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[Intervention Review]

Skin grafting for venous leg ulcers

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ABSTRACT

Background

Venous leg ulceration is a recurrent, chronic, disabling condition. It affects up to one in 100 people at some time in their lives. Standard treatments are simple dressings and compression bandages or stockings. Sometimes, despite treatment, ulcers remain open for months or years. Sometimes skin grafts are used to stimulate healing. These may be taken, or grown into a dressing, from the patient's own uninjured skin (autografts), or applied as a sheet of bioengineered skin grown from donor cells (allograft). Preserved skin from other animals, such as pigs, has also been used (xenografts).

Objectives

To assess the effect of skin grafts for treating venous leg ulcers.

Search methods

For this update we modified the search strategies and conducted searches of The Cochrane Wounds Group Specialised Register (searched 27 July 2012); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7); Ovid MEDLINE (2008 to July Week 3 2012); Ovid MEDLINE (In-Process & Other Non-Indexed Citations, July 26, 2012); Ovid EMBASE (2008 to 2012 Week 29); and EBSCO CINAHL (2008 to 26 July 2012). We did not apply date or language restrictions.

Selection criteria

Randomised controlled trials (RCTs) of skin grafts in the treatment of venous leg ulcers.

Data collection and analysis

Two review authors independently undertook data extraction and assessment of study quality.

Main results

For this update of the review, we identified one new trial, bringing the total to 17 trials (1034 participants) - all of which were generally at moderate or high risk of bias. In 12 trials participants also received compression bandaging.

Eleven trials compared a graft with standard care in which no graft was used. Two of these trials (102 participants) compared a dressing with an autograft; three trials (80 participants) compared frozen allografts with dressings, and two trials (45 participants) compared fresh allografts with dressings. Two trials (345 participants) compared tissue-engineered skin (bilayer artificial skin) with a dressing. In two trials (97 participants) a single-layer dermal replacement was compared with standard care.

Six trials compared alternative skin grafting techniques. The first trial (92 participants) compared autografts with frozen allograft, a second (51 participants) compared a pinch graft (autograft) with porcine dermis (xenograft), the third (110 participants) compared growth-arrested human keratinocytes and fibroblasts with placebo, the fourth (10 participants) compared an autograft delivered on porcine pads with an

autograft delivered on porcine gelatin microbeads, the fifth trial (92 participants) compared a meshed graft with a cultured keratinocyte autograft, and the sixth trial (50 participants) compared a frozen keratinocyte allograft with a lyophilised (freeze-dried) keratinocyte allografts.

Significantly more ulcers healed when treated with bilayer artificial skin than with dressings. There was insufficient evidence from the other trials to determine whether other types of skin grafting increased the healing of venous ulcers.

Authors' conclusions

Bilayer artificial skin, used in conjunction with compression bandaging, increases venous ulcer healing compared with a simple dressing plus compression. Further research is needed to assess whether other forms of skin grafts increase ulcer healing.

PLAIN LANGUAGE SUMMARY

Skin grafts to improve leg ulcer healing

Approximately 1% of people in industrialised countries have a leg ulcer at some time, mainly caused by poor blood flow back from the legs towards the heart. Skin grafts, either using the patient's own skin, artificial skin or donor skin/cells, have been evaluated to see whether they improve the healing of ulcers. The review of trials found evidence that tissue-engineered skin composed of two layers increases the chance of healing. There was not enough evidence to recommend any other type of graft, and further research is required.

BACKGROUND

The prevalence of active leg ulceration in the UK and Australia has been estimated at 1.5/1000 (Baker 1992; Callam 1985; Lees 1992) and it is estimated that one in 100 people will suffer from leg ulcers at some time in their lives. Prevalence increases with age and is higher among women. Typically, leg ulceration is a chronic, recurring condition; indeed 45% of participants in a Scottish study reported episodes of ulceration over more than 10 years (Callam 1989). There is a considerable cost both to the patient (Charles 1995) and to the health service (Bosanquet 1992). Most leg ulcers are associated with venous disease. Venous insufficiency has been shown to be associated with increased hydrostatic pressure in the veins of the legs; application of externally applied compression to reverse this is largely successful in healing venous leg ulcers. Standard therapy involves the use of dressings to protect the wound bed from trauma and absorb exudate, and compression bandages to treat the venous insufficiency and promote healing.

Whilst compression therapy undoubtedly addresses the underlying pathology, it may be insufficient to heal all ulcers caused by venous disease in instances where the patient's own, intrinsic, wound-healing mechanism is inadequate. Additional treatments such as venous surgery to correct the high venous pressure, drug therapy to improve blood flow, or skin grafting to promote healing and close the wound may be used in this group of patients. However, it needs to be established whether skin grafts have an effect on the rate of healing and other outcomes.

A number of skin replacements and substitutes are available: these are generally classified as autografts (skin or cells taken from another site on the same patient); allografts (skin or cells taken from another person); and xenografts (skin or cells taken from one species to an unlike species; for example, from pig to human). These grafts may be applied in the form of layers of cells grown in the laboratory, pinches of skin, or dressings incorporating skin cells. The ulcer is usually debrided (cleaned) prior to application of the graft to remove dead tissue and allow the cells in the graft to make intimate contact with the ulcer bed and blood supply.

The types of skin grafts considered in this review include the following.

- Autografts taken from the patient during a minor surgical procedure (pinch grafts, split-thickness mesh grafts, full-thickness skin grafts) or after growing the patients' cells (including keratinocytes from hair follicles) to form a thin film in the laboratory (cultured keratinocyte autograft, or a cultured epidermal autograft).
- Allografts (allogeneic) taken from other human sources (cultured keratinocytes, cultured epidermal fibroblasts), grown in the laboratory and kept ready for use when necessary.
- Xenografts, usually taken from pigs, as their skin has a similar structure to human skin.
- Artificial skin, also called tissue-engineered skin, bioengineered skin or human skin equivalents (such as Apligraf (Novartis), Dermagraft (Smith & Nephew) or Orcel (Ortec International) (all trademarks)). These products all feature a matrix into which cells important for skin repair are 'seeded'. There are both single and bilayer products. The bilayer products, such as Apligraf (Novartis) and Orcel (Ortec International) contain epidermal as well as dermal skin components. For example,

Apligraf (Novartis) consists of Type 1 bovine collagen and human allogeneic cells (keratinocytes and fibroblasts) with an epidermis (upper layer) of cornified differentiated keratinocytes and a lower, dermal matrix of a collagen lattice containing viable fibroblasts. Dermagraft (Smith and Nephew) contains only a lower, dermal component. The most serious concern with allogeneic skin is the possibility of transmission of infection, particularly of the human immunodeficiency virus (HIV) or hepatitis. Even with rigorous screening it is still possible that skin could be harvested from an HIV-infected but seronegative donor (Falanga 1998).

OBJECTIVES

To assess the effects of skin grafting on the healing of venous ulcers.

Specific questions addressed by the review were:

1. Does the application of a skin graft aid venous ulcer healing, when compared with standard care?
2. What is the comparative benefit of one type of skin graft compared with another?

METHODS

Criteria for considering studies for this review

Types of studies

We included trials if the allocation of participants was described as randomised. We included cross-over trials only if the outcomes at the point of cross-over were given, as data after this point were not based on comparable baseline groups. There was no restriction on study reports based on language or publication status.

Types of participants

We included studies involving participants of any age, in any care setting, and with venous leg ulceration (which may also be described as stasis or varicose ulceration). As the method of diagnosis of venous ulceration varies between studies, we did not apply a standard definition. We included trials that included participants with arterial, mixed, neuropathic and diabetic ulcers *only* if the outcomes for those with venous ulcers were reported separately.

Types of interventions

The primary intervention was skin grafts or skin replacements applied to venous leg ulcers.

We included studies which compared the following types of grafts with any other intervention:

1. pinch grafts (autografts);
2. split-thickness grafts (autografts);
3. full-thickness grafts (autografts and xenografts);
4. cultured keratinocytes/epidermal grafts (allografts and xenografts);
5. artificial skin (allografts).

We also considered studies that compared skin grafting with no other intervention, and comparisons between skin grafts.

We excluded studies that evaluated cell lysate products against dressings or each other as these do not retain cell or skin structure. We excluded studies of interventions to improve graft survival (e.g. dressing A compared with dressing B over newly-applied skin grafts), as this does not compare grafts against non-graft therapies or against other graft treatments, and therefore provides little information on the effectiveness of the graft itself.

Types of outcome measures

Primary outcomes

In order to be included in the review, a trial had to report at least one of the primary outcomes: i.e. objective measures of healing such as relative or absolute rate of change in ulcer area; time to complete healing; or proportion of ulcers healed within the trial period.

Secondary outcomes

Secondary outcomes included: costs; quality of life; pain; side effects; adverse events; withdrawals and acceptability of treatment.

Search methods for identification of studies

The search methods section for the third update of this review can be found in [Appendix 1](#).

For this fourth update we searched the following electronic databases:

- The Cochrane Wounds Group Specialised Register (searched 27 July 2012);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7);
- Ovid MEDLINE (2008 to July Week 3 2012);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, July 26, 2012);
- Ovid EMBASE (2008 to 2012 Week 29);
- EBSCO CINAHL (2008 to 26 July 2012).

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):

```
#1 MeSH descriptor Leg Ulcer explode all trees
#2 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXT extremity*) NEAR/2 ulcer*) or (crural NEXT ulcer*) or "ulcus cruris":ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Skin Transplantation explode all trees
#5 (skin NEXT graft*) or (pinch NEXT graft*):ti,ab,kw
#6 (split NEXT thickness) or (full NEXT thickness):ti,ab,kw
#7 allograft* or dermagraft* or apligraf*:ti,ab,kw
#8 tissue NEAR/2 engineer*:ti,ab,kw
#9 cultured NEAR/2 keratinocyte*:ti,ab,kw
#10 artificial NEXT skin:ti,ab,kw
#11 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 (#3 AND #11)
```

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#) respectively. 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); Ovid format ([Lefebvre 2011](#)). We combined the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) ([SIGN 2011](#)). We applied no date or language restrictions.

Data collection and analysis

Selection of studies

We assessed titles and abstracts of studies identified by the search strategy in terms of their relevance and design according to the selection criteria. We obtained (and translated if necessary) copies of all relevant and potentially relevant abstracts. We obtained full versions of articles if, from this initial assessment, they satisfied the inclusion criteria. Another review author repeated the processes of (a) identifying potentially relevant papers and (b) selecting papers based on the full text independently for verification. We resolved any disagreements by discussion.

Data extraction and management

The primary review author (JEJ) extracted details of eligible studies and summarised them using a data extraction sheet. The second review author (EAN) checked data extraction.

We extracted the following data for each study:

1. patient inclusion/exclusion criteria;
2. care setting;
3. key baseline variables by group, e.g. age, sex, baseline area of ulcer, duration of ulcer;
4. description of the interventions and numbers of participants randomised to each intervention;
5. follow-up period;
6. outcomes.

If studies were published more than once, we used all reports in order to extract the maximum amount of data describing the trial and participants.

Assessment of risk of bias in included studies

For this review update two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias ([Higgins 2011](#)). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance). We assessed blinding and completeness of outcome data for each outcome separately. We completed a 'Risk of bias' table for each eligible study and discussed any disagreement to achieve a consensus. We presented an assessment of risk of bias using a 'Risk of bias' summary figure ([Figure 1](#)), which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Brown-Etris 2000	?	?	?	?	?	?	?
Burdge 2000	?	?	?	?	?	?	?
Duhra 1992	?	?	+	+	+	+	+
Falanga 1998	+	?	-	+	+	-	?
Goedkoop 2010	?	?	+	+	+	+	+
Jankunas 2007	?	?	+	+	?	-	?
Krishnamoorthy 2003	+	?	+	+	+	-	-
Lindgren 1998	?	?	+	+	?	?	?
Liu 2004	+	?	+	+	+	-	+
Navratilova 2004	?	?	+	+	+	?	?

Figure 1. (Continued)

Navratilova 2004	?	?	+	+	+	?	?
Omar 2004	+	?	+	+	+	-	+
Paquet 2005	?	?	+	+	+	-	+
Poskitt 1987	+	?	+	+	+	?	?
Salomon 2002	?	?	-	+	?	?	?
Tausche 2003	+	?	?	+	+	?	?
Teepe 1993	?	-	-	+	+	?	?
Warburg 1994	?	?	+	+	+	?	?

Assessment of heterogeneity

Where two or more studies undertook similar comparisons in comparable populations using similar outcome measures, we assessed heterogeneity using the χ^2 test. Where clinical and methodological heterogeneity were absent, but there was statistical heterogeneity (defined as a P value less than 0.1), we applied a random-effects model; in the absence of clinical, methodological and statistical heterogeneity, we applied a fixed-effect model. In addition, we assessed heterogeneity between study results using the I^2 statistic (Higgins 2003). This examines the percentage of total variation across studies due to heterogeneity rather than to chance. Values of I^2 over 75% indicate a high level of heterogeneity.

Data synthesis

For each trial, we calculated the risk ratio (RR) with 95% confidence intervals (CI) for all dichotomous variables. The risk ratio indicates the relative benefit of a therapy but not the actual benefit. The absolute risk reduction (ARR) equals the arithmetic difference in healing rates between the experimental and control groups. The ARR tells us how much the difference is due to the graft itself and its inverse is the number needed to treat to benefit (NNTB). Thus a healing rate of 30% with a control dressing increased to 50% with a skin graft translates into an ARR of 50 to 30 = 20%, or 0.2. The NNT is therefore 1/0.2, or five participants. In other words, five participants would need to receive a skin graft in order for one additional ulcer to be healed.

When study reports failed to state the outcomes of patients who had withdrawn from the studies, we considered them to be treatment failures and included them in the analysis as such.

RESULTS

Description of studies

For this fourth update we identified one additional, eligible study (Goedkoop 2010). In reviewing the studies included in the review during the update process, we have excluded Mol 1991 as, on closer inspection, it appears not to be a randomised trial. One study (Wille 2011) is awaiting assessment.

The following comparisons were made:

1. Grafts compared with standard care

1.1 Autograft compared with standard care (two trials) (Jankunas 2007; Warburg 1994).

1.2 Fresh or frozen allograft compared with standard care (five trials) (Burdge 2000; Duhra 1992; Lindgren 1998; Paquet 2005; Teepe 1993).

1.3 Bilayered human skin equivalent compared with standard care (two trials) (Brown-Etris 2000; Falanga 1998).

1.4 Single-layered dermal skin replacement compared with standard care (two trials) (Krishnamoorthy 2003; Omar 2004).

1.5 Growth-arrested human keratinocytes and fibroblasts compared with placebo equivalent (one trial) (Goedkoop 2010).

2. Comparison between grafts

2.1 Autograft compared with frozen allograft (one trial) (Tausche 2003).

2.2 Autograft compared with xenograft (one trial) (Poskitt 1987).

2.3 Autograft delivered on porcine pads compared with autograft delivered on porcine gelatin microbeads (one trial) (Liu 2004).

2.4 Autograft compared with cultured keratinocyte autograft (one trial) (Salomon 2002).

2.5 Frozen allograft compared with lyophilised keratinocyte allograft (one trial) (Navratilova 2004).

Study setting

Three studies involved both inpatients and outpatients (Jankunas 2007; Poskitt 1987; Warburg 1994), one included inpatients only (Navratilova 2004) and five included outpatients only (Duhra 1992; Falanga 1998; Krishnamoorthy 2003; Lindgren 1998; Teepe 1993). Eight studies provided insufficient data on population or setting (Brown-Etris 2000; Burdge 2000; Goedkoop 2010; Liu 2004; Omar 2004; Paquet 2005; Salomon 2002; Tausche 2003).

Diagnosis of venous ulceration

Three studies failed to report the way in which venous ulceration was confirmed (Brown-Etris 2000; Mol 1991; Salomon 2002; Tausche 2003). Four studies diagnosed venous ulceration by excluding arterial disease by means of a hand-held Doppler, together with clinical examination (Falanga 1998; Krishnamoorthy 2003; Lindgren 1998; Navratilova 2004). Nine studies excluded arterial disease on the basis of hand-held Doppler, and used an objective test of venous insufficiency, e.g. venous Doppler, Duplex or plethysmography (Burdge 2000; Duhra 1992; Goedkoop 2010; Jankunas 2007; Liu 2004; Omar 2004; Paquet 2005; Poskitt 1987; Teepe 1993).

Inclusion and exclusion criteria

Inclusion and exclusion criteria were clearly listed in eight trials (Burdge 2000; Duhra 1992; Falanga 1998; Goedkoop 2010; Krishnamoorthy 2003; Navratilova 2004; Tausche 2003; Warburg 1994). The external validity of the remaining nine trials could not be easily assessed (Brown-Etris 2000; Jankunas 2007; Lindgren 1998; Liu 2004; Omar 2004; Paquet 2005; Poskitt 1987; Salomon 2002; Teepe 1993).

The majority of studies (15/17) included participants with ulcers which were 'hard to heal'. The means by which participants with 'hard to heal' ulcers were detected was either area/duration at baseline or during a washout period. Five studies recruited people with ulcers of longer than six months' duration (Duhra 1992; Falanga 1998; Goedkoop 2010; Jankunas 2007; Poskitt 1987), and six studies used a three-month or 12-week qualifying period (Liu 2004; Navratilova 2004; Omar 2004; Paquet 2005; Tausche 2003; Teepe 1993). One study used a one-month duration inclusion criterion (Burdge 2000). Two studies used a washout period, one of which included people whose ulcer failed to decrease in area by at least 30% with two weeks' compression (Brown-Etris 2000), while the other included those in whom ulcer area failed to decrease by 50% in 14 days (Krishnamoorthy 2003). Two trials did not describe attempts to exclude ulcers on the basis of chronicity (Lindgren 1998; Warburg 1994).

Study duration

The studies had a variety of duration of active treatment and follow-up. Falanga 1998, for example, had eight weeks' treatment with the skin equivalent and six months' follow-up. The trial duration ranged from six weeks (Duhra 1992; Goedkoop 2010) to 12 months (Warburg 1994). Where there were differences in trial duration, the results from pooled studies should be interpreted cautiously.

Sample size

The sample sizes used in most of these trials were a major deficiency in their design. Only two trials described an a priori sample size calculation (Poskitt 1987; Teepe 1993). The sample size

calculations performed by these authors sought to detect very large effect sizes, e.g. doubling the healing rate, and hence the required sample sizes were 40 (Teepe 1993) and 80 (Poskitt 1987). Since it is unlikely that an effect size of this magnitude would be realised in a trial of an intervention for healing chronic wounds - where a RR of 1.1 is typical and up to 1.5 is rare - these sample size calculations may be unrealistic. Twelve trials included a maximum of 51 participants. The smallest included trial in this review had four participants (Paquet 2005), while the largest had 309 participants (Falanga 1998).

Adverse events

Adverse events were reported by treatment group in four studies (Duhra 1992; Falanga 1998; Krishnamoorthy 2003; Tausche 2003). Other trials made general statements such as "no infections", or "no contact dermatitis", or failed to mention adverse effects (Burdge 2000; Lindgren 1998; Teepe 1993; Warburg 1994).

Risk of bias in included studies

Further details of each study are documented in Table 1 and 'Risk of bias' summary figure (Figure 1).

Allocation

Randomisation sequence

Only six trials reported a method of random sequence generation (Falanga 1998; Krishnamoorthy 2003; Liu 2004; Omar 2004; Poskitt 1987; Tausche 2003) which ranged from computer-generated sequences to random number tables. No method of random sequence generation was reported in the remaining 11 trials.

Allocation concealment

True randomisation with allocation concealment was explicitly reported in only one RCT (Krishnamoorthy 2003). Another trial reported that "randomisation schedules were held by the sponsor" and the allocation may, therefore, have been concealed (Falanga 1998) but the judgement remains unclear. Poskitt 1987 reported the use of sealed envelopes to conceal allocation however failed to specify whether the envelopes were opaque or sequentially numbered. The remaining 14 trials did not report the method of randomisation.

Blinding

Participants/care givers

Blinding of participants/care givers was achieved in two trials (Duhra 1992; Goedkoop 2010) which mentioned double-blinding. Due to the nature of some of the interventions, it can be difficult to blind the participants/care givers. Patients receiving grafts can be subject to a surgical procedure and in this event this would make blinding almost impossible and this was the case in one trial (Jankunas 2007). Secondly, the method of application of some interventions meant that patients and care givers could be aware of the allocation (Falanga 1998; Krishnamoorthy 2003; Liu 2004). Paquet 2005 reported its trial as open label. The remaining trials were judged to be unclear as there was insufficient information in the report to make a judgement.

Outcome assessment

Blinded outcome assessment is rarely used in wound care studies as it can be difficult to disguise a graft - particularly

a pinch or split-thickness graft - as these leave a characteristic pattern even in the fully healed state (sometimes described as a cobblestone appearance). Nevertheless, various attempts were made to blind the outcome assessment. Five studies (Duhra 1992; Goedkoop 2010; Liu 2004; Omar 2004; Paquet 2005) reported blinding of outcome assessor by using various means such as identical dressings (Duhra 1992), measuring outcomes using a remote computerised system (Liu 2004) or by blinding the data directly (Goedkoop 2010). The remaining trials involving a form of surgical intervention made blinding outcome assessment impossible (Jankunas 2007; Lindgren 1998; Poskitt 1987; Tausche 2003; Warburg 1994). The rest of the trials provided insufficient evidence to ascertain whether outcome assessors were blind.

Incomplete outcome data

Intention to treat (ITT) analysis, in which people are analysed in the group to which they were allocated, regardless of whether or not they received the allocated treatment, is the most robust analysis to conduct in an effectiveness trial. An ITT analysis of a surgical treatment, such as grafting, requires people to be analysed in the surgery group even if they did not receive the treatment (e.g. change of mind, got better on waiting list, became unfit for surgery). Such an analysis is necessary to maintain the balanced prognosis in the two groups achieved by randomisation, and any systematic exclusion of some participants from the analysis threatens the validity of the subsequent results. The alternative, a per-protocol analysis, includes people in the analysis according to the treatment they actually received and their availability at follow-up. In seven trials, all randomised participants were included in and accounted for in the final analysis (Duhra 1992; Goedkoop 2010; Jankunas 2007; Liu 2004; Navratilova 2004; Omar 2004; Paquet 2005). In four trials, there were dropouts and withdrawals but were assessed to be low risk of bias in this domain as they accounted for 10% or fewer of the sample size (Krishnamoorthy 2003; Lindgren 1998; Tausche 2003; Warburg 1994). The trial by Teepe 1993 reported losses to follow-up amounting to around 19% which was adjudged to be high risk of bias. The trials by Brown-Etris 2000; Burdge 2000 and Salomon 2002 were only available in abstract form, and subsequent, fuller reports may contain more information about the fate of withdrawals. The number of withdrawals from a study can affect the internal validity. If there is a high proportion of withdrawals in comparison to the event rate, one cannot be confident of the result. In these trials, follow-up rates ranged from 81% (Teepe 1993) to 100% (Duhra 1992; Lindgren 1998) and in two studies the number of withdrawals was not stated (Brown-Etris 2000; Burdge 2000) with no information on this supplied from authors.

Selective reporting

All trials reported their primary and secondary (if applicable) outcomes adequately with no suggestion of selective outcome reporting. All trials had reasonable primary outcomes with no omissions or absences.

Other potential sources of bias

In studies of treatment of venous leg ulcers, it is essential to ensure baseline comparability for ulcer area, and duration and history of previous ulceration, as these factors are likely to affect the outcome (Margolis 2004; Skene 1992).

Fifteen studies reported ulcer area at baseline; the remaining two did not (Paquet 2005; Salomon 2002). There were obvious imbalances in the ulcer areas in eight trials at baseline (Jankunas 2007; Krishnamoorthy 2003; Lindgren 1998; Liu 2004; Omar 2004; Poskitt 1987; Tausche 2003; Warburg 1994) identified by simple inspection of the baseline characteristics. Authors commonly stated there was "no significant difference" in baseline ulcer areas after applying statistical tests to compare these (inappropriate since, by definition, it is already known that where participants were randomised any baseline imbalance has arisen by chance). Only one of the included studies reported using ulcer area as a covariate in the analysis to account for any differences in the distribution of important predictors such as ulcer area or duration at randomisation (Falanga 1998). In large trials, randomised allocation should ensure that the mean wound size and variance in each group is similar. In a small trial, random allocation is unlikely to result in an even distribution of wound sizes and incorporating area into the analysis is recommended. If baseline data are not given, then it is not possible to determine the direction of bias and the validity of the result cannot be determined.

The duration of ulceration by allocation group was reported in fifteen trials (Brown-Etris 2000; Burdge 2000; Duhra 1992; Falanga 1998; Goedkoop 2010; Jankunas 2007; Krishnamoorthy 2003; Lindgren 1998; Liu 2004; Navratilova 2004; Omar 2004; Poskitt 1987; Tausche 2003; Teepe 1993; Warburg 1994) and, of these, three had well-balanced ulcer duration in the two groups (Falanga 1998; Omar 2004; Teepe 1993). In five trials the control group had ulcers of longer duration (Brown-Etris 2000; Burdge 2000; Krishnamoorthy 2003; Lindgren 1998; Warburg 1994). In six other studies there were variations in ulcer duration between the study groups (Duhra 1992; Jankunas 2007; Liu 2004; Navratilova 2004; Poskitt 1987; Tausche 2003). Only one of the included studies reported using ulcer duration as a covariate in the analysis to account for any differences in the distribution of ulcer duration at randomisation (Falanga 1998).

Effects of interventions

The results will be presented in the following comparisons.

1. Grafts compared with standard care

1.1 Autograft compared with standard care (two trials) (Jankunas 2007; Warburg 1994).

1.2 Fresh or frozen allograft compared with standard care (five trials) (Burdge 2000; Duhra 1992; Lindgren 1998; Paquet 2005; Teepe 1993).

1.3 Bilayered human skin equivalent compared with standard care (two trials) (Brown-Etris 2000; Falanga 1998).

1.4 Single-layered dermal skin replacement (two trials) (Krishnamoorthy 2003; Omar 2004).

1.5 Growth-arrested human keratinocytes and fibroblasts compared with placebo equivalent (one trial) (Goedkoop 2010).

2. Comparison between grafts

2.1 Autograft compared with frozen allograft (one trial) (Tausche 2003).

2.2 Autograft compared with xenograft (one trial) (Poskitt 1987).

2.3 Autograft delivered on porcine pads compared with autograft delivered on porcine gelatin microbeads (one trial) (Liu 2004).

2.4 Autograft compared with cultured keratinocyte autograft (one trial) (Salomon 2002).

2.5 Frozen allograft compared with lyophilised keratinocyte allograft (one trial) ([Navratilova 2004](#)).

1. Grafts compared with standard care

1.1 Autografts compared with standard care of hydrocolloid dressing

Two trials compared split-thickness autografts with a hydrocolloid dressing in 102 participants ([Jankunas 2007](#); [Warburg 1994](#)). In [Warburg 1994](#), both groups had vein surgery and they found no evidence of a significant benefit for autografts over a dressing in this small trial (102 participants) (risk ratio (RR) of healing with autografts 0.89, 95% confidence interval (CI) 0.34 to 2.31) ([Analysis 1.1](#)). [Jankunas 2007](#) reported a large difference in healing rates (RR of healing 42.93, 95% CI 2.72 to 677.16) ([Analysis 1.1](#)). Looking at these trials together, there was very high heterogeneity ($I^2 = 93\%$), therefore pooling was inappropriate. Both had follow-up periods of six months but the control groups (both receiving compression) had differing healing rates: 0% in [Jankunas 2007](#) (which is lower than commonly reported in other trials) and 38% in [Warburg 1994](#). This might indicate a different severity of ulcers seen in the [Jankunas 2007](#) group, or potentially reflect performance bias.

These trials provide no firm evidence of benefit rather than firm evidence of lack of benefit. At baseline, the [Warburg 1994](#) trial had larger ulcers in the skin graft group, which may have biased the results against grafting, or it may indicate that allocation was subverted as there was no indication whether allocation was concealed.

1.2 Fresh or frozen allografts compared with standard care of low-adherent dressing or hydrocolloid

Frozen allografts

Three trials compared frozen allografts with control dressings (Mepitel, petroleum jelly-impregnated gauze or hydrocolloid) in 80 participants ([Lindgren 1998](#); [Paquet 2005](#); [Teepe 1993](#)). Pooling the three trials using a fixed-effect model (Chi^2 0.76; degrees of freedom (df) = 1; P value 0.38; $I^2 = 0\%$) showed that there was no significant difference in healing with allografts over standard care (RR 1.62, 95% CI 0.79 to 3.33) ([Analysis 2.1](#)).

Fresh allografts

Three trials (45 participants) compared fresh allografts with standard care of non-adherent dressing soaked in culture medium, or petroleum jelly-impregnated gauze ([Burdge 2000](#); [Duhra 1992](#); [Paquet 2005](#)). Pooling these three trials using a fixed-effect model (Chi^2 0.02; df = 1; P value 0.88; $I^2 = 0\%$) showed that there was no significant difference in healing with allografts over standard care (RR 3.73, 95% CI 0.80 to 17.45) ([Analysis 2.1](#)).

Pooled analysis: pooling all five trials (125 participants) using a fixed effect model (Chi^2 1.65; df = 3; P value 0.65; $I^2 = 0\%$) indicated significantly higher healing rates with allografts than dressings (RR 2.00, 95% CI 1.04 to 3.84) ([Analysis 2.1](#)). Given the methodological problems with these trials, this result should be confirmed by large, well-designed and conducted trials.

1.3 Bilayered human skin equivalent compared with standard care of foam or placebo dressing

Two trials (345 participants) compared a bilayered skin equivalent with standard care of foam or a dressing made to look like the skin

equivalent ([Brown-Etris 2000](#); [Falanga 1998](#)). Apligraf (Novartis), used by [Falanga 1998](#), is described as having a lower layer to replace the dermis and an upper layer to replace the epidermis. Orcel (Ortec International), used by [Brown-Etris 2000](#), has a collagen matrix onto which donor fibroblast and keratinocytes are seeded and cultured. These were compared with a simple dressing underneath compression therapy ([Brown-Etris 2000](#); [Falanga 1998](#)). [Falanga 1998](#) randomised 309 participants, of whom 275 were available for evaluation of efficacy. [Brown-Etris 2000](#) described a trial in which 36 people with "hard to heal" ulcers were randomised. [Falanga 1998](#) reported that the ulcers of 92/146 (63%) participants in the treatment group had healed completely at six months compared with 63/129 (49%) in the control group. In the second trial, 12/17 (71%) of people with tissue-engineered skin plus compression had healed completely at six months compared with 7/19 (37%) in the compression therapy group ([Brown-Etris 2000](#)).

Pooling the results from these two trials using a fixed-effect model ($\text{Chi}^2 = 0.55$; df = 1; P value 0.46; $I^2 = 0\%$) yields a RR of healing with the artificial skin compared with simple dressings of 1.51 (95% CI 1.22 to 1.88) ([Analysis 3.1](#); [Figure 1](#)). The increase in healing rate from approximately 40% to 60% represents a number needed to treat to benefit (NNTB) of 1/0.2, or 5 for six months' treatment. This means that five participants would need to be treated with artificial skin rather than a simple dressing, in order for one additional ulcer to heal at six months. These two trials provide reasonable evidence that a greater proportion of venous ulcers heal with artificial skin than a simple dressing. The lack of an intention-to-treat analysis for the [Falanga 1998](#) trial reduces our certainty of the results. However, as participants in the trial who were not accounted for in the analysis may have dropped out for reasons related to the treatments, we contacted the authors to ask if data were available for an intention-to-treat analysis; they replied that the study sponsor had these data and had not made them available to the authors.

There was no concurrent economic analysis in the trials comparing tissue-engineered skin with standard care.

1.4 Single-layered dermal skin replacement compared with low-adherent dressing

Two trials (71 participants) compared a single-layered dermal replacement ([Krishnamoorthy 2003](#); [Omar 2004](#)) with standard care of four-layer compression and a low-adherent dressing. Both trials evaluated Dermagraft (Smith and Nephew), described as a human fibroblast-derived dermal replacement; the origin of the cells being newborn foreskin. The first study compared three different regimens with standard care (12 pieces, four pieces or one piece of Dermagraft (Smith and Nephew), and the second trial compared the four-piece regimen with standard care. There was no evidence of benefit associated with 12 pieces of dermal skin replacement (weekly for 11 weeks) compared with standard care in the small (26 participants) [Krishnamoorthy 2003](#) trial (RR 2.5, 95% CI 0.59 to 10.64) ([Analysis 4.1](#)). There was no evidence of overall benefit associated with four pieces of dermal skin replacement (at baseline, one, four and eight weeks) in the two studies (RR 3.04, 95% CI 0.95 to 9.68) ([Analysis 4.1](#)), when pooled using a fixed-effect model (44 participants). There was no evidence of benefit associated with one piece of dermal skin replacement (at baseline) compared with standard care in the [Krishnamoorthy 2003](#) trial, which made this comparison in 26 people (RR 0.46, 95% CI 0.05 to 4.53) ([Analysis 4.1](#)).

There is therefore insufficient evidence, based on two small studies, that single-layered dermal skin replacement heals venous ulcers more quickly than a simple low-adherent dressing.

1.5 Growth-arrested human keratinocytes and fibroblasts compared with placebo equivalent

One trial ([Goedkoop 2010](#)) compared growth-arrested human keratinocytes and fibroblasts (HP802-247) with placebo equivalent in 110 participants. This multi-centre, double-blind study randomised participants to seven treatment groups that varied in the composition of the intervention (ratio of keratinocytes: fibroblasts and the concentration of cells per intervention). The results showed that percentage of ulcers healed at 12 and 24 weeks were greater in participants receiving the interventions compared with placebo in all comparisons. For the purposes of the analysis we combined the results of the six intervention groups and compared them with the placebo group; there was no statistically significant difference between the two groups at either 12 weeks or 24 weeks ([Analysis 5.1](#)).

2. Comparisons between skin graft

Five trials compared an autograft (such as split-thickness mesh grafts) with other grafting methods.

2.1 Autograft compared with frozen allograft

One trial with 92 participants compared autograft with frozen allograft and found no difference in healing rates ([Tausche 2003](#)), expressed as proportions healed (RR 1.04, 95% CI 0.56 to 1.94) ([Analysis 6.1](#)) or percentage reduction in area (14.37% greater reduction with autograft, 95% CI -13.76 to 42.5).

2.2 Autograft compared with xenografts

We identified one trial (51 people) comparing pinch grafts with a porcine dermis (xenograft) dressing ([Poskitt 1987](#)). The increase in ulcers healed at 12 weeks with pinch grafting (72% (18/25) compared with 46% (13/28) xenograft) just missed the traditional cut-off for statistical significance (χ^2 3.55; df = 1; P value 0.06). The risk ratio for healing with autograft was 1.55 (95% CI 0.97 to 2.47) ([Analysis 6.1](#)). There was, however, a significant benefit associated with pinch grafts when the data were analysed by time to healing and the number of ulcers healed (authors' log rank χ^2 4.1; P value < 0.05). The larger and older ulcers were in the pinch graft group (difference of 10 cm² in mean area and 10 months in mean duration) biasing the study against pinch grafting and therefore increasing our confidence in the result. It is not clear what the withdrawal rate was, as it was stated that 51 patients with 60 ulcers entered the study but as four people "refused the study", 53 legs were "available for randomisation". If the four refusals were post-randomisation refusals of graft or xenograft, then they should have been included in the analysis on an intention-to-treat basis regardless of the treatment received. The exclusion of these participants threatens the validity of the results. In addition, it is not clear whether the authors accounted for the fact that there were more legs than participants in the study. The trial did randomise legs rather than participants, but the subsequent analysis should not have assumed that each piece of information, e.g. healing time, was independent, as data from both legs of the same participant are not independent.

2.3 Autograft delivered on porcine pads compared with autograft delivered on porcine gelatin microbeads

One trial made this comparison in 10 people ([Liu 2004](#)). There was no difference in the number of people healed at the end of the trial (RR 1.0, 95% CI 0.08 to 11.93), with only 20% healing in each group ([Analysis 7.1](#)).

2.4 Autograft compared with cultured autologous keratinocytes

One trial compared Epidex, an autologous epidermal equivalent grown from the outer root sheath keratinocytes of plucked hair follicles, with a meshed autograft in 92 people (reported outcomes only on 77) ([Salomon 2002](#)). There was no statistically significant difference in the number of people healed at the end of the trial (RR 1.04, 95% CI 0.56 to 1.94: our intention-to-treat analysis - assuming the non-healing of dropouts) ([Analysis 8.1](#)).

2.5 Frozen allograft compared with lyophilised keratinocyte

One trial (50 people) compared a cryopreserved graft with lyophilised keratinocytes ([Navratilova 2004](#)). This found no difference in healing rates at the end of the trial (RR 1.05, 95% CI 0.81 to 1.36) ([Analysis 9.1](#)).

DISCUSSION

Concerns regarding the quality of (and therefore risk of bias inherent in) the included trials affect the strength of the conclusions we can make. The quality of reporting was generally poor; many trials did not report inclusion criteria, so we could not tell whether the patients in the various trials were similar or representative. Little information was given on randomisation methods, and whether trialists took steps to conceal allocation from those recruiting patients into the studies. Other common methodological flaws were lack of baseline comparability and lack of blinded outcome assessment. Withdrawals and adverse events were poorly reported. Lack of clarity about withdrawals and the tendency to conduct per-protocol analyses - rather than intention-to-treat analyses - mean that the results reported in the original trial documentation may be biased.

The clearest conclusion is that bilayer tissue-engineered skin increased the chance of healing compared with a simple dressing made to look like the skin equivalent (under compression). A meta-analysis of five small trials comparing fresh or frozen allografts found a higher healing rate with allografts than standard care, but these small trials were of poor quality and hence this result should be treated with caution. Most of the trials provided insufficient evidence of benefit, rather than firm evidence of lack of benefit. Fifteen of the 17 included trials were under-powered and, therefore, clinically important differences were unlikely to reach statistical significance and be detected. This point is illustrated by the trial by [Falanga 1998](#), who found that human skin equivalent increased the risk of healing by 14% (from 49% to 63% at six months). If we consider that a 14% difference in healing is worthwhile, a sample size calculation determines that 210 participants would be needed in each group to detect such a difference. This estimate is based on 80% power (i.e. an 80% probability that this difference will be detected if it really exists) and a 5% probability of concluding that a difference does exist when, in fact, it does not. Having said this, [Falanga 1998](#) actually came quite close to this sample size estimate; however, the other 16 trials in this review were significantly smaller.

A number of outcome measures that may be of importance to patients were not measured, e.g. the pain of a pinch graft, or the creation of the graft site, which gives the patient an additional wound and may impinge on quality of life. Graft sites are at risk of infection and management of them increases costs. The cosmetic appearance of graft sites may also be problematic, since pinch grafts result in the creation of a cobblestone-like irregular surface.

The use of autologous keratinocytes in patients with venous leg ulcers causes several difficulties; each patient undergoes a biopsy, followed by a necessary delay of three to four weeks whilst the cells are cultivated. Furthermore, cultured keratinocytes from older individuals grow to confluence more slowly, and produce cultures that have reduced mitogen responsiveness and life spans - characteristics that are likely to persist after grafting in the wound bed (Phillips 1989). It is worth emphasising, however, that whilst adult cells may be slower initially to culture, once grown, they produce the same amount of growth factors as neonatal cells (Compton 1995). The culture lifetime of keratinocytes declines with the age of the donor; this may be due in part to loss of holoclones, the clonal cell type that has the greatest growth potential with increasing age (Barrandon 1987). Moreover, cultured neonatal keratinocytes release factors that stimulate the growth of other keratinocytes, whereas adult keratinocytes do not.

Allografts and bioengineered skin equivalents allow patients with chronic venous ulceration the chance to receive skin grafts without the additional injuries caused by harvesting, a stay in hospital, or the morbidity and mortality risks of anaesthesia. However, the preparation of ulcers for skin grafts is an important factor, since clean and granulating wounds are required for the procedure (Apligraf 2010). Whilst venous ulcers frequently occur on, or around, the ankle, these ulcers may not be suitable for artificial skin since it is difficult to anchor and immobilise the material on these areas. However, since the application of artificial skin is a noninvasive procedure that can be performed on an outpatient basis, it may offer significant advantages over split-thickness skin grafting in that it avoids the creation of a painful donor site, which can take a long time to heal in elderly people. Issues such as cost and the need for specialised storage facilities for artificial skin (which needs to be kept frozen until used) were not discussed by either Brown-Etris 2000 or Falanga 1998. Some people may not accept the use of xenografts because of religious or cultural beliefs (Enoch 2005).

Schonfeld et al (Falanga 1998) developed an economic model to estimate the costs and benefits of using Apligraf (Novartis)/Graftskin compared with a simple zinc oxide dressing (Unna's boot - standard therapy in the USA); both groups receiving compression. This model used healing data from Falanga 1998 and estimated that direct treatment costs were USD 20,041 per annum for people treated with Apligraf, compared with USD 27,493 for people treated with standard care. The higher treatment cost for Apligraf (USD 1425 per application) compared with Unna's boot (USD 12.05 per application) was more than offset by the need for fewer dressing changes, as a greater proportion of people healed more quickly with Apligraf. The results from this model need to be confirmed in a prospective economic analysis.

Compression therapy remains the mainstay of treatment for venous ulceration in clinical practice, with high-compression therapy being more effective at healing than low-compression systems. However, some 20% of ulcers remain unhealed after more than 50 weeks of appropriate compression therapy (Barwell 2004).

Margolis et al (Margolis 2004) was able to demonstrate, using the parameters of ulcer size and duration, that longstanding ulcers had only a 22% chance of healing at 24 weeks compared with small recent ulcers, which had a 71% chance. Therefore, it may be appropriate to identify those patients with "hard-to-heal" ulcers early, so that they may benefit from early adjunctive therapies such as grafting, rather than using this therapy as an early adjunct in ulcers that are not classed as recalcitrant where it may be unnecessary.

AUTHORS' CONCLUSIONS

Implications for practice

Bilayer tissue-engineered skin replacement, used with compression, increases the rate of healing of venous leg ulcers compared with simple dressings used with compression. There is insufficient evidence for the effectiveness of any other skin graft material or procedure for the treatment of venous leg ulcers.

Implications for research

Large randomised controlled trials (RCTs) comparing the interventions listed below would be valuable:

- Autografts: pinch grafting plus compression compared with compression alone.
- Allografts: cultured allografts compared with simple dressings.
- Bioengineered skin replacements: effectiveness and cost-effectiveness of the various artificial skin products compared with simple dressings.

Methods to identify people with ulcers amenable to treatment with skin grafts need to be developed, e.g. selecting people without infection (if this is shown to increase the probability of successful graft take), and identifying people who will heal without adjuvant therapies such as skin grafts.

New RCTs should follow CONSORT reporting guidelines and ensure that they report baseline comparability of treatment groups for important prognostic factors (such as ulcer area and duration); measure and analyse time to complete healing by appropriate (survival) methods; and report pain, acceptability, cosmetic outcomes, adverse events such as infection rates and recurrence, cost-effectiveness and quality of life.

Research is also needed into the identification of patients for whom grafting may be required and is effective. We know little about the feasibility of using artificial skin in primary care and other 'low tech' settings.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brown-Etris 2000

Methods	RCT with 6-month follow-up. Method of randomisation unclear.
Participants	36 patients from 8 centres. Only people with "hard to heal ulcers" included. Exclusion criteria: people whose ulcers had reduced in area by > 30% over 2 weeks with standard care Inclusion criteria: people with "hard to heal" venous ulcers Median size of ulcers: Group 1: = 4.5 cm ² ; Group 2: = 4.5 cm ² Median duration of ulcers: Group 1: = 9 months; Group 2: = 10 months
Interventions	Group 1: allogenic bilaminar Composite Cultured Skin (CCS: OrCel (trademark)), plus foam dressing and compression (CCS given as a single application each week for up to 4 weeks) Group 2: standard care, i.e. absorptive foam dressing and compression
Outcomes	Numbers of participants totally healed at 6 months: Group 1: = 71%; Group 2: = 37% (Probable that Group 1 had 12/17 healed and Group 2: had 7/19 healed)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The objective of this randomised, parallel group, feasibility study..." Comment: no mention of method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no evidence of allocation concealment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no data available
Selective reporting (reporting bias)	Unclear risk	Comment: no data available
Other bias	Unclear risk	Comment: no data available

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Brown-Etris 2000 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Burdge 2000

Methods	RCT (allocated in 2:1 ratio)
Participants	<p>Inclusion criteria: people with venous leg ulcers diagnosed by venous Duplex scan; min duration 1 month; age 18 or over; ulcer area at least 6 cm²; ulcer at least stage II or III as defined by IAET ulcer score; life expectancy of at least 12 months; Karnofsky score of at least 50 (0 to 100 scale that measures a person's ability to perform common tasks); BMI between 19 and 36</p> <p>Exclusion criteria: immuno-compromised patients; pregnancy/lactation; received chemotherapy within 30 days; history of irradiation of the ulcer area; uncontrolled diabetes; exposed bone, tendon, or fascia; osteomyelitis; active vasculitis; receiving haemodialysis; received corticosteroids >15 mg/d in last 30 days; ABPI < 0.65</p> <p>Patient age in years: Group 1: = 62 (SEM 6); Group 2: = 64 (SEM 9)</p> <p>Wound duration in months: Group 1: = 25 (SEM 8); Group 2: = 32 (SEM 16)</p>
Interventions	<p>Group 1: (n = 10) cultured epidermal autograft (Autoderm - trademark) (Compression bandages applied for 7 to 21 days (graft is harvested and grown during this time), then autograft applied on backing of tulle gras, weekly for 8 weeks)</p> <p>Group 2: (n = 5) standard care (debridement and compression)</p>
Outcomes	<p>Number of ulcers healed completely at 12 weeks:</p> <p>Group 1: = 8/10 (80%)</p> <p>Group 2: = 1/5 (20%)</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "An IRB approved clinical protocol called for the random assignment of 5 patients to the control group and 10 patients to the autoderm treatment group"</p> <p>Comment: no evidence of method of randomisation mentioned</p>
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: not stated
Selective reporting (reporting bias)	Unclear risk	Comment: not stated

Skin grafting for venous leg ulcers (Review)

Burdge 2000 (Continued)

Other bias	Unclear risk	Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Duhra 1992

Methods	RCT with 6 weeks' follow-up Method of randomisation unclear
Participants	22 participants with 30 ulcers treated in outpatients department Groups matched at baseline for age, sex, mean ulcer area and ulcer duration
Interventions	Group 1: (n = 15) allograft (cultured keratinocytes placed on a N-A dressing) Group 2: (n = 15) placebo (NA dressing soaked in culture medium) All participants received paraffin ointment impregnated tulle, gauze, absorbent pad, tubular elasticated bandage and compression
Outcomes	Healing rate over 6 weeks: a) Numbers healed at 6 weeks: Group 1: = 1/15 Group 2: = 0/15 b) Reduction in ulcer area (mean and SE): presented as a graph only in paper
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The ulcers were randomly allocated to receive the allograft or placebo in a double blind fashion" Comment: it appears unclear which method, if any, was used for randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants accounted for in the final analysis. N = 30. Therefore ITT assumed to be used.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported (healing rate and pain)
Other bias	Low risk	Comment: it appears that the groups were balanced in baseline variables

Duhra 1992 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The ulcers were randomly allocated to receive the allograft or placebo in a double blind fashion" Comment: double-blinding referred to and assumed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ulcers were examined by the same observer at 2wkly intervals" Comment: judged observer to be likely blinded as dressings were of identical appearance

Falanga 1998

Methods	RCT with 8 weeks' treatment and a 6-month follow-up Method of randomisation: used computer-generated randomisation schedules	
Participants	309 participants randomised with 293 treated as outpatients in 15 centres Groups well matched at baseline for age, sex, mean ulcer area and ulcer duration	
Interventions	Group 1: (n = 146) human skin equivalent and compression Group 2: (n = 129) dressing (made to look the same as intervention) and compression	
Outcomes	a) Incidence of complete healing by 6 months: Group 1: = 92/146 Group 2: = 63/129 b) Time required for complete healing to occur (days): Group 1: = 61 days (range 9 to 233 days) Group 2: = 181 days (range 10 to 232 days)	
Notes	Authors stated result as number of participants available for final analysis rather than number randomised, i.e. not an intention-to-treat analysis	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation schedules" Comment: clear evidence of method of randomisation given
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "309 were randomised for the trial and 293 were treated; for final statistical analysis 275 patients who met inclusion/exclusion criteria were evaluated" Comment: 18 patients were treated but no outcome data for them materialised. As a result, they are deemed as loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported (wound healing at 6 months)
Other bias	Low risk	Quote: "no significant differences between control and HSE groups in demographics at baseline"

Falanga 1998 (Continued)

		Comment: it appears that the groups were comparable in terms of variables at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "In the HSE group, the HSE was applied directly to the ulcer" Comment: since the control was compression alone, it is judged to be highly likely that patients were not blinded to the addition of HSE as it was not made clear that the control looked identical to the HSE
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: it is unclear whether the outcome assessor can see dressings at time of measuring the outcome. There is not enough evidence to suggest risk either way.

Goedkoop 2010

Methods	Double-blind and placebo-controlled RCT with up to 24-week follow-up
Participants	110 participants Inpatient and outpatients settings The groups were matched at baseline for important variables such as duration of ulcer and ulcer size
Interventions	Group 1: (n = 15) control receiving placebo (vials containing the spray without the cells) Intervention groups listed below varied in the ratio of keratinocytes (K) to fibroblasts (F) and in the concentration of cells (x 10 ⁶ cells/ml) Group 2: (n = 14) received intervention at K/F ratio 1:9, concentration 2.5 Group 3: (n = 17) received intervention at K/F ratio 1:9, concentration 5 Group 4: (n = 15) received intervention at K/F ratio 1:9, concentration 10 Group 5: (n = 17) received intervention at K/F ratio 1:1, concentration 2.5 Group 6: (n = 16) received intervention at K/F ratio 1:1, concentration 5 Group 7: (n = 16) received intervention at K/F ratio 1:1, concentration 10 The results comprised pooling into 2 intervention groups according to the K/F ratio
Outcomes	Percentage of ulcers completely healed at 12 weeks: Group 1: 38% 3/8 Groups 2 to 4 (pooled): 47% 15/32 Groups 5 to 7 (pooled): 47% 16/34 Percentage of ulcers completely healed at 24 weeks: Group 1: 50% 4/8 Groups 2 to 4 (pooled): 66% 21/32 Groups 5 to 7 (pooled): 56% 19/34
Notes	Group 3 displayed the highest levels of ulcer healing and the most favourable primary outcome findings (a combination of K:F of 1:9 and concentration 5 x 10 ⁶ cells)

Goedkoop 2010 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All 118 were randomised to treatment" Comment: method of generating the randomisation sequence is not clear
Allocation concealment (selection bias)	Unclear risk	Quote: "Centrally randomised" Comment: no reference to concealment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients randomised to treatment on an intention to treat data set" Comment: all patients randomised were accounted for in the statistical analysis. No evidence of loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported (complete closure at 12 weeks, reduction in ulcer size, wound healing rate)
Other bias	Low risk	Quote: "the demographic limb and reference ulcer characteristics at baseline were similar across treatment group" Comment: it appears that the groups were balanced in baseline variables
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind" Comment: the study reported the study as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded data" Comment: the outcome assessor measured complete ulcer closure. Blinded data referred to and assumption made that the outcomes were assessed via blind fashion

Jankunas 2007

Methods	RCT with 6-month follow-up. Method of randomisation: card picked by nurse
Participants	71 people treated as either inpatients or outpatients
Interventions	Rate of complete healing by 6 months Group 1: surgical skin autograft Group 2: hydrocolloid dressing All received compression therapy throughout
Outcomes	Group 1: = 27/40 Group 2: = 0/31
Notes	Ulcers in the surgical group 1 were larger and older with patients remaining in hospital for 10.7 days compared to 10.3 days for the control group

Risk of bias

Bias	Authors' judgement	Support for judgement
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Skin grafting for venous leg ulcers (Review)

Jankunas 2007 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "a nurse working with the instigator, pulled out 1 or 2 cards that had either a + (surgery) or - (conservative)" Comment: unclear description of method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two patients were diagnosed with SCC after fundus biopsies... Those patients were eliminated from the study. Histological analysis revealed lesions described as chronic inflammation." Comment: 2 patients eliminated from the study but the circumstances of exclusion adequately addressed and outcome data incorporated into the data set (n = 71). The loss to follow-up is less than 5%.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported (speed of epithelialisation)
Other bias	Unclear risk	Comment: although the groups were comparable in age (62 vs 69 years), the mean ulcer area at baseline was 236 cm ² (surgery) vs 182.3cm ² (conservative), it is unclear what impact, if any, this can have on the data
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were introduced to the study and the treatment (conservative or surgery)" Comment: patients aware which group they were allocated to therefore blinding likely not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not clear whether outcome assessor can distinguish between intervention and control. Not stated

Krishnamoorthy 2003

Methods	RCT with 12-week follow-up. RCT with 12-week follow-up. Method of randomisation: sealed envelopes.
Participants	53 people from 6 centres in UK and Canada treated in outpatients departments
Interventions	Group 1: Dermagraft, weekly for 11 weeks (total of 12 applications) Group 2: Dermagraft at 0, 1, 4 and 8 weeks (4 applications) Group 3: Dermagraft at time 0 (1 application) Group 4: no Dermagraft All received 4-layer compression bandaging throughout
Outcomes	Incidence of complete healing by 12 weeks: Group 1: = 5/13 Group 2: = 5/13 Group 3: = 1/14 Group 4: = 2/13 Percentage reduction in ulcer area: Group 1: = 81.4 Group 2: = 88.6 Group 3: = 59.4 Group 4: = 78.1

Krishnamoorthy 2003 (Continued)

Notes Ulcers in the control group were larger and older. Median area of control group was 31% larger than the total group average. Median duration was also 54% longer than total group average.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...computer generated scheme" Comment: clear method of randomisation identified
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "six patients were withdrawn from the study and did not complete treatment. 3 due to adverse effects, 2 non compliant, one withdrew" Comment: 6 withdrawals – all accounted for in the final analysis therefore ITT performed. Losses to follow-up represent 10% of final data set.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported (number of ulcers healed, duration of ulceration, ulcer area)
Other bias	Low risk	Quote: "patients were reasonably well matched at randomisation with respect to baseline clinical and demographic characteristics" Comment: it appears that the groups were comparable in terms of variables at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Blinding not possible in the study because the characteristics of the dermagraft preclude the use of a placebo" Comment: blinding not possible to the nature of the dermagraft
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open-label, prospective, multi centre, randomised, controlled clinical trial" Comment: open label. Blinding not done

Lindgren 1998

Methods	RCT with 8 weeks' treatment. Method of randomisation: unclear.
Participants	27 participants with venous ulcers treated in outpatient department Groups matched at baseline for age, sex, ulcer duration and mean ulcer area
Interventions	Group 1: (n = 15) cryopreserved allografts, dressing (Mepitel) and compression Group 2: (n = 12) dressing (Mepitel) and compression
Outcomes	a) Number with ulcer healed at 8 weeks: Group 1: = 2/15 Group 2: = 2/12 b) Number with a reduction in ulcer area: Group 1: = 8/15 Group 2: = 6/12

Skin grafting for venous leg ulcers (Review)

Lindgren 1998 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised to two groups" Comment: randomisation mentioned however no method outlined
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "two patients in each group were excluded as the end stage of healing produced multiple small wounds not allowing analysis with this method" Comment: 4 patients excluded which comprises 12% of the total sample. Assumed to be low risk due to small proportion of the total.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported adequately (wound healing as percentage of initial wound area)
Other bias	Unclear risk	Comment: all variables balanced except mean initial wound area (4.4 cm ² vs 7.9 cm ²). It is unclear what impact, if any, this can have on the data.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Liu 2004

Methods	12-week follow-up. Randomisation schedule was computer-generated, but not clear if allocation was concealed.
Participants	10 people with ulcers of at least 3 months' duration
Interventions	Group 1: (n = 5) single dose of autograft of keratinocytes cultured on porcine gelatin microbeads Group 2: (n = 5) single dose of autograft of keratinocytes cultured on porcine collagen pads Ulcers in both groups were surgically cleansed and debrided under local anaesthetic. A non-adherent, antibiotic impregnated tulle was used to cover graft, with a cotton gauze. Both groups had an elastic multilayer-bandage wrap. Dressings were changed 3 days after transplantation and daily thereafter.
Outcomes	Healed by 12 weeks: Group 1: = 1/4 Group 2: = 1/4 Reduction in area: Group 1: = 83% Group 2: = 50% Adverse effects: none in either group

Liu 2004 (Continued)

Notes Study reports on 15 people: after recruitment of 10 patients (randomised trial) 5 people were treated with multiple doses of keratinocytes on porcine gelatin microbeads

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomization schedules" Comment: evidence of adequate method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All ulcers were evaluated weekly during the first 4 weeks and followed thereafter for up to 12 weeks..." Comment: all participants were followed up. No evidence of loss to follow-up. All 15 participants accounted for in the final statistical analysis
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported adequately (complete wound healing, mean reduction in initial wound area)
Other bias	Low risk	Quote: "There were no significant differences between the treatment groups in patient demographics and baseline ulcer size" Comment: it appears that the groups were comparable in terms of variables at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...in the Bio – MCCS group...GMB was administered using a pipette". "in the CP group, the autologous graft was placed directly onto the wound" Comment: different methods of administering the materials therefore participant blinding likely not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The wound surface was were calculated using computerised image analysis" Comment: assessors were judged to be blind as calculations were made remotely using a computerised system

Navratilova 2004

Methods	RCT with 3 months' follow-up. Method of randomisation: unclear.
Participants	50 hospitalised participants (18 male) Ulcer area at baseline: Group 1: = 12.41 cm ² Group 2: = 9.04 cm ² Mean duration at baseline: Group 1: = 30.7 months Group 2: = 16.7 months Inclusion criteria: ulcer larger than 2 cm ² and of at least 3 months' duration Exclusion criteria: arterial ulcer; uncompensated diabetes; pronounced anaemia; uncompensated heart insufficiency; pronounced hypoproteinaemia; ABPI < 0.8; metastatic malignant tumour; systemic immunosuppressive therapy Mean age 63 years

Skin grafting for venous leg ulcers (Review)

Navratilova 2004 (Continued)

Mean BMI 30.1

Interventions	Group 1: (n = 25) cryopreserved cultured epidermal keratinocytes (allograft) Group 2: (n = 25) lyophilised cultured epidermal keratinocytes (allograft) Allografts applied when ulcer bed had a granulating base. Graft dressings covered with nonadherent silicone dressing, layers of dry gauze, a gauze bandage and a low-strength sterile bandage. Patients were advised to rest in bed for 48 hours after grafting. Dressings removed at 5 days, then replaced at 3-day intervals
Outcomes	Number with a healed ulcer at 90 days: Group 1: = 21/25 Group 2: = 20/25
Notes	Figure shows pain reducing over duration of trial but no detailed data provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was randomised (the patients were numbered in the order they entered the study)" Comment: unclear whether the sequence was randomly generated
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised patients accounted for in the final analysis. ITT assumed to be used. N = 50
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported (mean healing time, ulcer size, relief of pain)
Other bias	Low risk	Comment: size of ulcer prior to grafting comparable in both groups (my interpretation of table 6)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "sheets of Keratinocytes (cryopreserved or lyophilised) were applied on the wound bed" Comment: no comment as to difference in physical appearance of the dressings
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Omar 2004

Methods	RCT with 12 weeks' follow-up. Method of randomisation: unclear.
Participants	18 people with ulcers > 12 weeks' duration Inclusion criteria: clean ulcers with healthy granulation tissue; duplex finding of venous dysfunction; ABPI > 0.9 Mean ulcer duration at baseline: Group 1: = 118.8 weeks Group 2: = 120 weeks

Skin grafting for venous leg ulcers (Review)

Omar 2004 (Continued)

Mean ulcer area at baseline:
Group 1: = 9.5 cm² (SD 4.2)
Group 2: = 12.3 cm² (SD 7.6)

Interventions	Group 1: (n = 10) human fibroblast-derived dermal replacement (Dermagraft - trademark) Group 2: (n = 8) non-adherent dressing All patients received high compression, 4-layer bandaging
Outcomes	Number healed at week 12: Group 1: = 5/10 Group 2: = 1/8 Reduction in area over trial in cm ² per week: Group 1: = 0.82 (SD 0.33) Group 2: = 0.15 (SD 0.39)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Protocol-eligible patients were prospectively randomised to treatment (Dermagraft) according to the computer generated code on order of admittance to the study" Comment: clear method of randomisation identified
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed up weekly to 12 weeks..." Comment: all randomised patients' data included in final statistical analysis. N = 18. Therefore an ITT is assumed to be used. No evidence of loss to follow-up or withdrawals/drop-outs.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported adequately (healing rate, peri-ulcer skin blood flow)
Other bias	Low risk	Quote: "The patients were well matched at randomisation with respect to demographics and mean ulcer duration" Comment: the groups appear balanced in terms of variables at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients randomised to the Dermagraft group received Dermagraft at weeks 0, 1, 4 and 8 weeks...Control patients were treated with a local non-adherent dressing (Dermanet)" Comment: no mention whether the Dermanet and Dermagraft were distinguishable. As a result it cannot be ascertained whether the participants can distinguish between the dressings.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "ulcer measurements were made by a clinician blinded to the treatment group" Comment: the outcome assessors are said to be blinded

Paquet 2005

Methods	Split-ulcer RCT with 8 weeks' follow-up
Participants	4 women with venous ulcers of min 3 months' duration
Interventions	2-week run-in period of dressings and cleansing Group 1: half of ulcer (proximal or distal) had cultured allogenic keratinocyte dressing (1 had fresh, 3 had frozen) Group 2: half of ulcer (proximal or distal) had petrolatum gauze dressing Leg was wrapped with a Rosidal bandage Treatment reapplied weekly for 4 weeks
Outcomes	Reduction in area divided by initial perimeter: Group 1: = +1 mm (SD 6.2) Group 2: = -0.55 mm (SD 3.9) (an increase in area)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Four women aged 61-83 were enrolled". "The randomised investigational products were applied..." Comment: unclear whether the participants were randomised or the interventions
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants accounted for in the final analysis. No evidence of loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: all outcomes adequately reported
Other bias	Low risk	Quote: "The ulcers had an average diameter greater than 5cm but did not extend to the fascia" Comment: no evidence of comparison of baseline variables in text or figures. Unable to ascertain the demographics of the sample.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This open-label, randomised pilot study..." Comment: open labelled study is therefore unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "these measurements were made by one single-blind investigator" Comment: outcome assessor blind

Poskitt 1987

Methods	RCT with 12 weeks' follow-up. Allocation using random number tables to generate sealed envelopes.
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Skin grafting for venous leg ulcers (Review)

Poskitt 1987 (Continued)

Participants	51 participants with 53 venous ulcers Inpatient and outpatient settings used Groups well matched at baseline for important variables such as mean ulcer area, duration of ulcer and age of participants
Interventions	Group 1: (n = 25) pinch grafts and compression Group 2: (n = 28) porcine dermis (a xenograft) and compression
Outcomes	a) Number with ulcer healed at 6 weeks: Group 1: = 16/25 Group 2: = 8/28 b) Number with ulcer healed at 12 weeks: Group 1: = 18/25 Group 2: = 13/28
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number tables" Comment: randomisation achieved through random number tables
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed envelopes" Comment: although sealed envelopes were used, no mention was made regarding whether the envelopes were opaque and sequentially numbered
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised patients were accounted for in the final analysis. It is therefore assumed that an ITT was used. No evidence of loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: all outcomes addressed in results equally
Other bias	Low risk	Quote: "The treatment groups were closely comparable" Comment: it appears that the groups were balanced in baseline variables
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Salomon 2002

Methods	RCT with 12 weeks' follow-up
Participants	92 randomised. The analysis presented data on 77 patients but data available for 92 (a total of 13 in the meshed graft group dropped out and 2 in the Epidex group)

Skin grafting for venous leg ulcers (Review)

Salomon 2002 (Continued)

Interventions	Group 1: Epidex an autologous epidermal equivalent grown from keratinocytes of hair follicles Group 2: meshed skin autograft
Outcomes	Group 1: 14/45 Group 2: 14/47 Healed at week 12 - ITT analysis undertaken - all patients for whom the data were not presented at follow-up were assumed to be treatment failures
Notes	This report was available only as a conference abstract; we wrote to the author to request further information but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "92 eligible patients....were randomised to inpatient mesh graft or ambulatory epidex in 12 centres in Germany" Comment: method or random sequence generation not mentioned
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At unbinding of a 6-weeks run in period....patients dropped out of the study. Thus 77 were available for analysis" Comment: no evidence that dropouts were accounted for in final analysis. Loss to follow-up greater than 10%.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported
Other bias	Unclear risk	Comment: not clear if variables were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Tausche 2003

Methods	RCT with 6 months' follow-up. Allocation blinded to patients and investigators until 1 week prior to treatment.
Participants	99 people enrolled and 92 randomised. The analysis presented data on 77 who received treatment as randomised (15 dropped out between randomisation and treatment: 2 from Group 1, and 13 from Group 2).
Interventions	Group 1: autologous epidermal equivalents derived from hair follicles captured from plucked hairs (50 to 200 per patient) Group 2: meshed skin autograft

Skin grafting for venous leg ulcers (Review)

Tausche 2003 (Continued)

Outcomes	People with ulcers healed at 6 months: Group 1: = 19/45 Group 2: = 16/47
Notes	2 patients in Group 1 were excluded after randomisation compared with 13 patients in Group 2 (of whom 8 refused the surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients were randomised centrally to treatment...with a block size of 5" Comment: the study reported using block randomisation to generate the sequence
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "...15 dropped out prior to treatment. Eight patients in the mesh group dropped out because they refused to undergo the surgical procedure. Therefore the analyses was done on the 77 patients who received the treatment" Comment: statistical analysis was completed on all the treated patients but there were 23 patients (15 + 8) which were randomised that were not accounted for in the final analysis
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported adequately
Other bias	Low risk	Quote: "There were no significant differences between the treatment groups in the demographic CEAP classification" Comment: the demographics and variables appear comparable at baseline
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Treatment allocation was blinded to patients and investigators until 1 week prior to the treatment" Comment: it is unclear whether participants were blind at the time of treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not stated

Teepe 1993

Methods	RCT with 12 weeks' follow-up. Method of randomisation not stated.
Participants	43 participants with 47 ulcers treated in 2 outpatient departments Groups matched at baseline for ulcer area, ulcer duration, age and sex
Interventions	Group 1: cryopreserved allografts Group 2: hydrocolloid dressing Both groups received short stretch bandages

Skin grafting for venous leg ulcers (Review)

Teepe 1993 (Continued)

Outcomes	a) Number with ulcer healed at 6 weeks: Group 1: = 6/24 Group 2: = 5/23 b) Number with ulcer healed at 12 weeks: not relevant as cross-over at 6 weeks
Notes	Cross-over trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Both centres were randomised separately". "For each six consecutive patients, three were randomised to CCA, and three to HCD" Comment: although the method of allocation is present, the generation of the randomisation sequence is not mentioned
Allocation concealment (selection bias)	High risk	Quote: "For each consecutive 6 patients, three were randomised to CCA and 3 to HCD" Comment: allocation was not concealed as alternation was used to allocate
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "After completion of the therapy, 25 patients with 29 healed ulcers were followed up for 6 months" Comment: it appears only patients with healed ulcers were followed up. 9 patients (9 ulcers) dropped out and a further 9 did not heal at week 12. This means that 18 ulcers were not followed up. Losses to follow-up amounted to 19.1% and deemed unacceptable.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported adequately
Other bias	Low risk	Quote: "The two treatment groups showed similar characteristics, except a nearly significant difference between the initial ulcer sizes" Comment: there appear to be similarities in characteristics at baseline
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Ulcers treated with HCD were prepared in a similar fashion (to the CCA group)" Comment: although the method of preparation of ulcers is said to be "similar", it is still unclear as to the difference in appearance of the graft and dressing. Therefore, blinding is uncertain.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Ulcers treated with HCD were prepared in a similar fashion (to the CCA group)" Comment: although the method of preparation of ulcers is said to be "similar", it is still unclear as to the difference in appearance of the graft and dressing. Therefore, blinding of the outcome assessor is uncertain.

Warburg 1994

Methods	RCT with 12 months' follow-up. Method of allocation: unclear.
Participants	31 participants with venous leg ulcers, treated as inpatients and outpatients (3-arm trial - 3rd arm of 16 people not relevant to this review)

Skin grafting for venous leg ulcers (Review)

Warburg 1994 (Continued)

Groups appeared to be well matched at baseline for age and sex. Not well matched for ulcer duration or baseline ulcer area.

Median area (range):

Group 1: = 7 cm² (1.1 to 347 cm²)

Group 2: = 41.2 cm² (2.1 to 290 cm²)

Median duration (range):

Group 1: = 24 months (1 to 72 months)

Group 2: = 18 months (3 to 72 months)

Interventions	Group 1: (n = 16) meshed split-skin graft and surgery with compression Group 2: (n = 15) surgery for incompetent perforators and compression
Outcomes	Number healed at 12 months: Group 1: = 5/15 Group 2: = 6/16 Time to complete healing: Group 1: = 5.5 months (1.5 to 12 months) Group 2: = 3 months (1 to 12 months) Median ulcer area after 1 year: Group 1: = 6.5 cm ² (0-63) Group 2: = 4.1 cm ² (0-427) (Not clear if figures in brackets are ranges)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After informed consent, patients were randomised into 3 groups" Comment: method of generating the randomisation sequence is not clear
Allocation concealment (selection bias)	Unclear risk	Comment: not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During follow up, 4 patients dropped out" Comment: patients lost to follow-up were not accounted for in the analysis and final data set. LTF represents 10% of data and as a result, deemed at low risk
Selective reporting (reporting bias)	Low risk	Comments: all outcomes addressed in results equally
Other bias	Low risk	Quote: "no statistical significant differences of the variables between the 3 groups" Comment: it appears that the groups were balanced in baseline variables
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "all patients treated with compression bandage, patients in groups A and C were treated with hydrocolloid wound dressing" Comment: different dressing used in graft group (unclear whether distinguishable from original)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "all patients treated with compression bandage, patients in groups A and C were treated with hydrocolloid wound dressing"

Skin grafting for venous leg ulcers (Review)

Warburg 1994 (Continued)

Comment: different dressing used in graft group (unclear whether distinguishable from original)

Abbreviations

> = more than

< = less than

ABPI = ankle brachial pressure index

BMI = body mass index

CCA = cryopreserved allografts

CEAP = a system to classify the severity, cause, site and specific abnormality of venous disease

d = day(s)

h = hour(s)

HCD = hydrocolloid

HSE = human skin equivalent

IAET = International Association Enterostomal Therapy (IAET) staging classification

ITT = intention-to-treat

LTF = loss to follow up

min = minimum

NA = not applicable

N-A = non-adherent

RCT: randomised controlled trial

SCC = squamous cell carcinoma

SD = standard deviation

SEM = standard error

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahnlide 1997	Retrospective study
Altman 1997	Letter describing use of Apligraf
Andersen 1959	Not a RCT
Beele 1991	Not a RCT
Berretty 1979	Not a RCT
Boyce 1995	Not a RCT
Calonge 1993	The trial compared autografts and allografts in 15 patients, but no data were provided on the healing rates for the 2 groups. Abstract only available presenting insufficient data, authors contacted for further information, but no response received.
Carpentier 2009	Not a RCT
Carver 1991	Not a RCT
Chang 2000	Diabetic foot ulceration
Christiansen 1997	Retrospective study
Clancy 1988	No information provided on how patients were allocated to the 2 groups (see also Shehade 1989 which may report the same trial in more detail)

Study	Reason for exclusion
Coney 1990	Not a RCT
Dahlstrom 1992	Intervention was fibrin adhesive applied to grafts or not, therefore evaluation was of the treatment of grafts not grafts per se
Demling 2004	Not a graft but a dressing
Fahey 1998	Description of use of skin graft
Farah 2010	A review article, not a trial
Halter 2003	Not a RCT
Harris 1993	Not a RCT
Harrison 1988	Not a RCT
Henderson 1980	Intervention was antibacterial agent to clean graft site prior to grafting. Evaluation was of graft site preparation.
Kirsner 1997	Description of use of skin graft
Leigh 1986	Case study
Limova 1995	Not a RCT
Mahajan 1995	Not a RCT
Marcusson 1992	Not a RCT
Mekkes 1992	Evaluation was of graft site preparation
Millard 1977	Not a RCT
Mol 1991	Not a RCT
Mostow 2005	Intervention is a freeze-dried dressing made of intestinal mucosa - so will be considered as a dressing
Muhart 1998	Evaluated treatment of skin graft donor sites
O'Donnell 2006	Not a RCT
Oien 1998	Not a RCT
Ortega 2010	Not a RCT
Phillips 1991a	Non-systematic review
Phillips 1991b	Cohort study
Pojda 1994	Trial included only 1 person (out of 5 studied) with a venous ulcer. The study compared 3 methods of preparing split-thickness skin grafts, namely: the usual method; incubation in Iscoves medium, albumin and GM-CSF (a growth factor); and Iscoves medium and albumin alone. There was no information in this abstract about how the comparison was performed - was the ulcer divided into 3,

Study	Reason for exclusion
	or was each ulcer allocated to one form of graft? The authors were contacted for further information, but no response received.
Puonti 1998	Cohort study
Ruffieux 1997	Retrospective study
Shehade 1989	Not a RCT
Skene 1992	Interventions were 2 wound dressings
Slonkova 2002	Czech translator, no evidence that it is a RCT
Steele 1985	Not a RCT
Townsend 1970	Letter
Trent 1998	Review
Van den Hoogenband 1984	Retrospective study
Villeneuve 1998	Not a RCT
Vin 2002	Intervention was a collagen/oxidised regenerated cellulose dressing
Ward 1989	Intervention was amnion on graft site prior to grafting. Evaluation was of graft site preparation.

RCT: randomised controlled trial

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

Wille 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting full text retrieval

DATA AND ANALYSES

Comparison 1. Split-thickness autografts compared with standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Skin grafting for venous leg ulcers (Review)

Analysis 1.1. Comparison 1 Split-thickness autografts compared with standard care, Outcome 1 Healing.

Comparison 2. Frozen or fresh allografts compared with standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	5	125	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.04, 3.84]
1.1 Frozen allografts	3	80	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.79, 3.33]
1.2 Fresh allografts	2	45	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [0.80, 17.45]

Analysis 2.1. Comparison 2 Frozen or fresh allografts compared with standard care, Outcome 1 Healing.

Comparison 3. Bilayered human skin equivalent compared with standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Bilayer skin replacement	2	345	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.22, 1.88]

Analysis 3.1. Comparison 3 Bilayered human skin equivalent compared with standard care, Outcome 1 Healing.

Comparison 4. Single-layered dermal skin replacement compared with standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Twelve pieces of Dermagraft	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.59, 10.64]
1.2 Four pieces of Dermagraft	2	44	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.95, 9.68]
1.3 One piece of Dermagraft	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.05, 4.53]

Analysis 4.1. Comparison 4 Single-layered dermal skin replacement compared with standard care, Outcome 1 Healing.

Comparison 5. Allogenic tissue product compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete wound closure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Allogenic tissue product compared with placebo, Outcome 1 Complete wound closure.

Comparison 6. Autograft versus comparator graft

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion fully healed in trial	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Autograft versus frozen allograft	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Autograft versus xenograft	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Reduction in ulcer area	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Autograft versus frozen allograft	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Autograft versus comparator graft, Outcome 1 Proportion fully healed in trial.

Study or subgroup	Autograft n/N	Comparator graft n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Autograft versus frozen allograft				
Tausche 2003	14/45	14/47		0.94[0.39,2.28]
6.1.2 Autograft versus xenograft				
Poskitt 1987	18/25	13/28		0.34[0.11,1.06]
			Favours comparison graft	Favours autograft

Analysis 6.2. Comparison 6 Autograft versus comparator graft, Outcome 2 Reduction in ulcer area.

Study or subgroup	Autograft N	Autograft Mean(SD)	Comparator graft N	Comparator graft Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.2.1 Autograft versus frozen allograft						
Tausche 2003	45	65.9 (63)	47	51.5 (74.4)		14.37[-13.76,42.5]
					Favours experimental	Favours control

Comparison 7. Autograft on microbeads compared with autograft on pads

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 11.93]

Analysis 7.1. Comparison 7 Autograft on microbeads compared with autograft on pads, Outcome 1 Healing.

Comparison 8. Autograft versus cultured autologous keratinocytes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed at 12 weeks	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.56, 1.94]

Analysis 8.1. Comparison 8 Autograft versus cultured autologous keratinocytes, Outcome 1 Number of ulcers healed at 12 weeks.

Comparison 9. Frozen allograft compared with lyophilised keratinocyte

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.81, 1.36]

Analysis 9.1. Comparison 9 Frozen allograft compared with lyophilised keratinocyte, Outcome 1 Healing.

ADDITIONAL TABLES

Table 1. Quality appraisal

STUDY REF	Intention-to-treat	Blind outcome assessment	Groups comparable	Similar care	Clear entry criteria	Ulcer aetiology clear	Adverse events	Sample size OK	Follow-up %
Brown-Etris	No W/D reported	N/S	Area similar at baseline	Both received foam and compression	N/S	Criteria N/S	N/S	N/S	No information on withdrawals
Burdge	No W/D reported	N/S	Patient age and ulcer duration comparable. No information on area of ulcer.	Both received debridement and compression	Yes	Definition of venous ulcers by duplex	'No infections'	N/S	N/S
Duhra	Yes	Yes	Comparable for area and duration	Yes	Yes	No	Reported by group and type	N/S	100%
Falanga	No: 309 randomised, 293 treated, data on 275	N/S	Comparable for area and duration	Yes	Yes	Yes	Reported by group and type	N/S	89%
Goedkoop	No: 110 (randomised)	Yes	Comparable for area and duration	Yes	Yes	Yes	N/S	N/S	100%
Jankunas	No: 71 randomised	N/S	Larger and older ulcers in graft group	Both received compression	Yes	Yes	Squamous cell carcinoma	N/S	N/S
Krishnamoorthy	No: 53 randomised, 52 analysed	N/S	Ulcer duration longer in control group	Both received compression	Yes	Yes	Infections, skin problems	N/S	98%
Lindgren	Yes	N/S	Larger and older ulcers in graft group	Yes	No	No	Types of adverse events reported but no numbers	N/S	100%
Liu	Yes	Yes	Older but smaller ulcers in microbead group	Yes	Yes	Definition of venous ulcers by both continuous wave Doppler	No "contact dermatitis or infection throughout entire treatment period"	N/S	100%

Table 1. Quality appraisal (Continued)

Quality appraisal (continued)						and Duplex ultra-sound			
Navratilova	No W/D reported	N/S	Longer duration and larger ulcers in frozen graft group	Yes	Yes	Yes	N/S	N/S	100%
Omar	Yes	Yes	Comparable for ulcer duration and area	Dressing and compression	Yes	Yes	N/S	N/S	100%
Paquet	Yes	Yes	Comparable	Dressing and compression	Yes	Yes	None	N/S	100%
Poskitt	Unclear: 51 people (60 legs) 'entered study' but data on 53 'available for randomisation'	N/S	Larger and older ulcers in graft group	Both received compression	Yes	No	N/S	Stated they needed 40 per group	88%
Salomon	92 randomised, data on 77	N/S	N/S abstract only	N/S abstract only	No	No	N/S	N/S	N/S
Tausche	No	N/S	Larger ulcers in graft group	Compression therapy	Yes	Yes	None	N/S	100%
Teepe	Yes - but unit of analysis error	N/S	Larger ulcers in graft group	Both received tulle and compression		Definition of venous ulcer by clinical findings/LRR/Doppler	"Side effects not observed"	Stated they needed 20 per group	81%
Warburg	No	N/S	Ulcer areas not similar at baseline (7 vs 41 cm ²)	Both received surgery to incompetent perforators		Definition of venous ulcers by phlebography	"No thrombosis or sepsis"	N/S	90%

LRR = light reflection rheography

N/S = not stated

W/D = withdrawal

APPENDICES

Appendix 1. Search strategy - third update 2009

For this third update we searched the following electronic databases:

- Cochrane Wounds Group Specialised Register (Searched 22/5/09)
- The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library Issue 2 2009
- Ovid MEDLINE - 1950 to May Week 2 2009
- Ovid EMBASE - 1980 to 2009 Week 20
- Ovid CINAHL - 1982 to May Week 3 2009

The following search strategy was used in The Cochrane Central Register of Controlled Trials (CENTRAL):

```
#1 MeSH descriptor Leg Ulcer explode all trees
#2 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXT extremity*)
NEAR/2 ulcer*) or (crural NEXT ulcer*) or "ulcus cruris":ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Skin Transplantation explode all trees
#5 (skin NEXT graft*) or (pinch NEXT graft*):ti,ab,kw
#6 (split NEXT thickness) or (full NEXT thickness):ti,ab,kw
#7 allograft* or dermagraft* or apligraf*:ti,ab,kw
#8 tissue NEAR/2 engineer*:ti,ab,kw
#9 cultured NEAR/2 keratinocyte*:ti,ab,kw
#10 artificial NEXT skin:ti,ab,kw
#11 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 (#3 AND #11)
```

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in [Appendix 4](#), [Appendix 5](#) and [Appendix 6](#) respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN). No date or language restrictions were applied.

Appendix 2. Ovid MEDLINE search strategy

```
1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremity* adj ulcer*) or crural
ulcer* or ulcus cruris).ti,ab.
3 or/1-2
4 exp Skin Transplantation/
5 (skin graft$ or pinch graft$).ti,ab.
6 (split thickness or full thickness).ti,ab.
7 (allograft$ or dermagraft$ or apligraf$).ti,ab.
8 (tissue adj2 engineer$).ti,ab.
9 (cultured adj2 keratinocyte$).ti,ab.
10 artificial skin.ti,ab.
11 or/4-10
12 3 and 11
```

Appendix 3. Ovid EMBASE search strategy

```
1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremity* adj ulcer*) or crural
ulcer* or ulcus cruris).ti,ab.
3 or/1-2
4 exp Skin Graft/
5 (skin graft* or pinch graft*).ti,ab.
6 (split thickness or full thickness).ti,ab.
7 (allograft* or dermagraft* or apligraf*).ti,ab.
8 exp Tissue Engineering/
9 (tissue adj2 engineer*).ti,ab.
10 (cultured adj2 keratinocyte*).ti,ab.
```


11 exp Artificial Skin/
12 artificial skin.ti,ab.
13 or/4-12
14 3 and 13

Appendix 4. EBSCO CINAHL search strategy

S13 S4 and S12
S12 S5 or S6 or S7 or S8 or S9 or S10 or S11
S11 TI artificial skin or AB artificial skin
S10 TI cultured N2 keratinocyte* or AB cultured N2 keratinocyte*
S9 TI tissue N2 engineer* or AB tissue N2 engineer*
S8 TI (allograft* or dermagraft* or apligraf*) or AB (allograft* or dermagraft* or apligraf*)
S7 TI (split thickness or full thickness) or AB (split thickness or full thickness)
S6 TI (skin graft* or pinch graft*) or AB (skin graft* or pinch graft*)
S5 (MH "Skin Transplantation")
S4 S1 or S2 or S3
S3 lower extremity N3 ulcer* or AB lower extremity N3 ulcer*
S2 TI (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet N1 ulcer*) or stasis ulcer* or crural ulcer*) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet N1 ulcer*) or stasis ulcer* or crural ulcer*)
S1 (MH "Leg Ulcer+")

Appendix 5. Risk of Bias definitions

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

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. if 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

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 - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Any one of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- 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.
- 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.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- 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.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- 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.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Any one of the following.

- 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).
- The study did not address this outcome.

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

Low risk of bias

Any of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
30 July 2012	New citation required but conclusions have not changed	Conclusions remain unchanged.
30 July 2012	New search has been performed	Fourth update, new search, one new trial included (Goedkoop 2010); one trial previously included now excluded (Mol 1991); one study is awaiting assessment (Wille 2011).

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 1, 2000

Date	Event	Description
19 August 2009	New search has been performed	Third update, two new trials added, no change to conclusions
16 February 2007	New citation required and conclusions have changed	Substantive amendment For this second update, new searches were carried out in February 2006. Twenty-six potentially relevant citations were identified, of these six studies (Krishnamoorthy 2003 ; Liu 2004 ; Navratilova 2004 ; Omar 2004 ; Paquet 2005 ; Tausche 2003) were included in the review. Two studies (Calonge 1993 ; Pojda 1994) previously awaiting assessment have now been excluded. The review authors' conclusions remain unchanged.
28 June 2004	New search has been performed	For the first update, new searches were carried out in June 2004. Three new studies were identified. Of these, two studies (Brown-Etris 2000 ; Burdge 2000) were included in the review and one study (Halter 2003) was excluded.

CONTRIBUTIONS OF AUTHORS

June Jones (JEJ) and Andrea Nelson (EAN) checked the search results for inclusion and exclusion. JEJ extracted data from the included trials and this was checked by EAN. Analysis, data entry, drafting and editing of the review were undertaken by both JEJ and EAN. Updating the review was undertaken by both JEJ and EAN.

Aws Al-Hity contributed to the fourth update by checking the search results, extracting data and undertaking a risk of bias assessment on all included studies and adding these data to the review update.

JEJ is the guarantor for the review.

Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review and review update prior to submission.

Liz McInnes, Editor: approved the recent updated review for submission.

Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the review and the updated review.

Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section for the update.

DECLARATIONS OF INTEREST

Andrea Nelson was co-applicant and trial co-ordinator for one of the trials included in this review ([Iglesias 2004](#)); this trial was commissioned after the first version of this review was completed. Andrea Nelson was trial co-ordinator and author of the main publication for one of the trials included in this review ([Nelson 2007a](#)).

June Jones and Aws Al-Hity - none.

SOURCES OF SUPPORT

Internal sources

- Department of Health Sciences, University of York, UK.
- School of Healthcare, University of Leeds, Leeds, UK.

External sources

- NHS Health Technology Assessment Programme, England, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Skin Transplantation; Leg Ulcer [*surgery]; Occlusive Dressings; Randomized Controlled Trials as Topic; Transplantation, Autologous

MeSH check words

Adult; Humans