Alginate dressings for venous leg ulcers (Review)

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[Intervention Review]

Alginate dressings for venous leg ulcers

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ABSTRACT

Background

Venous leg ulcers are a common and recurring type of chronic, complex wound associated with considerable cost to patients and healthcare providers. To aid healing, primary wound contact dressings are usually applied to ulcers beneath compression devices. Alginate dressings are used frequently and there is a variety of alginate products on the market, however, the evidence base to guide dressing choice is sparse.

Objectives

To determine the effects of alginate dressings compared with alternative dressings, non-dressing treatments or no dressing, with or without concurrent compression therapy, on the healing of venous leg ulcers.

Search methods

For this first update, in March 2015, we searched the following databases: The Cochrane Wounds Group 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. There were no restrictions based on language or date of publication.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) that evaluated the effects of any type of alginate dressing in the treatment of venous ulcers were included.

Data collection and analysis

Two review authors independently performed study selection, data extraction and risk of bias assessment. Meta-analysis was undertaken when deemed feasible and appropriate.

Main results

Five RCTs (295 participants) were included in this review. All were identified during the original review. The overall risk of bias was high for two RCTs and unclear for three. One RCT compared different proprietary alginate dressings (20 participants), three compared alginate and hydrocolloid dressings (215 participants), and one compared alginate and plain non-adherent dressings (60 participants). Follow-up periods were six weeks in three RCTs and 12 weeks in two. No statistically significant between-group differences were detected for any comparison, for any healing outcome. Meta-analysis was feasible for one comparison (alginate and hydrocolloid dressings),

with data from two RCTs (84 participants) pooled for complete healing at six weeks: risk ratio 0.42 (95% confidence interval 0.14 to 1.21). Adverse event profiles were generally similar between groups (not assessed for alginate versus plain non-adherent dressings).

Authors' conclusions

The current evidence base does not suggest that alginate dressings are more or less effective in the healing of venous leg ulcers than hydrocolloid or plain non-adherent dressings, and there is no evidence to indicate a difference between different proprietary alginate dressings. However, the RCTs in this area are considered to be of low or unclear methodological quality. Further, good quality evidence is required from well designed and rigorously conducted RCTs that employ - and clearly report on - methods to minimise bias, prior to any definitive conclusions being made regarding the efficacy of alginate dressings in the management of venous leg ulcers.

PLAIN LANGUAGE SUMMARY

Alginate dressings for venous leg ulcers

Venous leg ulcers are a common and recurring type of chronic or complex wound which can be distressing for patients and costly to healthcare providers. Compression therapy, in the form of bandages or stockings, is considered to be the cornerstone of venous leg ulcer management. Dressings are applied underneath bandages or stockings with the aim of protecting the wound and providing a moist environment to aid healing. Alginate dressings contain substances derived from seaweed and are one of several types of wound dressings available. We evaluated the evidence from five randomised controlled trials that compared either different brands of alginate dressings, or alginate dressings with other types of dressings. In terms of wound healing, we found no good evidence to suggest that there is any difference between different brands of alginate dressings, nor between alginate dressings and hydrocolloid or plain non-adherent dressings. Adverse events were generally similar between treatment groups (but not assessed for alginate versus plain non-adherent dressings). Overall, the current evidence is of low quality. Further, good quality evidence is required before any definitive conclusions can be made regarding the use of alginate dressings in the management of venous leg ulcers.

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

alginate dressing (Sorbsan®) compared to alternative alginate dressing (Tegagen ™ High Gelling) for venous leg ulceration

Patient or population: people with venous leg ulceration
Settings: outpatient clinics
Intervention: Alginate dressing (Sorbsan®)
Comparison: alternative alginate dressing (Tegagen ™ High Gelling)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Alternative alginate dressing (Tegagen ™High Gelling)	Alginate dressing (Sorbsan®)				
Time to healing	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported.
Proportion of participants with healed ulcers Follow-up: 6 weeks	**Study population**[1]		**RR 6.00** (0.32 to 111.04)	20 (1 study)	⊕◯◯◯ **very low**[2,3,4,5]	
	Low[1]					
	91 per 1000	**546 per 1000** (29 to 1000)				
	High[1]					
	204 per 1000	**1000 per 1000** (65 to 1000)				

Mean change in wound size, with adjustment for baseline size	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported (only reported mean percentage change in ulcer area, with no variance estimate, and no adjustment for baseline area)
Adverse effects	See comment	See comment	Not estimable	0 (0)	See comment	Limited information provided.
Health-related quality of life	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Note: lower risk of the outcome is less favourable (i.e. lower risk of healing) than higher risk. Estimates for baseline low and high risks of healing at 30 days have been taken from a meta-analysis of RCTs evaluating different types of compression. The low risk estimate is based on a subset of participants with larger baseline ulcer area (greater than 5 cm squared). The high risk estimate is based on a subset of participants with smaller baseline ulcer surface area (5 cm squared or smaller). Most participants received a simple, low-adherent dressing plus four-layer bandage (O'Meara 2007). Estimate of baseline risk could not be estimated from study population because no participants healed in the Tegagen ™ HG group.
[2] Overall risk of bias was unclear.
[3] Risk ratio estimate based on single RCT; unable to assess heterogeneity.
[4] Risk ratio estimate based on single very small RCT (N = 20).
[5] Risk ratio estimate based on single RCT; unable to formally assess presence of publication bias.

BACKGROUND

For definitions of terminology see Glossary (Appendix 1).

Description of the condition

Venous leg ulcers are a common and recurring type of chronic or complex wound. They are usually caused by venous insufficiency (impaired venous blood flow) brought about by venous hypertension. Predisposing factors for venous hypertension include a history of deep vein thrombosis (DVT), thrombophlebitis, leg trauma, arthritis, obesity, pregnancy and a sedentary lifestyle. These factors can result in damage to the valves in the leg veins allowing pathological two-way blood flow instead of the normal one-way movement. A related issue is diminished calf muscle pump action. Both valvular and calf muscle pump impairment can result in reduced venous blood flow leading to venous hypertension. This causes distension of the leg veins, oedema (swelling due to fluid accumulation) of the lower limb and leakage of circulatory fluids from the capillaries into the surrounding tissues. This in turn induces irritation and increased fragility of the epidermis (the outer layer of skin) leading to ulceration (Doughty 2007). The duration of venous leg ulceration ranges from a matter of weeks to more than 10 years, and some people never heal (Moffatt 1995; Ruckley 1998; Vowden 2009a). Older patient age, longer wound duration and larger ulcer surface area have been reported as independent risk factors for delayed ulcer healing (Gohel 2005; Margolis 2004). A review of 11 venous leg ulceration prevalence studies conducted in Australia and Europe estimated point prevalence as 0.1% to 0.3% (Nelzen 2008). Surveys undertaken in the UK estimated prevalence of venous leg ulceration as 0.023% in Wandsworth, London (Moffatt 2004), 0.044% in Hull and East Yorkshire (Srinivasaiah 2007), 0.039% in Bradford and Airedale (Vowden 2009a; Vowden 2009b), and 0.029% in Leeds (Hall 2014). The lower estimates reported in the UK surveys relative to the worldwide literature might be explained by differences in disease management or case definition, or both. The epidemiological data have consistently suggested that prevalence increases with age and is higher among women (Graham 2003; Lorimer 2003; Margolis 2002; Moffatt 2004; Vowden 2009a). We were unable to identify contemporary prevalence data for non-western countries.

Diagnosis of venous leg ulceration can be made according to the appearance and location of the ulcer. Clinical practice guidelines recommend the use of clinical history, physical examination and haemodynamic assessment (SIGN 2010; O'Donnell 2014). The latter typically includes an assessment of arterial supply to the leg using the ankle brachial pressure index (ABPI), measured using a hand-held Doppler ultrasound scanner. Measuring ABPI in addition to visual inspection, clinical history and physical assessment can aid confirmation of ulcer aetiology (cause). In arterial disease, Doppler might be used to assess the extent of the arterial disease or to confirm the diagnosis. Venous and arterial disease can co-exist in the same person (SIGN 2010; O'Donnell 2014). An ABPI measurement of greater than 0.8 at rest is generally used to rule out the co-existence of clinically significant peripheral arterial disease in a leg ulcer that has been diagnosed as being due to venous insufficiency (Moffatt 2007); some sources suggest a more stringent threshold for this purpose (greater than 0.9) (SIGN 2010; O'Donnell 2014).

Leg ulcers are associated with considerable cost to patients and to healthcare providers. Two systematic reviews summarised the literature on health-related quality of life in patients with leg ulcers (Herber 2007; Persoon 2004). Both included qualitative and quantitative evaluations and reported that presence of leg ulceration was associated with pain, restriction of work and leisure activities, impaired mobility, sleep disturbance, reduced psychological well-being and social isolation.

The cost of treating an unhealed leg ulcer in the UK has been estimated to be around GBP 1300 per year at 2001 prices (Iglesias 2004). Another evaluation estimated the average cost of treating a venous leg ulcer (based on cost of dressings) as varying between EUR 814 and EUR 1994 in the UK and EUR 1332 and EUR 2585 in Sweden (price year 2002), with higher costs associated with larger and more chronic wounds (Ragnarson Tennvall 2005). This reflected findings from a more recent evaluation conducted in Hamburg, Germany, recruiting 502 community based adult patients with any type of leg ulcer. The total mean annual cost of illness for leg ulcers was estimated as EUR 9060 per patient (price year 2006), taking account of direct, indirect and intangible costs from a societal perspective. Direct costs included all expenses directly related to leg ulcer care (dressings, bandages, topical agents, systemic treatment, diagnostic procedures, clinician fees, in-patient treatment costs and transport); indirect costs related to loss of productivity; and intangible costs included impact on health-related quality of life. Estimates ranged from zero cost (i.e. no treatment) to EUR 44,462, with higher costs associated with ulcers with arterial aetiology, larger wound size and no history of wound closure (Augustin 2012). A large part of ulcer treatment cost comprises nursing time. For the financial year 2006-2007 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, not just venous leg ulcers) (Vowden 2009c). We were unable to identify additional, contemporary, international cost data.

Description of the intervention

Compression therapy (bandages or stockings) is now considered to be the cornerstone of venous leg ulcer management (Moffatt 2007; O'Meara 2012). Primary wound contact dressings (i.e. dressings in direct contact with the wound bed) are usually applied underneath compression devices. A range of other interventions may be used concurrently with compression, including debriding agents (Davies 2005), vasoactive drugs (Robson 2006), fibrinolytic ther-

apy (Robson 2006), physical therapies (Cullum 2010; Aziz 2015), and topical applications (Robson 2006).

Primary wound contact dressings are applied beneath compression devices with the aim of aiding healing, providing comfort, controlling exudate (the fluid produced by wounds) and helping to prevent bandages and stockings from adhering to the wound bed. The ideal conditions required for wound healing in terms of dressing application are proposed as follows: maintenance of a moist wound environment without risk of maceration (excessive softening of skin because of being constantly wet); avoidance of toxic chemicals, particles or fibres in the dressing fabric; minimisation of number of dressing changes; and maintenance of an optimum pH level (balanced acidity and alkalinity) (BNF 2015).

Several types of wound dressing are available and costs vary (Appendix 2). For example, there can be a six-fold difference in the UK unit price of a 9.5 cm x 9.5 cm non-adherent (knitted viscose) dressing compared with a 10 cm x 10 cm calcium alginate dressing (BNF 2015).

Alginate dressings are available as flat, freeze-dried porous sheets, or as flexible fibre dressings (e.g. packing tape), designed for packing cavity wounds. The base constituents include calcium alginate or calcium sodium alginate, derived from brown seaweed. Alginate dressings are designed to form a soft gel once in contact with wound exudate. Purported benefits of alginate dressings include high absorbency of fluid from moderately to heavily exuding wounds and the ability to maintain a moist wound environment, thereby promoting autolytic debridement (the body's own process of breaking down dead tissue lying on top of the wound bed). Calcium ions present in the dressings help to control bleeding by aiding blood clotting; a potential disadvantage is that blood clots may cause the dressing to adhere to the wound surface. Alginate dressings are designed to function most effectively in a moist environment, and are not suitable for use with dry wounds, or those covered with hard, necrotic tissue; heavy bleeding is a contraindication to use (BNF 2015; Boateng 2008). In the UK, alginate dressings are common to many wound care formularies, where they are often recommended for the management of wounds with moderate to high amounts of exudate.

Examples of alginate dressings currently available in the UK include Algosteril® (Smith and Nephew) and Tegaderm® Alginate (3M). Appendix 2 provides a description of all wound dressings categorised by the British National Formulary (BNF 2015).

How the intervention might work

Findings from research based on animal models suggest that acute wounds heal more quickly if the wound surface is kept moist in order to prevent the formation of a hard scab or eschar. A moist environment is also thought to provide optimal conditions for promoting autolytic debridement, which is sometimes considered to be an important part of the healing pathway (König 2005). It has been suggested that alginate dressings may control bleeding, manage exudate, promote autolytic debridement, provide a moist wound healing environment and promote healing (BNF 2015; Boateng 2008).

Why it is important to do this review

Wound dressings are a key part of the treatment pathway when caring for venous leg ulcers. Most will be used in combination with compression systems and guidelines are necessary to help make decisions regarding the value and best use of available dressings. Several types of wound dressing are available, and costs vary considerably. However, the evidence base to guide dressing choice is sparse. A previous systematic review evaluating different wound dressings for venous leg ulcers concluded that the type of dressing applied beneath compression did not influence ulcer healing (Palfreyman 2007). The authors concluded that there was insufficient evidence to permit firm recommendations for the use of alginate dressings compared with other dressings.

This review updates part of the previous systematic review by Palfreyman 2007 and is one of several Cochrane reviews investigating the use of dressings in the treatment of venous leg ulcers (O'Meara 2013; Ribeiro 2013; Ribeiro 2014).

OBJECTIVES

The primary objective of this review was to determine the effects of alginate dressings compared with alternative dressings, non-dressing treatments or no dressing, with or without concurrent compression therapy, on the healing of venous leg ulcers. Secondary objectives were to determine the effects of alginate dressings compared with alternatives on: health-related quality of life, costs (e.g. cost-effectiveness estimations), pain (e.g. at dressing change), debridement, haemostasis (control of bleeding), dressing performance (management of wound exudate and ease of removal) and adverse effects (e.g. infection, eczema, maceration).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), either published or unpublished, that evaluated the effects of any type of alginate dressing in the treatment of venous ulcers, irrespective of language of report. RCTs reported in abstract form only were eligible for inclusion, provided adequate information was either presented in

the abstract or available from the trial author. Studies using quasi-randomisation were excluded.

Types of participants

We considered RCTs recruiting people described in the primary report as having venous leg ulcers, managed in any care setting, to be eligible for inclusion. As the method of diagnosis of venous ulceration may vary, we accepted definitions as used in the RCTs. We included RCTs recruiting samples that comprised people with venous leg ulcers and people with other types of wounds (e.g. arterial ulcers, diabetic foot ulcers) if the results for people with venous ulcers were presented separately (or available from the trial authors), or if the majority of participants (75% or more in each arm) had leg ulcers of venous aetiology.

Types of interventions

The primary intervention of interest was alginate wound dressings. For ease of comparison, we grouped included RCTs according to the comparator intervention using categories presented in the British National Formulary (BNF 2015). We have reported generic names for all products where possible, also providing trade names and manufacturers, where available. However, it is important to note that manufacturers and distributors of dressings may vary from country to country, and dressing names may also differ. We have not included RCTs assessing alginate dressings impregnated with antibiotic, antiseptic or analgesic agents as these interventions are evaluated in other Cochrane reviews (Briggs 2012; O'Meara 2014). RCTs evaluating foam dressings, hydrocolloid dressings and hydrogels are covered in other Cochrane reviews (O'Meara 2013; Ribeiro 2013; Ribeiro 2014) and were included in this review only if they involved a comparison with an alginate dressing.

We included any RCT in which the presence or absence of an alginate dressing was the only systematic difference between treatment groups; and in which an alginate dressing was compared with other wound dressings (including alternative alginate dressings), non-dressing treatments (for example, topical applications) or no dressing. We included RCTs of alginate dressings, irrespective of whether compression was reported as a concurrent therapy.

Types of outcome measures

Primary outcomes

The primary outcome for the review was wound healing. Wound healing is measured and reported by trial authors in many different ways, including time to complete wound healing, the proportion of wounds healed during follow-up, change in wound size and rate of change in wound size. For this review, we regarded RCTs that reported one or more of the following as providing the best measures of outcome in terms of relevance and rigour:

- time to complete wound healing (correctly analysed using censored data and preferably with adjustment for prognostic covariates such as baseline size);
- the proportion of ulcers healed during follow-up (frequency of complete healing);
- and change (and rate of change) in wound size, with adjustment for baseline size.

We considered evidence from RCTs that reported mean or median time to healing without survival analysis (i.e. they regarded time to healing as a continuous measure without censoring), and those that reported change or rate of change in wound size without adjustment for baseline size, as less rigorous assessments of these outcomes. Data reported in this manner have not been used to populate the 'Summary of findings' tables.

Secondary outcomes

The secondary outcomes for the review were:

- health-related quality of life (measured using a validated standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6 or validated disease-specific questionnaire) preferably with follow-up estimates adjusted for baseline scores;
- costs (including cost or cost-effectiveness estimations as well as measurements of resource use such as number of dressing changes, dressing wear time and nurse time);
- pain (e.g. at dressing change, in between dressing changes or over the course of treatment);
- debridement (e.g. measured as percentage of sloughy or necrotic material remaining on the wound bed);
- haemostasis (control of bleeding);
- dressing performance (exudate management and ease of removal/adherence to the wound bed); and
- rates of adverse events together with descriptions (e.g. infection, eczema, maceration).

Search methods for identification of studies

Electronic searches

In March 2015, for this first update, we searched the following electronic databases for potentially relevant RCTs:

- The Cochrane Wounds Group Specialised Register (searched 4 March 2015);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2015, Issue 2);
- Ovid MEDLINE (1946 to 3 March 2015);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations searched 3 March 2015);
- Ovid EMBASE (1980 to 3 March 2015);
- EBSCO CINAHL (1982 to 4 March 2015)

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor Alginates explode all trees
#2 (alginate* or activheal or algisite or algosteril or curasorb or kaltostat or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb a or tegaderm or tegagel or urgosorb):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Leg Ulcer explode all trees
#5 ((varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (stasis NEXT ulcer*) or (crural NEXT ulcer*) or "ulcus cruris" or "ulcer cruris"):ti,ab,kw
#6 (#4 OR #5)
#7 (#3 AND #6)
We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL (Appendix 3). 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 2014). We did not restrict searches with respect to language or date of publication.
We searched for ongoing RCTs in the following clinical trial registries using the search term 'leg ulcer':

- World Health Organization International Trial Registry Platform (http://www.who.int/ictrp/en/);
- ISRCTN (International Standard Randomised Controlled Trial Number) register (http://www.controlled-trials.com/);
- ClinicalTrials.gov (http://www.clinicaltrials.gov).

All registries were accessed on 1st August 2012 for the original review and on 17th July 2015 for this update.

Searching other resources

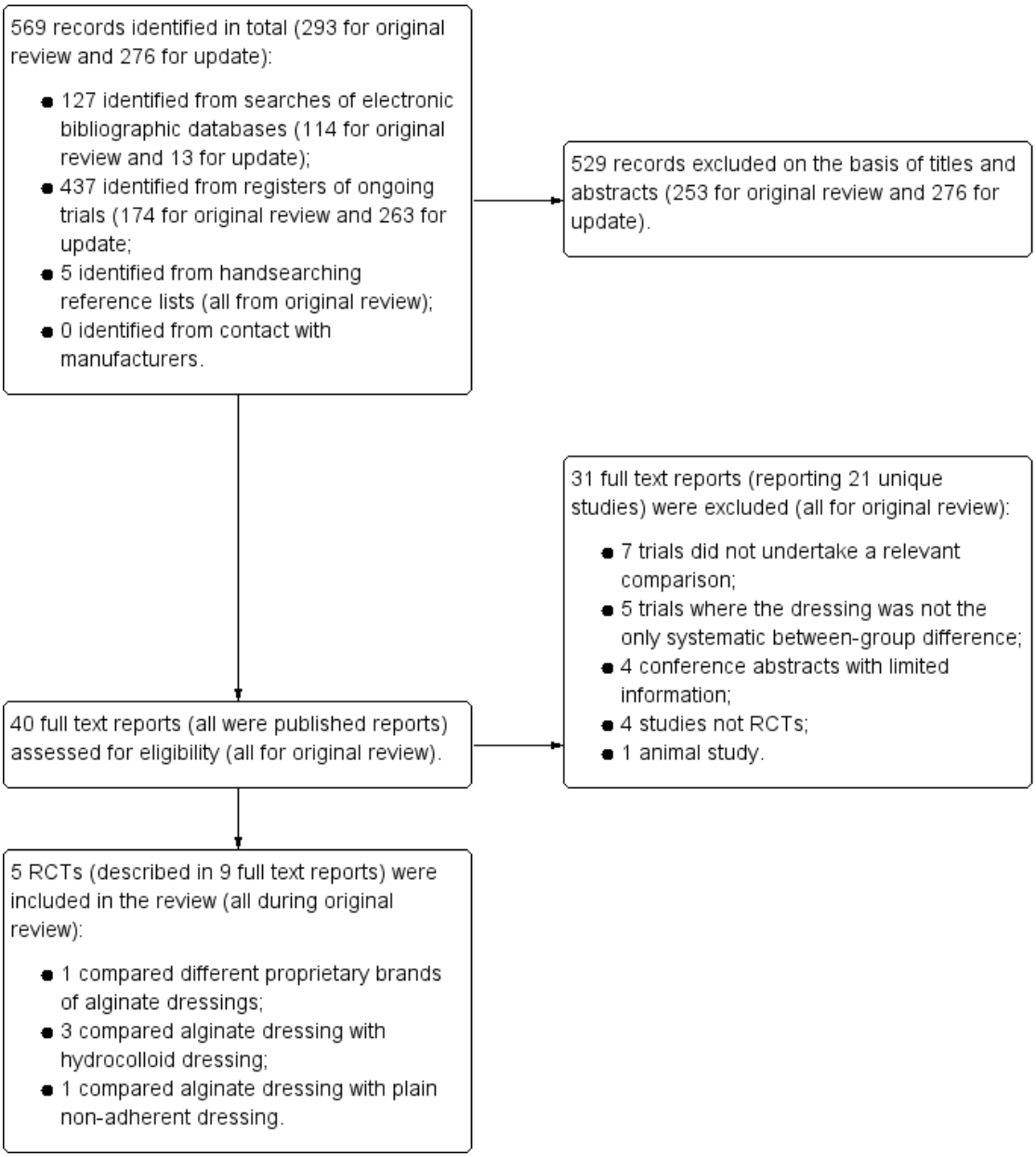
We attempted to contact trial authors to obtain unpublished data and other information as required. For the first version of this review, we contacted manufacturers to request information about ongoing or unpublished RCTs (for a list of manufacturers see Appendix 4). We also examined the reference lists of eligible RCTs and relevant review articles.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts for relevance. After this initial assessment, we obtained the full text of all RCT reports felt to be potentially relevant. Two review authors then independently checked the full papers for eligibility, with all disagreements resolved by discussion. We recorded all reasons for exclusion.
We have presented our study selection process as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Liberati 2009) (Figure 1).

Figure 1. Flow diagram of the trial selection process.



Data extraction and management

We extracted and summarised details of the eligible RCTs using a standardised data extraction form (Appendix 5). We extracted the data from RCT reports using an Excel spreadsheet designed to capture the RCT information detailed below. Initially, we piloted the spreadsheet with a sample of eligible RCTs, to explore any issues that might arise in relation to the data extraction process. We expanded and amended the spreadsheet as necessary after the piloting process. Two review authors performed independent data extraction of all included RCTs after which both data extractions were compared for agreement. We resolved any disagreements by discussion. If data were missing from reports we attempted to contact the trial authors to obtain the missing information. We included RCTs published as duplicate reports (parallel publications) once, using all associated RCT reports to extract the maximum amount of information, but ensuring that data were not duplicated in the review. We extracted the following information:

- trial authors;
- year of publication;
- country where trial was undertaken;
- setting of care;
- trial design details (e.g. pragmatic, pilot);
- ethical approval;
- participant consent;
- unit of investigation - participant, leg or ulcer;
- overall sample size and methods used to estimate statistical power (relates to the target number of participants to be recruited, the clinical difference to be detected and the ability of the RCT to detect this difference);
- participant selection criteria;
- number of participants randomised to each treatment arm;
- baseline characteristics of participants per treatment arm (gender, age, baseline ulcer area, ulcer duration, prevalence of co-morbidities such as diabetes, prevalence of clinically infected wounds or colonised wounds, previous history of ulceration, baseline levels of wound exudate, and participant mobility);
- details of the dressing/treatment regimen prescribed for each arm including details of any concomitant therapy, for example, compression;
- duration of treatment;
- duration of follow-up;
- statistical methods used for data analysis;
- primary and secondary outcomes measured;
- primary and secondary outcome data by treatment arm;
- adverse effects of treatment (per treatment arm with numbers and type);
- withdrawals (per treatment arm with numbers and reasons); and
- source of trial funding.

Assessment of risk of bias in included studies

Two review authors independently assessed each included RCT report using The Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool addresses specific domains, namely: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting (see Appendix 6 for details of the criteria on which judgements were based). For blinded outcome assessment we made separate judgements for primary and secondary outcomes. As assessment of healing (the primary outcome) is likely to be subject to potential observer/measurement bias, blinding of outcome assessment is important. Similarly we made separate judgements for primary and secondary outcomes for the domain of incomplete outcome data. In order to assess selective outcome reporting, we sought protocols for all included RCTs. Where protocols were unavailable, we made a judgement based on congruence of information in methods and results sections of reports of RCTs. We classified RCTs as being at overall high risk of bias if they were rated as 'high' for any one of three key domains (allocation concealment, blinding of outcome assessors and completeness of outcome data).

We have presented our assessment of risk of bias findings using 'Risk of bias' figures (Figure 2 is a summary of information across all included RCTs and Figure 3 shows a cross-tabulation of each individual RCT with each risk of bias item). This display of internal validity indicates the weight the reader may give the results of each RCT.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

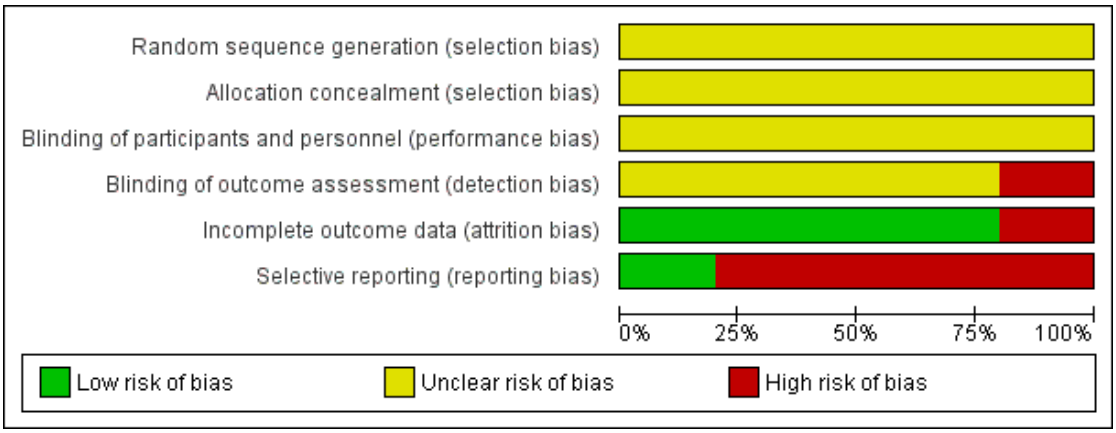
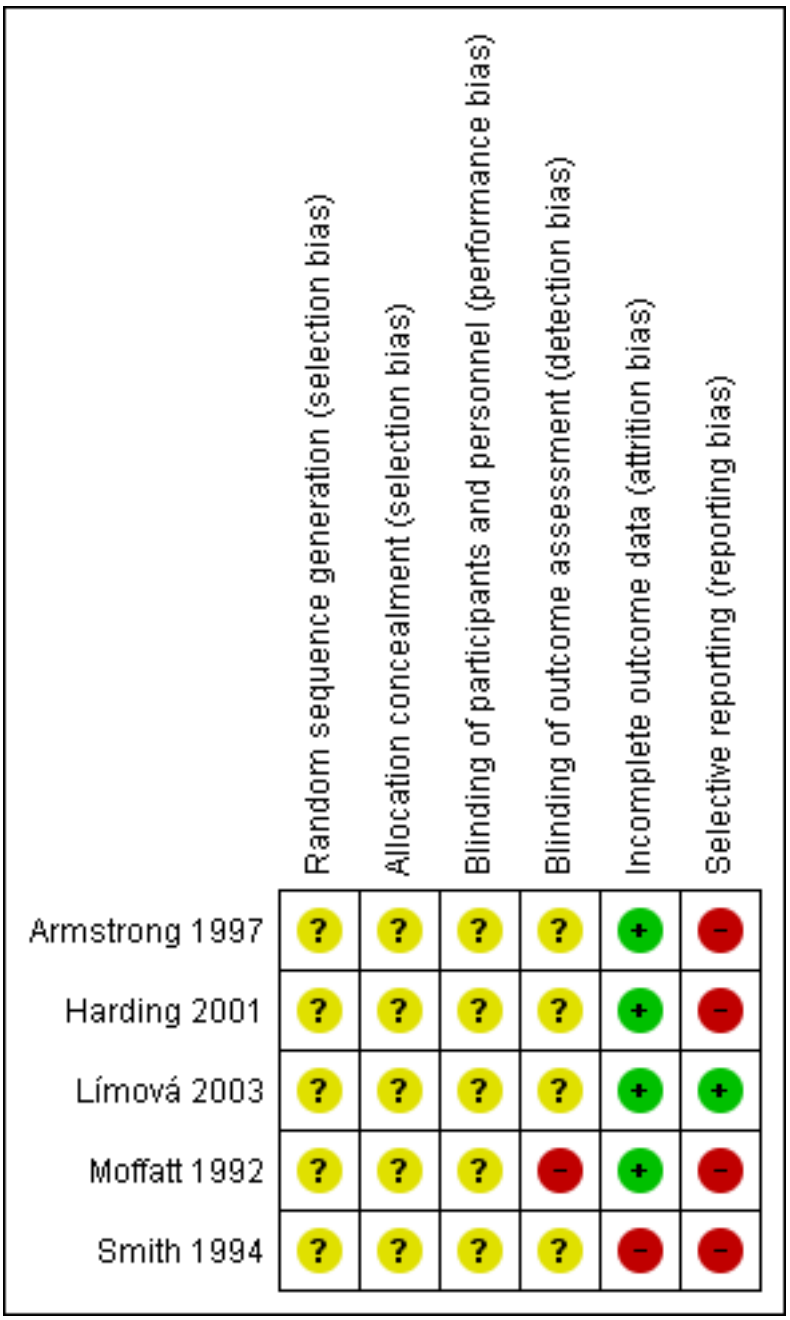


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Measures of treatment effect

We reported estimates for dichotomous outcomes (e.g. number of ulcers healed) as risk ratio (RR) with associated 95% confidence interval (CI). We reported estimates for continuous data outcomes (e.g. absolute or relative change in ulcer area and healing rate) as mean difference (MD) with 95% CI. We planned to report estimates of time to healing and hazard ratios where available. Where RCTs reported adverse events in sufficient detail (e.g. the number of participants who experienced at least one adverse event) we analysed these data as dichotomous. Where adverse events were reported as dressing-related we planned to analyse these data separately. We calculated measures of effect using Cochrane RevMan software (version 5.1) (RevMan 2014). We reported data narratively as provided in the RCT reports, without additional estimation of treatment effect, in the following instances:

- where time to healing estimates were based on non-censored data;
- where count data were provided (e.g. where the denominator was the total number of adverse events or total number of dressing changes per group);
- and where it was unclear whether the denominator was the total number of events (such adverse events or dressing changes) or the number of participants.

Unit of analysis issues

We recorded whether RCT reports specified participants, limbs or ulcers as the units of allocation and analysis. In cases where multiple limbs or ulcers on the same individual were studied, we planned to note whether the trial authors' analysis was appropriate (i.e. correctly taking account of highly correlated data) or inappropriate (i.e. considering outcomes for multiple ulcers on the same participant as independent). Where the number of wounds appeared to be equal to the number of participants, we have assumed that the ulcer was the unit of analysis, unless otherwise stated.

Dealing with missing data

Missing data are a common problem in RCTs. Excluding randomised participants from the analysis, or ignoring those lost to follow-up, can compromise the process of randomisation and introduce bias. Where RCTs reported the outcome of complete healing only for participants who completed the RCT (i.e. participants withdrawing and lost to follow-up were excluded from the analysis), we treated the excluded participants as if their wound did not heal (that is, they were included in the denominator but not the numerator). Where results were reported for participants who completed the RCT without specifying the numbers initially randomised per group, we presented complete case data. For other outcomes we presented data for all participants randomised where reported; otherwise we based our estimates on complete case data.

Assessment of heterogeneity

We considered clinical heterogeneity (that is the degree to which RCTs vary in terms of participant, intervention and outcome characteristics) and statistical heterogeneity. We assessed statistical heterogeneity using the Chi^2 test (a significance level of $P < 0.10$ was considered to indicate statistically significant heterogeneity) in conjunction with the I^2 statistic (Higgins 2003). The I^2 statistic examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance (Higgins 2003). We considered that I^2 values of 40%, or less, indicated a low level of heterogeneity, and values of 75%, or more, indicated very high heterogeneity (Deeks 2011).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of 'small study effects', that is, a tendency for estimates of the intervention effect to be more beneficial in smaller RCTs. Funnel plots allow a visual assessment of whether small study effects may be present in a meta-analysis. A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of each trial's size or precision (Sterne 2011). We planned to present funnel plots for meta-analyses comprising 10 RCTs or more using RevMan 5.1.

Data synthesis

We have presented a narrative synthesis of all included RCTs, with results grouped according to type of comparator (e.g. foam dressings compared with alginates, hydrocolloids compared with alginates). We undertook statistical pooling of outcome data on groups of RCTs with available data and considered to be sufficiently similar in terms of design and characteristics of participants, interventions and outcomes. The decision to undertake meta-analysis depended on the availability of outcome data and assessment of heterogeneity. For comparisons where there was no apparent clinical heterogeneity and the I^2 value was 40%, or less, we applied a fixed-effect model. Where there was no apparent clinical heterogeneity and the I^2 value was over 40%, we planned to apply a random-effects model. However, we planned not to pool data where heterogeneity was very high (I^2 values of 75% or above).

For dichotomous outcomes we have presented the summary estimate as a risk ratio (RR) with 95% CI. Where continuous outcomes were measured in the same way across RCTs, we planned to present a pooled mean difference (MD) with 95% CI; we planned to pool standardised mean difference (SMD) estimates where RCTs measured the same outcome using different methods. For time to event data, we planned to plot (and, if appropriate, pool) estimates of hazard ratios and 95% CIs as presented in the RCT reports using the generic inverse variance method in RevMan 5.1. Where hazard ratios were not reported we planned to extrapolate estimates, where possible, using other reported data (Parmar 1998). Pooled estimates of treatment effect were obtained using Cochrane RevMan software (version 5.1) (RevMan 2014).

'Summary of findings' tables

We have presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We planned to present the following outcomes in the 'Summary of findings' tables:

- time to complete ulcer healing where analysed using appropriate survival analysis methods;
- proportion of ulcers completely healing during the trial period;
- change in wound size, when adjusted for baseline size;
- adverse events; and
- health-related quality of life.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis for complete healing according to whether compression was used as a concurrent treatment, excluding any RCTs in which use of compression was unclear.

Sensitivity analysis

We planned two sensitivity analyses for the outcome of complete healing: one where RCTs classified as being at overall high risk of bias were excluded; and one where RCTs that possibly, or definitely, reported outcomes only for participants who completed the trial were excluded.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The total number of records identified from the search strategy is 569; the breakdown in relation to the original review and this update is as follows. For the original review, the search strategy generated 293 records in total. Of these, 114 were retrieved from electronic bibliographic databases, 174 from registers of ongoing trials, and five from examination of reference lists. No references were obtained as a result of contact with wound dressing manufacturers (Appendix 4). Two manufacturers out of 11 contacted confirmed that there were no ongoing or recently completed RCTs of alginate dressings; no replies were received from the remainder. Two hundred and fifty-three records were excluded because of irrelevance on the basis of information in titles and abstracts or records of ongoing trials (all records of ongoing trials were deemed irrelevant). Forty records were retrieved as full text reports (all were published). Following assessment of full text reports against the review's study selection criteria, 31 were excluded that reported 21 unique studies. Five RCTs (described in nine full text reports) were included in the review (see next section for further details). No studies were classified as awaiting assessment, or ongoing. Reasons for exclusion of full text reports (21 unique studies) were as follows:

- seven did not undertake a relevant comparison (Capillas Pérez 2000; de la Brassinne 2006; Límová 2002; Romanelli 2008; Romero-Cerecero 2012; Sibbald 2005; Wild 2010);
- five indicated that the dressing was not the only systematic difference between the treatment groups (Bull 1996; Dmochowska 1999; Schulze 2001; Scurr 1994; Stacey 1997);
- four were reported as abstracts with limited information, and the full RCT report was not available (Chaloner 1992; Kammerlander 2000; Mulder 1995; Petres 1994);
- four studies were not RCTs (Anonoymous 1997; Kordestani 2008; Moody 1991; Thomas 1989);
- and one was an animal study (Barnett 1987).

See Characteristics of excluded studies for further information. For this first review update, database searching generated 13 records. All were excluded after screening titles and abstracts. Two hundred and sixty three records were identified from registers of ongoing trials; all were irrelevant to the review.

The study selection process in shown in Figure 1.

Included studies

Five RCTs (295 participants) were included (Armstrong 1997; Harding 2001; Límová 2003; Moffatt 1992; Smith 1994). One was undertaken in the USA (Límová 2003), one in France and the UK (Armstrong 1997), and the remaining three solely in the UK (Harding 2001; Moffatt 1992; Smith 1994). Three were multicentre RCTs (Armstrong 1997; Harding 2001; Límová 2003). One RCT was described as a pilot study (Moffatt 1992). The included RCTs were reported between 1992 and 2003.

Sample sizes ranged from 20 participants to 131 participants. Only one RCT reported performing a sample size calculation (Harding 2001). The participant was the unit of randomisation and analysis in all five RCTs.

Where reported, the mean age of participants ranged from 73.1 years to 76.6 years. One RCT did not report on the age of the participants (Smith 1994). The proportion of female participants ranged from 47% to 71%. Only one RCT reported on participant mobility, stating that 55% of participants recruited had limited mobility or were immobile (Armstrong 1997).

With the exception of two RCTs that recruited participants with ulcers of venous, mixed or other aetiology (Armstrong 1997; Harding 2001), all participants had leg ulcers that were of venous aetiology. An ABPI of less than 0.8 was an exclusion criterion in two RCTs (Límová 2003; Moffatt 1992). Where reported, ulcer aetiology was assessed using Doppler or patient history, or both.

The dressing comparisons evaluated by the included RCTs were as follows:

- one RCT compared one alginate dressing (Tegagen ™ HG) with another (Sorbsan®) (Límová 2003);
- three RCTs compared hydrocolloid dressings with alginate dressings (Armstrong 1997; Harding 2001; Smith 1994);
- and one RCT compared a plain non-adherent dressing with an alginate dressing (Moffatt 1992).

All RCTs reported that all participants received compression therapy as part of the intervention, and so the planned subgroup analysis according to use versus non use of compression as a concurrent treatment with dressings could not be undertaken. Length of treatment was six weeks in three RCTs (Armstrong 1997; Límová 2003; Smith 1994), and twelve weeks in two (Harding 2001; Moffatt 1992). Treatment settings were outpatient clinics, dermatology departments and the community.

All RCTs reported the proportion of ulcers completely healed at the end of treatment. Time to complete ulcer healing was assessed by two RCTs (Harding 2001; Moffatt 1992), and change in ulcer size was assessed by four RCTs (Armstrong 1997; Harding 2001; Límová 2003; Smith 1994).

See Characteristics of included studies for further details.

Risk of bias in included studies

A summary of the risk of bias assessment is presented in Figure 2 and Figure 3.

Allocation

Generation of the randomisation sequence

None of the included RCTs reported a method for generation of the randomisation sequence, and were, therefore, all judged as being at unclear risk of bias for this domain.

Concealment of the allocation process

Two RCTs reported the use of sealed envelopes, but did not report whether these were opaque and sequentially numbered, and were, therefore, judged as being at unclear risk of bias for this domain (Armstrong 1997; Harding 2001). The remaining RCTs did not report on the method of allocation concealment at all, and were also considered as being at unclear risk of bias.

Blinding

Blinding of participants and personnel

Four of the included RCTs were described as 'open' but did not provide any statements regarding blinding of participants or study personnel, and were, therefore, judged as being at unclear risk of bias for this domain (Armstrong 1997; Harding 2001; Límová 2003; Smith 1994). The RCT by Moffatt 1992 provided no statement regarding blinding of participants or study personnel, and was also judged at being unclear risk of bias.

Blinding of outcome assessment

Four of the included RCTs did not provide any statement regarding blinding of outcome assessment, and were, therefore, judged as being at unclear risk of bias for this domain (Armstrong 1997; Harding 2001; Límová 2003; Smith 1994). The RCT report by Moffatt 1992 indicated that the outcome assessment was not blinded and was judged to be at a high risk of bias for this domain.

Incomplete outcome data

Three of the included RCTs described analysis on an intention-to-treat basis and were considered to be at a low risk of bias for this domain (Armstrong 1997; Harding 2001; Moffatt 1992). One RCT reported that only one participant who left the trial in the first week was not included in the analysis, and was also considered to be at a low risk of bias (Límová 2003). The RCT by Smith 1994

stated that the analyses excluded 12 participants who withdrew from the trial, so was judged to be at a high risk of bias.

Selective reporting

We were unable to obtain any RCT protocols, and so judgements were based on agreement between the methods and results sections of RCT reports. One RCT presented results for all of the outcomes described in the methods section of the report and was classified as being at a low risk of bias (Límová 2003). The remaining RCTs were classified as being at high risk of bias for this domain, for the following reasons.

Armstrong 1997 reported an outcome that was not described in the methods section (seven-day wear time). Conversely, there were no data reported for two outcomes relating to dressing performance (exudate handling and ease of removal) that were mentioned in the methods section of the secondary reference.

Harding 2001 mentioned that secondary outcomes were assessed by both participants and investigators, but only presented one set of results for which the assessor was not specified. The full range of data were not provided for the outcome of ease of dressing removal, which used a four-point scale for assessments; only the proportion recorded as 'excellent' was presented.

Moffatt 1992 indicated that time to healing was assessed, but minimal information was presented (no data and no P value).

Smith 1994 described assessing the mean number of dressing changes, but did not report the results as mean values (ranges were provided). Health-related quality of life was assessed using a five-point scale but only the proportion of participants reporting the most favourable outcome category was presented at the end of the trial. Similarly, the full range of data for dressing performance outcomes (exudate handling and ease of removal) were not provided.

Overall risk of bias

Two RCTs were considered as being at high risk of bias overall (Moffatt 1992; Smith 1994), and the other three were classified as unclear (Armstrong 1997; Harding 2001; Límová 2003).

Effects of interventions

See: **Summary of findings for the main comparison** Alginate dressing (Sorbsan®) compared to alternative alginate dressing (Tegagen™ High Gelling) for venous leg ulceration; **Summary of findings 2** Alginate dressing compared to hydrocolloid dressing for venous leg ulceration; **Summary of findings 3** Alginate dressing compared to plain non-adherent dressing for venous leg ulceration

Five RCTs that evaluated alginate dressings were included in this review (Armstrong 1997; Harding 2001; Límová 2003; Moffatt 1992; Smith 1994). The results are grouped according to the comparator dressing, starting with alginate dressings compared with alternative alginate dressings (Límová 2003). This is followed by comparisons with hydrocolloid (Armstrong 1997; Harding 2001; Smith 1994), and plain non-adherent dressings (Moffatt 1992). Details of primary and secondary outcome data are presented in Table 1 and Table 2. Reporting of secondary outcomes was often inadequate, with no presentation of variance estimates or results of tests of statistical significance between treatment groups; where available, we have reported these values below.

We were unable to undertake several of our planned analyses because of a lack of data available. These analyses included plotting and pooling hazard ratio estimates, separate analyses for dressing- and non-dressing-related adverse events, and assessment of publication bias using funnel plots. Meta-analyses of continuous data and the planned sensitivity analyses could not be performed for the same reason.

Comparison between different alginate dressings

One RCT that compared different alginate dressings was identified (Límová 2003), and classified as having an unclear overall risk of bias.

Primary outcomes

Proportion of ulcers completely healed

Límová 2003 randomised 20 participants: 11 received a Tegagen ™ high-gelling (HG) alginate dressing and nine received a Sorbsan® alginate dressing. The potential difference between these dressings was not clear from the RCT report, and there was no stated rationale for comparing them. Product information does not draw attention to any obvious differences (3M Healthcare 2010; SMTL 2002). All participants received a secondary dressing (hydrocolloid), and compression consisting of a paste bandage covered by an elastic cohesive bandage. Participants were assessed every seven days for six weeks, or until the ulcer no longer required the use of an alginate dressing. It should be noted that some participants were recruited with ulcer areas smaller than the size described as eligible for inclusion to the trial (the specified eligible range was 3 cm^2 to 100 cm^2). The number of ulcers healed at six weeks was 0/11 (0%) in the Tegagen ™ HG group compared with 2/9 (22%) in the Sorbsan® group. The between-group difference in the proportion of ulcers healed at six weeks was not statistically significant (RR 6.00, 95% CI 0.32 to 111.04) (Analysis 1.1).

Change in ulcer size

The mean percentage change in ulcer area at six weeks was -33.7% in the Tegagen ™ HG alginate dressing group compared with -29.6% in the Sorbsan® alginate dressing group (Límová 2003).

Secondary outcomes

Costs (resource use): number of dressing changes

Límová 2003 reported that 69 (65 scheduled and four unscheduled) dressing changes occurred in the Tegagen ™ HG alginate dressing group compared with 61 (60 scheduled and one unscheduled) in the Sorbsan® alginate dressing group.

Pain

The between-group differences in comfort score, both during dressing wear time and at dressing removal, were both statistically significant in favour of the Tegagen ™ HG alginate dressing (score range 1 to 5, lower score better). The respective differences in means were: -0.90 (95% CI -1.29 to -0.51), P value < 0.00001 (Analysis 1.2); and -0.70 (-0.88 to -0.52), P value < 0.00001 (Analysis 1.3) (Límová 2003).

Debridement

There were no statistically significant between-group differences in the percentage of visits where necrotic tissue was observed (Tegagen ™ HG 60%, Sorbsan® 69%, P value 0.57), or in the percentage of visits where debridement was required (19% and 41% respectively, P value 0.18). Improvement in necrotic tissue was measured using a scale of 0 (none) to 5 (100%); mean scores were 2.5 and 1.5 respectively, again with no statistically significant difference observed between treatment groups (P value 0.38) (all P values as reported by trial author) (Límová 2003).

Dressing performance

Límová 2003 reported a statistically significant between-group difference in favour of Tegagen ™ HG for exudate absorption score (score range 1 to 5, lower score better): difference in means -0.80 (95% CI -1.22 to -0.38), P value 0.0002 (Analysis 1.4). However, the difference between groups for percentage of clinic visits with medium or large amounts of exudate observed was not statistically significant (72% for Tegagen ™ HG, 86% for Sorbsan® (P value 0.25, reported by trial author).

The between-group difference for ease of dressing removal was in also favour of Tegagen ™ HG (score range 1 to 5, lower score better): difference in means -0.90 (95% CI -1.28 to -0.52), P value < 0.00001 (Analysis 1.5). No participants in the Tegagen ™ HG dressing group reported dressing adherence to the wound, but 28% in the Sorbsan® group did (P value < 0.05, reported by trial author).

Adverse events

There was a statistically significantly lower percentage of clinic visits with observations of denuded peri-wound skin in the Tegagen ™ HG group than in the Sorbsan® group (9% versus 32%, P value 0.04). However, no statistically significant between-group differences were observed for visits with observation of maceration or peri-wound skin requiring medication, respective values being: 36% versus 54% (P value 0.30); and 31% versus 65% (P value 0.07 - all P values as reported by trial author) (Límová 2003).

Comparison between different alginate dressings: summary of results

Evidence from one RCT of overall unclear risk of bias suggested no statistically significant difference between Tegagen ™ HG and Sorbsan® alginate dressings in the proportion of ulcers completely healed at six weeks (Límová 2003). In terms of secondary outcomes, Tegagen ™ HG appeared to be statistically significantly better than Sorbsan® for pain/comfort scores, exudate absorption score, ease of removal, adherence to the wound bed and instances of denuded peri-wound skin. Groups did not differ for other adverse effects (maceration and requirement for medication for peri-wound skin) or for outcomes relating to debridement. Costs (in terms of resource use, i.e. number of dressing changes) also appeared to be similar between groups, but data were difficult to interpret because no variance estimate or P value were provided. All data should be interpreted with caution because of the small number of participants recruited (n = 20).

Hydrocolloid dressings compared with alginate dressings

We identified three RCTs that compared hydrocolloid dressings with alginate dressings, one judged to be at high overall risk of bias (Smith 1994), and the other two classified as unclear (Armstrong 1997; Harding 2001).

Primary outcomes

Time to healing

Harding 2001 recruited participants with various types of leg ulcers, but the majority (79%) had venous ulceration. After randomisation, 66 participants received a fibrous hydrocolloid dressing, and 65 an alginate dressing. All participants had an absorbent pad as a secondary dressing and those eligible for compression received orthopaedic padding and a high-compression elastic bandage. Participants were assessed every seven days for a maximum of 12 weeks, or until the ulcer healed. Time to healing estimates based on healed participants only, generated the following values: mean days to healing were 41.8 (standard deviation (SD) 21.3) for hydrocolloid and 56.6 (SD 21.6) for alginate dressings (P value 0.053); respective median values (ranges) were 42 (14 to 87) and 56 (14 to 85) days. The trial authors mentioned undertaking an analysis of Kaplan-Meier survival curves based on all randomised participants. The results of this analysis were not presented in full; the log rank test for the difference between curves generated a P value of 0.05.

Proportion of ulcers completely healed

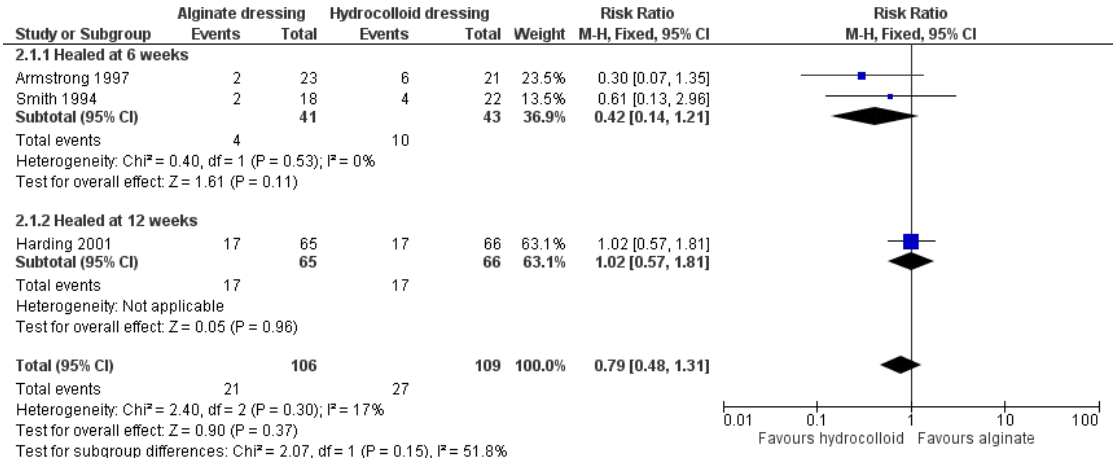
Smith 1994 randomised 40 participants; 22 received a hydrocolloid dressing and 18 an alginate dressing. Compression bandaging

was applied to each participant, but no details of the type used were reported. Treatment continued for six weeks, or until the ulcer healed. The number of ulcers healed at six weeks was 4/22 (18%) in the hydrocolloid dressing group compared with 2/18 (11%) in the alginate dressing group.

Armstrong 1997 recruited 44 participants with leg ulcers of different aetiologies, the majority being venous (82%). Twenty-one participants were randomised to receive a fibrous hydrocolloid dressing and 23 to receive an alginate dressing. All participants received an occlusive hydrocolloid dressing as a secondary dressing and compression (orthopaedic padding followed by a high compression elastic bandage). Participants were assessed on days 14 and 28, and on completion of the trial period. Treatment was for six weeks, or until healing if sooner. At six weeks the number of ulcers healed in the hydrocolloid dressing group was 6/21 (29%) compared with 2/23 (9%) in the alginate dressing group.

When these two RCTs were pooled, no statistically significant between-group difference was detected: RR 0.42 (95% CI 0.14 to 1.21), Chi^2 test for heterogeneity P value 0.53, I^2 = 0% (Analysis 2.1, Figure 4).

Figure 4. Forest plot of comparison: 2 Hydrocolloid dressings compared with alginate dressings, outcome: 2.1 Proportion of ulcers healed at 6 and 12 weeks.



In the RCT by Harding 2001, 17 participants (26%) had healed in both groups at 12 weeks: RR 1.02 (95% CI 0.57 to 1.81) (Analysis 2.1, Figure 4).

Change in ulcer size

At six weeks Smith 1994 reported a mean percentage change in ulcer area of -57.1% in the hydrocolloid dressing group compared with -34.9% in the alginate dressing group. The trial authors reported that the between-group difference was not statistically different, but the P value was not provided.

At six weeks Armstrong 1997 reported a median change in ulcer area of -205 mm^2 in the hydrocolloid dressing group compared with -162 mm^2 in the alginate dressing group. In terms of percentage change in area from baseline, the respective values were -42% and -26%. The trial authors reported that the between-group difference was not statistically significant for either outcome, but P values were not provided.

At 12 weeks Harding 2001 reported a mean change in ulcer area of -516.86 (SD 1202.72) mm^2 in the hydrocolloid dressing group compared with -347.30 (SD 1382.69) mm^2 in the alginate dressing group. The between group difference in means was not statistically significant: MD -169.56 (95% CI -613.61 to 274.49) (Analysis 2.2). In terms of percentage change in area from baseline, the finding was similar with mean respective values being -38.18% (SD 92.36) and -30.54 (SD 84.08), generating MD -7.64% (95% CI -37.88 to 22.60) (Analysis 2.3).

Secondary outcomes

Health-related quality of life

In one RCT, 42.9% of participants in the hydrocolloid dressing group improved markedly (to the fifth category of a five-point scale) compared with 40.0% of participants in the alginate dressing group. The trial authors did not report the number of participants

completing the quality of life assessment, and the measurement instrument was not specified (Smith 1994).

Costs (resource use): mean wear time/number of dressing changes

Smith 1994 reported that both dressings were equivalent in terms of mean wear time, but no data by group, or P value for the between-group difference, were reported.

Armstrong 1997 reported a mean wear time of four days in the hydrocolloid group compared with three days in the alginate group, and the number of participants achieving a seven-day wear time on at least one occasion was 9/21 (43%) and 3/23 (13%) respectively. The between-group differences for both outcomes were described as statistically significant in the RCT report, but P values were not presented.

During the Harding 2001 trial, the total number of dressing changes was 1093 in the hydrocolloid dressing group compared with 1186 in the alginate group. Respective values for mean number of dressing changes per healed ulcer were 7.4 and 12.1, whilst mean wear times for all ulcers (healed and unhealed) were 3.632 (SD 1.878) and 3.271 (SD 1.944) days. Although the RCT report presented the latter between-group difference as statistically significant, this was not confirmed by the review authors' calculation in RevMan: (MD 0.36, 95% CI -0.29 to 1.02) (Analysis 2.4).

Cost: material costs

Smith 1994 reported on cost of materials used at each dressing change, but did not include nursing time. The mean cost in the hydrocolloid group was GBP 431.73 compared with GBP 364.08 in the alginate group (price year/tariff not provided).

Armstrong 1997 reported a total cost per treatment group to achieve ulcer healing based on material costs (1995 Drug Tariff) and nursing time. The estimated cost to heal one ulcer was GBP 237.66 in the hydrocolloid dressing group compared with GBP 687.31 in the alginate dressing group (values calculated by review authors from information in the RCT report).

Harding 2001 reported a mean cost to achieve ulcer healing based on material costs (2000 Drug Tariff) and nursing time of GBP 1184.09 (USD 1699.71) in the hydrocolloid dressing group compared with GBP 1200.73 (USD 1723.59) in the alginate dressing group.

Pain

Smith 1994 used an 11-point visual analogue scale, that ranged from 0 (no pain) to 10 (worst possible pain), to assess pain at baseline and at six weeks; both assessments were based on pain experienced during the previous two weeks. In addition, the trial evaluated pain during dressing change. Mean scores at baseline appeared comparable: 4.74 for hydrocolloid and 4.86 for alginate dressing. The changes from baseline at six weeks were -3.28 and -2.71 respectively (calculated by review authors). The mean scores at dressing change assessed at week six were 1.73 and 2.16, respectively.

In the Armstrong 1997 trial, pain at dressing change was recorded as one of seven categories (i.e. no pain, mild pain, moderate pain, severe pain, excruciating pain, unable to respond, missing data). The proportion of dressing changes across these categories appeared to be similar between treatment groups, the majority of dressing changes were associated with no pain (79%) or mild pain (16%) (Table 2).

Harding 2001 used a four-point scale, that ranged from 'no pain' to 'severe pain', to assess pain during dressing removal. The percentage of dressing changes associated with no pain was 82% in the hydrocolloid dressing group compared with 62% in the alginate dressing group (trial authors reported P value < 0.001 for the between-group difference). The trial authors did not provide full data from all parts of the scale, or present raw data (so denominators for calculations were unclear).

Dressing performance: exudate handling

Harding 2001 used a four-point scale, that ranged from 'poor' to 'excellent', to assess exudate handling. A rating of 'excellent' was given in 44% of instances in the hydrocolloid dressing group compared with 20% in the alginate dressing group, however, it was unclear whether the denominator was the number of participants or the number of dressing changes (P value 0.002 reported by RCT authors for the between-group difference).

Smith 1994 provided minimal details of assessment of exudate handling performance, and mentioned only that the alginate dressing was 'slightly superior' in terms of ability to contain exudate.

Dressing performance: sticking/adherence

In the Smith 1994 RCT, ease of dressing removal was assessed using a six-point scale that ranged from 'excellent' to 'awful'. The proportion of participants reporting 'excellent' for ease of dressing removal was 56.3% in the hydrocolloid dressing group compared with 8.3% in the alginate dressing group (trial authors' reported P value for between-group difference < 0.001). The RCT authors did not report raw numbers, and so it was not clear whether the denominator was the number of participants or number of dressing changes, they also did not provide the findings from the full assessment scale.

Harding 2001 reported a percentage recording of 'excellent' for overall ease of dressing removal of 51% in the hydrocolloid dressing group compared with 24% in the alginate dressing group but did not report if the denominator was the number of participants or the number of dressing changes (reported P value for between-group difference 0.006). The percentage of dressing changes with some adhesion to the wound bed was 38% in the hydrocolloid dressing group compared with 74% in the alginate dressing group (reported P value for between-group difference < 0.001).

Adverse events

Smith 1994 reported that the number of participants who experienced the adverse events of pain, allergy, wound infection or erythema was 5/22 (23%) in the hydrocolloid dressing group compared with 6/18 (33%) in the alginate dressing group. The between-group difference was not statistically significant (RR 1.47, 95% CI 0.53 to 4.03) (Analysis 2.5).

Armstrong 1997 reported 32 adverse events in the hydrocolloid dressing group, four of which were attributed to the primary dressing; 32 adverse events were recorded in the alginates dressing group, with three attributed to the primary dressing. The number of participants experiencing adverse events was not reported.

Hydrocolloid dressings compared with alginate dressings: summary of results

Evidence from one RCT with an overall high risk of bias (Smith 1994), and two with unclear risk of bias (Armstrong 1997; Harding 2001), suggested no difference between hydrocolloid and alginate dressings for any healing outcomes (maximum follow-up 12 weeks). In terms of secondary outcomes, removal of hydrocolloid dressings was easier, whilst rates of adverse events appeared to be similar between treatment groups. Findings were difficult to interpret for exudate handling and pain (results were conflicting), health-related quality of life (used unspecified measurement instrument) and costs (no rigorously conducted economic evaluations reported). Interpretation of all secondary outcomes was hampered further by lack of data in terms of variance estimates and P values for tests of between-group differences. In addition, findings were not always presented across all parts of the various assessment scales used (e.g. pain, exudate handling and ease of removal) and denominators were unclear for some dichotomous outcomes - often because of ambiguity concerning whether the rating was based on numbers of participants, or numbers of events such as dressing changes.

Plain non-adherent dressings compared with alginate dressings

We identified one RCT that compared plain non-adherent dressings with alginate dressings; it had an overall high risk of bias (Moffatt 1992).

Primary outcomes

Time to healing and proportion of ulcers completely healed

Moffatt 1992 randomised 60 participants: 30 received a plain non-adherent dressing and 30 an alginate dressing. All participants were fitted with a graduated compression bandaging system designed to provide 40 mmHg ankle pressure; treatment duration was 12 weeks. The number of ulcers healed at 12 weeks was 24/30 (80%) in the plain non-adherent dressing group compared with 26/30 (87%) in the alginate dressing group. The between-group difference was not statistically significant (RR 1.08, 95% CI 0.86 to 1.36) (Analysis 3.1). Analyses relating to time to healing were mentioned briefly, with trial authors stating that the cumulative proportions healed (estimated from life table analysis) were similar to those in the above analysis. This could not be verified from the trial report since no data or P value for the between-group difference were presented.

Secondary outcomes

None reported.

Plain non-adherent dressings compared with alginate dressings: summary of results

Evidence from one RCT, with an overall high risk of bias, suggested no statistically significant difference between plain non-adherent dressings compared with alginate dressings in the proportion of ulcers completely healed at 12 weeks (Moffatt 1992). No secondary outcomes were reported.

'Summary of findings' tables

In order to provide a concise overview and synthesis of the volume and quality of the evidence, we have included a 'Summary of findings' table for each of the dressing comparisons: comparison between different alginate dressings (Summary of findings for the main comparison); alginate compared with hydrocolloid dressing (Summary of findings 2); and alginate compared with non-adherent dressing (Summary of findings 3). We had planned to include estimates of time to healing, complete healing, change in wound size, adverse events, and change in health-related quality of life in the 'Summary of findings' tables. Due to limitations of reported data, we were only able to include estimates of complete healing (for all comparisons) and adverse events (for alginate compared with hydrocolloid). Data in the 'Summary of findings' tables suggest that the evidence for all comparisons is of very low quality, meaning that there is much uncertainty around all estimates included. On balance, there is no strong evidence of a benefit of using alginate dressings compared with hydrocolloid or plain low-adherent dressings for treating venous leg ulcers, and there is no evidence to suggest that one brand of alginate dressing may be better than another.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

alginate dressing compared to hydrocolloid dressing for venous leg ulceration

Patient or population: people with venous leg ulceration
Settings: outpatient clinics or community
Intervention: Alginate dressing
Comparison: hydrocolloid dressing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hydrocolloid dressing	Alginate dressing				
Time to healing	See comment	See comment	Not estimable	0 (0)	See comment	One RCT presented time to healing, but did not report a reliable estimate (not based on censored data)
Proportion of participants with healed ulcers at 6 weeks Follow-up: 6 weeks	**Study population**[1]		**RR 0.42** (0.14 to 1.21)	84 (2 studies)	⊕◯◯◯ **very low**[2,3,4]	
	233 per 1000	**98 per 1000** (33 to 281)				
	Low[1]					
	91 per 1000	**38 per 1000** (13 to 110)				
	High[1]					
	204 per 1000	**86 per 1000** (29 to 247)				

Proportion of participants with healed ulcers at 12 weeks Follow-up: 12 weeks	**Study population**		**RR 1.02** (0.57 to 1.81)	131 (1 study)	⊕○○○ **very low**[5,6,7,8]	
	258 per 1000	**263 per 1000** (147 to 466)				
	Low					
	311 per 1000	**317 per 1000** (177 to 563)				
	High					
	696 per 1000	**710 per 1000** (397 to 1000)				
Mean change in wound size, with adjustment for baseline size	See comment	See comment	Not estimable	0 (0)	See comment	Three RCTs reported change in wound area, but not with baseline adjustment
Proportion of participants experiencing adverse effects at 6 weeks Follow-up: 6 weeks	**227 per 1000**	**334 per 1000** (120 to 916)	**RR 1.47** (0.53 to 4.03)[9]	40 (1 study)	⊕○○○ **very low**[10,11,12,13]	
Health-related quality of life	See comment	See comment	Not estimable	0 (0)	See comment	One RCT assessed health-related quality of life but did not use a validated tool, and only reported percentages of participants who had improved

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Note: lower risk of the outcome is less favourable (i.e. lower risk of healing) than higher risk. Estimates for baseline low and high risks of healing at 30 days (and 90 days for the 12 week outcome) have been taken from a meta-analysis of RCTs evaluating different types of compression. The low risk estimate is based on a subset of participants with larger baseline ulcer area (greater than 5 cm squared). The high risk estimate is based on a subset of participants with smaller baseline ulcer surface area (5 cm squared or smaller). Most participants received a simple, low-adherent dressing plus four-layer bandage (O'Meara 2007).
[2] One RCT had overall unclear risk of bias and one had overall high risk of bias.
[3] Underpowered comparison (N = 84).
[4] Risk ratio estimate based on 2 RCTs; not possible to assess publication bias.
[5] RCT had overall unclear risk of bias.
[6] Risk ratio estimate based on single RCT; not possible to assess heterogeneity.
[7] Underpowered comparison (N = 131).
[8] Risk ratio estimate based on single RCT; not possible to assess publication bias.
[9] Baseline event rate is taken from the control group in the RCT.
[10] Estimate based on single RCT with overall high risk of bias.
[11] Risk ratio estimate based on single RCT; not possible to assess heterogeneity.
[12] Underpowered comparison (N = 40).
[13] Risk ratio estimate based on single RCT; not possible to assess publication bias.

alginate dressing compared to plain non-adherent dressing for venous leg ulceration

Patient or population: people with venous leg ulceration
Settings: community
Intervention: Alginate dressing
Comparison: plain non-adherent dressing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Plain non-adherent dressing	Alginate dressing				
Time to healing	See comment	See comment	Not estimable	0 (0)	See comment	Assessment of time to healing mentioned in RCT report, but estimates not provided
Proportion of participants with healed ulcers Follow-up: 12 weeks	**Study population**[1]		**RR 1.08** (0.86 to 1.36)	60 (1 study)	⊕◯◯◯ **very low**[2,3,4,5]	
	800 per 1000	**864 per 1000** (688 to 1000)				
	Low[1]					
	311 per 1000	**336 per 1000** (267 to 423)				
	High[1]					
	696 per 1000	**752 per 1000** (599 to 947)				

Mean change in wound size, with adjustment for baseline size	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported.
Adverse effects	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported.
Health-related quality of life	See comment	See comment	Not estimable	0 (0)	See comment	Outcome not reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Note: lower risk of the outcome is less favourable (i.e. lower risk of healing) than higher risk. Estimates for baseline low and high risks of healing at 90 days have been taken from a meta-analysis of compression RCTs. The low risk estimate is based on a subset of participants with larger baseline ulcer surface area (greater than 5 cm squared). The high risk estimate is based on a subset of participants with smaller baseline ulcer surface area (5 cm squared or smaller). Most participants received a simple, low-adherent dressing plus four-layer bandage (O'Meara 2007).
[2] RCT was at overall high risk of bias.
[3] Risk ratio estimate based on single RCT; not possible to assess heterogeneity.
[4] Underpowered comparison (N = 60).
[5] Risk ratio estimate based on single RCT; not possible to assess publication bias.

DISCUSSION

Summary of main results

In this review we included five RCTs that recruited participants with venous leg ulceration (all identified during the original review): one compared different proprietary alginate dressings (Límová 2003), three compared alginate and hydrocolloid dressings (Armstrong 1997; Harding 2001; Smith 1994), and one compared alginate and plain non-adherent dressings (Moffatt 1992). The primary outcome for the review was wound healing, which could be reported as time to healing, proportion of participants with complete healing, change in wound size and rate of healing. All the included RCTs assessed complete healing, three at six weeks (Armstrong 1997; Límová 2003; Smith 1994), and two at 12 weeks (Harding 2001; Moffatt 1992). Reporting of other healing outcomes varied across RCTs. No statistically significant between-group differences were detected for any comparison for any healing outcome. Meta-analysis was feasible for one comparison (alginate and hydrocolloid dressings), with data from two RCTs pooled for complete healing at six weeks: RR 0.42 (95% CI 0.14 to 1.21) (Analysis 2.1; Figure 4).

We included a range of secondary outcomes of potential importance in clinical decision making. These included costs, health-related quality of life, pain, debridement, haemostasis, dressing performance (management of wound exudate and adherence to the wound bed) and adverse events. Assessment and reporting varied across RCTs; one RCT did not report any secondary outcomes (Moffatt 1992), and there were no evaluations of haemostasis. Interpretation of data was often hindered because of poor reporting of methods and findings. It is possible, however, that hydrocolloid dressings are better than alginate dressings for ease of dressing removal, whereas adverse event profiles and dressing wear times appeared to be similar between groups for the same comparison (Armstrong 1997; Harding 2001; Smith 1994). The rationale for the comparison between two proprietary alginate dressings (Tegagen ™ HG and Sorbsan®) was not stated, and the information available suggests little difference between the two devices. However, Tegagen ™ HG appeared to be superior in terms of some secondary outcomes (pain/comfort, exudate handling, ease of removal and incidence of denuded peri-wound skin). The two dressings appeared to be similar for other types of adverse effects (including maceration) and debridement. These findings should be viewed with caution because this RCT was very small (20 participants) and so there is much uncertainty around the estimates (Límová 2003).

Overall completeness and applicability of evidence

Participant and intervention characteristics

With regard to confirmation of venous ulcer diagnosis, two RCTs provided no information about methods of ascertainment (Armstrong 1997; Smith 1994), one described using patient history and Doppler (Harding 2001), and the remaining two stated a participant exclusion criterion of ABPI less than 0.8, but did not describe methods of obtaining the measurement (Límová 2003; Moffatt 1992). Three RCTs mentioned presence of moderate or high wound exudate as a participant inclusion criterion (Armstrong 1997; Harding 2001; Límová 2003). Only one RCT reported participant mobility, in which around half of the participants had limited mobility or were immobile (Armstrong 1997). Presence of ulcer infection was an exclusion criterion in two RCTs (Límová 2003; Smith 1994), but was not mentioned in the remaining three RCTs (Armstrong 1997; Harding 2001; Moffatt 1992). The majority of RCTs imposed a limit to the baseline wound size of 10 cm^2 or less, to ensure that wound sizes would not exceed the study dressing dimensions (Harding 2001). These factors may limit applicability to clinical practice, where patients with infected wounds - and a wide range of wound sizes - are likely to be encountered. Imbalance of prognostic baseline covariates may have confounded the treatment effect in two RCTs, both comparing alginate and hydrocolloid dressings: Armstrong 1997 reported participants having larger and more chronic ulcers in the alginate group, whilst Smith 1994 indicated larger ulcers in the hydrocolloid group (ulcer duration at baseline not reported). No imbalances were apparent in two other RCTs (Límová 2003; Moffatt 1992), and another did not present any data on ulcer area or duration (Harding 2001).

All of the RCTs included reported the use of compression therapy as part of the intervention, and we were unable to undertake our planned subgroup analysis for the concurrent presence or absence of compression. The type of compression therapy differed across trials, and included orthopaedic padding covered by a high-compression elastic bandage (Armstrong 1997; Harding 2001), paste bandage plus an elastic cohesive bandage (Límová 2003), and an unspecified bandage system designed to provide graduated compression exerting 40 mmHg at the ankle (Moffatt 1992). The remaining RCT indicated the use of compression, but presented no details about the specific device used (Smith 1994).

It is important to note that this review only identified evidence on alginate dressings compared with alternative alginates, hydrocolloids and non-adherent dressings: no comparisons were identified with other dressings, for example foam or hydrogel, therefore, some potential data are lacking. In addition, the most recent of the included RCTs was published in 2003 (Límová 2003), which may limit the external validity of this review, if manufacturers have made changes to alginate and comparator dressings in the interim period. No new RCTs were identified during this first review update.

Primary outcomes

Time to healing was assessed in only two of the five included RCTs (Harding 2001; Moffatt 1992), one employed a log rank test to

compare survival curves (Harding 2001), and the other analysed this outcome by life table (Moffatt 1992). However, whilst both RCTs suggested that the results for time to healing were similar across groups, Moffatt 1992 reported no outcome data by group, and neither RCT reported the associated P value. One of these RCTs also evaluated this outcome as a mean time to healing (Harding 2001). This analysis approach would only account for those participants whose ulcers healed. Participants whose ulcers did not heal during the trial (censored data) would not have been accounted for by this analysis method, which could result in a biased effect estimate (Deeks 2011). The limited way in which this outcome was analysed and reported impedes any inference regarding the efficacy of alginate dressings in terms of time to healing.

All included RCTs reported the proportion of ulcers healed, enabling us to estimate between-group differences. The comparison between hydrocolloid dressings and alginate dressings comprised three RCTs (Armstrong 1997; Harding 2001; Smith 1994). For the other two comparisons, estimates were based on a single RCT: Tegagen ™ HG versus Sorbsab alginate dressings (Límová 2003); and alginate versus plain non-adherent dressings (Moffatt 1992). The follow-up period was short in all included RCTs (six or 12 weeks).

Four RCTs reported change in wound size; interpretation of this outcome was often hampered by incomplete presentation of data (i.e. lack of variance estimates or P values, or both) (Armstrong 1997; Límová 2003; Smith 1994). One RCT provided sufficient information on absolute and percentage area changes for us to calculate mean differences with associated 95% CIs (Harding 2001). None of the included RCTs reported rate of healing over time.

Secondary outcomes

One RCT reported a health-related quality of life assessment, but did not clarify the number of participants on which it was based, and presented only the proportion that had achieved the most favourable outcome category of its five-point scale (Smith 1994). The scale used was an unspecified instrument that was unlikely to be valid and reliable. Whilst outcomes appeared to be similar between groups, no variance estimates or P value for the between-group differences were reported.

One RCT reported mean cost to heal one ulcer (material costs and nursing costs), but lacked the necessary variance data to estimate a between-group difference (Harding 2001). The same RCT reported mean wear time with a variance estimate, and we were able to calculate a between-group difference that indicated no statistically significant difference between alginate and hydrocolloid dressings.

Across the RCTs that reported pain as an outcome, the mode and timing of the assessment was very varied, as was the reporting of data. Estimation of difference in means was feasible for one small RCT (Límová 2003), that indicated that Tegagen ™ HG alginate dressing was statistically significantly better than Sorbsan® alginate dressing in terms of comfort during wear time and dressing removal.

One RCT reported the percentage of visits at which debridement was required and where necrotic tissue was observed, but did not report the numbers of participants concerned (Límová 2003). Haemostasis was not reported by any of the included RCTs.

The included RCTs assessed and reported dressing performance (exudate management and ease of removal/adherence to the wound bed) in a variety of ways. These outcomes were often assessed subjectively and were sometimes reported as count data. Estimation of difference in means was undertaken for one small RCT (Límová 2003), that suggested that Tegagen ™ HG alginate dressing was statistically significantly better than Sorbsan® alginate dressing in terms of exudate absorption and ease of dressing removal.

The reporting of adverse events across the three RCTs that assessed this outcome was disparate (Armstrong 1997; Límová 2003; Smith 1994). In two RCTs it was unclear how many participants experienced adverse events because the denominators were events and assessments (Armstrong 1997; Límová 2003, respectively). Only one report of this outcome permitted an assessment of between-group difference, which indicated no statistically significant difference between alginate and hydrocolloid dressings (Smith 1994).

Cautious interpretation of secondary outcome data is required because of the subjective nature of many of the assessments. Most of the scales used appear to have been designed solely for the use of the trial and were unlikely to have been demonstrated to be valid and reliable instruments. In addition, poor reporting was common with a lack of data for variance estimates, P values for between group differences, and failure to present the complete set of data for some assessment scales (in some cases only the most favourable outcome category was presented).

Quality of the evidence

Two of the five included RCTs were considered to be at overall high risk of bias, one because some randomised participants had not been accounted for in the analysis (Smith 1994), and the other because the outcome assessment was not blinded (Moffatt 1992). Missing outcome data, due to attrition (drop-out) during the trial or exclusion of participants from the analysis, can bias the effect estimate, and lack of blinding of participants or healthcare providers can bias the results by influencing outcomes (Higgins 2011). The other three RCTs were classified as having an unclear overall risk of bias (Armstrong 1997; Harding 2001; Límová 2003).

All five included RCTs were published prior to the current CONSORT (Consolidated Standards of Reporting Trials) guidelines (Schulz 2010). Key aspects of best practice in RCT design to minimise bias include a robust randomisation method, concealment of treatment group allocation, blinding of participants and trial personnel, and blinded outcome assessment, all of which should

be clearly stated in the RCT report. None of the included RCTs in this review reported the method of generation of the random sequence, or an adequate method of allocation concealment, and there was evidence of selective outcome reporting in four of the five included RCTs.

The 'Summary of findings' tables indicate that the current evidence base for the effects of alginate dressings compared with alternatives on the healing of venous leg ulcers is of very low quality (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Potential biases in the review process

In addition to the electronic searches of bibliographic databases, the search for evidence for the original review and this first update included: examination of reference lists of eligible RCTs and review articles; contact with trial authors; and ongoing trials registers. During the original review we also contacted manufacturers of alginate dressings. Although this search strategy was comprehensive, the possibility of publication bias cannot be discounted. However, given the low quality of the RCTs identified for inclusion (all were published reports), coupled with the absence of any observed statistically significant treatment effects on ulcer healing, it is unlikely that any additional unpublished data would contribute substantially to the overall findings of this review.

Agreements and disagreements with other studies or reviews

The evidence base to guide dressing choice suggests that there is no evidence to support alginate dressings as being better or worse than other dressing treatments for the healing of venous leg ulcers. This observation is in agreement with the Palfreyman 2007 systematic review, which reported that there was insufficient data available to conclude that any one dressing type was more effective than any other in healing venous leg ulcers. There is some overlap between our review and the Palfreyman 2007 review, with three RCTs common to both (Límová 2003; Moffatt 1992; Smith 1994).

AUTHORS' CONCLUSIONS

Implications for practice

At present, there is no evidence to suggest any differences in terms of wound healing between different alginate dressings, or between alginate dressings and hydrocolloid dressings, or alginate dressings and non-adherent dressings. It is possible that dressing performance, in terms of ease of removal, is better for hydrocolloid dressings than alginate dressings. Adverse event profiles were generally similar between treatment groups (not assessed for alginate versus plain non-adherent dressings).

The current evidence base is of low quality. The lack of good quality evidence limits any specific recommendations regarding the use of any of the dressing types reviewed here for the healing of venous leg ulcers. Further, good quality evidence is required from well designed randomised controlled trials (RCTs) before any definitive conclusions regarding the efficacy of alginate dressings in the management of venous leg ulcers can be drawn.

Implications for research

All of the RCTs included in this review have methodological and reporting problems. Future RCTs that compare wound dressings should employ robust randomisation methods and concealment of allocation procedures to minimise bias. In addition, blinded outcome assessment and use of the intention-to-treat principle for data analysis should be adopted in order to minimise bias. These methodological aspects should be reported clearly, in line with the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Schulz 2010). Assessment of time to healing should be measured and reported using appropriate survival analysis with adjustment for prognostic covariates such as ulcer area and duration. Future RCTs should be adequately powered in order to detect treatment effects, and estimations that guide decisions regarding sample size should be reported clearly. Those planning future RCTs should consider the extent to which the recruited population is likely to represent patients seen in clinical practice, particularly with respect to mobility, ulcer size and duration, and the presence of ulcer infection.

Further research is required to investigate the safety and tolerability of wound dressings for venous leg ulcers. Health-related quality of life assessment should be undertaken using a valid and reliable assessment instrument, with findings reported in full. As dressing choice for the management of venous leg ulcers may be guided by cost, those planning future RCTs should consider incorporation of meaningful cost-effectiveness information.

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CHARACTERISTICS OF STUDIES

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

Armstrong 1997

Methods	Design: open, multicenter RCT - 3 centres Country: UK (2 centres) and France (1 centre) Setting: centres specialising in the treatment of leg ulceration Sample size calculation: not reported Ethical approval: not reported Informed consent: not reported
Participants	44 patients recruited from centres specialising in the treatment of leg ulceration. Inclusion criteria: males and females over 18 years of age presenting with an ulcer of any aetiology $\leq$ 7.5 cm in diameter, producing moderate to heavy amounts of exudate. Exclusion criteria: none specified Numbers randomised: Group 1 (hydrocolloid dressing): 21 participants Group 2 (alginate dressing): 23 participants Mean participant age: Group 1 (hydrocolloid dressing): 71 years (SD 10) Group 2 (alginate dressing): 65 years (SD 11) Number male: Group 1 (hydrocolloid dressing): 10/21 (48%) Group 2 (alginate dressing): 13/23 (57%) Number of participants with ulcers of venous, mixed or other aetiology: Group 1 (hydrocolloid dressing): 17/21 (81%), 3/21 (14%), 1/21 (5%) Group 2 (alginate dressing): 19/23 (83%), 3/23 (13%), 1/23 (4%) ABPI: not reported Unit of analysis: Participant Number of participants who had limited mobility or were immobile: Group 1 (hydrocolloid dressing): 13/21 (62%) Group 2 (alginate dressing): 11/23 (48%) Baseline ulcer area mm^2 - median (range): Group 1 (hydrocolloid dressing): 491 (64-2081) Group 2 (alginate dressing): 611 (60-1830) Baseline ulcer duration months - median (range): Group 1 (hydrocolloid dressing): 9 (1-47) Group 2 (alginate dressing): 12 (1-120)

	Ulcer infection: not reported Participant ulcer history: not reported Number of participants with heavily exuding ulcers: Group 1 (hydrocolloid dressing): 1/21 (5%) Group 2 (alginate dressing): 5/23 (22%) Comments: a moderately-exuding wound was defined as one requiring a dressing change every second day with a conventional dressing (tulle), or every third day with an absorbent dressing. A heavily-exuding wound was defined as needing a dressing change daily, or more frequently, with a conventional dressing, or every second day with a more absorbent dressing The trial authors reported that there was an imbalance as participants in Group 1 had ulcers which were smaller and of shorter duration at baseline
Interventions	Group 1: hydrocolloid-fibrous dressing (Aquacel, manufacturer not reported) Group 2: alginate dressing (Kaltostat, ConvaTec) The dressing was changed if there had been leakage, if infection was suspected, if a participant complained of pain, or once it had been in place for 7 days. A standardised secondary dressing and bandaging regimen applied over the primary dressing consisted of an occlusive hydrocolloid (DuoDerm Extra Thin) as the secondary dressing and, if indicated, orthopaedic padding and a Class 3C compression bandage (Tensopress) Description of compression therapy: Class 3C compression bandage (Tensopress) Length of treatment: 6 weeks, or until healing if sooner Follow-up: 6 weeks
Outcomes	Review-relevant outcomes: Time to healing: not reported. Proportion of ulcers healed: reported, photography and planimetry used to measure the wound on enrolment, on days 14 and 28, and on completion of the trial period Change in ulcer size: reported. Healing rate: not reported. Quality of life: not reported. Costs: reported, direct costs (primary dressings, compression treatment and saline wound cleanser) and indirect costs (nurse time, calculated at GBP 2.03 per dressing change) measured. Costs based on 1995 Drug Tariff prices and manufacturer's costs for the hydrocolloid dressing.Total dressing cost was calculated per participant. Mean cost to achieve a healed ulcer was calculated by treatment group. Mean wear time was estimated from the first to last dressing change Pain: reported, pain on dressing removal assessed on a scale of 0-5 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = excruciating, 5 = unable to respond) Debridement: not reported. Haemostasis: not reported. Dressing performance - exudate handling: secondary reference mentions 'noting leakage', but exudate levels not reported in the results Dressing performance - adherence/sticking: secondary reference mentions 'ease of removal', but not reported in the results

	Adverse events: reported, safety monitored by documenting all adverse events Other outcomes assessed by the trial: none reported.
Notes	Sponsor: ConvaTec Ltd (trial number not reported) Number participants withdrawing and reasons: Group 1 (hydrocolloid dressing): 5/21 (24%) participant request, 1; adverse events, 4 Group 2 (alginate dressing): 7/23 (30%) all due to adverse events Adverse events that prompted withdrawal described as: bleeding; increased erythema; and deterioration of the ulcer (not reported by group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Twenty-one patients were randomized to the Hydrocolloid dressing and 23 to the alginate." (Armstrong 1996) Comment: sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were then randomized to the primary dressings under investigation by the use of sealed envelopes opened in a numerical order." Comment: no statements about whether the envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "An open, comparative, randomized, multi-centre trial design was adopted. " (Armstrong 1996) Comment: no statement regarding blinding of participants or study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "An open, comparative, randomized, multi-centre trial design was adopted. " (Armstrong 1996) Comment: no statement regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data were analysed on an intention-to-treat basis."
Selective reporting (reporting bias)	High risk	Comment: the reported outcome of proportion of participants achieving a 7-day wear time was not mentioned in the methods section. Two outcomes in the secondary reference (exudate handling ability of the dressing and ease of removal) were

		not reported. Trial protocol not available (email communication with trial sponsor)

Harding 2001

Methods	Design: open, multicenter RCT - 4 centres Country: UK (4 centres) Setting: community Sample size calculation: a sample size of 90 evaluable participants (i.e. either completed the 12 week trial or healed) estimated as having 80% power to detect between-group difference in mean wear time of 1 day at 5% significance, assuming a SD of 1.7 days Ethical approval: ethical approval was granted from the relevant local ethics committees Informed consent: participants were recruited once written informed consent was obtained
Participants	Recruited 131 participants with moderately- to heavily-exuding leg ulcers Inclusion criteria: people with moderately- to heavily-exuding leg ulcers of varying aetiology, provided they were suitable for treatment with either dressing. Wound aetiology assessed using patient history and Doppler Exclusion criteria: people who had been in the trial previously and those with: a known history of poor compliance with treatments, wounds too large for the dressings, or dry eschar on the wound Numbers randomised: Group 1 (hydrocolloid dressing): 66 participants Group 2 (alginate dressing): 65 participants Mean participant age (range): Group 1 (hydrocolloid dressing): 75.53 years (35-93) Group 2 (alginate dressing): 77.6 years (43-97) Number male: Group 1 (hydrocolloid dressing): 21/66 (32%) Group 2 (alginate dressing): 12/65 (18%) Number participants with ulcers of venous, mixed, arterial or diabetic aetiology: Group 1 (hydrocolloid dressing): 54/66 (82%), 9/66 (13%), 2/66 (3%), 1/66 (2%) Group 2 (alginate dressing): 49/65 (75%), 6/65 (10%), 9/65 (13%), 1/66 (2%) ABPI: not reported Unit of analysis: participant Participant mobility: not reported Baseline ulcer area: not reported Exclusion criteria included wounds that were too large for the dressings. Dressings used were 5 cm x 5 cm and 10 cm x 10 cm Baseline ulcer duration: not reported Ulcer infection: not reported

	Participant ulcer history: not reported Participant baseline exudate levels: not reported Comments: trial authors reported that participants were well matched in terms of baseline wound characteristics, but no data were reported
Interventions	Group 1: hydrocolloid fibre dressing (Aquacel, ConvaTec) Group 2: alginate dressing (Sorbsan®, Maersk) Both dressings available in 5 cm x 5 cm and 10 cm x 10 cm sizes. Both groups received an absorbant pad as a secondary dressing (Release, Johnson & Johnson). Dressings could be left in place for up to 7 days (according to manufacturers' instructions) and were changed according to clinical need. If the wound became infected, dressings in Group 2 were changed daily (manufacturers' instructions). If the wound became infected during the trial, systemic antibiotics were prescribed and the participant remained in the trial. If topical antibiotic treatment was required, the participant was withdrawn from the trial Description of compression therapy: where clinically indicated, compression provided using orthopaedic padding and a Class 3C elastic bandage (SurePress, ConvaTec) Length of treatment: 12 weeks, or until healing Follow-up: participants were followed up until they healed, or for a maximum of 12 weeks
Outcomes	Review relevant outcomes reported: Time to healing: reported, wound size assessed using acetate tracings. Wound assessments performed on a weekly basis. Analysed using log rank test to compare Kaplan-Meier survival curves Proportion of ulcers healed: reported Change in ulcer size: reported Healing rate: not reported Quality of life: not reported Costs: reported, cost -effectiveness calculated by comparing clinical costs with costs in the International Committee on Wound Management and the Health economic UK Guidelines. All materials used at each dressing change were used to estimate mean costs. Included an additional GBP 15 (USD 21.53) at each dressing change to reflect cost of nursing staff. Costs calculated using May 2000 Drug Tariff prices (with the exception of the orthopaedic wool). Estimated a mean cost associated with a 1 cm^2 reduction and a 10% reduction in ulcer area per treatment group, and the mean cost of a healed ulcer Pain: reported, pain on dressing removal was assessed by participant self-reporting on a four-point scale ('no pain' to 'severe pain'). Also, pain on dressing removal was assessed by the participant on a "yes/no" basis Debridement: not reported Haemostasis: not reported Dressing performance - exudate handling: reported, assessed by investigator using 4-point scale ranging from "poor" to "excellent" on a patient-by-patient basis Dressing performance - adherence/sticking: reported, assessed by investigator using 4-point scale ranging from "poor" to "excellent" on a patient-by-patient basis. Also, at each dressing change dressings were assessed for adhesion on a "yes/no" basis

	Adverse events: not reported Other outcomes assessed by the trial: ease of application and residue observed on dressing change Review authors' comment: the trial authors stated that ease of dressing removal, exudate handling and level of pain on dressing removal were assessed by both the investigator and participant
Notes	Sponsor: ConvaTec (trial number not reported) Participant withdrawal: trial authors did not report on participant withdrawal in the primary reference. Secondary reference reported a larger sample size described as "mainly community based". Possibility that primary reference only reported on the community-based participants (not stated) Number participants withdrawing based on review authors' comparison between primary and secondary references: Group 1 (hydrocolloid dressing): 1/67 (1.5%) Group 2 (alginate dressing): 4/69 (6%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to one of the following dressings:" Comment: sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization to study treatment using sealed envelopes was made at this point and the patients' wounds dressed accordingly, . . . " Comment: no statement that envelopes were opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This paper reports the results of an open, prospective, randomized, controlled, multicenter evaluation . . ." Comment: no statement regarding blinding of participants or study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Both the investigator and patient measured the secondary outcomes" Comment: no statement regarding blinded outcome assessment of primary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data were processed on an 'intention to treat' basis so that all information relating to a subject who participated in the

Harding 2001 (*Continued*)

		study was retained
Selective reporting (reporting bias)	High risk	Quote: "Both the investigator and patient measured the secondary outcomes." Comment: only one set of results was presented for the secondary outcomes and it was not reported whether these were assessed by the participants or investigators Quote: "Overall ease of application and removal was assessed by the investigator using a four-point scale ranging from 'poor' to 'excellent' on a patient-by-patient basis. " Comment: results were not presented for the full 4-point scale for ease of application - only the proportion recorded as "excellent" was reported

Límová 2003

Methods	Design: open RCT Country: USA (2 centres) Setting: outpatients Sample size calculation: not reported Ethical approval: not reported Informed consent: one of the inclusion criteria was that participants should be willing to sign informed consent before enrolment
Participants	Recruited 20 people from wound clinics. Inclusion criteria: outpatients ≥ 21 years, able to understand the product application and assessment procedures, and willing to sign informed consent. Required to have a venous insufficiency ulcer of at least 1 month duration, with area 3 cm^2 to 100 cm^2 and moderate (3-5 ml) to large amount (> 5 ml) of exudate. Initial assessment included recording ulcer history and determination of ulcer status (stable, improving or worsening) Exclusion criteria: ABPI < 0.8, uncontrolled diabetes, underlying vasculitis, on immunosuppressive therapy, ulcer showing signs of infection, presence of pre-existing local skin disease or condition that could affect trial results, or an allergy to the trial materials Numbers randomised: Group 1 (alginate dressing, Tegagen ™ HG): 11 participants Group 2 (alginate dressing, Sorbsan®): 9 participants Baseline data were reported for participants completing the trial: Group 1 (Tegagen ™ HG): 10 participants Group 2 (Sorbsan®): 9 participants Participant age - mean (range):

	Group 1 (alginate dressing, Tegagen ™ HG): 75.4 years (51-88) Group 2 (alginate dressing, Sorbsan®): 72.1 years (45-93) Number male: Group 1 (alginate dressing, Tegagen ™ HG): 3/10 (30%) Group 2 (alginate dressing, Sorbsan®): 0/9 (0%) ABPI: ABPI < 0.8 amongst exclusion criteria. No data reported by group Unit of analysis: participant Participant mobility: not reported Baseline ulcer area cm^2 - mean (range): Group 1 (alginate dressing, Tegagen ™ HG): 6.9 (1.0-16.8) Group 2 (alginate dressing, Sorbsan®): 8.5 (1.6-21.7) Baseline ulcer duration - mean (range): Group 1 (alginate dressing, Tegagen ™ HG): 6.1 months (2-14) Group 2 (alginate dressing, Sorbsan®): 9.1 months (1-24) Participant ulcer history: not reported Number of ulcers categorised as worsening, stable, improving (exact nature of this variable unclear from RCT report): Group 1 (alginate dressing, Tegagen ™ HG): 4/10 (40%), 6/10 (60%), 0/10 (0%) Group 2 (alginate dressing, Sorbsan®): 7/9 (77.8%), 2/9 (22.2%), 0/9 (0%) Ulcer infection: participants with ulcers showing signs of infection were excluded Number of participants with ulcers with foul odour: Group 1 (alginate dressing, Tegagen ™ HG): 1/10 (10.0%) Group 2 (alginate dressing, Sorbsan®): 2/9 (22.2%) Number participants with medium to large amounts of exudate: Group 1 (alginate dressing, Tegagen ™ HG): 10/10 (100%) Group 2 (alginate dressing, Sorbsan®): 9/9 (100%) Breakdown by medium and large levels of exudate not reported Number of participants with purulent serosanguineous exudate: Group 1 (alginate dressing, Tegagen ™ HG): 3/10 (30%) Group 2 (alginate dressing, Sorbsan®): 6/9 (66.7%) Number of participants with macerated peri-wound skin: Group 1 (alginate dressing, Tegagen ™ HG): 5/10 (50%) Group 2 (alginate dressing, Sorbsan®): 4/9 (44.4%) Number of participants with necrotic tissue: Group 1 (alginate dressing, Tegagen ™ HG): 10/10 (100%) Group 2 (alginate dressing, Sorbsan®): 9/9 (100%)

	Number of participants with ulcers that required debridement: Group 1 (alginate dressing, Tegagen ™ HG): 7/10 (70%) Group 2 (alginate dressing, Sorbsan®): 3/9 (33.3%) Comment: recruited some participants with ulcers smaller than those described as eligible for inclusion
Interventions	Group 1: alginate dressing (Tegagen ™ HG (High Gelling),3M) Group 2: alginate dressing (Sorbsan®, Dow Hickman) Need for debridement (surgical debridement not requiring anaesthesia) of fibrin or necrotic tissue from wounds assessed at weekly dressing changes. Dressing changes completed weekly. The secondary dressing (Tegasorb hydrocolloid dressing, 3M) the same for both groups. Applied 3M Cavilon No Sting Barrier Film (3M) if peri-wound skin was denuded or macerated Description of compression therapy: Medicopaste Bandage (Graham-Field) and 3M Coban Self-Adhesive Wrap (3M) Length of treatment: 6 weeks, or until ulcer no longer required the use of an alginate dressing Follow-up: participants followed up for a maximum of 6 weeks, or until the venous leg ulcer no longer required the use of a calcium alginate dressing
Outcomes	Review-relevant outcomes reported: Time to healing: not reported Proportion of ulcers healed: reported, wounds assessed weekly using a wound tracing and a photograph Change in ulcer size: reported Healing rate: not reported Quality of life: not reported Costs: reported, recorded the number of dressing changes over the course of the trial Pain: reported, comfort during dressing wear and at removal assessed by asking participants if they experienced itching, pain, or other problems. Dressings rated on a scale of 1 (very good) to 5 (very poor) Debridement: reported, recorded the percentage of visits where necrotic tissue was observed and debridement required. The amount of necrotic tissue was graded as 0 = none, 1 = ≤25%, 2 = 26%-50%, 3 = 51%-75%, 4 = 76%-99%, 5 = 100% Haemostasis: not reported Dressing performance - exudate handling: reported, estimated by observation of the wound and dressing at dressing removal (dry wound; small amount, 1-2 ml exudate; medium amount, 3-5 ml exudate; large, > 5 ml exudate). Dressings rated on scale ranging from 1 (very good) to 5 (very poor) in terms of exudate absorption Dressing performance - ease of removal: reported, rated during weekly assessment visits on a scale ranging from 1 (very good) to 5 (very poor). Dressing adherence to wound bed rated as 'yes' or 'no' Adverse events: reported, peri-wound skin condition classified as normal, denuded, macerated, or flaky/dry. Reported whether peri-wound skin required medication

	Other outcomes assessed by the trial: condition of the wound edge; type and amount of necrotic tissue; amount of granular tissue and epithelialisation; dressing comfort; ease of application; conformability of dressing to the site; itching or other problems; and dressing residue on wound bed
Notes	Sponsor: a 'company sponsor' is mentioned as having provided training to evaluators, but name not provided Number of participants withdrawing and reasons: Group 1 (alginate dressing, Tegagen ™ HG): 1/11(9%), left after 1 week due to an unrelated adverse event Group 2 (alginate dressing, Sorbsan®): no details regarding participant withdrawal reported, assume 0/9 (0)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients provided informed consent and were randomized to one of the treatment groups according to the protocol randomization schedule." Comment: sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The purpose of this open, randomized, controlled clinical study was to compare the performance characteristics and clinical effect of two calcium alginate dressings in the management of venous leg ulcers:" Comment: no statement regarding blinding of participants or study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All wound assessments and dressing performance evaluations were undertaken by either the primary investigator or her designate (RN staff member)." Comment: no statement regarding blinding of the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in the Alginate A group (Group 1) left the study after 1 week due to an unrelated adverse event and was not included in the analyses." Comment: reason for drop-out stated as unrelated to treatment (although nature of

Límová 2003 (*Continued*)

		the adverse event not reported)
Selective reporting (reporting bias)	Low risk	Comment: outcomes described in the methods section matched those reported in the results section Unable to obtain trial protocol

Moffatt 1992

Methods	Design: RCT (pilot study) Country: UK Setting: community Sample size calculation: not reported, trial was a pilot study Ethical approval and informed consent: trial authors described methods used in the discussion section of the paper, and indicated that ethical approval and informed consent were both obtained
Participants	Recruited 60 patients from the community Inclusion criteria: people with ulcers < 10 cm^2. All participants had ABPI measurements Exclusion criteria: ABPI < 0.8 Numbers randomised: Group 1 (plain non-adherent dressing): 30 participants Group 2 (alginate dressing): 30 participants Median participant age (range): Group 1 (plain non-adherent dressing): 70 years (38-88) Group 2 (alginate dressing): 78 years (44-88) Number of males: Group 1 (plain non-adherent dressing): 13/30 (43%) Group 2 (alginate dressing): 10/30 (33%) ABPI: ABPI < 0.8 an exclusion criterion. No data reported by group Unit of analysis: participant Participant mobility: not reported Baseline ulcer size - median (range): Group 1 (Plain non-adherent dressing): 6.4 (1.1-9.9) Group 2 (alginate dressing): 3.6 (0.9-9.8) Unit of measurement not stated, assume cm^2 Baseline ulcer duration, unit of measurement not stated, assume months - median (range) : Group 1 (plain non-adherent dressing): 3 (1-20) Group 2 (alginate dressing): 2 (1-192) Ulcer infection: not reported

Moffatt 1992 (*Continued*)

	Participant ulcer history: not reported Participant baseline exudate levels: not reported
Interventions	Group 1: plain non-adherent dressing (proprietary name not reported, Johnson and Johnson) Group 2: alginate dressing (Tegagel, 3M) Weekly cleaning and re-dressing of ulcers unless excessive exudate or infection occurred, in which case dressing and bandage changes were more frequent Description of compression therapy: All participants fitted with a graduated compression bandaging system to produce and sustain 40 mmHg at the ankle (exact device not specified) Length of treatment: 12 weeks Follow-up: 12 weeks
Outcomes	Review-relevant outcomes reported: Time to healing: reported, healing assessment method not described. Data analysis was by life table, with comparison between-groups by the log rank method Proportion of ulcers healed: reported Change in ulcer size: not reported Healing rate: not reported Quality of life: not reported Costs: not reported Pain: not reported Debridement: not reported Haemostasis: not reported Dressing performance - exudate handling: not reported Dressing performance - adherence/sticking: not reported Adverse events: not reported Other outcomes assessed by the trial: none reported.
Notes	Sponsor: 3M Health Care Ltd (trial number not reported) Number of participants withdrawing and reasons: trial authors did not report on participant withdrawal

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Following assessment for arterial disease, patients were entered into the trial and randomised to either of the two dressing types." Comment: sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation method not reported

Moffatt 1992 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no statement regarding blinding of participants or study personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "One of the difficulties of running trials of this nature is that the person assessing efficacy cannot be 'blind' to the treatment that is being offered to the patient." Comment: trial authors described the methods used in the discussion, and indicated that outcome assessment was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analysis based on 'intention to treat' is a standard method." Comment: trial authors described the methods used in the discussion, and indicated that ITT was undertaken
Selective reporting (reporting bias)	High risk	Quote: "Data analysis was by life table for time to healing, with comparison between-groups by the log rank method." Comment: trial authors described the methods used to assess time to healing, but no results data presented

Smith 1994

Methods	Design: open RCT Country: UK Setting: hospital dermatology department Sample size calculation: not reported Ethical approval: not reported Informed consent: recruited consenting adults
Participants	Recruited 40 people from a hospital dermatology department Inclusion criteria: people with a venous leg ulcer > 2.5 cm in diameter Exclusion criteria: any condition that might affect wound healing (infection, immune deficiency, treatment with steroids, malignant disease), ulcer not clearly of venous origin, systemic treatment that might affect ulcer healing (fibrinolytic or anticoagulant therapy) , or if other treatment was deemed better Numbers randomised: Group 1 (hydrocolloid dressing): 22 participants Group 2 (alginate dressing): 18 participants Baseline participant age, % male, and mobility: The trial authors reported that there were no statistically significant differences at baseline

	in participants in terms of sex, age or mobility. No data were reported ABPI: not reported Unit of analysis: participant Baseline ulcer area cm^2 - mean: Group 1 (hydrocolloid dressing): 22.17 Group 2 (alginate dressing): 12.74 Baseline ulcer size, ulcer duration, and participant ulcer history: not reported Baseline ulcer infection: presence of infection was an exclusion criterion Mean ulcer pain score at baseline (during previous 2weeks, lower score better): Group 1 (hydrocolloid dressing): 4.74 Group 2 (alginate dressing): 4.86 Participant baseline exudate levels: not reported Comments: trial authors commented that the mean ulcer size at enrolment was considerably larger in Group 1
Interventions	Group 1: hydrocolloid dressing: (Improved Formulation Granuflex, ConvaTec) Group 2: alginate dressing (type and manufacturer not reported) Wounds cleaned with physiological saline and dressings applied according to manufacturers' instructions. Participants re-attended dermatology clinic for ulcer dressing whenever necessary Description of compression therapy: Compression bandaging applied to each participant, but details of type not reported Length of treatment: 6 weeks Follow-up: trial dressing continued for 6 weeks, or until the ulcer healed
Outcomes	Review relevant outcomes reported: Time to healing: not reported Proportion of ulcers healed: reported, an acetate tracing of the ulcer made on the first and last day of the trial, and the ulcer area calculated using an image analyser Change in ulcer size: reported Healing rate: not reported Quality of life: reported, assessed over the previous 2 weeks at weeks 0, 2, 4 and 6 on a 5-point scale (deteriorated markedly, deteriorated somewhat, no change, improved somewhat or improved markedly). Name of scale not provided and no mention of using a validated instrument to assess health-related quality of life Costs: reported, completed a costing sheet, listing all materials used, at each dressing change. Nursing time not included and price year/tariff not provided. Frequency of dressing changes assessed as the mean number of changes over 2 weeks Assessment of wear time mentioned, but no details of assessment provided Pain: reported, pain was assessed over the previous 2 weeks at weeks 2, 4, and 6 using a 10-point visual analogue scale (0 = no pain to 10 = worse pain). Pain that disturbed

	sleep assessed (as: often, sometimes, rarely) and also pain at dressing change (10-point VAS as before) Debridement: not reported Haemostasis: not reported. Dressing performance - exudate handling: reported, the ability of dressings to contain exudate rated on a 6-point scale (excellent, very good, good, fair, poor or awful) Dressing performance - adherence/sticking: reported, ease of removal assessed on a 6-point scale (excellent, very good, good, fair, poor, awful) Adverse events: reported, all adverse events recorded, including severe pain and suspected infection of the ulcer Other outcomes assessed by the trial: convenience of dressing changes; participant comfort; ease of application
Notes	Sponsor: ConvaTec Ltd (trial number not reported) Number of participants withdrawing and reasons: Group 1 (hydrocolloid dressing): 6/22 (27%) - pain, 1; ulcer infection, 1; possible allergy, 1; dressing leakage, 1; misdiagnosis, 1; participant default, 1 Group 2 (alginate dressing): 6/18 (33%) - pain, 4; ulcer infection, 2 Note: pain, ulcer infection and possible allergy classified by trial authors as adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were allocated randomly to treatment with either the alginate or Granuflex." Comment: sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "It was an open, randomised, parallel group trial . . . " Comment: no statement regarding blinding of participants or study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "It was an open, randomised, parallel group trial . . . " Comment: no statement regarding blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Statistical analysis was carried out on results from patients who completed the trial . . . " Quote: "Twelve patients were withdrawn before completion, six on the alginate and

Smith 1994 (*Continued*)

		six on Granuflex . . . " Comment: the analysis did not include all randomised participants
Selective reporting (reporting bias)	High risk	Comment: mean number of dressing changes assessed over 2-week periods, but was not reported as such (e.g. "one or two alginate dressings"). Did not report all outcome categories for quality of life assessment, or data for outcomes of exudate handling and ease of dressing removal Trial protocol not available (email communication with trial sponsor)

Abbreviations
> = greater than
< = less than
≤ = less than or equal to
ITT = intention-to-treat analysis
RCT = randomised controlled trial
VAS = visual analogue scale

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

Study	Reason for exclusion
Anonoymous 1997	Not an RCT (review article translated from German).
Barnett 1987	Animal study.
Bull 1996	Alginate dressing not the only systematic difference across treatment arms (different compression systems used at different participating centres)
Capillas Pérez 2000	Compared moist dressings (a mix of hydrocolloids, hydrogels, and alginates) with traditional dressings. Results not available separately for participants receiving alginate dressings. Information confirmed with author (RCT report published in Spanish)
Chaloner 1992	Did not report sufficient information to be judged as eligible for inclusion in this review. Unable to obtain the necessary information to make a judgement (no response to email to sent trial author)
de la Brassinne 2006	Not treatment of interest (topical agents not alginate dressings)
Dmochowska 1999	Alginate dressing not the only systematic difference across treatment groups (alginate group only received secondary absorbant dressing)

(*Continued*)

Kammerlander 2000	Did not report sufficient information to be judged as eligible for inclusion in this review. Unable to obtain the necessary information to make a judgement (no response to email to sent trial author)
Kordestani 2008	Not an RCT (participants allocated to groups on an alternating basis)
Límová 2002	Not treatment of interest (comparison of hydrocolloid dressings)
Moody 1991	Not an RCT (single-arm trial of alginate dressings in pressure ulcers and non-healing burns)
Mulder 1995	Abstract with limited information. Full RCT report no longer available (email communication with trial author)
Petres 1994	Abstract with limited information. Full RCT report no longer available (email communication with trial sponsor)
Romanelli 2008	Not treatment of interest (protease-modulating matrix dressing)
Romero-Cerecero 2012	Not treatment of interest (antifungal agent).
Schulze 2001	Alginate dressing not the only systematic difference across treatment arms (alginate group only received secondary film dressing that was changed to a sterile swab dressing for 50% of the group half-way through the trial)
Scurr 1994	Alginate dressing not the only systematic difference across treatment arms (different secondary dressings used in each treatment group)
Sibbald 2005	Not treatment of interest (freeze-dried alginate not dressings)
Stacey 1997	Alginate dressing not the only systematic difference across treatment arms (different compression systems used in each treatment group)
Thomas 1989	Not an RCT (participants allocated to groups on alternating basis)
Wild 2010	Not treatment of interest (hydrocolloid dressing).

DATA AND ANALYSES

Comparison 1. Tegagen HG alginate dressing compared with Sorbsan alginate dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed at 6 weeks	1	20	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.32, 111.04]
2 Score for comfort of dressing during wear time at 6 weeks	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.29, -0.51]
3 Score for comfort during dressing removal at 6 weeks	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-0.88, -0.52]
4 Exudate absorption score at 6 weeks	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.22, -0.38]
5 Ease of dressing removal score at 6 weeks	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.28, -0.52]

Comparison 2. Hydrocolloid dressings compared with alginate dressings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed at 6 and 12 weeks	3	215	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]
1.1 Healed at 6 weeks	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.14, 1.21]
1.2 Healed at 12 weeks	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.57, 1.81]
2 Change in ulcer area in mm^2 at 12 weeks	1	131	Mean Difference (IV, Fixed, 95% CI)	-169.56 [-613.61, 274.49]
3 Percentage change in ulcer area at 12 weeks	1	131	Mean Difference (IV, Fixed, 95% CI)	-7.64 [-37.88, 22.60]
4 Mean wear time (days)	1	131	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.29, 1.02]
5 Proportion of participants experiencing adverse events	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.53, 4.03]

Comparison 3. Plain non-adherent dressings compared with alginate dressings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed at 12 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.86, 1.36]

Analysis 1.1. Comparison 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing, Outcome 1 Proportion of ulcers healed at 6 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing

Outcome: 1 Proportion of ulcers healed at 6 weeks

Study or subgroup	Sorbsan alginate dressing n/N	Tegagen HG alg dressing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
L mov 2003	2/9	0/11		100.0 %	6.00 [0.32, 111.04]
Total (95% CI)	**9**	**11**		**100.0 %**	**6.00 [0.32, 111.04]**

Total events: 2 (Sorbsan alginate dressing), 0 (Tegagen HG alg dressing)

Heterogeneity: not applicable

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing, Outcome 2 Score for comfort of dressing during wear time at 6 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing

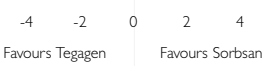
Outcome: 2 Score for comfort of dressing during wear time at 6 weeks

Study or subgroup	Tegagen HG alginate dressing N	Mean(SD)	Sorbsan alginate dressing N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
L mov 2003	10	1.2 (0.35)	9	2.1 (0.5)		100.0 %	-0.90 [-1.29, -0.51]
Total (95% CI)	**10**		**9**			**100.0 %**	**-0.90 [-1.29, -0.51]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.50 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing, Outcome 3 Score for comfort during dressing removal at 6 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing

Outcome: 3 Score for comfort during dressing removal at 6 weeks

Study or subgroup	Tegagen HG alginate dressing N	Mean(SD)	Sorbsan alginate dressing N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
L mov 2003	10	1.2 (0.22)	9	1.9 (0.19)		100.0 %	-0.70 [-0.88, -0.52]
Total (95% CI)	**10**		**9**			**100.0 %**	**-0.70 [-0.88, -0.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.44 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing, Outcome 4 Exudate absorption score at 6 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing

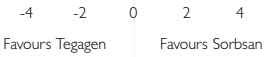
Outcome: 4 Exudate absorption score at 6 weeks

Study or subgroup	Tegagen HG alginate dressing N	Mean(SD)	Sorbsan alginate dressing N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
L mov 2003	10	1.3 (0.45)	9	2.1 (0.48)		100.0 %	-0.80 [-1.22, -0.38]
Total (95% CI)	**10**		**9**			**100.0 %**	**-0.80 [-1.22, -0.38]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.74 (P = 0.00019)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing, Outcome 5 Ease of dressing removal score at 6 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 1 Tegagen HG alginate dressing compared with Sorbsan alginate dressing

Outcome: 5 Ease of dressing removal score at 6 weeks

Study or subgroup	Tegagen HG alginate dressing N	Mean(SD)	Sorbsan alginate dressing N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
L mov 2003	10	1.1 (0.16)	9	2 (0.56)		100.0 %	-0.90 [-1.28, -0.52]
Total (95% CI)	**10**		**9**			**100.0 %**	**-0.90 [-1.28, -0.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.65 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Hydrocolloid dressings compared with alginate dressings, Outcome 1 Proportion of ulcers healed at 6 and 12 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 2 Hydrocolloid dressings compared with alginate dressings

Outcome: 1 Proportion of ulcers healed at 6 and 12 weeks

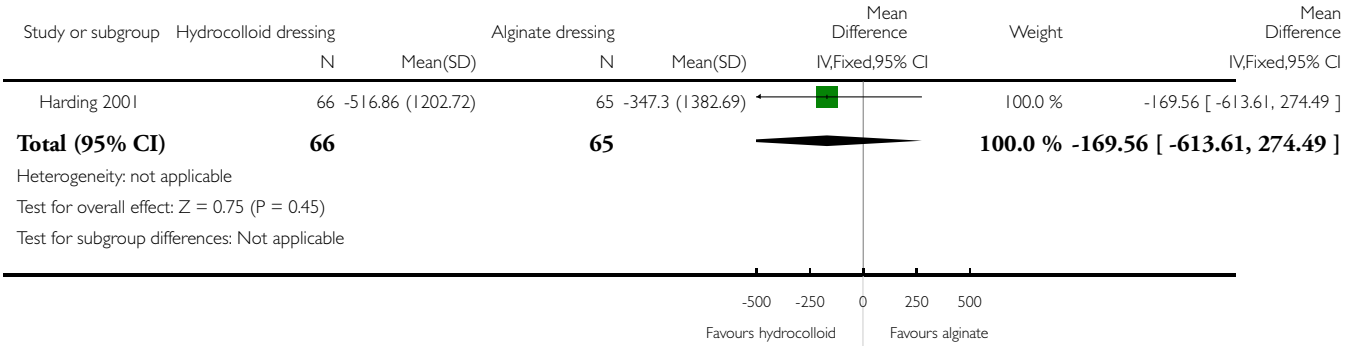
Study or subgroup	Alginate dressing n/N	Hydrocolloid dressing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Healed at 6 weeks					
Armstrong 1997	2/23	6/21		23.5 %	0.30 [0.07, 1.35]
Smith 1994	2/18	4/22		13.5 %	0.61 [0.13, 2.96]
Subtotal (95% CI)	**41**	**43**		**36.9 %**	**0.42 [0.14, 1.21]**
Total events: 4 (Alginate dressing), 10 (Hydrocolloid dressing)					
Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					
2 Healed at 12 weeks					
Harding 2001	17/65	17/66		63.1 %	1.02 [0.57, 1.81]
Subtotal (95% CI)	**65**	**66**		**63.1 %**	**1.02 [0.57, 1.81]**
Total events: 17 (Alginate dressing), 17 (Hydrocolloid dressing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**106**	**109**		**100.0 %**	**0.79 [0.48, 1.31]**
Total events: 21 (Alginate dressing), 27 (Hydrocolloid dressing)					
Heterogeneity: Chi^2 = 2.40, df = 2 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Chi^2 = 2.07, df = 1 (P = 0.15), I^2 =52%					

Analysis 2.2. Comparison 2 Hydrocolloid dressings compared with alginate dressings, Outcome 2 Change in ulcer area in mm2 at 12 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 2 Hydrocolloid dressings compared with alginate dressings

Outcome: 2 Change in ulcer area in mm^2 at 12 weeks

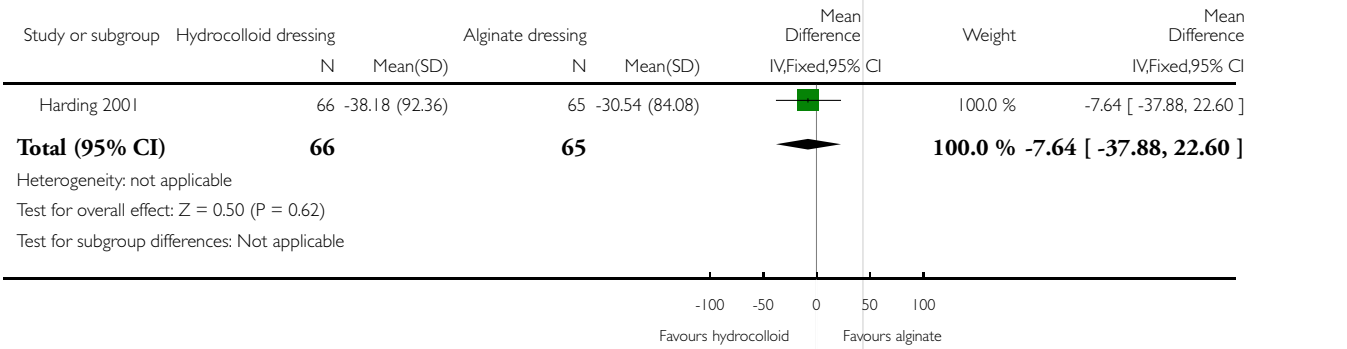


Analysis 2.3. Comparison 2 Hydrocolloid dressings compared with alginate dressings, Outcome 3 Percentage change in ulcer area at 12 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 2 Hydrocolloid dressings compared with alginate dressings

Outcome: 3 Percentage change in ulcer area at 12 weeks

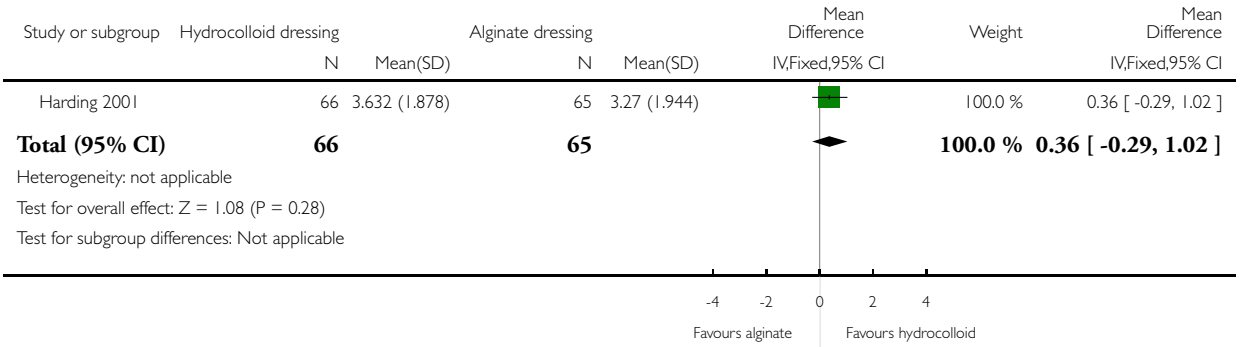


Analysis 2.4. Comparison 2 Hydrocolloid dressings compared with alginate dressings, Outcome 4 Mean wear time (days).

Review: Alginate dressings for venous leg ulcers

Comparison: 2 Hydrocolloid dressings compared with alginate dressings

Outcome: 4 Mean wear time (days)

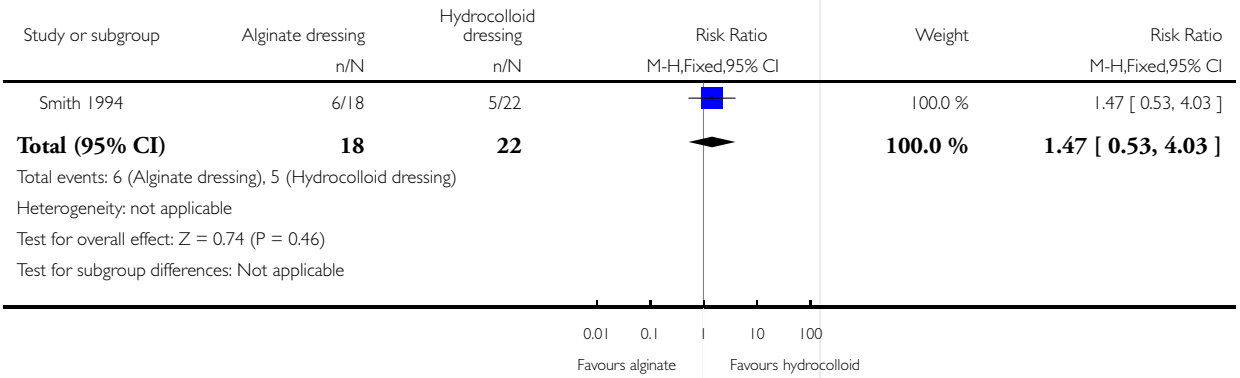


Analysis 2.5. Comparison 2 Hydrocolloid dressings compared with alginate dressings, Outcome 5 Proportion of participants experiencing adverse events.

Review: Alginate dressings for venous leg ulcers

Comparison: 2 Hydrocolloid dressings compared with alginate dressings

Outcome: 5 Proportion of participants experiencing adverse events



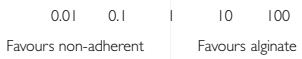
Analysis 3.1. Comparison 3 Plain non-adherent dressings compared with alginate dressings, Outcome 1 Proportion of ulcers healed at 12 weeks.

Review: Alginate dressings for venous leg ulcers

Comparison: 3 Plain non-adherent dressings compared with alginate dressings

Outcome: 1 Proportion of ulcers healed at 12 weeks

Study or subgroup	Alginate dressing n/N	Plain non-adherent n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Moffatt 1992	26/30	24/30		100.0 %	1.08 [0.86, 1.36]
Total (95% CI)	**30**	**30**		**100.0 %**	**1.08 [0.86, 1.36]**
Total events: 26 (Alginate dressing), 24 (Plain non-adherent)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					



ADDITIONAL TABLES

Table 1. Outcome data reported by included trials: primary (healing) outcomes

Armstrong 1997	**Number of ulcers healed at 6 weeks:** Group 1 (hydrocolloid dressing): 6/21 (29%) Group 2 (alginate dressing): 2/23 (9%) P value for between-group difference not reported. **Change in ulcer size - median change in area:** Group 1 (hydrocolloid dressing): -205 mm^2 Group 2 (alginate dressing): -162 mm^2 The trial authors reported that the between-group difference was not statistically significant. P value not reported. **Change in ulcer size - median percentage change in ulcer area:** Group 1 (hydrocolloid dressing): -42% Group 2 (alginate dressing): -26% The trial authors reported that the between-group difference was not statistically significant. P value not reported. Review authors' comment: there was a reporting discrepancy between primary and secondary references for this outcome. The respective values in the secondary reference were -30.5% and -28.1%
Harding 2001	**Time to healing days - mean (SD) [median (range)] (analysis based on healed participants only):** Group 1 (hydrocolloid dressing): 41.823 days (SD 21.302) [42 (14 to 87)]; n = 17 Group 2 (alginate dressing): 56.588 days (SD 21.569) [56 (14 to 85)]; n = 17 Reported P value for between-group difference in means = 0.053 P = 0.05 (log rank test) for difference in Kaplan-Meier survival curves (analysis based on all randomised patients) **Number of ulcers healed at 12 weeks:** Group 1 (hydrocolloid dressing): 17/66 (26%)

Table 1. Outcome data reported by included trials: primary (healing) outcomes *(Continued)*

	Group 2 (alginate dressing): 17/65 (26%) P value for between-group difference not reported **Change in ulcer area mm^2 - mean (SD) [median (range)]:** Group 1 (hydrocolloid dressing): -516.86 mm^2 (SD 1202.72) [-301.13 (-2494.84 to 5285.82)]; n = 66 Group 2 (alginate dressing): -347.30 mm^2 (SD 1382.69) [-132.83 (-5144.08 to 5946.24)]; n = 65 P value for between-group difference in means P = 0.48, reported by trial authors **Percentage change in ulcer area - mean (SD) [median (range)]:** Group 1 (hydrocolloid dressing): -38.18% (SD 92.36) [-67.67 (374.84 to -100.00)]; n = 66 Group 2 (alginate dressing): -30.54% (SD 84.08) [-43.33 (411.74 to -100.00)]; n = 65 P value for between-group difference in means = 0.64, reported by trial authors
Límová 2003	**Number of ulcers healed at 6 weeks:** Group 1 (alginate dressing, Tegagen ™ HG): 0/11 (0%) Group 2 (alginate dressing, Sorbsan®): 2/9 (22%) P value for between-group difference not reported. **Mean percentage change in wound area at 6 weeks:** Group 1 (alginate dressing, Tegagen ™ HG): -33.7%, n = 10 Group 2 (alginate dressing, Sorbsan®): -29.6%, n = 9 The trial authors reported a P value of 0.88 for between-group difference
Moffatt 1992	**Time to healing/number of ulcers healed at 12 weeks:** Group 1 (plain non-adherent dressing): 24/30 (80%) Group 2 (alginate dressing): 26/30 (87%) P value for between-group difference not reported The trial authors reported that results were similar for cumulative proportions healed estimated using life table analysis (no data or P value for between-group difference presented)
Smith 1994	**Number of ulcers healed at 6 weeks:** Group 1 (hydrocolloid dressing): 4/22 (18%) Group 2 (alginate dressing): 2/18 (11%) P value for between-group difference not reported **Mean percentage change in ulcer area:** Group 1 (hydrocolloid dressing): -57.1 Group 2 (alginate dressing): -34.9 The trial authors reported that the between-group difference was not statistically different. P value not reported

Table 2. Outcome data reported by included trials - secondary outcomes

Armstrong 1997	**Mean wear time days:** Group 1 (hydrocolloid dressing): 4.112 days Group 2 (alginate dressing): 3.051 days The trial authors reported a between-group difference of 1.029 days (95% CI 0.385 to 1.672), and that the difference was statistically significant in favour of Group 1 but the P value was not reported. Reviewer authors' comment: the difference in means reported by the trial authors does not follow from the mean values for each group **Number participants achieving a 7-day wear time on at least one occasion:** Group 1 (hydrocolloid dressing): 9/21 (43%) Group 2 (alginate dressing): 3/23 (13%) The trial authors reported that the between-group difference (30%, 95% CI 5% to 55%) was statistically significant but P value not reported **Cost to heal one ulcer:** Group 1 (hydrocolloid dressing): GBP 237.66 (total direct and indirect costs = GBP 1425.97 for total of 6 wounds healed) Group 2 (alginate dressing): GBP 687.31 (total direct and indirect costs = GBP 1374.61 for total of 2 wounds healed) Cost per wound healed calculated by review authors. Taking into account the number of participants completely healed in each group, the trial authors reported that the cost to achieve a healed wound using the Group 1 dressing was approximately one-third of the cost of Group 2. **Number dressing changes with no pain, mild pain, moderate pain, severe pain, excruciating pain, unable to respond, missing data:** Group 1 (hydrocolloid dressing): (total of 192 dressing changes) 144 (75%), 38 (20%), 6 (3%), 2 (1%), 0 (0%) , 0 (0%), 2 (1%) Group 2 (alginate dressing): (total of 224 dressing changes) 186 (83%), 29 (13%), 8 (3.5%), 0 (0%), 0 (0)%, 0 (0%), 1 (0.5%) **Number of adverse events during the trial:** Group 1 (hydrocolloid dressing): 32 adverse events reported during the trial. 4 were related to the primary dressing and 28 to the secondary dressing, of which 8 were attributed to maceration Group 2 (alginate dressing): 32 adverse events reported during the trial. 3 were related to the primary dressing and 29 to the secondary dressing, of which 9 were attributed to maceration
Harding 2001	**Total number of dressing changes:** Group 1 (hydrocolloid dressing): 1093 Group 2 (alginate dressing): 1186 **Mean wear time days (SD) [median (range)]:** Group 1 (hydrocolloid dressing): 3.632 days (1.878) [3 (1 to 13)]; n = 66 Group 2 (alginate dressing): 3.271 days (1.944) [3 (1 to 9)]; n = 65 The trial authors reported that the between-group difference in means was P value < 0.001 **Mean number of dressing changes per healed ulcer:** Group 1 (hydrocolloid dressing): 7.4 Group 2 (alginate dressing): 12.1 P value for between-group difference not reported **Mean cost to achieve ulcer healing (based on patients healed):** Group 1 (hydrocolloid dressing): GBP 1184.09 (USD 1699.71) Group 2 (alginate dressing): GBP 1200.73 (USD 1723.59) **Mean cost per 1cm^2 reduction in ulcer size (all patients randomised):**

Table 2. Outcome data reported by included trials - secondary outcomes (*Continued*)

	Group 1 (hydrocolloid dressing): GBP 59.22 (USD 85.01) Group 2 (alginate dressing): GBP 92.27 (USD 132.46) **Mean cost per 10% reduction in ulcer area:** Group 1 (hydrocolloid dressing): GBP 80.15 (USD 115.06) Group 2 (alginate dressing): GBP 104.92 (USD 150.62) **Percentage of dressing changes associated with no pain:** Group 1 (hydrocolloid dressing): 82% Group 2 (alginate dressing): 62% The trial authors reported that the between-group difference was statistically significant (P value < 0.001). Numbers of dressings not reported **Dressing performance - percentage recording "excellent" for overall ability to contain exudate:** Group 1 (hydrocolloid dressing): 44% Group 2 (alginate dressing): 20% Unclear whether denominator was the number of participants or the number of dressing changes Reported P value for between-group difference = 0.002 **Dressing performance - percentage recording "excellent" for overall ease of dressing removal:** Group 1 (hydrocolloid dressing): 51% Group 2 (alginate dressing): 24% Unclear whether denominator was the number of participants or the number of dressing changes Reported P value for between-group difference = 0.006 **Percentage of dressing changes with some adhesion to the wound bed:** Group 1 (hydrocolloid dressing): 38% Group 2 (alginate dressing): 74% The trial authors reported that the between-group difference was statistically significant (P value < 0.001) Number of dressing changes not reported Review authors' comments: there were some minor discrepancies between numbers in main text and tables for cost information (data from main text were recorded here); discrepancies between primary and secondary references for outcomes of ease of removal and exudate handling (data from primary reference recorded here); unclear whether reported outcomes relating to pain at dressing change, exudate handling, ease of dressing removal and adhesion were rated by participants or investigators (or both)
Límová 2003	**Total number of dressing changes over the course of the trial:** Group 1 (alginate dressing, Tegagen ™ HG): 69 (65 scheduled and 4 unscheduled) Group 2 (alginate dressing, Sorbsan®): 61 (60 scheduled and 1 unscheduled) **Mean (SD) comfort score during wear over number of visits:** Group 1 (alginate dressing, Tegagen ™ HG): 1.2 (SD 0.35) over 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 2.1 (SD 0.50) over 51 visits; n = 9 The trial authors reported a P value of 0.0005 for the between-group difference **Mean (SD) comfort score during dressing removal over number of visits:** Group 1 (alginate dressing, Tegagen ™ HG): 1.2 (SD 0.22) over 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 1.9 (SD 0.19) over 51 visits; n = 9 The trial authors reported a P value of 0.003 for the between-group difference **Percentage of visits where necrotic tissue was observed:** Group 1 (alginate dressing, Tegagen ™ HG): 59.7% of 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 68.9% of 51 visits; n = 9 The trial authors reported a P value of 0.57 for the between-group difference **Percentage of visits where debridement was required:** Group 1 (alginate dressing, Tegagen ™ HG): 18.7% of 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 40.7% of 51 visits; n = 9

Table 2. Outcome data reported by included trials - secondary outcomes (*Continued*)

	The trial authors reported a P value of 0.18 for the between-group difference **Mean improvement in amount of necrotic tissue (lower score is better):** Group 1 (alginate dressing, Tegagen ™ HG): 2.5 over 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 1.5 over 51 visits; n = 9 The trial authors reported a P value of 0.38 for the between-group difference **Mean (SD) exudate absorption score over number of visits (lower score better):** Group 1 (alginate dressing, Tegagen ™ HG): 1.3 (SD 0.45) over 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 2.1 (SD 0.48) over 51 visits; n = 9 The trial authors reported a P value of 0.002 for the between-group difference **Percentage of clinic visits with medium or large amount of exudate observed:** Group 1 (alginate dressing, Tegagen ™ HG): 71.7% of 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 86.3% of 51 visits; n = 9 The trial authors reported a P value of 0.25 for the between-group difference **Mean (SD) ease of removal score over number of visits (lower is better):** Group 1 (alginate dressing, Tegagen ™ HG): 1.1 (SD 0.16) over 55 visits; n = 10 Group 2 (alginate dressing, Sorbsan®): 2.0 (SD 0.56) over 51 visits; n = 9 The trial authors reported a P value of 0.002 for the between-group difference **Proportion of participants reporting dressing adherence to the wound bed:** Group 1 (alginate dressing, Tegagen ™ HG): 0% Group 2 (alginate dressing, Sorbsan®): 27.8% The trial authors reported that the average percentage of dressing changes with adherence to the wound bed was significantly less in Group 1 (P value < 0.05) **Percentage of clinic visits with observation of peri-wound skin as macerated, denuded, requiring medication:** Group 1 (alginate dressing, Tegagen ™ HG): 36.0%, 9.0%, 31.3% Group 2 (alginate dressing, Sorbsan®): 54.4%, 31.9%, 65.2% Reported P values for between-group difference: macerated skin P value 0.30; denuded skin P value 0.04, medication required P value 0.07
Moffatt 1992	None reported
Smith 1994	**Proportion of participants "improved remarkably" in quality of life at week 6:** Group 1 (hydrocolloid dressing): 42.9% Group 2 (alginate dressing): 40.0% The trial authors did not report the number of participants completing the quality of life assessment. P value for between-group difference not reported. There was a reporting discrepancy between "improved remarkably" and the pre-defined categories for this outcome (deteriorated markedly, deteriorated somewhat, no change, improved somewhat or improved markedly) **Number of dressings used per week:** Group 1 (hydrocolloid dressing): 1-3 Group 2 (alginate dressing): 1-2 **Wear time:** The trial authors reported that both dressings were equivalent in terms of wear time, but no data by group or P value for between-group difference were reported **Mean total approximate cost of materials:** Group 1 (hydrocolloid dressing): GBP 431.73 Group 2 (alginate dressing): GBP 364.08 P value for between-group difference not reported **Mean ulcer pain score over past 2 weeks at 6 weeks:** Group 1 (hydrocolloid dressing): 1.46

Table 2. Outcome data reported by included trials - secondary outcomes (*Continued*)

	Group 2 (alginate dressing): 2.15 The trial authors reported that the between-group difference was not statistically significant. P value not reported **Change from baseline in mean ulcer pain score over past 2 weeks at 6 weeks:** Group 1 (hydrocolloid dressing): -3.28 Group 2 (alginate dressing): -2.71 Estimated by review authors **Mean pain score at dressing change at week 6:** Group 1 (hydrocolloid dressing): 1.73 Group 2 (alginate dressing): 2.16 P value for between-group difference not reported **Change from baseline in mean pain score at dressing change at 6 weeks:** Not reported and reviewer unable to estimate as data at week 6 only reported (no baseline) **Proportion of participants reporting no sleep disturbance due to pain at week 2 and week 6:** Group 1 (hydrocolloid dressing): 31.25%, 78.6% Group 2 (alginate dressing): 8.8%, 40.0% The trial authors did not report whether the proportions were for all participants enrolled or only those completing the trial. Reported P value for between-group difference = 0.0721, but unclear to which time point this refers or if it is for the test across time points **Dressing performance (exudate handling):** The trial authors reported that the Group 2 dressing was "slightly superior" in terms of ability to contain exudate. However, no data by group or P value for between-group difference were reported **Proportion of participants reporting 'excellent' for ease of dressing removal:** Group 1 (hydrocolloid dressing): 56.3% Group 2 (alginate dressing): 8.3% The trial authors did not report raw numbers and the denominator was not clear. Reported P value for between-group difference was < 0.001. The trial authors reported that the Group 2 dressing often needed to be soaked off the ulcer. **Number participants experiencing adverse events:** Group 1 (hydrocolloid dressing): 5/22 (23%) (withdrawals: pain, 1; ulcer infection, 1; possible allergy, 1; not thought to warrant withdrawal - wound infection, 1; pain and erythema at the final visit, 1) Group 2 (alginate dressing): 6/18 (33%) (withdrawals: pain, 4; ulcer infection, 2)

APPENDICES

Appendix 1. Glossary

The source for all definitions is The Free Dictionary 2015.

Aetiology: the underlying cause of diseases and disorders.

Autolytic: the destruction of tissues or cells of an organism by the action of substances, such as enzymes, that are produced within the organism.

Debride/debridement: the removal of foreign material and dead or damaged tissue from a wound.

Exudate: fluid, which leaks out of a wound.

Fibrinolytic therapy: the use of special drugs to break up blood clots.

Haemodynamic(s): the study of the forces involved in the circulation of blood.

Haemostatic: retarding or stopping bleeding.

Macerate/maceration: the softening and breaking down of skin resulting from prolonged exposure to moisture.
Slough: a layer or mass of dead tissue separated from surrounding living tissue, as in a wound, a sore, or an inflammation.
Vasoactive: causing constriction or dilation of blood vessels.

Appendix 2. British National Formulary categories of dressings

Basic wound contact dressings

Low-adherence dressings

Low-adherence dressings are usually cotton pads that are placed directly in contact with the wound. These dressings can be used as interface layers under secondary absorbent dressings and are suitable for clean, granulating, lightly exuding wounds without necrosis; they protect the wound bed from direct contact with secondary dressings. Variants include tulle dressings (manufactured from cotton or viscose fibres impregnated with soft white or yellow paraffin) and knitted viscose dressings (BNF 2015). Examples include Atrauman® (Hartmann) and Tricotex® (Smith and Nephew).

Absorbent dressings

Absorbent dressings have an absorbent cellulose or polymer wadding layer and are suitable for use on moderately to heavily exuding wounds. These may be applied directly to the wound and may be used as secondary absorbent layers in the management of heavily exuding wounds (BNF 2015). Examples include DryMax® Extra (Aspen Medical) and KerraMax® (Ark Therapeutics).

Advanced wound dressings

Hydrogel dressings

Hydrogel dressings consist of cross-linked insoluable polymers (i.e. starch or carboxymethylcellulose) and up to 96% water. They are supplied in flat sheets, or as an amorphous hydrogel or as beads. These dressings are generally used to donate liquid to dry, sloughy wounds and facilitate autolytic debridement of necrotic tissue. Some also have the ability to absorb very small amounts of exudate. A secondary, non-absorbent dressing is required with these dressings (BNF 2015). Examples include ActiFormCool® (Activa) and Intrasite Hydrosorb® (Hartmann).

Vapour-permeable films and dressings

Vapour-permeable dressings come in the form of a transparent film, usually with an adhesive base, which is applied to the wound. Vapour-permeable films and membranes allow the passage of water vapour and oxygen but are impermeable to water and micro-organisms. They are suitable for lightly-exuding wounds, but not for infected, large, heavily-exuding wounds. Most commonly, they are used as a secondary dressing over alginates or hydrogels (BNF 2015). Examples include OpSite® (Smith and Nephew) and Tegaderm® (3M).

Soft polymer dressings

Dressings with soft polymer, often a soft silicone polymer, in a non-adherent or gently-adherent layer are suitable for use on lightly- to moderately-exuding wounds. For moderately- to heavily-exuding wounds, an absorbent secondary dressing can be added, or a soft polymer dressing with an absorbent pad can be used (BNF 2015). Examples include Mepilex® (Mölnlycke) and Urgotul® (Urgo).

Hydrocolloid dressings

Hydrocolloid dressings are occlusive dressings usually composed of a hydrocolloid matrix bonded onto a vapour-permeable film or foam backing. When in contact with wound exudate these dressings form a gel to facilitate rehydration in lightly- to moderately-exuding wounds (BNF 2015). Examples include DuoDERM® Extra Thin (ConvaTec) and Tegaderm® Hydrocolloid (3M).

Foam dressings

Foam dressings contain hydrophilic foam and are suitable for all types of exuding wounds. They vary in their ability to absorb exudates; some are suitable only for lightly to moderately exuding wounds, while others have a greater fluid-handling capacity. These can be used in combination with other primary wound contact dressings, but are usually placed over ulcers prior to the application of compression bandages or hosiery, with the intention of promoting healing, and preventing the bandages from sticking to the wound. Saturated foam dressings can cause maceration of healthy skin if left in contact with the wound. If used under compression bandaging or compression garments, the fluid-handling capacity of foam dressings may be reduced (BNF 2015). Examples include and Biatain® Non-Adhesive (Coloplast) and Tielle® Plus (Systagenix).

Alginate dressings

Alginate dressings are available as flat, freeze-dried porous sheets, or as flexible fibre dressings (e.g. packing tape), designed for packing cavity wounds. The base constituents include calcium alginate or calcium sodium alginate, derived from brown seaweed. Alginate dressings are designed to form a soft gel once in contact with wound exudate. Purported benefits of alginate dressings include high absorbency of fluid from moderately to heavily exuding wounds and the ability to maintain a moist wound environment, thereby promoting autolytic debridement (the body's own process of breaking down dead tissue lying on top of the wound bed). Calcium ions present in the dressings help to control bleeding by aiding blood clotting; a potential disadvantage is that blood clots may cause the dressing to adhere to the wound surface. Alginate dressings are designed to function most effectively in a moist environment, and are not suitable for use with dry wounds, or those covered with hard, necrotic tissue; heavy bleeding is a contraindication to use (BNF 2015; Boateng 2008). In the UK, alginate dressings are common to many wound care formularies, where they are often recommended for the management of wounds with moderate to high amounts of exudate. Examples of alginate dressings currently available in the UK include Algosteril® (Smith and Nephew) and Tegaderm® Alginate (3M).

Capillary-action dressings

Capillary-action dressings consist of an absorbent core of hydrophilic fibres held between two low-adherent wound-contact layers to ensure no fibres are shed on to the wound surface. Wound exudate is taken up by the dressing and retained within the highly absorbent central layer. Capillary-action dressings are suitable for use on all types of exuding wounds, but particularly on sloughy wounds where removal of fluid from the wound aids debridement (BNF 2015). Examples include Advadraw® (Advancis) and Vacutex® (Protex).

Odour-absorbant dressings

Dressings containing activated charcoal are used to absorb odour from wounds. Many odour absorbent dressings are intended for use in combination with other dressings, and are often used in conjunction with a secondary dressing to improve absorbency (BNF 2015). Examples include CarboFLEX® (ConvaTec) and CliniSorb® Odour Control Dressings (CliniMed).

Antimicrobial dressings

Honey

Medical-grade honey has antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. It is available in sheet-dressing form or as a honey-base topical application applied directly to the wound and covered with a primary low-adherence wound dressing (BNF 2015). Examples include Medihoney® (Medihoney) and Mesitran® (Aspen Medical).

Iodine

Iodine has a long history of use as a skin and wound disinfectant. It is thought to have a wide spectrum of antimicrobial activity but is deactivated by wound exudate. There are currently two types of iodine-based preparations used in wound management: povidone iodine and cadexomer iodine. Povidone iodine is available as various topical applications (solution, ointment and spray) and as an impregnated wound dressing. The impregnated dressing may be used as a wound contact layer for abrasions and superficial burns, and has also been used with chronic wounds (BNF 2015; Jeffcoate 2009). An example is Inadine® (Systagenix). Cadexomer iodine is available as different topical applications (paste, ointment and powder) and is used to absorb exudate and for debridement (BNF 2015). Examples include Iodoflex® (Smith and Nephew) and Iodosorb® (Smith and Nephew).

Silver

Antimicrobial dressings containing silver are available as: low-adherent dressings, with knitted fabric of activated charcoal, soft polymer dressings, hydrocolloid dressings, foam dressings and alginate dressings. Silver ions exert an antimicrobial effect in the presence of wound exudate. Antimicrobial dressings containing silver should be used only when infection is suspected on the basis of clinical signs or symptoms (BNF 2015). Examples include Acticoat® (Smith and Nephew), Aquacel® Ag (ConvaTec) and Biatain® Ag (Coloplast).

Other antimicrobial dressings

A number of dressings that are impregnated with other antimicrobial agents, such as chlorhexidine and polyhexanide, are also available (BNF 2015). Examples include chlorhexidine gauze dressing, BP 1993 and Suprasorb® X + PHMB (Activa).

Specialised dressings

Protease-modulating matrix dressings

Protease-modulating matrix dressings alter the activity of proteolytic enzymes in chronic wounds (BNF 2015). Examples include Promogran® (Systagenix) and UrgoStart® (Urgo).

Appendix 3. Search strategies for Ovid Medline, Ovid Embase and EBSCO CINAHL

Ovid Medline

1 exp Alginates/ (4449)
2 (alginate* or activheal or algisite or algosteril or curasorb or kalostat or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb a or tegaderm or tegagel or urgosorb).tw. (6053)
3 or/1-2 (6601)
4 exp Leg Ulcer/ (9728)
5 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris or ulcer cruris).tw. (3571)
6 or/4-5 (10421)
7 3 and 6 (68)
8 randomized controlled trial.pt. (238104)
9 controlled clinical trial.pt. (39335)
10 randomized.ab. (193802)
11 placebo.ab. (90703)
12 clinical trials as topic.sh. (79028)
13 randomly.ab. (133232)
14 trial.ti. (71766)
15 or/8-14 (538944)
16 (animals not (humans and animals)).sh. (1600596)
17 15 not 16 (490866)

18 7 and 17 (21)
19 2012*.ed. (680299)
20 18 and 19 (3)

Ovid Embase

1 exp alginic acid/ (8396)
2 (alginate* or activheal or algisite or algosteril or curasorb or kalostat or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb a or tegaderm or tegagel or urgosorb).tw. (9024)
3 or/1-2 (11076)
4 exp leg ulcer/ (5951)
5 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris or ulcer cruris).tw. (5370)
6 or/4-5 (7825)
7 3 and 6 (121)
8 Randomized controlled trials/ (22788)
9 Single-Blind Method/ (15232)
10 Double-Blind Method/ (84730)
11 Crossover Procedure/ (31212)
12 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab. (920231)
13 (doubl$ adj blind$).ti,ab. (88524)
14 (singl$ adj blind$).ti,ab. (9443)
15 or/8-14 (952716)
16 animal/ (716985)
17 human/ (8455793)
18 16 not 17 (478469)
19 15 not 18 (920958)
20 7 and 19 (27)
21 2012*.em. (1182739)
22 20 and 21 (1)

EBSCO CINAHL

S7S3 AND S6
S6S4 OR S5
S5TI (alginate* or activheal or algisite or algosteril or curasorb or kalostat or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb a or tegaderm or tegagel or urgosorb) OR AB (alginate* or activheal or algisite or algosteril or curasorb or kalostat or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb a or tegaderm or tegagel or urgosorb)
S4(MH “Alginates”)
S3S1 OR S2
S2TI (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris or ulcer cruris) OR AB (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris or ulcer cruris)
S1(MH “Leg Ulcer+”)

Appendix 4. Dressing manufacturers contacted regarding ongoing or recently completed trials of alginate dressings

3M
Activa
Aspen Medical
Coloplast
ConvaTec
Covidien
Hartmann
MedLogic
Mölnlycke
Smith & Nephew Healthcare
Urgo

Appendix 5. Data extraction form

Trial identifier	First author and year (country where trial undertaken)
Methods	Design (number of study centres): e.g. pragmatic RCT (5 study centres) Sample size calculation: yes or no, if yes, summarise estimation details Treatment setting. Ethical approval reported: yes or no. Informed consent reported: yes or no.
Participant characteristics at baseline	Number of patients randomised overall and recruitment setting: Inclusion criteria: Ulcer diagnosis method: e.g. Doppler Exclusion criteria: Unit of randomisation/analysis: Numbers randomised per treatment group: Group 1 (comparator dressing): xx participants/limbs/ulcers Group 2 (alginate dressing): xx participants/limbs/ulcers Participant age in years - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) male: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of participants with co-morbidities such as diabetes: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of participants with ulcer aetiology venous/mixed/arterial/other: Group 1 (comparator dressing):

(*Continued*)

	Group 2 (alginate dressing): ABPI: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of participants according to different categories of mobility (e.g. fully mobile, walks with aid, confined to bed or wheelchair): Group 1 (comparator dressing): Group 2 (alginate dressing): Health-related quality of life score (instrument) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of participants with previous history of leg ulceration: Group 1 (comparator dressing): Group 2 (alginate dressing): Ulcer surface area (in, e.g. cm^2) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Ulcer duration (in, e.g. months) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of participants with ulcer infection: Group 1 (comparator dressing): Group 2 (alginate dressing): Ulcer-related pain score (instrument) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Percentage of sloughy or necrotic material on the wound bed - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Participant baseline exudate levels (instrument) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Comments:
Intervention characteristics	Group 1: description of comparator dressing, e.g. hydrocolloid dressing (proprietary name, manufacturer) Group 2: description of alginate dressing (proprietary name, manufacturer) Details of other care, common to all treatment groups (e.g. wound cleansing, debridement,

(*Continued*)

	compression, also planned frequency of dressing changes) Length of treatment: Length of follow-up: Comments:
Outcomes	Reporting of outcomes specified in the review - yes or no; if yes, give details of assessment and statistical methods: Time to healing: Proportion of ulcers healed: Change in ulcer size: Healing rate: Health-related quality of life: Costs: e.g. including cost or cost-effectiveness estimations as well as measurements of resource use such as number of dressing changes, dressing wear time and nurse time Pain: e.g. at dressing change, in between dressing changes or over the course of treatment Debridement: e.g. measured as percentage of sloughy or necrotic material remaining on the wound bed Haemostasis: management of bleeding Dressing performance - exudate handling: Dressing performance - adherence/sticking to wound bed: Adverse events - number per group together with descriptions: Other outcomes assessed by the trial:
Outcome data	Time to healing (in, e.g. weeks) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) of ulcers healed at (state time point): Group 1 (comparator dressing): Group 2 (alginate dressing): Change in ulcer size (either as absolute change, e.g. in cm^2 or as % change relative to baseline) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Healing rate (e.g. cm^2 per week) - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Health-related quality of life score - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Cost or other resource use estimation - mean (SD) [median (range)]: Group 1 (comparator dressing):

(*Continued*)

	Group 2 (alginate dressing): Ulcer-related pain score - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Debridement, e.g. percentage of sloughy or necrotic material on the wound bed - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Haemostasis, as reported: Group 1 (comparator dressing): Group 2 (alginate dressing): Dressing performance (exudate handling) exudate levels/score - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Dressing performance (adherence/sticking to wound bed), using score as reported - mean (SD) [median (range)]: Group 1 (comparator dressing): Group 2 (alginate dressing): Number (%) patients experiencing adverse events (with description of events): Group 1 (comparator dressing): Group 2 (alginate dressing): Comments:
Notes	Name of trial sponsor: Trial registration number: Number (%) participants withdrawing and reasons: Group 1 (comparator dressing): Group 2 (alginate dressing):

Appendix 6. 'Risk of bias' criteria

1. Was the allocation sequence randomly generated?

Low risk of bias: the investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.
High risk of bias: the investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.
Unclear risk of bias: insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias: participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.
High risk of bias: participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. envelopes were unsealed or non-opaque or not sequentially-numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
Unclear risk of bias: insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially-numbered, opaque and sealed.

3. Blinding of participants and personnel - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias: no blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding or blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
High risk of bias: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk', or the study did not address this outcome.

4. Blinding of outcome assessment - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
High risk of bias: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk', or the study did not address this outcome.

5. Were incomplete outcome data adequately addressed?

Low risk of bias: no missing outcome data, or reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias), or missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; or (for dichotomous outcome data), the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; or (for continuous outcome data), plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; or missing data have been imputed using appropriate methods.
High risk of bias: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; or (for dichotomous outcome data), the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; or (for continuous outcome data), plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; or 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation, or potentially inappropriate application of simple imputation.
Unclear risk of bias: insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided), or the study did not address this outcome.

6. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias: either the trial protocol is available and all of the pre-specified outcomes that are in the protocol have been reported in the pre-specified manner or, if the protocol is not available, it is clear that the published report includes all outcomes in the results section that are described as being assessed in the methods section.

High risk of bias: if the trial protocol is available either, not all of the pre-specified outcomes that are in the protocol are reported, or one or more outcomes are reported using measurements, analysis methods or subsets of the data that are not pre-specified; or one or more reported outcomes were not pre-specified (unless there is justification for their reporting, such as an unexpected adverse event). If the trial protocol is not available either, not all of the trial's outcomes have been reported in the results section that are described in the methods section, or one or more of the outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not described in the methods section of the report; or one or more of the reported outcomes were not described in the methods section.

Unclear risk of bias: insufficient information to permit judgement of low or high risk of bias.

WHAT'S NEW

Last assessed as up-to-date: 4 March 2015.

Date	Event	Description
19 August 2015	New citation required but conclusions have not changed	No new trials identified, references updated, conclusions unchanged
19 August 2015	New search has been performed	First update, new search, new author joined the team.

CONTRIBUTIONS OF AUTHORS

Susan O'Meara is guarantor of the review. She conceived, designed and co-ordinated the original review; extracted the data, checked the quality of data extraction, undertook and checked quality assessment and analysed and interpreted data. She performed statistical analysis and checked quality of statistical analysis; completed the first draft of the review; made an intellectual contribution to, and approved final review prior to submission, and advised on the review. She performed previous work that was the foundation of the current review. She screened records for inclusion and edited the review for the first update.

Marrisa Martin St. James contributed the following to the original review: extracted data, undertook quality assessment and analysed data; contributed to writing or editing of the review; made an intellectual contribution to the review and wrote to study authors/experts/companies.

Una Adderley screened records for inclusion and edited the review for the first update.

Contributions of editorial base

Nicky Cullum: edited the protocol; advised on methodology, interpretation and content.
Joan Webster (Editor): approved the final review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol and review versions.
Ruth Foxlee: designed the search strategy, edited the search methods section and ran the searches.

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INDEX TERMS

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*Bandages, Hydrocolloid [adverse effects]; Alginates [adverse effects; *therapeutic use]; Compression Bandages; Pain Measurement; Randomized Controlled Trials as Topic; Varicose Ulcer [*therapy]

MeSH check words

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