel	1 (24)	Taddeucci 2004	2.00 (0.21 to 19.23)	0.79 (0.39 to 1.62)

Table 3. Direct comparisons for individual interventions compared with NMA results (*Continued*)

PMM	1 (74)	Vin 2002	1.42 (0.80 to 2.51)	1.31 (0.93 to 1.84)
SSD	1 (60)	Blair 1988b	0.79 (0.57 to 1.10)	0.81 (0.57 to 1.15)
Growth factor[a]	3 (460)	Robson 1995; Robson 2001; Robson 2004	0.96 (0.81 to 1.14) I² = 0%; P = 0.65	0.95 (0.72 to 1.25)
Comparisons with ***alginate: RR*** *> 1 indicates greater proportion healing with specified alternative treatment*				
Foam	1 (113)	Schulze 2001	0.55 (0.10 to 2.86)	0.94 (0.72 to 1.23)
Hydrocolloid	2 (80)	Scurr 1994; Smith 1994	0.72 (0.15 to 3.42) I² = 52%; P = 0.15	0.86 (0.68 to 1.11)
Hydrofibre	2 (175)	Armstrong 1997; Harding 2001	1.47 (0.48 to 4.47) I² = 54%; P = 0.14	1.15 (0.77 to 1.72)
Paste bandage	1 (133)	Stacey 1997	1.22 (0.91 to 1.63)	1.39 (1.01 to 1.90)
PMM	2 (140)	Petkov 1997; Romanelli 2015a	1.10 (0.84 to 1.46) I² = 0%; P = 0.87	1.08 (0.83 to 1.40)
Comparisons with ***cadexomer iodine: RR*** *> 1 indicates greater proportion healing with specified alternative treatment*				
Hydrocolloid	1 (104)	Hansson 19980	0.73 (0.26 to 2.08)	0.90 (0.39 to 2.10)
Gentian violet	1 (60)	Ormiston 1985	0.58 (0.27 1.28)	0.58 (0.26 to 1.29)
Comparisons with ***foam: RR*** *> 1 indicates greater proportion healing with specified alternative treatment*				
Hydrocolloid	6 (458)	Bowszyc 1995; Charles 2002; Norkus 2005; Sopata 2016; Thomas 1997; Zuccarelli 1992	0.92 (0.77 to 1.08) I² = 0%; P = 0.84	0.91 (0.78 to 1.07)
Ibuprofen	2 (242)	Fogh 2012; Gottrup 2008	0.88 (0.48 to 1.61) I² = 0%; P = 0.79	0.88 (0.48 to 1.62)
Octenidine	1 (126)	Vanscheidt 2012	1.03 (0.56 to 1.90)	1.03 (0.55 to 1.92)
Paste bandage	1 (36)	Rubin 1990	2.30 (1.29 to 4.10)	1.47 (0.99 to 2.17)
PMM	1 (187)	Meaume 2012	0.87 (0.30 to 2.48)	1.14 (0.82 to 1.60)
PMM silver	1 (30)	Lanzara 2008	1.57 (0.84 to 2.92)	1.15 (0.78 to 1.71)

Table 3. Direct comparisons for individual interventions compared with NMA results (*Continued*)

Silver	4 (397)	Dimakakos 2009;Ivins 2006; Jørgensen 2005; Senet 2014	1.65 (1.08 to 2.52) I^2 = 0%; P = 0.77	2.12 (1.46 to 3.07)
Comparisons with ***hyaluronic acid: RR*** > *1 indicates greater proportion healing with specified alternative treatment*				
Saline gauze	1 (88)	Humbert 2013	0.52 (0.23 to 1.17)	0.57 (95% CI 0.28 to 1.14)
Emollient cream	1 (101)	Dereure 2012a	1.31 (0.31 to 5.55)	1.75 (0.87 to 3.52)
Comparisons with ***hydrocolloid: RR*** > *1 indicates greater proportion healing with specified alternative treatment*				
PMM silver	1 (49)	Hanft 2006	1.07 (0.69 to 1.67)	1.27 (0.87 to 1.85)
Povidone iodine	1 (200)	Smith 1992	0.92 (0.69 to 1.23)	0.92 (0.68 to 1.26)
Saline gauze	1 (28)	Ohlsson 1994	0.29 (0.07 to 1.14)	0.34 (95% CI 0.15 to 0.8)
Silver	1 (58)	Kucharzewski 2013	4.39 (2.23 to 8.65) Note 100% events in silver arm	2.32 (1.58 to 3.41)
Zinc oxide	1 (43)	Brandrup 1990	0.95 (0.27 to 3.33)	0.95 (0.27 to 3.35)
Blood product[a]	1 (13)	Senet 2003	0.86 (0.07 to 10.96)	0.38 (95% CI 0.17 to 0.88)
Growth factor[a]	1 (29)	Rasmussen 1991	1.83 (0.22 to 15.51)	0.91 (0.71 to 1.17)
Comparisons with***hydrogel: RR*** > *1 indicates greater proportion healing with specified alternative treatment*				
Sucralfate	1 (100)	Tumino 2008	8.60 (3.72 to 19.90)	8.60 (3.68 to 20.07)
Blood product[a]	1 (44)	De Araujo 2016	0.47 (0.14 to 1.58)	0.51 (CI 0.21 to 1.23)
Growth factor[a]	1 (59)	Senet 2011	1.38 (0.64 to 3.01)	1.20 (0.61 to 2.35)
Comparisons with ***blood product***: *RR > 1 indicates greater proportion healing with specified alternative treatment*				
Saline gauze	1 (67)	Stacey 2000	0.93 (0.74 to 1.16)	0.89 (0.68 to 1.17)
Emollient cream	1 (147)	Biland 1985	0.76 [0.55, 1.06]	0.79 (0.56 to 1.11)
Comparisons with ***emollient cream: RR*** > *1 indicates greater proportion healing with specified alternative treatment*				

Table 3. Direct comparisons for individual interventions compared with NMA results (*Continued*)

SSD	1 (57)	Bishop 1992	6.21 (0.80 to 48.38)	2.56 (1.01 to 6.53)

Abbreviations: **PMM:** protease modulating matrix; **RR:** relative risk; **SSD:** silver sulphadiazine
[a]Non-eligible linking intervention

Table 4. Interventions in the included studies

Intervention	Number of included studies	Included studies	Number of participants in included studies
A. Pichinchensis	1	Romero-Cerecero 2012	34
Alginate	10	Armstrong 1997; Harding 2001; Moffatt 1992b; Petkov 1997; Romanelli 2015a; Romero-Cerecero 2012; Schulze 2001; Scurr 1994; Smith 1994; Stacey 1997	735
Blood product[a]	5	Arenbergerova 2013; Biland 1985; De Araujo 2016; Senet 2003; Stacey 2000	431
Cadexomer iodine	7	Hansson 1998; Harcup 1986; Lindsay 1986; Moss 1987; Ormiston 1985; Steele 1986; Tarvainen 1988	433
Cellulose	1	Alvarez 2012	48
Collagen	2	Caprio 1992; Robson 1995	132
Dextranomer	3	Kalis 1993; Moss 1987; Tarvainen 1988	171
Emollient cream	3	Biland 1985; Bishop 1992; Dereure 2012a	384
Film	1	Banerjee 1997	56
Foam	18	Bowszyc 1995; Callam 1992; Charles 2002; Dimakakos 2009; Fogh 2012; Gottrup 2008; Ivins 2006; Jørgensen 2005; Lanzara 2008; Meaume 2012; Norkus 2005; Rubin 1990; Schulze 2001; Senet 2014; Sopata 2016;	1672

Table 4. Interventions in the included studies (*Continued*)

		Thomas 1997; Vanscheidt 2012; Zuccarelli 1992	
Gentian violet	1	Ormiston 1985	60
Growth factor[a]	5	Rasmussen 1991; Robson 1995; Robson 2001; Robson 2004; Senet 2011	560
Honey	1	Jull 2008	368
Hyaluronic acid	2	Dereure 2012a; Humbert 2013	189
Hyaluronic acid + povidone iodine	1	Casoni 2002	65
Hydrocolloid	25	Backhouse 1987; Blair 1988a; Bowszyc 1995;Brandrup 1990; Caprio 1992; Charles 2002; Greguric 1994; Hanft 2006; Hansson 1998; Kalis 1993; Kucharzewski 2013; Leaper 1991; Meredith 1988; Moffatt 1992a; Nelson 2007; Norkus 2005; Ohlsson 1994; Rasmussen 1991; Scurr 1994; Senet 2003; Smith 1992; Smith 1994; Sopata 2016; Thomas 1997; Zuccarelli 1992	2044
Hydrofibre	4	Arenbergerova 2013; Armstrong 1997; Harding 2001; Kelechi 2012	329
Hydrogel	6	Beckert 2006; De Araujo 2016; Luiza 2015; Senet 2011; Taddeucci 2004; Tumino 2008	393
Ibuprofen	2	Fogh 2012; Gottrup 2008	222
Magnesium sulphate	1	Greguric 1994	110
Nonadherent	20	Alvarez 2012; Arnold 1994; Backhouse 1987; Banerjee 1997; Blair 1988a; Blair 1988b; Callam 1992; Casoni 2002; Hansson 1998; Kelechi 2012; Leaper 1991; Moffatt 1992a; Moffatt 1992b; Meredith 1988; Nelson	1725

Table 4. Interventions in the included studies (*Continued*)

		2007; Robson 1995; Robson 2001; Robson 2004; Taddeucci 2004; Vin 2002	
Non silver	1	Michaels 2009	208
No treatment	1	Hokkam 2011	104
Octenidine	1	Vanscheidt 2012	106
Ozonated oil	1	Solovastru 2015	29
Papain	2	De Araujo 2016; Luiza 2015	70
Paste bandage	2	Rubin 1990; Stacey 1997	149
Phenytoin	1	Hokkam 2011	104
Povidone iodine	1	Smith 1992;	200
PMM	4	Meaume 2012; Petkov 1997; Romanelli 2015a; Vin 2002	400
PMM-silver	2	Hanft 2006; Lanzara 2008;	79
Saline gauze	3	Humbert 2013; Ohlsson 1994; Stacey 2000	202
Shale oil	1	Beckert 2006	119
Silica gel fibre	1	Brown 2014	120
Silver	6	Dimakakos 2009; Ivins 2006; Jørgensen 2005; Kucharzewski 2013; Michaels 2009; Senet 2014;	663
SSD	2	Bishop 1992; Blair 1988b	146
Standard care/mixed treatments	6	Arnold 1994; Brown 2014; Harcup 1986; Jull 2008; Lindsay 1986; Steele 1986	715
Sucralfate	1	Tumino 2008	100
Suphadryl	1	Salim 1992	137
Tripeptide copper	1	Bishop 1992	86

Table 4. Interventions in the included studies (*Continued*)

Zinc oxide	2	Brandrup 1990; Solovastru 2015	72

Abbreviations: **PMM:** protease modulating matrix; **SSD:** silver sulphadiazine
[a] Ineligible intervention included in expanded base-case to improve network connectivity

Table 5. Comparison of NMA results for base-case and two sensitivity analyses

NMA contrast	Base-case RR (95% CI)	Narrow sensitivity analysis RR (95% CI)	Extended sensitivity analysis RR (95% CI)
Sucralfate versus hydrogel	8.60 (3.66 to 20.2)	---	8.60 (3.68 to 20.1)
Sucralfate versus silver	6.99 (0.60 to 82.0)	---	2.80 (0.88 to 8.97)
Sucralfate versus foam	14.83 (1.30 to 169)	---	5.94 (1.96 to 18.0)
Sucralfate versus hydrocolloid	16.24 (1.43 to 185)	---	6.51 (2.17 to 19.6)
Sucralfate versus nonadherent	17.15 (1.52 to 193)	---	6.80 (2.24 to 20.7)
Hydrogel versus silver	0.81 (0.08 to 8.19)	0.81 (0.08 to 8.20)	0.33 (0.15 to 0.72)
Hydrogel versus foam	1.73 (0.18 to 16.9)	1.72 (0.18 to 16.9)	0.69 (0.34 to 1.41)
Hydrogel versus hydrocolloid	1.89 (0.19 to 18.4)	1.88 (0.19 to 18.4)	0.76 (0.38 to 1.53)
Hydrogel versus nonadherent	1.99 (0.21 to 19.3)	2.00 (0.21 to 19.4)	0.79 (0.39 to 1.62)
Silver versus foam	2.12 (1.46 to 3.09)	2.12 (1.45 to 3.10)	2.12 (1.46 to 3.07)
Silver versus hydrocolloid	2.32 (1.58 to 3.43)	2.32 (1.57 to 3.44)	2.32 (1.58 to 3.41)
Silver versus nonadherent	2.45 (1.58 to 3.82)	2.47 (1.58 to 3.86)	2.43 (1.58 to 3.74)
Foam versus hydrocolloid	1.10 (0.93 to 1.28)	1.09 (0.93 to 1.29)	1.10 (0.94 to 1.28)
Foam versus nonadherent	1.16 (0.91 to 1.47)	1.16 (0.91 to 1.49)	1.15 (0.91 to 1.44)
Hydrocolloid versus nonadherent	1.06 (0.84 to 1.32)	1.06 (0.85 to 1.33)	1.04 (0.85 to 1.29)

Abbreviations: **CI:** confidence interval; **RR:** relative risk

Table 6. Ranks of treatments - base-case and two sensitivity analyses (ordered by mean rank)

Treatment	Base-case (rank of 22) Mean rank (SUCRA) and maximum probability and its corresponding rank	Narrow sensitivity analysis (rank of 17) Mean rank (SUCRA) and maximum probability and its corresponding rank	Extended base-case (rank of 25)# Mean rank (SUCRA) and maximum probability and its corresponding rank
Sucralfate	1.5 (1.0) 91% (rank 1)	---	1.1 (1.0) 93% (rank 1)
Silver	3.2 (0.9) 38% (rank 3)	1.9 (0.9) 40% (rank 2)	2.7 (0.9) 50% (rank 2)
Hyaluronic acid + povidone iodine	5.8 (0.8) 32% (rank 21)	---	5.3 (0.8) 21% (rank 3)
Paste bandage	5.8 (0.8) 19% (rank 5)	4.0 (0.8) 26% (rank 3)	5.4 (0.8) 22% (rank 4)
Hydrofibre	8.3 (0.7) 14% (rank 7)	5.9 (0.7) 17% (rank 5)	8.1 (0.7) 16% (rank 6)
Hydrogel	8.9 (0.6) 39% (rank 2)	6.4 (0.7) 39% (rank 1)	16.9 (0.3) 15% (rank 20)
PMM	9.4 (0.6) 15% (rank 9)	7.0 (0.6) 19% (rank 6)	9.0 (0.7) 16% (rank 8)
PMM silver	9.5 (0.6) 12% (rank 8)	6.8 (0.6) 15% (rank 5)	8.9 (0.7) 13% (rank 7)
Film	10.1 (0.6) 9% (rank 5)	7.5 (0.6) 10% (rank 3)	10.2 (0.6) 9% (rank 5)
Alginate	10.9 (0.5) 17% (rank 10)	8.1 (0.6) 20% (rank 7)	10.5 (0.6) 16% (rank 10)
Octenidine	11.4 (0.5) 7% (rank 7)	---	11.4 (0.6) 9% (rank 6)
Foam	12.0 (0.5) 18% (rank 11)	9.0 (0.5) 20% (rank 9)	11.5 (0.6) 17% (rank 11)
Cadexomer iodine	12.1 (0.5) 9% (rank 19)	9.0 (0.5) 9% (rank 4)	11.8 (0.5) 8% (rank 19)
Zinc oxide	13.3 (0.4) 13% (rank 20)	10.5 (0.4) 14% (rank 15)	14.4 (0.4) 8% (rank 25)
Ibuprofen-releasing foam	14.1 (0.4) 12% (rank 18)	---	14.3 (0.4) 9% (rank 18)
Hydrocolloid	14.3 (0.4) 21% (rank 15)	11.0 (0.4) 25% (rank 11)	14.0 (0.5) 18% (rank 14)
Nonadherent	15.2 (0.3) 18% (rank 15)	11.8 (0.3) 25% (rank 13)	15.3 (0.4) 15% (rank 15)
Povidone iodine	15.2 (0.3) 14% (rank 17)	11.8 (0.3) 17% (rank 13)	15.5 (0.4) 12% (rank 17)
Hyaluronic acid	15.7 (0.3) 18% (rank 4)	12 (0.3) 38% (rank 16)	17.0 (0.3) 19% (rank 22)
Gentian violet	17.4 (0.2) 19% (rank 21)	---	18.4 (0.3) 16% (rank 25)

Table 6. Ranks of treatments - base-case and two sensitivity analyses (ordered by mean rank) (*Continued*)

SSD	18.1 (0.2)_____23% (rank 19)	14 (0.2)_____28% (rank 15)	18.8 (0.3)_____16% (rank 19)
Saline gauze	21.0 (0)_____69% (rank 22)	16.3 (0)_____77% (rank 17)	23.0 (0.1)_____33% (rank 24)

Abbreviations:**PMM:** protease modulating matrix; **SSD:** silver sulphadiazine; **SUCRA** surface under the cumulative ranking curve
ranks for extra treatments not reported

Table 7. Contributions matrix

Mixed treatment comparisons ⇨ Direct comparisons (risk of bias) ⇩	**Silver vs HC**	**HC vs NA**	**Foam vs NA**	**HC vs Foam**	**Silver vs foam**	**Sucralfate vs HC**	**Silver vs NA**	**Sucralfate vs NA**	**Sucralfate vs silver**	**Sucralfate vs foam**
Hyaluronic + povidone iodine vs nonadherent (low)										
Hydrocolloid vs nonadherent (high)	3.0	80.6	32.7	6.2	1.2	17.9	28.9	2.7	11.1	10.9
Hyaluronic acid vs saline gauze (high)										
Hydrofibre vs nonadherent	0.2	0.6	1.0	0.3	0.1	0.1	0.7	0.4	0.2	0.2

Table 7. Contributions matrix (*Continued*)

(high)										
Hydrogel vs nonadherent (very high)						3.4		5.2	2.6	3.4
PMM vs nonadherent (low)	0.3	0.8	2.1	0.6	0.1	0.3	1.3	0.1	0.5	0.8
PMM silver vs hydrocolloid (high)	1.0	0.1	1.2	2.2	0.4	0.1	0.4		0.3	0.6
Hydrocolloid vs povidone iodine (very high)										
Hydrocolloid vs saline gauze (low)		0.2	0.1			2.7	0.1	1.9	1.8	1.9
Silver vs hydrocolloid (high)	32.5	0.1	0.9	2.2	12.9	0.1	15.9		7.2	0.5
Hydrocolloid vs zinc oxide (high)										
SSD vs nonadherent (high)		0.1				0.5		0.9	0.4	0.5

Table 7. Contributions matrix (*Continued*)

Cadexomer iodine vs nonadherent (high)		0.8	0.3			0.2	0.3		0.1	0.1
Sucralfate vs hydrogel (high)						25.1		32.4	18.7	21.4
Film vs nonadherent (very high)										
Foam vs nonadherent (very high)	2.5	5.4	21.4	5.3	1.0	1.8	9.1	0.3	3.3	5.8
Growth factor vs nonadherent (low)		0.5	0.2			16.2	0.2	22.7	12.2	13.8
Hydrocolloid vs alginate (high)	0.3	0.5		0.5	0.1	0.3	0.1			
Hydrofibre vs alginate (very high)	0.2	0.6	1.0	0.3	0.1	0.4	0.7	0.1	0.5	0.6
Paste bandage vs alginate (high)	0.4	0.4	1.3	0.7	0.2	0.2	0.8		0.5	0.6

Table 7. Contributions matrix (*Continued*)

PMM vs alginate (low)	0.1	0.4	0.7	0.1		0.1	0.5	0.1	0.2	0.2
Foam vs alginate (very high)	0.1	0.1	0.4	0.3	0.1	0.1	0.2		0.1	0.2
Hydrocolloid vs blood product (low)		0.1				1.2		0.8	0.9	0.9
Hydrofibre vs blood product (very high)						0.4		0.5	0.3	0.4
Hydrogel vs blood product (low)		0.2	0.1			4.8	0.1	4.2	3.4	3.7
Blood product vs saline gauze (high)		0.2	0.1			2.7	0.1	1.9	1.8	1.9
Blood product vs emollient cream (high)		0.1				0.6		1.0	0.5	0.5
Hydrocolloid vs cadexomer iodine (high)		0.8	0.3			0.2	0.3		0.1	0.1

Table 7. Contributions matrix (*Continued*)

Gentian violet vs cadexomer iodine (high)										
Hyaluronic acid vs emollient cream (low)										
SSD vs emollient cream (low)		0.1				0.5		0.9	0.4	0.5
Hydrocolloid vs foam (very high)	26.6	6.0	31.2	75.5	11.1	2.1	13.3	0.3	7.0	13.1
Ibuprofen foam vs foam (high)										
Octenidine vs foam (high)										
Paste bandage vs foam (high)	0.4	0.4	1.3	0.7	0.2	0.2	0.8		0.5	0.6
PMM vs foam (high)	0.3	0.4	1.4	0.5	0.1	0.1	0.8		0.4	0.5
PMM silver vs foam (high)	1.0	0.1	1.2	2.2	0.4	0.1	0.4		0.3	0.6

Table 7. Contributions matrix (*Continued*)

Silver vs foam (low)	31.0	0.1	0.9	2.2	71.9	0.1	24.7		11.6	0.5
Hydrocolloid vs growth factor (high)		0.4	0.1			0.7	0.1	0.3	0.5	0.5
Hydrogel vs hydrocolloid (high)		0.1	0.1			16.9	0.1	23.0	12.7	14.3
RISK OF BIAS FOR Mixed Treatment Comparison	**High**	**High**	**High**	**Very high**	**Low**	**High**	**High**	**High**	**High**	**High**

Abbreviations:**HC:** hydrocolloid; **NA:** nonadherent; **PMM:** protease modulating matrix; **SSD:** silver sulphadiazine

Table 8. Inconsistency factors - base-case and extended base-case

Loop	RoRR and 90%CI	P value	Loop heterogeneity tau² (loop)
Foam-hydrocolloid-silver	2.44 (90%CI 1.23 to 4.84)	0.033	0
Nonadherent-alginate-foam	2.28 (90%CI 0.54 to 9.67)	0.349	0
Alginate-foam-PMM	2.26 (90%CI 0.43 to 11.94)	0.419	0
Nonadherent-cadexomer-hydrocolloid	1.81 (90%CI 0.25 to 13.24)	0.625	0.104
Nonadherent-alginate-hydrocolloid	1.66 (90%CI 0.35 to 7.74)	0.59	0.103
Foam-hydrocolloid-PMM silver	1.60 (90%CI 0.83 to 3.08)	0.24	0
Alginate-foam-hydrocolloid	1.40 (90%CI 0.26 to 7.39)	0.74	0

Table 8. Inconsistency factors - base-case and extended base-case (*Continued*)

Nonadherent-alginate-PMM	1.26 (90%CI 0.72 to 2.21)	0.503	0
Nonadherent-foam-PMM	1.25 (90%CI 0.43 to 3.62)	0.73	0
Nonadherent-alginate-hydrofibre	1.18 (90%CI 0.61 to 2.26)	0.684	0
Nonadherent-foam-hydrocolloid	1.06 (90%CI 0.55 to 2.06)	0.878	0.042
Alginate-foam-paste bandage	1.03 (90%CI 0.23 to 4.58)	0.974	0
Extended base-case only			
Nonadherent-growth factor-hydrogel	3.00 (90%CI 0.40 to 22.43)	0.370	0
Blood product-hydrocolloid-saline gauze	2.78 (90%CI 0.24 to 31.92)	0.491	0
Nonadherent-growth factor-hydrocolloid	2.23 (90%CI 0.21 to 23.65)	0.577	0.078
Quadratic loops			
Alginate-blood product-hydrocolloid-hydrofibre	7.34 (90%CI 0.12 to 460.27)	0.428	0.487
Nonadherent-blood product-hydrofibre-hydrogel	4.7 (90%CI 0.15 to 148.15)	0.461	0
Nonadherent-blood product-hydrocolloid-hydrofibre	4.09 (90%CI 0.03 to 493.5)	0.629	0.096
Blood product-emollient cream-hyaluronic acid-saline gauze	3.68 (90%CI 0.89 to 15.16)	0.131	0
Blood product-growth factor-hydrocolloid-hydrogel	1.38 (90%CI 0.07 to 28.86)	0.862	0
Nonadherent-blood product-hydrocolloid-hydrogel	1.15 (90%CI 0.02 to 82.36)	0.957	0.096

Abbreviations:**CI:** confidence interval; **PMM:** protease modulating matrix; **RoRR:** ratio of relative risks

Table 9. Node splitting

Comparison	Direct RR (95% CI)	Indirect RR (95% CI)	RoRR (90% CI)
Alginate vs nonadherent	1.08 (95% CI 0.86 to 1.36)	1.52 (95% CI 1.07 to 2.15)	0.71 (90% CI 0.50 to 1.02)
Foam vs nonadherent	1.35 (95% CI 0.87 to 2.08)	1.10 (95% CI 0.83 to 1.47)	1.22 (90% CI 0.79 to 1.89)
Hydrocolloid vs nonadherent	0.94 (95% CI 0.72 to 1.23)	2.01 (95% CI 0.56 to 7.23)	0.47 (90% CI 0.16 to 1.39)
Hydrofibre vs nonadherent	1.47 (95% CI 0.84 to 2.56)	1.35 (95% CI 0.71 to 2.56)	1.09 (90% CI 0.53 to 2.23)
Hydrogel vs nonadherent	2.00 (95% CI 0.21 to 19.1)	0.76 (95% CI 0.36 to 1.64)	2.62 (90% CI 0.35 to 19.5)
PMM vs nonadherent	1.46 (95% CI 0.80 to 2.67)	1.29 (95% CI 0.85 to 1.96)	1.13 (90% CI 0.61 to 2.11)
Foam vs alginate	0.55 (95% CI 0.10 to 2.87)	0.95 (95% CI 0.72 to 1.27)	0.57 (90% CI 0.14 to 2.36)
Hydrocolloid vs alginate	0.70 (95% CI 0.24 to 2.06)	0.87 (95% CI 0.67 to 1.14)	0.81 (90% CI 0.31 to 2.05)
Hydrofibre vs alginate	1.18 (95% CI 0.66 to 2.10)	1.09 (95% CI 0.57 to 2.10)	1.08 (90% CI 0.51 to 2.29)
Paste bandage vs alginate	1.22 (95% CI 0.91 to 1.63)	2.41 (95% CI 1.28 to 4.53)	0.51 (90% CI 0.28 to 0.91)
PMM vs alginate	1.08 (95% CI 0.76 to 1.53)	1.07 (95% CI 0.57 to 1.98)	1.01 (90% CI 0.55 to 1.85)
Hydrocolloid vs foam	0.92 (95% CI 0.76 to 1.12)	0.90 (95% CI 0.64 to 1.28)	1.02 (90% CI 0.73 to 1.42)
Paste bandage vs foam	2.30 (95% CI 1.29 to 4.09)	1.17 (95% CI 0.79 to 1.72)	1.97 (90% CI 1.10 to 3.55)
PMM vs foam	0.87 (95% CI 0.30 to 2.51)	1.19 (95% CI 0.81 to 1.74)	0.73 (90% CI 0.28 to 1.90)
PMM silver vs foam	1.57 (95% CI 0.83 to 2.96)	0.96 (95% CI 0.59 to 1.57)	1.64 (90% CI 0.83 to 3.21)
Silver vs foam	1.65 (95% CI 1.08 to 2.51)	4.12 (95% CI 2.06 to 8.22)	0.40 (90% CI 0.20 to 0.79)
PMM silver vs hydrocolloid	1.07 (95% CI 0.68 to 1.7)	1.75 (95% CI 0.91 to 3.37)	0.61 (90% CI 0.31 to 1.2)
Silver vs hydrocolloid	4.39 (95% CI 2.23 to 8.62)	1.76 (95% CI 1.12 to 2.75)	2.50 (90% CI 1.26 to 4.95)
Emollient cream vs blood product	0.76 (95% CI 0.54 to 1.09)	2.78 (95% CI 0.53 to 14.62)	0.28 (90% CI 0.07 to 1.15)
Hydrocolloid vs blood product	1.17 (95% CI 0.09 to 14.81)	2.39 (95% CI 0.91 to 6.32)	0.49 (90% CI 0.05 to 4.84)
Hydrofibre vs blood product	0.33 (95% CI 0.01 to 7.82)	3.65 (95% CI 1.31 to 10.19)	0.09 (90% CI 0.01 to 1.5)
Hydrogel vs blood product	2.13 (95% CI 0.63 to 7.25)	1.33 (95% CI 0.33 to 5.42)	1.6 (90% CI 0.33 to 7.69)

Table 9. Node splitting (*Continued*)

Saline gauze vs blood product	0.93 (95% CI 0.71 to 1.21)	0.34 (95% CI 0.1 to 1.18)	2.71 (90% CI 0.93 to 7.85)
Hyaluronic acid vs emollient cream	0.76 (95% CI 0.18 to 3.24)	2.78 (95% CI 1.13 to 6.8)	0.28 (90% CI 0.07 to 1.15)
Hydrocolloid vs growth factor	0.55 (95% CI 0.06 to 4.6)	1.11 (95% CI 0.84 to 1.46)	0.49 (90% CI 0.08 to 3.01)
Hydrogel vs growth factor	0.72 (95% CI 0.33 to 1.6)	1.55 (95% CI 0.39 to 6.11)	0.47 (90% CI 0.12 to 1.78)
Hyaluronic acid vs saline gauze	2.32 (95% CI 1.06 to 5.07)	0.64 (95% CI 0.14 to 2.89)	3.63 (90% CI 0.87 to 15.21)
Hydrocolloid vs saline gauze	3.5 (95% CI 0.87 to 14.06)	1.91 (95% CI 0.57 to 6.39)	1.84 (90% CI 0.39 to 8.7)

Abbreviations:**CI:** confidence interval**; PMM:** protease modulating matrix; **RoRR:** ratio of relative risks; **RR:** relative risk

CONTRIBUTIONS OF AUTHORS

Gill Norman: co-ordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing and editing the review; approved the final review prior to submission; and is a guarantor of the review.

Maggie Westby: designed the review; analysed or interpreted data; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing or editing the review; approved the final review prior to submission; and is a guarantor of the review.

Amber Rithalia: extracted data; checked the quality of data extraction; checked the quality of the statistical analysis; and approved the final review prior to submission.

Nikki Stubbs: analysed or interpreted data; advised on the review; and approved the final review prior to submission.

Marta Soares: designed the review; analysed or interpreted data; advised on the review; performed previous work that was the foundation of the current review; and approved the final review prior to submission.

Jo Dumville: conceived and designed the review; analysed or interpreted data; contributed to writing or editing the review; secured funding; and approved the final review prior to submission.

Contributions of editorial base

Nicky Cullum (Co-ordinating Editor): edited the protocol and the review; advised on methodology, interpretation and content; approved the final review prior to submission.
Gill Rizzello (Managing Editor): co-ordinated the editorial process, advised on content; edited the protocol and the review.
Reetu Child and Naomi Shaw: (Information Specialists) designed the search strategy, ran the searches and edited the search methods section.
Ursula Gonthier (Editorial Assistant): edited the Plain Language Summary, tables and reference sections.

DECLARATIONS OF INTEREST

Gill Norman: my employment at the University of Manchester while completing this work was funded by the NIHR and focused on high-priority Cochrane reviews in the prevention and treatment of wounds.

Maggie Westby: my employment at the University of Manchester while completing this work was funded by the NIHR and focused on high-priority Cochrane reviews in the prevention and treatment of wounds.

Amber Rithalia: none known.

Nikki Stubbs: I have received consultancy payments from Cogora, a healthcare marketing agency, and expenses for conference attendance. Funding from pharmaceutical companies supports training and education events in the service and I have received payments for non product-related educational sessions. These have been unrelated to the subject matter of the systematic review and have never been in support or in pursuit of the promotion of products.

Marta Soares: none known.

Jo Dumville: I received research funding from the NIHR for the production of systematic reviews focusing on high-priority Cochrane reviews in the prevention and treatment of wounds.

Andrew Jull (peer reviewer): I was lead author of an excluded study. No other conflicts to declare.

Clifford Richardson (peer reviewer): I work at the University of Manchester and know some of the members of the author team, but do not work with them in any capacity.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following decisions were made which represent differences between the review and the published protocol (Norman 2017).

Establishment of a narrower base-case of interventions for the main network: after mapping the network of eligible interventions we made the decision to restrict the network to interventions in use in clinical practice rather than primarily research contexts. This both increased the clinical relevance of the results of the analysis and rendered it more amenable to analysis. The number of included interventions remained high, and was further increased by a sensitivity analysis using an expanded data set to examine the stability of the network. Studies which were not included in the network remained in the review and are summarised by direct evidence. We additionally conducted a sensitivity analysis using a narrower set of interventions which were more widely used.

We also made the decision to treat as excluded studies those trials which included only one relevant intervention and which did not perform a linking function in the network; we had planned to list these as included studies with limited data extraction. This was a pragmatic decision made because of the large number of these studies; they are instead clearly identifiable in the list of excluded studies.

We had considered performing a grouped analysis which would have looked at wider groupings of dressing types. Experience (Westby 2017) suggested that this was unlikely to provide useful additional information so we did not conduct this.

We had planned for the potential to conduct various sensitivity analyses which were not in practice appropriate, full details of these are nevertheless provided in the methods.

We had planned to search trials registers and to contact review groups working on ongoing relevant reviews. Time constraints due to the very large number of identified studies meant that this was not undertaken; however a full update search was conducted and all other reference cross-checking was undertaken.