ClinicalEvidence

Venous leg ulcers

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ABSTRACT

INTRODUCTION: Leg ulcers usually occur secondary to venous reflux or obstruction, but 20% of people with leg ulcers have arterial disease, with or without venous disorders. Between 1.5 and 3.0/1000 people have active leg ulcers. Prevalence increases with age to about 20/1000 in people aged over 80 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of standard treatments, adjuvant treatments, and organisational interventions for venous leg ulcers? What are the effects of interventions to prevent recurrence of venous leg ulcers? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 80 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: compression bandages and stockings, cultured allogenic (single or bilayer) skin replacement, debriding agents, dressings (cellulose, collagen, film, foam, hyaluronic acid-derived, semi-occlusive alginate), hydrocolloid (occlusive) dressings in the presence of compression, intermittent pneumatic compression, intravenous prostaglandin E1, larval therapy, laser treatment (low-level), leg ulcer clinics, multilayer elastic system, multilayer elastomeric (or non-elastomeric) high-compression regimens or bandages, oral treatments (aspirin, flavonoids, pentoxifylline, rutosides, stanozolol, sulodexide, thromboxane alpha$_2$ antagonists, zinc), peri-ulcer injection of granulocyte-macrophage colony-stimulating factor, short-stretch bandages, single-layer non-elastic system, skin grafting, superficial vein surgery, systemic mesoglycan, therapeutic ultrasound, self-help (advice to elevate leg, advice to keep leg active, advice to modify diet, advice to stop smoking, advice to reduce weight), and topical treatments (antimicrobial agents, autologous platelet lysate, calcitonin gene-related peptide plus vasoactive intestinal polypeptide, freeze-dried keratinocyte lysate, mesoglycan, negative-pressure recombinant keratinocyte growth factor, platelet-derived growth factor).

QUESTIONS

INTERVENTIONS

STANDARD TREATMENTS

Beneficial

Likely to be beneficial

Unknown effectiveness

Unlikely to be beneficial

Key points

- Leg ulcers are usually secondary to venous reflux or obstruction, but 20% of people with leg ulcers have arterial disease, with or without venous disorders.
- Compression bandages and stockings heal more ulcers compared with no compression, but we don't know which bandaging technique is most effective.

  Compression is used for people with ulcers caused by venous disease who have an adequate arterial supply to the foot, and who don't have diabetes or rheumatoid arthritis.

  The effectiveness of compression bandages depends on the skill of the person applying them.

  We don't know whether intermittent pneumatic compression is beneficial compared with compression bandages or stockings.
- Occlusive (hydrocolloid) dressings are no more effective than simple low-adherent dressings in people treated with compression, but we don't know whether semi-occlusive dressings are beneficial.
- Peri-ulcer injections of granulocyte-macrophage colony-stimulating factor may increase healing, but we don't know whether other locally applied agents, or therapeutic ultrasound are beneficial, as we found few studies.
- Oral pentoxifylline increases ulcer healing in people receiving compression, and oral flavonoids, sulodexide, and mesoglycan may also be effective.

  We don't know whether oral aspirin, rutosides, thromboxane alpha$_2$ antagonists, zinc, debriding agents, intravenous prostaglandin E1, superficial vein surgery, skin grafting, leg ulcer clinics, larval therapy, laser treatment, or advice to elevate legs, increase activity, lose weight, change diet, or give up smoking increase healing of ulcers in people treated with compression.

- Compression bandages and stockings reduce recurrence of ulcers compared with no compression, and should ideally be worn for life.

  Superficial vein surgery may also reduce recurrence, but we don't know whether systemic drug treatment is effective.

DEFINITION

Definitions of leg ulcers vary, but the following is widely used: loss of skin on the leg or foot that takes more than 6 weeks to heal. [1] Some definitions exclude ulcers confined to the foot, whereas others include ulcers on the whole of the lower limb. This review deals with ulcers of venous origin in people without concurrent diabetes mellitus, arterial insufficiency, or rheumatoid arthritis.

INCIDENCE/ PREVALENCE

Between 1.5 and 3.0/1000 people have active leg ulcers. Prevalence increases with age to about 20/1000 in people aged over 80 years. [2] Most leg ulcers are secondary to venous disease; other causes include arterial insufficiency, diabetes, and rheumatoid arthritis. [3] The annual cost to the NHS in the UK has been estimated at £300 million. [4] This does not include the loss of productivity due to illness.

AETIOLOGY/ RISK FACTORS

Leg ulceration is strongly associated with venous disease. However, about a fifth of people with leg ulceration have arterial disease, either alone or in combination with venous problems, which may require specialist referral. [2] Venous ulcers (also known as varicose or stasis ulcers) are caused by venous reflux or obstruction, both of which lead to poor venous return and venous hypertension.

PROGNOSIS

People with leg ulcers have a poorer quality of life than age-matched controls because of pain, odour, and reduced mobility. [5] In the UK, audits have found wide variation in the types of care (hospital inpatient care, hospital clinics, outpatient clinics, home visits), in the treatments used (topical agents, dressings, bandages, stockings), and in healing rates and recurrence rates (26–69% in 1 year). [6] [7]

AIMS OF INTERVENTION

To promote healing; to reduce recurrence; to improve quality of life, with minimal adverse effects.

OUTCOMES

Ulcer area; number of ulcers healed; time to complete ulcer healing; number of ulcer-free limbs; recurrence rates; number of new ulcer episodes; number of ulcer-free weeks or months; number of people who are ulcer free; frequency of dressing/bandage changes; quality of life; adverse effects of treatment.

METHODS

BMJ Clinical Evidence search and appraisal September 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2007, Embase 1980 to September 2007, and The Cochrane Library (all databases) 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — all databases, Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, including open studies (as most interventions cannot be effectively blinded) and containing more than 20 people. We included studies with fewer than 20 people if limbs were randomised. There was no maximum loss to follow-up or minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 32).

QUESTION What are the effects of standard treatments for venous leg ulcers?

OPTION COMPRESSION BANDAGES AND STOCKINGS VERSUS NO COMPRESSION

Healing rates

Compared with no compression Compression (bandages, stockings, Unna's boot) is more effective at increasing healing rates (high-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Compression bandages and stockings versus no compression:

We found one systematic review [8] and one additional RCT. [9] Overall, the studies found that compression (e.g. multilayer elastomeric high-compression bandages, short-stretch bandages,

double-layer bandages, compression stockings, or Unna's boot) healed more venous leg ulcers compared with no compression (dressing alone, non-compressive bandages, usual care). The review (search date 2000, 6 RCTs, 267 people) compared all forms of compression versus no compression. [8] The RCTs included in the review were heterogeneous, using different forms of compression in different settings and populations. Therefore, the results were not pooled. The first RCT (50 people) identified by the review found that compression healed a significantly higher proportion of ulcers compared with no compression (19/27 [70%] with compression *v* 6/23 [26%] with no compression; RR 2.70, 95% CI 1.30 to 5.60). The second RCT (34 people) identified by the review found no significant difference in healing between compression and no compression (9/17 [53%] with compression *v* 7/17 [41%] with no compression; RR 1.29, 95% CI 0.62 to 2.65). The third RCT (69 people) found that compression healed a significantly higher proportion of ulcers compared with no compression (21/30 [70%] with compression *v* 15/39 [38%] with no compression; RR 1.82, 95% CI 1.15 to 2.89). The fourth RCT (36 people) found significantly higher healing with compression compared with no compression (18/19 [95%] with compression *v* 7/17 [41%] with no compression; RR 2.30, 95% CI 1.29 to 4.10). The fifth RCT (42 people) found no significant difference in healing between compression and no compression (17/21 [81%] with compression *v* 15/21 [71%] with no compression; RR 1.13, 95% CI 0.81 to 1.59). The sixth RCT (36 people) found significantly higher healing with compression compared with no compression (12/18 [67%] with compression *v* 4/18 [22%] with no compression; RR 3.00, 95% CI 1.19 to 7.56). [8] The additional RCT (200 people) found that, over 12 weeks, four-layer elastomeric high-compression bandaging healed a significantly higher proportion of ulcers compared with no compression (54% with compression *v* 34% with no compression; P less than 0.001). [9] A sub-analysis of this RCT (reported in a 2nd publication) focused on the effect of four-layer elastomeric high-compression bandaging on quality of life. This RCT found that people treated with compression had a greater improvement in the physical dimensions of quality of life compared with people continuing with their usual care (no compression) as measured by condition-specific and generic questionnaires. [10]

Harms:

High levels of compression applied to limbs with insufficient arterial supply or inexpert application of bandages can lead to tissue damage and, at worst, amputation. [11] One observational study (194 people) found that four-layer compression bandaging for several months was associated with toe ulceration in 12 (6%) people. [12]

Compression bandages and stockings versus no compression:
No adverse effects were reported for this comparison in either the review [8] or RCT. [9] [10]

Comment:

People thought to be suitable for high-compression therapies (bandages, stockings, and compression leggings) are those with clinical signs of venous disease (ulcer in the gaiter region, from the upper margin of the malleolus to the bulge of the gastrocnemius; staining of the skin around an ulcer; or eczema), no concurrent diabetes mellitus or rheumatoid arthritis, and adequate arterial supply to the foot as determined by ankle/brachial pressure index. The precise ankle/brachial pressure index below which compression is contraindicated is often quoted as 0.8; however, many RCTs used the higher cut-off of 0.9. [8] Effectiveness is likely to be influenced by the ability of those applying the bandage to generate safe levels of compression, and by the fitting of appropriately sized compression stockings or leggings. Bandages may be applied by the person with the leg ulcer, their carer, nurse, or doctor. We found no comparisons of healing rates between specialist and non-specialist application of compression. Training improves bandaging technique among nurses. [13] Bandages containing elastomeric fibres can be applied weekly as they maintain their tension over time. Bandages made of wool, cotton, or both, such as short-stretch bandages, may need to be reapplied more frequently as they do not maintain their tension.

OPTION COMPRESSION STOCKINGS VERSUS SHORT-STRETCH BANDAGES

Healing rates
Compared with short-stretch bandages We don't know whether compression stockings are more effective at increasing healing rates (very low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Compression stockings versus short-stretch bandages:
We found two RCTs. [14] [15] The first RCT (134 people) reported a higher proportion of people healing with a stocking than with short-stretch bandages (29/66 [44%] with stocking *v* 19/68 [28%] with short-stretch bandages), but the results were only significant if a one-sided test was performed (P = 0.0129). [14] These results should, therefore, be approached with caution, as a one-sided test is less conservative than a two-sided test, the RCT reported the outcomes for only 121/134 (90%) people randomised, and people using short-stretch bandages had larger and older ulcers than people using compression stockings. The second RCT (188 people randomised; 178 analysed) found similar rates of complete healing of ulcers at 12 weeks with short-stretch bandagescompared

with a heel-less open-toed elastic compression stocking (51/88 [58%] with stocking *v* 51/90 [57%] with short stretch bandage; significance not assessed). [15] This result should be treated with caution, as only one short-stretch bandage was applied, which may have delivered less compression than is commonly used. In addition, the bandage was replaced once a week, despite other studies finding that more frequent replacement is required for this treatment to maintain compression.

Harms: High levels of compression applied to limbs with insufficient arterial supply, or inexpert application of bandages, can lead to tissue damage and, at worst, amputation. [11]

Compression stocking versus short-stretch bandages:
The RCT reported a suspected causal relationship between the study treatment and four adverse events: increased pain from the ulcer (U-Stocking); enlarged ulcer due to poor wrapping of the bandage; restricted flexibility of the ankle due to pain (bandages); and an intolerance reaction to the compression material with suspected delayed allergic reaction. [14] In the second RCT, 14% of people in the heelless-stocking group complained of pain, and were subsequently given a larger stocking. [15]

Comment: None.

OPTION MULTILAYER ELASTOMERIC HIGH-COMPRESSION REGIMENS VERSUS EACH OTHER

Healing rates
Multilayer elastomeric high-compression regimens compared with each other Four-layer compression bandages (including Charing Cross four-layer bandages) and other multilayer high-compression bandages are equally effective at increasing healing rates (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Multilayer elastomeric high-compression regimens versus each other:**
We found one systematic review (search date 2000, 3 RCTs, 285 people) [8] and three subsequent RCTs. [16] [17] [18] The RCTs identified by the review compared the original "Charing Cross" four-layer bandages versus other types of four-layer compression, and one compared four-layer versus three-layer compression bandages. The review found no significant difference in the proportion of people healed with four-layer elastomeric bandages compared with other multilayer high-compression bandages (99/142 [70%] with 4-layer "Charing Cross" bandages *v* 98/143 [68%] with other high-compression multilayer bandages; RR 1.02, 95% CI 0.87 to 1.18). [8] The first subsequent RCT (149 people) found no significant difference in healing rates at 20 weeks between an original Charing Cross four-layer bandage and two commercial "kits" making a four-layer bandage (87% with Charing Cross system *v* 84% and 83% with the two commercial kits; P = 0.56). [17] The second subsequent RCT (133 people) found that three-layer paste significantly increased healing rates compared with four-layer bandages, and reduced time to complete ulcer healing (healing rates: 80% with 3-layer paste *v* 65% with 4-layer bandage; P = 0.031; median time to complete ulcer healing: 12 weeks with 3-layer paste *v* 16 weeks with 4-layer bandage). [16] The third subsequent RCT (112 people) found no significant difference in healing rates at 24 weeks between a four-layer compression bandage and a two-layer system (HR for healing in 4-layer system 1.18, 95% CI 0.69 to 2.02). [18]

Harms: High levels of compression applied to limbs with insufficient arterial supply, or inexpert application of bandages, can lead to tissue damage and, at worst, amputation. [11] One observational study (194 people) found that four-layer compression bandaging for several months was associated with toe ulceration in 12 (6%) people. [12]

Multilayer elastomeric high-compression regimens versus each other:
The review [8] and the first and second subsequent RCTs [16] [17] gave no information on adverse effects for this comparison. The third subsequent RCT reported that the number of people with at least one device-related adverse incident was significantly greater in the two-layer bandaging system compared with four-layer bandaging (15/54 [28%] with 2-layer *v* 5/54 [9%] with 4-layer; P = 0.01). The adverse incidents included irritation, pain/discomfort, slippage, tissue breakdown, and excessive pressure. [18]

Comment: None.

OPTION MULTILAYER ELASTOMERIC HIGH-COMPRESSION BANDAGES VERSUS SINGLE-LAYER BANDAGES

Healing rates

Compared with single-layer bandage Multilayer compression bandages are more effective at increasing the proportion of people with healed ulcers (high-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Multilayer elastomeric high-compression bandages versus single-layer bandage:
We found one systematic review (search date 2000, 4 RCTs, 280 people), which compared multilayer high-compression bandages versus a single layer of bandage. [8] It found a significant increase in the proportion of people whose reference ulcer had healed with multilayer compression bandages compared with single-layer bandages (82/139 [59%] with multilayer compression bandages *v* 59/141 [42%] with single-layer bandages; RR 1.41, 95% CI 1.12 to 1.77; NNT for variable periods of treatment 6, 95% CI 4 to 18).

Harms:

High levels of compression applied to limbs with insufficient arterial supply, or inexpert application of bandages, can lead to tissue damage and, at worst, amputation. [11] One observational study (194 people) found that four-layer compression bandaging for several months was associated with toe ulceration in 12 (6%) people. [12]

Multilayer elastomeric high-compression bandages versus single-layer bandage:
The review gave no information on adverse effects for this comparison. [8]

Comment:

None.

OPTION MULTILAYER ELASTOMERIC HIGH-COMPRESSION BANDAGES VERSUS SHORT-STRETCH BANDAGES OR UNNA'S BOOT

Healing rates

Compared with short-stretch bandages or Unna's boot We don't know whether multilayer elastomeric high-compression stockings are more effective at increasing healing rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Multilayer elastomeric high-compression bandages versus short-stretch bandages or Unna's boot:
We found one systematic review (search date 2000, 4 small RCTs, 164 people) [8] and five subsequent RCTs (744 people). [19] [20] [21] [22] [23] The review found no significant difference in healing rate between multilayer elastomeric compression bandages, and short-stretch bandages or Unna's boot (37/83 [44%] with multilayer elastomeric bandages *v* 33/81 [41%] with short-stretch bandages or Unna's boot; RR 1.10, 95% CI 0.78 to 1.55). [8] The first subsequent RCT (116 people) found no significant difference in healing rates between four-layer compression bandages and short-stretch bandages (33/53 [62%] with compression bandages *v* 43/59 [73%] with short-stretch bandages; P = 0.49). [19] The second subsequent RCT (89 people) found that four-layer elastomeric multilayer compression bandages significantly increased healing at 12 weeks compared with short-stretch bandages (30% with elastomeric multilayer compression bandages *v* 22% with short-stretch bandages; HR 2.9, 95% CI 1.1 to 7.5). [20] The third subsequent RCT (156 people) found no significant difference in healing over 24 weeks between four-layer bandages and cohesive short-stretch bandages (51/74 [69%] with 4-layer bandages *v* 60/82 [73%] with cohesive short-stretch bandages; HR 1.08, 95% CI 0.63 to 1.85). [21] The fourth subsequent RCT (68 people) found no significant difference in healing at 24 weeks with a four-layer bandage compared with Unna's boot (HR for healing in 4-layer 1.62, 95% CI 0.87 to 3.02). [22] The fifth subsequent RCT (387 people) found a significantly higher healing rate with a four-layer bandage than with a short-stretch bandage (HR for healing with short-stretch bandage 0.72, 95% CI 0.57 to 0.91). [23]

Harms:

Multilayer elastomeric high-compression bandages versus short-stretch bandages or Unna's boot:
The review gave no information on adverse effects for this comparison. [8] The first subsequent RCT reported the withdrawal of two people (1 from each group) because of adverse incidents, but did not report the type of incident. [19] The second subsequent RCT reported one withdrawal in the short-stretch bandage group attributable to pain. [20] The third subsequent RCT reported 12 adverse events in the four-layer bandage group, and nine adverse events in the short-stretch bandage group which were definitely bandage related. The adverse events included tissue damage/new ulcer, eczema/reaction to bandage, pain, and maceration. [21] The fourth subsequent RCT gave no information on adverse effects. [22] The fifth subsequent RCT reported 255 adverse events involving 76 people in the four-layer bandage group that were possibly related to compression treatment, compared with 337 adverse events involving 91 people in the short-stretch bandage group. The adverse events included maceration, excoriation, skin damage, bandage failure, ulcer

deterioration (including infection), skin deterioration, dryness, non-surgical admission to hospital related to leg ulceration, occurrence of new ulcer, and a medical event relating to the leg. [23]

Comment: None.

OPTION MULTILAYER ELASTOMERIC VERSUS NON-ELASTOMERIC HIGH-COMPRESSION BANDAGES

Healing rates
Compared with non-elastomeric high-compression bandages We don't know whether multilayer elastomeric high-compression stockings are more effective at increasing healing rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Multilayer elastomeric versus non-elastomeric high-compression bandages:**
We found one systematic review (search date 2000, 3 RCTs, 273 people) [8] and one subsequent RCT. [24] The review found that elastomeric high-compression bandaging significantly increased healing rates compared with non-elastomeric bandaging (77/134 [57%] with elastomeric compression *v* 52/139 [37%] with non-elastomeric compression; RR 1.54, 95% CI 1.19 to 2.00, NNT for variable periods of treatment 5, 95% CI 3 to 12). The subsequent RCT (112 people) found no significant difference in healing rates between elastomeric and non-elastomeric layered compression (58% with elastomeric compression *v* 62% with non-elastomeric compression; P = 0.623). [24]

Harms: High levels of compression applied to limbs with insufficient arterial supply, or inexpert application of bandages, can lead to tissue damage and, at worst, amputation. [11] One observational study (194 people) found that four-layer compression bandaging for several months was associated with toe ulceration in 12 (6%) people. [12]

Multilayer elastomeric versus non-elastomeric high-compression bandages:
No adverse effects were reported in the review. [8] The subsequent RCT reported one withdrawal from the elastomeric group because of pretibial skin necrosis. [24]

Comment: None.

OPTION SINGLE-LAYER NON-ELASTIC SYSTEM VERSUS MULTILAYER ELASTIC SYSTEM

Healing rates
Compared with multilayer elastic system Non-elastic systems may be more effective at reducing areas of ulceration, but we don't know whether they are more effective at increasing the proportion of limbs with complete healing of ulcers at 12 weeks (very low-quality evidence). One RCT found that a non-elastic system increased ulcer healing rate compared with a four-layer elastic bandage. However, there was no difference between the non-elastic and the multilayered elastic systems in the proportion of limbs with complete healing of ulcers at 12 weeks.

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Single-layer non-elastic system versus multilayer elastic system:**
We found one RCT (12 people, 24 limbs). [25] The RCT compared a non-elastic compression device versus a four-layer elastic bandage. The RCT found that a similar proportion of limbs had complete healing of ulcers at 12 weeks with both the non-elastic and the multilayered elastic systems in the (4/12 [33%] with non-elastic system *v* 4/12 [33%] with elastic system; significance not assessed). The RCT found a significantly higher rate of ulcer-area reduction with the non-elastic system compared with the multilayer elastic system (HR 0.56, 95% CI 0.33 to 0.96).

Harms: **Single-layer non-elastic system versus multilayer elastic system:**
The RCT gave no information on adverse effects for this comparison. [25]

Comment: None.

OPTION SINGLE-LAYER NON-ELASTIC SYSTEM VERSUS MULTILAYER NON-ELASTIC SYSTEM

Healing rates
Compared with multilayer non-elastic system We don't know whether non-elastic legging systems are more effective than Unna's boot at increasing healing rates (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Single-layer non-elastic system versus multilayer non-elastic system:**
We found one RCT (38 people), which compared a single-layer non-elastic system versus Unna's boot (multilayer non-elastic system). [26] The RCT found similar healing rates between the non-elastic legging system and Unna's boot (17/19 [89%] with non-elastic legging system *v* 11/19 [58%] with Unna's boot; significance not assessed). [26]

Harms: **Single-layer non-elastic system versus multilayer non-elastic system:**
The RCT reported that five people withdrew from the study in the Unna's Boot (multilayer) arm of the study, because of allergy, weeping dermatitis, and increasing ulcer size, and two people withdrew from the single-layer arm of the study because of the ulcer not healing and the person being referred for surgery. [26]

Comment: None.

OPTION PERI-ULCER INJECTION OF GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

Healing rates
Compared with placebo Recombinant human granulocyte-macrophage colony-stimulating factors are more effective at increasing the proportion of people with completely healed ulcers at 13 weeks (high-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Peri-ulcer injection of granulocyte-macrophage colony-stimulating factor:**
One RCT (60 people) found that a 4-week course of injections of recombinant human granulocyte-macrophage colony-stimulating factor (rHuGM-CSF) 200 or 400 micrograms around the ulcer significantly increased the proportion of people whose ulcers had completely healed after 13 weeks' treatment compared with placebo (23/39 [59%] with rHuGM-CSF *v* 4/21 [19%] with placebo; combined RR for rHuGM-CSF 200 and 400 micrograms 3.21, 95% CI 1.23 to 8.34; NNT for 13 weeks' treatment 2, 95% CI 1 to 7). [27]

Harms: Granulocyte-macrophage colony-stimulating factor contains polyethylene glycol, which may be linked to allergic reactions.

Peri-ulcer injection of granulocyte-macrophage colony-stimulating factor:
Adverse effects were reported in 2/21 (9%) people receiving placebo, 8/21 (38%) people receiving rHuGM-CSF 200 micrograms, and 5/18 (26%) people receiving rHuGM-CSF 400 micrograms. The RCT reported that the most common treatment related adverse events were lumbar pain and malaise (5/21 [24%] people receiving rHuGM-CSF 200 micrograms *v* 3/19 [17%] people receiving rHuGM-CSF 400 micrograms). None of the adverse effects were considered life threatening; all were graded as mild to moderate. [27]

Comment: None.

OPTION COMPRESSION BANDAGES OR STOCKINGS VERSUS INTERMITTENT PNEUMATIC COMPRESSION

We found no clinically important results comparing compression stockings with intermittent pneumatic compression in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Compression bandages or stockings versus intermittent pneumatic compression:**
We found two systematic reviews (search date 2001), which identified the same RCT (16 people). [28] [29] The RCT identified by the reviews found no significant difference in the proportion of people with healed ulcers over 2–3 months between compression bandages and intermittent pneumatic compression (0/6 [0%] with compression bandages *v* 0/10 [0%] with intermittent pneumatic compression; P value not reported). However, the number of people in this trial is below *BMJ Clinical Evidence* inclusion criteria, and is too small to draw a reliable conclusion.

Harms: **Compression bandages or stockings versus intermittent pneumatic compression:**
The RCT identified by the reviews gave no information on adverse effects for this comparison. [28] [29]

Comment: None.

OPTION DEBRIDING AGENTS

We found no clinically important results about the effects of debriding agents in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Debriding agents versus usual care or versus each other:
We found one systematic review (search date 1997, 23 RCTs), which compared debriding agents versus traditional dressing in people with chronic non-healing wounds. [30] The review did not perform a meta-analysis specifically in people with venous leg ulcers. [30] Six RCTs (277 people) identified by the review compared dextranomer polysaccharide bead dressings with traditional dressings, but only two RCTs reported complete ulcer healing. The incomplete reporting of healing rates, and small sample sizes mean we cannot draw any firm conclusions from these trials. Seven RCTs (451 people) identified by the review compared cadexomer iodine versus traditional dressings, but only three RCTs reported complete ulcer healing. The incomplete reporting of healing rates means we cannot draw any firm conclusions from these trials. Two RCTs identified by the review compared enzymatic preparations versus traditional dressings (52 ulcers) and found no evidence of a difference in ulcer healing rates. [30]

Harms:

Preparations containing iodine may affect thyroid function if used over large surface areas for extended periods. [31] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [32]

Debriding agents versus usual topical care or versus each other:
The review reported adverse events such as pain, allergy, bacterial infection, and wound-size increase. [30]

Comment:

None.

OPTION FOAM, FILM, HYALURONIC ACID-DERIVED DRESSINGS, COLLAGEN, CELLULOSE, OR ALGINATE (SEMI-OCCLUSIVE) DRESSINGS

Healing rates
Semi-occlusive dressings compared with simple low-adherent dressings Semi-occlusive dressings (foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate) and simple low-adherent dressings (such as paraffin-tulle, or knitted viscose dressings) are equally effective at increasing wound healing rates in the presence of compression (high-quality evidence).

Alginate dressings compared with zinc oxide dressings We don't know whether alginate dressings are more effective at increasing ulcer healing (low-quality evidence).

Different occlusive or semi-occlusive dressing (excluding hydrocollids) compared with each other Occlusive and semi-occlusive dressings (excluding hydrocolloids) are equally effective at increasing healing rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Foam, film, hyaluronic acid-derived dressings, collagen, cellulose or alginate (semi-occlusive) dressings versus simple low-adherent dressings, in the presence of compression:
We found three systematic reviews (search date 1997, [33] 6 RCTs, search date 2003, [34] 7 RCTs, and search date April 2006, [35] 4 RCTs). The first review identified six RCTs comparing semi-occlusive dressings (foam, film, alginates) versus simple (traditional) low-adherent dressings (such as paraffin-tulle or knitted viscose dressings) in the presence of compression. [33] The second review identified these six RCTs plus one other RCT, which compared a collagen dressing versus a non-adherent dressing. The first RCT (71 people) identified by the reviews compared film versus saline-soaked gauze. It found no significant difference between dressings in wound healing (11/36 [31%] with film *v* 8/35 [23%] with gauze; OR 1.48, 95% CI 0.5 to 4.3). [33] The second RCT (11 people, 12 ulcers) compared film versus Unna's boot. It found that film significantly reduced the wound area compared with Unna's boot (mean reduction in wound area: 39% with film *v* 7% with Unna's boot; mean difference 32%, 95% CI 10% to 54%). [33] The third RCT (132 people) identified by the review compared foam versus a knitted viscose dressing. It found no significant difference between dressings in wound healing (31/66 [47%] with foam *v* 23/66 [35%] with knitted viscose; OR 1.67, 95% CI 0.80 to 3.30). [33] The fourth RCT (48 people) compared foam compress versus a sterile gauze compress. It found that foam significantly reduced the wound area compared with the sterile gauze (mean change in wound area: –66% with foam compress *v* +78% with sterile gauze compress; mean difference between treatments: 144%, 95% CI 49% to 239%). [33] The fifth RCT (60 people)

compared an alginate dressing versus a knitted viscose dressing. It found no significant difference between dressings in wound healing (26/30 [87%] with alginate *v* 24/30 [80%] with knitted viscose; OR 1.62, 95% CI 0.40 to 6.50). [33] The sixth RCT (113 people with 133 ulcerated limbs) compared alginate dressings versus zinc oxide paste applied as a bandage or stocking. It found a significant increase in the proportion of ulcers healed with the zinc oxide-impregnated bandage compared with alginate (25/43 [58%] with zinc oxide bandage *v* 16/46 [35%] with alginate; OR 2.6, 95% CI 1.1 to 6.1). However, the RCT found no significant difference in ulcers healed between the zinc oxide-impregnated stocking and alginate (19/44 [43%] with zinc oxide stocking *v* 16/46 [35%] with alginate; OR 1.42, 95% CI 0.61 to 3.34). The RCT (75 people) identified by the second review compared a collagen dressing versus a non-adherent dressing. It found no significant difference between the collagen dressing and the non-adherent dressing in the proportion of ulcers healed (RR 1.33, 95% CI 0.71 to 2.49). [34] The third review identified two RCTs. [35] The first RCT included in the review (17 people) compared hyaluronic dressings versus paraffin gauze. It found no significant difference in rates of ulcer healing between hyaluronic dressings and paraffin gauze (2/12 [17%] with hyaluronic dressing *v* 1/12 [8%] with paraffin gauze, no significance test performed). [36] The second RCT included in the review (73 people) compared a collagen-plus-cellulose dressing versus a modern low-adherent dressing. It found no significant difference between treatments in healing rates at 12 weeks (18/37 [49%] with collagen-plus-cellulose dressing *v* 12/36 [33%] with modern low-adherent dressing; risk difference +0.16, 95% CI –0.07 to +0.38). [37] However, the RCTs identified by the reviews may have been too small to detect anything but a large difference in effectiveness.

Comparisons between different occlusive or semi-occlusive dressings:
See benefits of hydrocolloid (occlusive) dressings in the presence of compression, p 14 .

Harms:

It is unlikely that low-adherent primary wound dressings cause harm, although dressings containing iodine may affect thyroid function if used over large surface areas for extended periods. [31] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [32]

Foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate (semi-occlusive) dressings versus simple low-adherent dressings, in the presence of compression:
The reviews reported adverse effects such as pain, infection, allergy, leakage, eczema, and odour. [33] [34] [35] Frequent changes of adhesive dressings may also damage the skin. [38]

Comparisons between different occlusive or semi-occlusive dressings:
See harms of hydrocolloid (occlusive) dressings in the presence of compression, p 14 .

Comment:

Simple primary dressings maintain a moist environment beneath compression bandages by preventing loss of moisture from the wound. [39]

OPTION INTERMITTENT PNEUMATIC COMPRESSION

Healing rates
Intermittent pneumatic compression plus compression stockings compared with compression stockings or bandages alone We don't know whether pneumatic compression plus compression stockings are more effective at increasing healing rates (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Intermittent pneumatic compression versus compression bandages:
See benefits of compression bandages versus intermittent compression, p 8 .

Intermittent pneumatic compression plus compression stockings versus compression stockings or bandages alone:
We found two systematic reviews (search date 2001, 3 RCTs, 115 people; [28] search date 2001, 2 RCTS, 99 people). [29] Two RCTs were included in both systematic reviews. The reviews did not perform a meta-analysis because of clinical and methodological differences among the trials. The first RCT identified by the reviews (45 people) found that intermittent pneumatic compression plus graduated compression stockings significantly increased the proportion of people with healed ulcers at 3 months compared with graduated compression stockings alone (10/21 [48%] with intermittent pneumatic compression plus graduated compression stockings *v* 1/24 [4%] with graduated compression stockings alone; RR 11.4, 95% CI 1.6 to 82.0). The second RCT (53 people) found no significant difference in the proportion of people healed at 6 months between intermittent pneumatic compression plus elastic stockings and Unna's boot (20/28 [71%] with intermittent pneumatic compression plus elastic stockings *v* 15/20 [75%] with Unna's boot; RR 0.95, 95% CI 0.67 to 1.34). The third RCT included in the first systematic review (22 people) found no significant difference in

healing at 6 months between intermittent pneumatic compression plus Unna's boot and Unna's boot alone (12/12 [100%] with intermittent pneumatic compression plus Unna's boot *v* 8/10 [80%] with Unna's boot alone; RR 1.25, 95% CI 0.92 to 1.70). [28]

Harms:

Intermittent pneumatic compression versus compression bandages:
See harms of compression bandages versus intermittent compression, p 8 .

Intermittent pneumatic compression plus compression stockings versus compression stockings or bandages alone:
One RCT identified by the review reported an adverse reaction to Unna's boot. [28] [29] Peroneal neuropathy and compartment syndrome have been associated with the use of intermittent pneumatic compression to prevent deep vein thrombosis during surgery. [40]

Comment:

Availability may vary widely in different healthcare settings. Treatment can be delivered in the home, in outpatient clinics, or in the hospital ward. RCTs have evaluated the use of intermittent pneumatic pressure for 1 hour twice weekly and 3–4 hours daily. Treatment requires resting for 1–4 hours daily, which may reduce quality of life.

OPTION ANTIMICROBIAL AGENTS (TOPICAL)

Healing rates
Compared with placebo or usual care Topical antimicrobial agents may be no more effective at increasing the proportion of people with completely healed ulcers (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Topical antimicrobial agents versus placebo or usual care:
We found two systematic reviews (search date 1997, 14 RCTs; [41] and search date 2006, 9 RCTS), [42] and two additional RCTs, [43] [44] which compared antimicrobial agents versus either placebo or usual care. The RCTs identified by the first review were small (25–153 people), and of poor quality, making it impossible to draw firm conclusions. [41] The second review (9 RCTs, 6 included in the first review) compared dressings impregnated with silver versus dressings not containing silver for venous ulcers. [42] It found no significant difference between groups in the proportion of ulcers completely healed (2 RCTs, 147 people, RR 1.66, 95% CI 0.68 to 4.05; P = 0.27). [42] The first subsequent RCT (251 people) compared topical ethacridin lactate (0.1% solution) applied twice daily versus placebo. [43] The authors defined responders as people with a greater than 20% reduction in ulcer area at 28 days. The RCT found a significantly higher proportion of responders with ethacridin lactate compared with placebo (104/129 [81%] with ethacridin lactate *v* 69/122 [57%] with placebo; P less than 0.0001). Ulcer healing was not reported. [43] The second subsequent RCT (119 people) compared daily application of 10% pale sulfonated shale oil (has antiseptic and anti-inflammatory properties) versus vehicle (non-ionic gel). [44] The RCT found no significant difference in the proportion of people with completely healed ulcers between pale sulfonated shale oil and vehicle (21/62 [34%] with pale sulfonated shale oil *v* 13/57 [23%] with vehicle; P = 0.177). However, the RCT found that pale sulfonated shale oil significantly reduced ulcer area compared with vehicle (72% with pale sulfonated shale oil *v* 19% with vehicle; P less than 0.001).

Harms:

Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [32]

Topical antimicrobial agents versus placebo or usual care:
The review reported adverse events such as erythema, pruritus, and severe irritation. [41] The second systematic review gave no information on adverse effects. [42] The first additional RCT gave no information on adverse effects of ethacridin lactate. [43] The second RCT found no difference in adverse effects between 10% pale sulfonated shale oil and vehicle (12% with pale sulfonated shale oil *v* 11% with vehicle). Two people in each group had eczema and pruritus. [44]

Comment:

Daily or twice-daily application of topical antiseptics requires considerable investment in nursing time, or involvement of patients/carer, because of the need to remove and reapply compression bandages.

OPTION CALCITONIN GENE-RELATED PEPTIDE (TOPICAL)

Healing rates
Compared with placebo Calcitonin gene-related peptide plus vasoactive intestinal polypeptide is no more effective at increasing the proportion of people with healed ulcers at 12 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Topical calcitonin gene-related peptide plus vasoactive intestinal polypeptide versus placebo:
We found one RCT (66 people) which compared calcitonin (salcatonin) gene-related peptide plus vasoactive intestinal polypeptide given by iontophoresis versus placebo iontophoresis. [45] It found no significant difference between treatments in the proportion of people with healed ulcers after 12 weeks (11/33 [33%] with calcitonin (salcatonin) gene-related peptide plus vasoactive intestinal polypeptide *v* 6/33 [18%] with placebo; RR 1.83, 95% CI 0.77 to 4.38). [45] However, the RCT may have been too small to detect a clinically important difference.

Harms:

Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [32]

Topical calcitonin gene-related peptide plus vasoactive intestinal polypeptide versus placebo:
The RCT gave no information on adverse effects for this comparison. [45]

Comment:

None.

OPTION MESOGLYCAN (TOPICAL)

Healing rates
Compared with plant-based extract We don't know whether topical mesoglycan (a profibrinolytic agent) is more effective at increasing ulcer healing at 2 months (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Topical mesoglycan versus a plant-based extract:
We found one RCT (40 people) which found similar cure rates at 2 months between topically applied mesoglycan, a profibrinolytic agent, and a plant-based extract (19/20 [95%] with topical mesoglycan *v* 16/20 [85%] with plant extract; CI not reported, significance assessment not performed). [46]

Harms:

Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [32]

Topical mesoglycan versus a plant based extract:
The RCT gave no information on adverse effects. [46]

Comment:

None.

OPTION TOPICAL NEGATIVE PRESSURE

Time to healing
Compared with usual care Topical negative pressure (vacuum-assisted closure [VAC]) may be more effective than conventional wound care techniques at reducing time to complete healing in people with venous or arterio-venous ulcers of at least 6 months' duration (very low-quality evidence).

Recurrence rates
Compared with usual care Topical negative pressure (VAC) may be no more effective at reducing median time to recurrence of ulcers in people with venous or arteriovenous ulcers of at least 6 months' duration (very low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Topical negative pressure versus usual care:
We found two systematic reviews (search date 2002 [47] and search date 2004 [48]) and one subsquent RCT. [49] Both reviews identified one RCT (24 people), which compared topical negative pressure versus simple dressings. [47] [48] The single RCT identified by the reviews was carried out in people with any type of chronic wound, but included some people with venous leg ulcers. However, it may have been too small to detect a clinically important difference in outcomes between topical negative pressure and simple dressings. The subsequent RCT (60 people with venous or arterio-venous ulcers of at least 6 months' duration) compared topical negative pressure (vacuum-assisted closure [VAC]) versus control (conventional wound care techniques). [49] The RCT found that VAC significantly reduced time to complete healing compared with control (29 days with VAC *v* 45 days with control, P = 0.001). However, there was no significant difference between groups for median length of time to recurrence (4 months with VAC *v* 2 months with control, P = 0.47). [49]

Harms:

Topical negative pressure versus usual care:
Two RCTs reported by the first review reported adverse events for topical negative pressure. [47] The first RCT reported that 3/18 (17%) wounds with topical negative pressure had osteomyelitis, calcaneal features, or both. Two people suffered calcaneal features while ambulating on the topical negative pressure dressing (against medical advice). Both people eventually required amputation. The second RCT reported pain in some people with topical negative pressure with initial collapse, foam dressing removal, or both. [47] The second review gave no information on adverse effects. [48] The subsequent RCT reported no significant differences for adverse effects for erysipelas, pain, wound infection, postoperative bleeding at donor site, and non-healing ulcers (erysipelas: 1 with VAC *v* 0 with control; pain: 3 with VAC *v* 1 with control; wound infection: 0 with VAC *v* 1 with control; postoperative bleeding at donor site: 0 with VAC *v* 2 with control; non-healing ulcers: 1 with VAC *v* 1 with control; all reported as non significant, no P values reported). However, the RCT reported that VAC significantly increased the risk of cutaneous damage secondary to treatment compared with control (7 with VAC *v* 2 with control, P less than 0.05). [49]

Comment:

One review reported that one of the 10 RCTs of topical negative therapy underway includes venous leg ulcers. [48] In the subsequent RCT, all the included people had chronic ulcers (more than 6 months' duration) and were hospitalised throughout. This limits the applicability of this evidence, as most ulcers are treated outside hospital, which reduces cost. [49]

OPTION RECOMBINANT KERATINOCYTE GROWTH FACTOR 2 (TOPICAL)

Healing rates
Compared with placebo Topical recombinant human keratinocyte growth factor 2 plus compression is no more effective at increasing complete ulcer healing rates at 12 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Topical recombinant human keratinocyte growth factor 2 plus compression versus placebo plus compression:
We found one RCT (94 people) which compared topically applied recombinant human keratinocyte growth factor 2 (repifermin 20 or 60 micrograms/cm^2) plus compression versus placebo plus compression). [50] It found no significant difference in the rate of complete ulcer healing after 12 weeks between human keratinocyte growth factor 2 and placebo (32% with repifermin 20 micrograms/cm^2 *v* 38% with repifermin 60 micrograms/cm^2 *v* 29% with placebo; for all doses of human keratinocyte growth factor 2 *v* placebo, P = 0.57).

Harms:

Topical recombinant human keratinocyte growth factor 2 plus compression versus placebo plus compression:
The RCT found no significant difference in adverse effects (leg pain, pruritus, skin ulcer, rash abrasion, and reopening of venous ulcer) between repifermin and placebo. [50] However, this study may have lacked power to detect a clinically important difference between groups.

Comment:

Clinical guide:
Growth factors may be expensive: for them to be cost effective in clinical practice, their use would need to reduce the time to healing, and therefore nursing costs.

OPTION PLATELET-DERIVED GROWTH FACTOR (TOPICALLY APPLIED)

Healing rates
Compared with placebo We don't know whether platelet-derived growth factors are more effective at increasing ulcer healing rates (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Platelet-derived growth factor versus placebo:
We found two RCTs (135 people) in one publication, which found similar healing rates between platelet-derived growth factor and placebo gel (first RCT: 12/35 [36%] healed with growth factor *v* 12/36 [34%] healed with placebo; second RCT: 18/32 [56%] healed with growth factor *v* 14/32 [44%] healed with placebo; CI not reported, significance assessment not performed). [51]

Harms:

Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [32]

Platelet-derived growth factor versus placebo:
In the first RCT, 11/35 (31%) people receiving becaplermin gel and 14/36 (39%) people receiving placebo had at least one treatment related, wound-related adverse event. In the second RCT,

17/32 (53%) people receiving becaplermin gel and 11/32 (34%) people receiving placebo had at least one such event. [51]

Drug safety alert:
A drug safety alert has been issued on the increased risk of cancer mortality associated with use of three or more tubes of becaplermin (http://www.fda.gov/bbs/topics/NEWS/2008/NEW01845.html).

Comment: None.

OPTION HYDROCOLLOID (OCCLUSIVE) DRESSINGS IN THE PRESENCE OF COMPRESSION

Healing rates
Compared with simple dressings Hydrocolloid dressings and simple low-adherent dressings in the presence of compression are equally effective at increasing ulcer healing rates (high-quality evidence).

Hydrocolloids compared with other occlusive or semi-occlusive dressings Hydrocolloids and other occlusive or semi-occlusive dressings are equally effective at increasing proportion of ulcers healed at 12–16 weeks (high-quality evidence).

Different occlusive or semi-occlusive dressing (excluding hydrocolloids) compared with each other Occlusive and semi-occlusive dressings (excluding hydrocolloids) are equally effective at increasing healing rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

We found three systematic reviews (search date 1997, 16 RCTs; [33] search date 2003, 15 RCTs; [34] and search date 2006, 27 RCTs [35]) comparing hydrocolloid dressings in the presence of compression.

Hydrocolloid (occlusive) dressings versus simple dressings in the presence of compression:
The first systematic review identified nine RCTs, the second review identified eight RCTs, and the third review identified nine RCTs comparing hydrocolloid dressings versus simple dressings in the presence of compression. Five RCTs were included in both the first and second reviews. A random-effects meta-analysis of seven of the nine studies identified by the first review (714 people) found no significant difference in rates of ulcer healing between hydrocolloid dressings and simple low-adherent dressings in the presence of compression (158/358 [44%] with hydrocolloid dressing *v* 140/356 [39%] with simple dressing; OR 1.45, 95% CI 0.83 to 2.54). [33] A meta-analysis of the eight RCTs (782 people) identified by the second review found no significant difference in ulcer healing between hydrocolloid dressings and simple low-adherent dressings in the presence of compression (172/397 [43.3%] with hydrocolloid dressing *v* 168/385 [43.6%] with simple dressing; RR 0.99, 0.85 to 1.15). [34] The third review found no significant difference in ulcer healing for hydrocolloid dressings compared with simple low-adherent dressings in the presence of compression (8 RCTs: 190/397 [48%] with hydrocolloid dressing *v* 170/395 [45%] with simple dressing; RR 1.09, 0.89 to 1.34). [35]

Hydrocolloids versus other occlusive or semi-occlusive dressings:
We found three systematic reviews (search date 1997, 6 RCTs; [33] search date 2003, 6 RCTs; [34] and search date 2006, 9 RCTs [35]), which compared hydrocolloids with other modern dressings and reported complete ulcer healing. The third review supersedes the first two reviews, so we only report the most recent data here. [35] The review found no significant difference between the two treatments in the proportion of ulcers healed between 12 and 16 weeks (4 RCTs; 311 people, 85/171 [50%] with hydrocolloid *v* 69/140 [49%] with foam; RR 0.98, 95% CI 0.79 to 1.22, P = 0.9). [35]

Different occlusive or semi-occlusive dressings (excluding hydrocolloids) versus each other:
We found two systematic reviews (search date 1997, 1 small RCT; [33] and search date 2006, 8 RCTs [35]), and three subsequent RCTs [52] [53] [54] comparing different occlusive or semi-occlusive dressings. The reviews found no significant difference in healing rates between dressings, or insufficient data were reported to calculate their significance. [33] [35] The first subsequent RCT (107 people) compared a foam dressing with a foam composite. It found no difference between treatments in healing rates at 12 weeks (healed: 39% with foam dressing *v* 36% with foam composite; CI not reported, significance assessment not performed). [52] The second subsequent RCT (159 people with chronic venous leg ulcers) compared a foam dressing versus a silicione foam dressing (both under compression) over 24 weeks. [53] The RCT found no significant difference between groups for complete ulcer healing (50/81 [62%] with foam dressing *v* 50/75 [67%] with silicone foam dressing; HR for healing 1.48, 0.87 to 2.54, P = 0.15). [53] The third subsequent crossover RCT (122 people with chronic venous leg ulcers of more than 8 weeks' duration) compared a foam

dressing containing ibuprofen versus a similar foam dressing with no ibuprofen. [54] People were randomised to the ibuprofen group (62) and non-ibuprofen group (60). The groups were assessed in one treatment on days 1–5, and then subsequently crossed over to the other treatment and were assessed at days 43–47. The people included in the RCT were allowed to take concomitant pain medication during the trial as long as it was constant at days 1–5 and 43–47 when pain was assessed. The RCT assessed chronic (persistent) and dressing change-related (temporary) pain on days 1–5 and on days 43–47. Chronic pain was rated on a pain-relief 5-point verbal rating scale (VRS) (0 = no relief to 4 = complete relief). Pain intensity was measured on an 11-point numeric box scale (NBS 0 to 10, 0 = no pain, 10 = worst pain imaginable). The RCT found that ibuprofen dressings significantly reduced chronic pain on days 1–5 compared with non-ibuprofen dressings (46/62 [74%] with ibuprofen *v* 35/60 [58%] with non-ibuprofen dressings, P = 0.0003). [54] The RCT found no significant difference between groups for ulcer healing at 24 weeks (11.2 cm^2 to 7.9 cm^2 with ibuprofen *v* 7.2 cm^2 to 3.8 cm^2 with non-ibuprofen, reported as non significant, RR, CI, and P value not reported). [54]

Harms: It is unlikely that low-adherent primary wound dressings cause harm, although dressings containing iodine may affect thyroid function if used over large surface areas for extended periods. [31] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [32]

Hydrocolloid (occlusive) dressings versus simple dressings, in the presence of compression:
The reviews reported adverse effects such as wound infection, cellulitis, increase in ulcer size, and dermatitis of peri-ulcer skin. [33] [34] [35]

Hydrocolloids versus other occlusive or semi-occlusive dressings:
The reviews reported adverse events such as pain, wound infection, allergy, dressing leakage, peri-wound eczema, injury/intolerance of peri-ulcer skin, and extensive exudates and odour leakage. [33] [34] [35]

Different occlusive or semi-occlusive dressings (excluding hydrocolloids) versus each other:
The two reviews gave no information on adverse effects. [33] [35] The first subsequent RCT reported that the most common adverse event in the foam-compress group was new wound development in different anatomical locations (6 people). In the foam-dressing group, the most common adverse event was maceration, which also affected six people. [52] The second subsequent RCT reported no difference between groups for adverse effects related to the dressings, with 11 events in each group definitely related to the dressing. [53] The third subsequent RCT reported 31 adverse effects in 19 people (12 people with ibuprofen [21 adverse effects] *v* 7 people with no ibuprofen [10 adverse effects], P value not reported). [54] Frequent changes of adhesive dressings may damage the skin on removal. [38]

Comment: Simple primary dressings maintain a moist environment beneath compression bandages as the layers of dressings and bandages prevent loss of moisture from the wound. [39] A foam dressing containing ibuprofen reduced pain intensity from 6.8 to 4.1, while a similar foam reduced pain from 6.6 to 4.6 (pain intensity measured on a 10-point scale), but required dressings to be changed every 48 hours. [54]

OPTION AUTOLOGOUS PLATELET LYSATE (TOPICALLY APPLIED)

Healing rates
Compared with placebo Topically applied autologous platelet lysate is no more effective at increasing the proportion of people with healed ulcers at 9 months (moderate-quality evidence).

Benefits: **Topically applied autologous platelet lysate versus placebo:**
We found one RCT (86 people), which found no significant difference in the proportion of people healed at 9 months between topical autologous platelet lysate and placebo (33/42 [78%] with topical autologous platelet lysate *v* 34/44 [77%] with placebo; RR 1.05, 95% CI 0.80 to 1.30). [55]

Harms: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [32]

Topically applied autologous platelet lysate versus placebo:
The RCT reported that there was no evidence of any adverse effects specifically related to the application of the lysate solution. [55]

Comment: None.

OPTION FREEZE-DRIED KERATINOCYTE LYSATE (TOPICALLY APPLIED)

Healing rates
Compared with placebo/usual care Topically applied freeze-dried keratinocyte lysate is no more effective at increasing healing rates at 24 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Topically applied freeze-dried keratinocyte lysate versus vehicle or usual care:**
We found one RCT (200 people) which compared three interventions: keratinocyte lysate plus usual care, placebo (vehicle) plus usual care, and usual care alone. [56] It found no significant difference between treatments in healing (37% with lysate *v* 27% with vehicle or usual care; P = 0.14).

Harms: **Topically applied freeze-dried keratinocyte lysate versus vehicle or usual care:**
In total, 47 (24%) people had at least one general adverse effect during the treatment phase (25% with usual care plus lysate *v* 25% with usual care plus vehicle *v* 22% with usual care alone) and 27 (15%) people during the follow-up period (16% with usual care plus lysate*v* 17% with usual care plus vehicle *v* 12% with usual care alone). [56] No significant differences were noted between the three treatment arms.

Comment: None.

QUESTION What are the effects of adjuvant treatments for venous leg ulcers?

OPTION PENTOXIFYLLINE (ORAL)

Healing rates
Compared with placebo Oral pentoxifylline plus compression is more effective at increasing the proportion of people with healed ulcers at 8–24 weeks (high-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral pentoxifylline versus placebo:**
We found one systematic review (search date 2007, 12 RCTs, 864 people). [57] The systematic review compared pentoxifylline (oxpentifylline) 1200 or 2400 mg daily versus placebo or versus other treatments, with or without compression. [57] It found that, in the presence of compression, pentoxifylline significantly increased the proportion of people with healed ulcers over 8–24 weeks compared with placebo (7 RCTs: 221/348 [64%] with pentoxifylline *v* 126/311 [40%] with placebo; RR 1.51; 95% CI 1.3 to 1.76). One RCT identified by the review found no significant difference in healing rates at 3 months in people receiving compression between pentoxifylline and defibrotide (11/12 [92%] with pentoxifylline *v* 9/11 [82%] with defibrotide; RR 1.12, 95% CI 0.81 to 1.55). [57]

Harms: **Oral pentoxifylline versus placebo:**
The review of oral pentoxifylline versus placebo found that people taking pentoxifylline had more adverse effects, although the difference was not significant (55/297 [18%] with pentoxifylline *v* 33/252 [13%] with placebo; RR 1.27, 95% CI 0.89 to 1.83). [57] Nearly half of the adverse effects were gastrointestinal (dyspepsia, vomiting, or diarrhoea).

Comment: None.

OPTION CULTURED ALLOGENIC BILAYER SKIN REPLACEMENT

Healing rates
Compared with non-adherent dressing Cultured allogenic bilayer skin replacement (containing both epidermal and dermal components) is more effective at increasing the proportion of healed ulcers at 6 months (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Cultured allogenic bilayer skin replacement versus non-adherent dressing:**
We found one systematic review (2 RCTs, 345 people, search date 2006). [58] It found that a cultured allogenic bilayer skin replacement, containing both epidermal and dermal components, significantly increased the proportion of ulcers healed completely in 6 months compared with a simple non-adherent dressing (pooling 2 trials using a fixed-effect model: RR 1.51, 95% CI 1.22 to 1.88). [58]

Harms: **Cultured allogenic bilayer skin replacement versus non-adherent dressing:**
Taking a skin graft leaves a wound that itself requires management, and may cause pain. We found no evidence of harm from tissue-engineered skin. [58]

Comment: None.

OPTION FLAVONOIDS (ORAL)

Healing rates
Flavonoids plus compression compared with compression alone We don't know whether flavanoids plus compession is more effective at increasing ulcer healing rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Flavonoids plus compression versus compression alone:**
We found one systematic review (search date 2003, 5 RCTs, 723 people). [59] Two RCTs included in the review compared micronised purified flavonoid fraction 1 g daily plus compression versus compression with or without placebo. [59] The first RCT (107 people) found no significant difference in cure rates at 2 months between adding flavonoids to compression and adding placebo, although cure rates were higher with flavonoids (14/53 [26%] with flavonoids *v* 6/52 [11%] with placebo; RR 2.29, 95% CI 0.99 to 5.43). [59] It found that flavonoids significantly reduced time to healing of ulcers less than 10 cm^2 compared with placebo (P = 0.037). The second RCT (202 people; previously unpublished) found similar cure rates at 2 months with flavonoid plus compression compared with compression plus placebo (21/103 [20%] with flavonoids *v* 25/99 [25%] with placebo; significance not assessed). [59] Three RCTs identified by the review compared flavonoids plus compression versus compression alone. The first RCT (140 people) found that flavonoids plus compression significantly increased cure rates at 6 months compared with compression alone (33/71 [47%] with adding flavonoids *v* 19/69 [28%] with compression alone; OR 2.3, 95% CI 1.1 to 4.6). [59] The second RCT (150 people) found similar cure rates at 2 months with flavonoids plus compression and compression alone (10/71 [14%] with flavonoids *v* 6/69 [9%] with compression alone; significance not assessed). The third RCT (124 people, previously unpublished) reported a higher proportion of people healing at 2 months with flavonoids plus compression compared with compression alone (25/62 [40%] with flavonoids *v* 13/62 [21%] with compression alone; significance not assessed). The systematic review performed a meta-analysis of healing rates at 2 months (follow-up was to 6 months in 4 of the trials), and the findings were dependent on the model used. Using a random-effects model, flavonoids increased ulcer healing by 54% (95% CI 0% to 137%), whereas, with a fixed-effect model, flavonoids increased ulcer healing by 44% (95% CI 7% to 94%). The review found that flavonoids significantly increased ulcer healing compared with compression plus placebo or compression alone (HR 1.38, 95% CI 1.11 to 1.70). However, the systematic review excluded two unpublished RCTs (271 people) from the meta-analysis because of missing data at baseline or intermediate time points, or study incompletion, and it is not clear what impact these RCTs might have on the meta-analysis.

Harms: **Flavonoids plus compression versus compression alone:**
The review reported adverse effects of flavonoids, such as gastrointestinal disturbance, in 10% of people. [59]

Comment: None.

OPTION SULODEXIDE (ORAL)

Healing rates
Oral sulodexide plus compression compared with compression alone Oral sulodexide plus compression is more effective at increasing healing rates at 2–3 months (high-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral sulodexide plus compression versus compression alone:**
We found four RCTs (488 people). [60] [61] [62] [63] The first RCT (235 people) found that adding sulodexide to compression significantly increased cure rates at 3 months compared with adding placebo (63/121 [52%] with adding sulodexide *v* 36/114 [32%] with adding placebo; RR 1.65, 95% CI 1.28 to 18.54). [60] The second RCT (95 people) also found that adding sulodexide to compression significantly increased cure rates at 2 months compared with compression alone (30/52 [58%] with adding sulodexide *v* 15/43 [35%] with adding placebo; RR 1.65, 95% CI 1.06 to 2.7; NNT for 3 months' treatment 4, 95% CI 3 to 9). [61] The third RCT (44 people) found that adding intramuscular and then oral sulodexide to a compression regimen significantly increased healing rates at 7 weeks

(16/23 [70%] with sulodexide *v* 7/21 [35%] with control; P less than 0.05). [62] The fourth RCT (114 people) found that oral sulodexide significantly increased healing at 30 days compared with compression alone (32/61 [52%] with sulodexide *v* 17/53 [32%] with compression alone; P less than 0.05) . [63]

Harms: **Oral sulodexide plus compression versus compression alone:**
One RCT reported 37 people with a total of 40 adverse events, 23 (19%) in the sulodexide group and 17 (15%) in the placebo group. Of these, four adverse events in the treatment group (1 cutaneous rash, 1 diarrhoea, 1 epigastric pain, and 1 headache) were considered treatment related. [60] Two RCTs gave no information on adverse effects. [61] [62] The fourth RCT found no severe adverse effects in the people included in the RCT [63]

Comment: Sulodexide is not widely available, and daily injections may be unacceptable to some people.

OPTION MESOGLYCAN (SYSTEMIC)

Healing rates
Systemic mesoglycan plus compression compared with placebo plus compression Systemic mesoglycan plus compression is more effective at increasing the proportion of people with healed ulcers at 24 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Systemic mesoglycan plus compression versus placebo plus compression:**
We found one RCT (183 people) comparing systemic mesoglycan (daily im for 21 days and then orally for 21 weeks) plus compression versus placebo plus compression. [64] It found that systemic mesoglycan significantly increased the proportion of people with healed ulcers after 24 weeks' treatment compared with placebo (82/92 [89%] with mesoglycan *v* 69/91 [76%] with placebo; RR 1.17, 95% CI 1.03 to 1.35).

Harms: **Systemic mesoglycan plus compression versus placebo plus compression:**
The RCT reported that total adverse-event incidence was 7/92 (8%) with mesoglycan and 6/91 (7%) with placebo. There were two serious (non-fatal) events in each group, and two people withdrew from mesoclycan treatment (road accident trauma and congestive heart failure), and four with placebo (skin rash, cerebral stroke, ischaemia, and rectal bleeding). Most of the events were considered unrelated to treatment. [64]

Comment: None.

OPTION CULTURED ALLOGENIC SINGLE-LAYER DERMAL REPLACEMENT

Healing rates
Compared with usual care We don't know whether human dermal skin replacements (12-, 4-, or 1-piece dermagrafts) are more effective at increasing ulcer healing rates at 8–11 weeks (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Cultured allogenic single-layer dermal replacement versus usual care:**
We found one systematic review (search date 2006, 2 RCTs, 71 people), which compared single layered dermal replacement with standard care. [65] The first RCT included in the review compared three different regimens versus usual care (12 pieces, 4 pieces and 1 piece of dermagraft) and the second RCT compared the four-piece regimen versus usual care. The first RCT found no significant difference in rates of healing at 11 weeks for 12 pieces of dermal skin replacement, or for one piece of dermal skin replacement at baseline compared with usual care (12 pieces: 1 RCT, 26 people, RR 2.5, 95% CI 0.59 to 10.64, P = 0.2; 1 piece: 1 RCT, 26 people, RR 0.46, 95% CI 0.05 to 4.53, P = 0.5). The review found no significant difference in rates of healing for the four-piece dermal skin replacement at baseline, or at 1, 4, and 8 weeks (2 RCTs, 44 people, RR 3.04, 95% CI 0.95 to 9.68, P = 0.06). [65]

Harms: Taking a skin graft leaves a wound that itself requires management and may cause pain. We found no evidence of harm from tissue-engineered skin. [58]

Cultured allogenic single-layer dermal replacement versus usual care:
The review gave no information on adverse effects. [65]

Comment: None.

OPTION PROSTAGLANDIN E1 (INTRAVENOUS)

Healing rates
Compared with placebo Intravenous prostaglandin E1 may be more effective at improving the number of healed ulcers at 120 days (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Intravenous prostaglandin E1 versus placebo:**
We found one RCT (87 people), which compared intravenous prostaglandin E1 (PGE1) 60 mg daily (infused over 2 hours) for 20 days versus a placebo infusion. [66] Participants received infusions as outpatients and stayed in hospital for 6 hours. Both groups were also treated with elastic bandaging and local treatment. The RCT found that intravenous PGE1 significantly improved the proportion of ulcers healed at 120 days compared with placebo (40/44 [91%] with PGE1 *v* 32/43 [74%] with placebo; P less than 0.05). However, the RCT did not include an analysis that was adjusted for effects of bandages and local treatment.

Harms: **Intravenous prostaglandin E1 versus placebo:**
Adverse effects reported in the RCT included headache, nausea, hypotension, diarrhoea, and vomiting (5/44 [11%] with PGE1 *v* 2/43 [5%] with placebo; significance not assessed). [66]

Comment: PGE1 improves local ischaemia, and so could be effective in the treatment of venous leg ulcers.

OPTION LARVAL THERAPY

We found no direct information about larval therapy in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: We found no systematic review or RCTs on larval therapy in the healing of venous leg ulcers.

Harms: We found no RCTs.

Comment: Larval therapy is available either “free range”, and subsequently isolated in the wound using dressings and netting, or supplied already placed in a net bag. Larval therapy is acceptable to about three quarters of people with leg ulcer. [67]

OPTION LASER TREATMENT (LOW-LEVEL)

Healing rates
Compared with sham treatment We don’t know whether low-level laser treatment is more effective at increasing ulcer healing rates at 4 weeks to 9 months (very low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Low-level laser treatment versus sham treatment:**
We found two systematic reviews [68] [69] and three subsequent RCTs (4 publications). [70] [71] [72] [73] Two RCTs identified by the first review (search date 1998, 4 RCTs, 139 people) compared low-level laser treatment versus sham treatment, and found no significant difference in healing rates over 12 weeks (17/44 [39%] with laser treatment *v* 14/44 [32%] with sham treatment; RR 1.21, 95% CI 0.73 to 2.03). [68] The third RCT (30 people) included in the first review compared three interventions: low-level laser treatment, low-level laser treatment plus infrared light, and non-coherent, unpolarised red light. It found a significantly higher proportion of ulcers healed completely after 9 months' treatment with a combination of laser plus infrared light compared with non-coherent, unpolarised red light (12/15 [80%] with laser plus infrared light *v* 5/15 [33%] with non-coherent, unpolarised red light; RR 2.40, 95% CI 1.12 to 5.13). The fourth RCT included in the first review compared laser versus ultraviolet light, and found no significant difference in healing over 4 weeks (reported as not significant; P value not reported). [68] The second review (search date 1999, 5 RCTs, 148 people) [69] identified, but did not describe fully, the four RCTs identified by the first review, and did not perform a meta-analysis. The fifth RCT identified by the second review (9 people, 12 venous leg ulcers) compared low-level laser treatment versus sham treatment, and found limited evidence that ulcer-area reduction was greater with laser over 10 weeks (ulcer area remaining unhealed: 25% with laser treatment *v* 85% with sham treatment; CI not reported, significance assessment not performed). [69] The RCT did not assess complete ulcer healing. The first subsequent RCT (15 people) compared low-level laser treatment plus phototherapy once-weekly for 4 weeks versus sham treatment. [70] It found no significant difference in ulcer area at 12 weeks between

laser and sham (P = 0.14). The second subsequent RCT (65 people receiving compression and drug treatment) compared three interventions: low-level laser, sham laser, and "no additional treatment" (although it is unclear if the "no additional treatment" was established by randomisation). [71] It found no significant difference between treatments in the change in area of ulceration (reduction in area: 4.25 cm^2 [27%] with laser *v* 5.21 cm^2 [39%] with sham laser *v* 2.98 cm^2 [18%] with no treatment; reported as not significant, P value not reported). The third subsequent RCT (44 people) compared compression plus low-level laser, compression plus placebo laser, and compression alone. [72] [73] The RCT found no significant difference between the treatment groups in reduction in ulcer size (reported as not significant; P value not reported).

Harms: **Low-level laser treatment versus sham treatment:**
The two reviews gave no information on adverse effects. [68] [69] The first subsequent RCT reported an increase in pain levels during the treatment period for both groups. [70] The second subsequent RCT gave no information on adverse effects. [71] The third subsequent RCT reported increases in ulcer area in 28% of people receiving laser treatment compared with 11% of people in the compression-alone group. [72] [73] Eye protection is required when using some types of laser, as the high-energy beam may damage the retina.

Comment: The laser power, wavelength, frequency, duration, and follow-up of treatment were different for all of the studies. The subsequent RCTs may have lacked power to detect clinically important differences between laser and sham treatment. The third subsequent RCT reported within-group rather than between-group differences. [72] [73]

OPTION ASPIRIN (ORAL)

Healing rates
Compared with placebo Aspirin may be more effective at increasing ulcer healing rates (very low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral aspirin versus placebo:**
We found one small RCT comparing aspirin (300 mg daily, enteric coated) versus placebo. [74] It found that aspirin significantly increased ulcer healing rates compared with placebo (38% with aspirin *v* 0% with placebo; P less than 0.007). However, the RCT had several methodological weaknesses, so the result should be treated with caution.

Harms: **Oral aspirin versus placebo:**
The RCT gave no information on adverse effects. [74]

Comment: None.

OPTION RUTOSIDES (ORAL)

Healing rates
Compared with placebo We don't know whether oral rutosides alone or with compression are more effective at increasing ulcer healing rates at 6–12 weeks (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral rutosides versus placebo:**
We found two reports of three RCTs. [75] [76] The two RCTs (119 people) reported in one publication compared two different doses of oral hydroxyethyl rutosides (500 and 1000 mg twice daily) with placebo. The RCTs found no significant difference in rates of complete ulcer healing at 12 weeks between either dose of rutosides and placebo (1 RCT, 55 people, 48 analysed: 12/23 [52%] with rutoside 1 g/day *v* 7/25 [28%] with placebo; P = 0.087; results for the second RCT not reported). The third RCT (107 people) compared oral rutosides 500 mg twice daily plus compression versus compression alone. The RCT found no difference in healing rates at 6 weeks between oral rutoside plus compression and compression alone (10/55 [18%] with rutoside plus compression *v* 12/52 [23%] with compression alone; significance not assessed). [76] The RCTs may have been too small to detect a clinically important difference.

Harms: **Oral rutosides versus placebo:**
One report of two RCTs (119 people) found no significant difference in adverse effects between oral rutosides and placebo (no details reported). [75] The third RCT gave no information on adverse effects. [76]

Comment: None.

OPTION THROMBOXANE ALPHA2 ANTAGONISTS (ORAL)

Healing rates
Compared with placebo We don't know whether oral thromboxane alpha$_2$ antagonists are more effective at increasing ulcer healing rates (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral thromboxane alpha$_2$ antagonists versus placebo:**
We found one RCT (165 people) comparing an oral thromboxane alpha$_2$ antagonist versus placebo. [77] It found no significant difference in the proportion of ulcers healed (55% with thromboxane alpha$_2$ antagonist *v* 54% with placebo; CI not reported). [77]

Harms: **Oral thromboxane alpha$_2$ antagonists versus placebo:**
The RCT gave no information on any adverse effects. [77]

Comment: None.

OPTION ZINC (ORAL)

We found no clinically important results about the effects of oral zinc in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral zinc versus placebo:**
We found one systematic review (search date 1997, 5 RCTs, 151 people) comparing daily doses of oral zinc sulphate 440–660 mg versus placebo. [78] The review found no evidence of benefit for oral zinc in people with venous leg ulcers (significance not assessed).

Harms: **Oral zinc versus placebo:**
The review gave no information on adverse effects. [78]

Comment: None.

OPTION SKIN GRAFTING

Healing rates
Compared with other treatments for leg ulcers We don't know whether different types of skin grafts are more effective at increasing healing of venous ulcers (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Different types of skin grafts versus other treatments for leg ulcers:**
We found one systematic review (search date 2006, 11 RCTs, 768 people) [58] of skin grafts (autografts, allografts, or xerografts) for venous leg ulcers, and one subsequent RCT. [79] In 11 RCTs identified by the review, people also received compression bandaging; one RCT (31 people) compared an autograft with a dressing, three RCTs (45 people) compared fresh allografts with dressings, three RCTs (80 people) compared frozen allografts with dressings, one RCT (92 people) compared an autograft with a frozen allograft, one RCT (51 people) compared a pinch autograft with a xenograft, one RCT (7 people) compared tissue-engineered skin with a split-thickness graft, and one RCT (50 people) compared a fresh allograft with a frozen allograft. [58] The review found insufficient evidence to determine whether skin grafting increased healing rates for venous ulcers, because studies were small and generally of poor quality. [58] In the additional RCT (120 people), a porcine extracellular matrix graft was compared with usual care (both groups received compression). There was a significantly higher proportion of people healed at 12 weeks with the matrix graft than with usual care (55% with matrix graft *v* 34% with usual care; RR for healing with matrix 1.59, 95% CI 1.06 to 2.42). [79]

Harms: **Different types of skin grafts versus other treatments for leg ulcers:**
Taking a skin graft leaves a wound that itself requires management and may cause pain. We found no evidence of harm from tissue-engineered skin. [58] The subsequent RCT gave no information on adverse effects. [79]

Comment: Porcine derived products may not be acceptable to some patient groups. [80]

OPTION SUPERFICIAL VEIN SURGERY TO TREAT VENOUS LEG ULCERS

Healing rates

Perforator ligation compared with no surgery or surgery plus skin grafting We don't know whether perforator ligation is more effective at increasing the proportion of ulcers healed at 1 year or at reducing time to ulcer healing (very low-quality evidence).

Minimally invasive surgery compared with compression bandages or usual care We don't know whether minimally invasive surgery may be more effective at reducing time to complete healing, or whether it is more effective at increasing ulcer healing rates (low-quality evidence).

Venous surgery (based on duplex scan) plus compression compared with compression alone Venous surgery (based on duplex scan) plus compression and compression alone are equally effective at increasing healing rates at 24 weeks and at 3 years (high-quality evidence).

Open perforator surgery compared with subfascial endoscopic perforator surgery We don't know whether open perforator surgery is more effective at increasing ulcer healing rates at 4 months (low-quality evidence).

Adverse effects

Open perforator surgery compared with subfascial endoscopic perforator surgery Open perforator surgery is associated with higher wound infection rates compared with subfascial endoscopic perforator surgery (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Perforator ligation versus no surgery or versus surgery plus skin grafting:
We found one RCT (47 people) which compared perforator ligation versus no surgery or surgery plus skin grafting. [81] All participants were also treated with a compression bandage. The RCT found no significant difference in the proportion of ulcers healed after 1 year or in the time to complete ulcer healing (reported as P greater than 0.05 for both outcomes). [81] The RCT did not perform an intention-to-treat analysis, and 7/47 (15%) people withdrew from the trial. It is likely to have been underpowered to detect a clinically important difference among groups.

Minimally invasive surgery versus compression bandages or usual care:
We found two RCTs (215 people), which compared minimally invasive surgery versus compression bandages. [82] [83] In the first RCT, people randomised to surgery were treated with a compression bandage before surgery, while in the second RCT they wore compression until ulcer healing. The first RCT found high healing rates in both groups (100% with surgery *v* 96% with compression); it randomised legs rather than people. [82] . It found that surgery significantly reduced time to complete healing compared with compression bandages (median: 31 days with surgery *v* 63 days with compression; P less than 0.005). [82] The second RCT (170 people with venous leg ulcers) compared subfascial endoscopic perforator surgery (SEPS) plus superficial venous surgery as required versus compression alone. It found no significant difference in the proportion of ulcers healed between groups (83% with surgery *v* 73% with conservative care: P = 0.24, absolute figures not reported). [83]

Venous surgery (based on duplex scan) plus compression versus compression alone:
We found one RCT (341 people), which compared venous surgery (type of surgery based on duplex scan) plus compression versus compression alone. [84] The RCT found no significant difference in healing rates between treatments at 24 weeks (ulcer healing rates: 65% in both arms; HR for healing: 0.84, 95% CI 0.77 to 1.24). [84] Long-term follow-up of this RCT also found no significant difference in healing rates between groups at 3 years (93% for surgery plus compression *v* 89% for compression alone, P = 0.73). [85]

Open perforator surgery versus subfascial endoscopic perforator surgery:
We found one systematic review (search date 2003, 1 RCT, 39 people). [86] The RCT identified by the review found no significant difference between treatments in healing rates at 4 months (17/20 [85%] with subfascial endoscopic perforator surgery *v* 17/19 [89%] with open surgery; CI not reported). [86]

Harms:

Vein surgery carries the usual risks of surgery and anaesthesia.

Perforator ligation:
The first RCT found no postoperative complications, but may have been too small to detect clinically important adverse effects. [81]

Minimally invasive surgery:
The RCTs gave no information on adverse effects. [82] [83]

Venous surgery (based on duplex scan):
The RCT reported that adverse events were minimal and about equal in each group; no further information was given. [84] The long-term follow-up gave no information on adverse effects. [85]

Open perforator surgery versus subfascial endoscopic perforator surgery:
One RCT (39 people) identified by a systematic review found higher wound infection rates with open surgery compared with subfascial endoscopic perforator surgery (0% with subfascial endoscopic perforator surgery *v* 53% with open surgery; P less than 0.001). [87] The review reported that deep vein thrombosis occurred in 1%, wound infection in 6%, neuralgia in 7%, and haematoma in 9% of all people with venous ulcers having surgical treatment involving subfascial endoscopic perforator surgery. [86]

Comment: Several operative approaches are commonly used, including perforator ligation, saphenous vein stripping, and a combination of both procedures. The RCT comparing open perforator surgery versus subfascial endoscopic perforator surgery found that hospital stay was shorter with subfascial endoscopic perforator surgery (4 days with subfascial endoscopic perforator surgery *v* 7 days with open surgery). [87] About 25% of people who were offered venous surgery in one study refused it. [88]

OPTION THERAPEUTIC ULTRASOUND

We found no clinically important results about the effects of therapeutic ultrasound in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: **Therapeutic ultrasound versus no or sham ultrasound:**
We found one systematic review (search date 1999, 7 RCTs, 470 people) comparing therapeutic ultrasound with no ultrasound or sham ultrasound for venous leg ulcers. [89] Ultrasound improved ulcer healing in all studies, but a significant difference was found in only four of the seven RCTs, and heterogeneity precluded pooling the seven RCTs.

Harms: **Therapeutic ultrasound versus no or sham ultrasound:**
Mild and severe erythema, local pain, and small areas of bleeding were reported in RCTs identified by the review. [90] [91]

Comment: None.

QUESTION What are the effects of organisational interventions for venous leg ulcers?

OPTION LEG ULCER CLINICS

Healing rates
Compared with usual care We don't know whether leg ulcer clinics are more effective at increasing ulcer healing rates (very low-quality evidence).

Note
Leg ulcer clinics and leg clubs may only be suitable for mobile people.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: **Leg ulcer clinics versus usual care:**
We found one systematic review (search date 2001, 1 RCT) [92] and one additional RCT. [93] The RCT identified by the review [92] randomised people with leg ulcers to usual care at home or high-compression bandaging in a leg ulcer clinic. The review found that attending a leg ulcer clinic significantly increased the probability of ulcer healing compared with usual care at home (Cox model, ulcers 1.65 times more likely to heal when attending a leg ulcer clinic, 95% CI 1.15 to 2.35). However, all people attending the leg ulcer clinic were treated with high-compression bandaging, whereas only half the people receiving usual care at home were treated with some type of compression bandaging. Compression bandaging is known to be beneficial in the treatment of leg ulcers, and so increased improvement rates in those attending the leg clinic would be expected. One additional RCT (33 people) compared community-based "Leg Clubs" versus usual care. [93] The RCT found a significantly greater reduction in ulcer area in the "Leg Club" group compared with the

usual-care group (P = 0.004). However, the RCT found no significant difference in the proportion of people healed at 12 weeks (7/16 [44%] with "Leg Club" *v* 4/17 [24%] with usual care; reported as not significant; P value not reported).

Harms: **Leg ulcer clinics versus usual care:**
The review [92] and RCT [93] gave no information on adverse effects.

Comment: **Clinical guide:**
Leg ulcer clinics and "Leg Clubs" may only be suitable for mobile people.

QUESTION **What are the effects of advice about self-help interventions in people receiving usual care for venous leg ulcers?**

OPTION **ADVICE TO ELEVATE LEG** New

We found no direct information about the effects of leg elevation in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found no RCT evidence to support the elevation of the leg, although this intervention makes sense as venous insufficiency is corrected if the leg is elevated above the heart. The advantages of leg elevation — such as reduced oedema and increasing venous return — must be weighed against the potential for harm if the cardiovascular system cannot cope with a sudden increase in circulating volume. Many people with venous disease have joint or other mobility problems which mitigate against their being able to elevate their legs for long periods.

OPTION **ADVICE TO KEEP LEG ACTIVE** New

We found no direct information about the effects of keeping the leg active in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found no RCT evidence about the effects of advice to keep the leg active, although this intervention makes sense, as venous insufficiency can be reduced by activation of the calf muscle pump. Potential advantages of activity may include reduced leg oedema, and increasing venous return. Many people with venous disease have joint or other mobility problems which may mitigate against increasing their activity levels.

OPTION **ADVICE TO MODIFY DIET** New

We found no direct information about the effects of diet modification in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found no RCT evidence on the impact of dietary modification on venous ulcer prevention or healing. A healthy diet is important for preventing arterial disease, which could, in turn, affect ulcer healing. It is not clear if people with venous ulceration have specific dietary needs, but a diet high in fruit and vegetables, and low in salt, fat, alcohol, and sugar, is likely to maintain vascular supply to support healing.

OPTION ADVICE TO STOP SMOKING New

We found no direct information about the effects of smoking cessation in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found no RCT evidence on the impact of smoking-cessation advice on venous ulcer prevention or healing. A healthy lifestyle, including avoidance of smoking, is important for preventing arterial disease, which could, in turn, affect ulcer healing.

OPTION ADVICE TO REDUCE WEIGHT New

We found no direct information about the effects of weight reduction in people with venous leg ulcers.

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found no RCT evidence on the impact of advice for weight loss on venous ulcer prevention or healing. A healthy lifestyle is important for preventing arterial disease, and increasing activity while maintaining a healthy diet could, in turn, affect ulcer healing.

QUESTION What are the effects of interventions to prevent recurrence of venous leg ulcers?

OPTION COMPRESSION BANDAGES AND STOCKINGS

Recurrence rates
Compared with no compression Compression stockings are more effective at reducing ulcer recurrence rates at 6 months (high-quality evidence).

Compression stockings compared with other forms of compression High-compression stockings (UK class 3), and moderate compression stockings (UK class 2) seem equally effective at reducing recurrence at 5 years (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, **see table, p 32 .**

Benefits: **Compression stockings versus no compression:**
We found one systematic review (search date 2000), [94] which found no RCTs comparing compression stockings versus no compression, and one subsequent RCT. [95] The RCT (153 people) found that wearing compression stockings significantly reduced recurrence at 6 months compared with not wearing compression stockings (21% with compression stockings *v* 46% with no compression stockings; RR 0.46, 95% CI 0.28 to 0.76; NNT for 6 months' treatment 2, 95% CI 2 to 5). [95]

Compression stockings versus other forms of compression:
We found one systematic review (search date 2000, 2 RCTs). [94] The first RCT identified by the review (166 people) compared two brands of UK Class 2 stockings (see comment below) and found no significant difference in recurrence after 18 months (22/92 [24%] with Medi *v* 27/74 [36%] with Scholl; RR 0.82, 95% CI 0.61 to 1.12). The second RCT identified by the review (300 people) compared Class 2 and Class 3 stockings (see comment below). With intention-to-treat analysis, the RCT found no significant difference in recurrence after 5 years with high-compression stockings (UK Class 3) compared with moderate-compression stockings (recurrence: 59/151 [39%] with Class 2 elastic compression *v* 48/149 [32%] with Class 3 compression cases; RR 0.74, 95% CI 0.45 to 1.20). This analysis may underestimate the effectiveness of the Class 3 stockings because a significant proportion of people changed from Class 3 to Class 2. Both RCTs found that non-compliance with compression stockings was associated with recurrence.

Harms: The application of high compression to limbs with reduced arterial supply may result in ischaemic tissue damage and, at worst, amputation. [57]

Compression stockings versus no compression:
The review [94] and subsequent RCT [95] gave no information on adverse effects.

Compression stockings versus other forms of compression:
The review gave no information on adverse effects. [94]

Comment: Compression hosiery is classified according to the magnitude of pressure exerted at the ankle; the UK classification states that Class 2 stockings are capable of applying 18–24 mm Hg pressure and Class 3 are capable of applying 25–35 mm Hg pressure at the ankle. Other countries use different classification systems. Stockings reduce venous reflux by locally increasing venous pressure in the legs relative to the rest of the body. This effect only takes place while hosiery is worn. The association between non-compliance with compression and recurrence of venous ulceration provides some indirect evidence of the benefit of compression in prevention. People are advised to wear compression stockings for life, and may be at risk of pressure necrosis from their compression stockings if they subsequently develop arterial disease. Regular reassessment of the arterial supply is considered good practice, but we found no evidence about the optimal frequency of assessment. Other measures designed to reduce leg oedema, such as resting with the leg elevated, may be useful (see comment on advice to elevate legs, p 24).

OPTION SUPERFICIAL VEIN SURGERY TO PREVENT RECURRENCE

Recurrence rates
Surgery plus compression compared with compression alone Superficial vein surgery plus compression is more effective at reducing ulcer recurrence rates at 12 months to 3 years (moderate-quality evidence).

Open compared with endoscopic surgery Open surgery is less effective at reducing ulcer recurrences at 12 months, and is associated with higher wound infection rates (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits:

Surgery plus compression versus compression alone:
We found one systematic review (search date 1997, 1 RCT) [96] and three subsequent RCTs. [82] [84] [83] The RCT (30 people) identified by the review compared surgery plus compression stockings versus compression stockings alone for prevention of recurrence (see comment below). [96] It found that surgery plus compression stockings significantly reduced recurrence rates compared with compression stockings alone (5% with surgery plus compression stockings *v* 24% with compression stockings alone; RR 0.21, 95% CI 0.03 to 0.80). [96] The first subsequent RCT (45 people) compared minimally invasive surgery versus compression bandages. [82] People randomised to surgery wore compression stockings immediately after surgery, and people randomised to compression wore compression stockings after ulcer healing was achieved. The RCT found that surgery significantly reduced recurrence rates over 3 years compared with compression (2/21 [10%] with surgery *v* 9/24 [38%] with compression bandages; P less than 0.05). [82] The second subsequent RCT (428 people), which compared superficial vein surgery plus compression versus compression alone, found significantly lower recurrence rates after 12 months with surgery plus compression compared with compression alone (12% with surgery plus compression *v* 28% with compression alone; HR –2.76, 95% CI –1.78 to –4.27). [84] Long-term follow-up of this RCT found that this difference was sustained at 3 years (31% recurrence in surgery group *v* 56% recurrence in compression group, P less than 0.01). [85] The third subsequent RCT (170 people), which compared subfascial endoscopic perforating vein surgery (SEPS) plus compression versus compression alone, found no significant difference in recurrence rates between groups at 27 months (22% with surgery and compression *v* 23% with compression alone, reported as non-significant, all other data presented graphically). [83]

Open versus endoscopic surgery:
We found one systematic review (search date 2003, 1 RCT, 39 people), [86] which compared open surgery versus SEPS, and a subsequent long-term follow-up report [97] of the RCT identified by the review. The RCT found four (22%) recurrences at 12 months in the open surgery group, and two (12%) in the SEPS group (reported as P = 0.044). [86] [97]

Harms:

One RCT gave information on adverse effects. [87] It found significantly higher wound infection rates with open surgery compared with subfascial endoscopic perforator surgery (SEPS) (53% with open surgery *v* 0% with SEPS; P less than 0.001). [87] Vein surgery has the usual risks of surgery and anaesthesia.

Surgery plus compression versus compression alone:
The review, [96] three subsequent RCTs, [82] [84] [83] and the long-term follow-up RCT [85] gave no information on adverse effects.

Open versus endoscopic surgery:
The review found that deep vein thrombosis was reported in 1%, wound infection in 6%, neuralgia in 7%, and haematoma in 9% of people having surgical treatment involving SEPS. [86] [97]

Comment: The small RCT identified by the review, which compared surgery plus compression versus compression alone, was poorly controlled, and its results should be interpreted with caution. [96] The subsequent small RCT randomised legs rather than people. [82]

OPTION RUTOSIDE (ORAL)

Recurrence rates
Compared with placebo Oral rutosides are no more effective at reducing ulcer recurrence at 18 months (moderate-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral rutoside versus placebo:**
We found one systematic review (search date 1997, 1 RCT, 139 people). [96] The RCT found no significant difference in recurrence at 18 months between rutoside and placebo (32% with rutoside *v* 34% with placebo; P = 0.93).

Harms: **Oral rutoside versus placebo:**
One RCT (31 people with obstructive arm lymphoedema) found that rutoside was associated with headache, flushing, rashes, and mild gastrointestinal disturbances. [98] The review gave no information on adverse effects. [96]

Comment: None.

OPTION STANOZOLOL (ORAL)

Recurrence rates
Compared with placebo Stanozolol may be no more effective at reducing ulcer recurrence at 18 months (low-quality evidence).

For GRADE evaluation of interventions for venous leg ulcers, see table, p 32 .

Benefits: **Oral stanozolol versus placebo:**
We found one systematic review (search date 1997, 1 RCT, 60 people). [96] The RCT found no significant difference in ulcer recurrence between 6 months' treatment with stanozolol and placebo (length of follow-up not reported; recurrence: 7/25 [28%] legs with stanozolol *v* 4/23 [17%] legs with placebo; RR 1.61, 95% CI 0.54 to 4.79). [96]

Harms: **Oral stanozolol versus placebo:**
Stanozolol is an anabolic steroid; adverse effects include acne, hirsutism, amenorrhoea, oedema, headache, dyspepsia, rash, hair loss, depression, jaundice, and changes in liver enzymes. The review gave no information on adverse effects. [96]

Comment: None.

GLOSSARY

Cultured allogenic bilayer skin replacement Also called human skin equivalent. This is made of a lower (dermal) layer of bovine collagen containing human living dermal fibroblasts, and an upper (epidermal) layer of human living keratinocytes.
Intermittent pneumatic compression External compression applied by inflatable leggings or boots either over, or instead of, compression bandages or stockings. A pump successively inflates and deflates the boots to promote the return of blood from the tissues. Newer systems have separate compartments in the boots so that the foot is inflated before the ankle, which is inflated before the calf.
Iontophoresis The delivery of an ionic substance by application of an electrical current.
Minimally invasive surgery Surgery in which small incisions are made in the skin, and the use of surgical instruments with cameras or direct viewing through eyepieces allows the surgeon to operate. Often performed under local anaesthetic and as a day case.
Subfascial endoscopic perforator surgery is a minimally invasive endoscopic procedure, which eliminates the need for a large incision in the leg. An endoscope is used to visualise directly and tie off incompetent medial calf perforating veins to decrease venous reflux, and reduce ambulatory venous pressure.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Laser treatment (low-level) Application of treatment energy (less than 10 J/cm^2) using lasers of 50 mW or less.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Multilayer elastomeric high-compression bandages Usually a layer of padding material followed by one to four additional layers of elastomeric bandages.
Non-elastic legging Compression device consisting of a series of interlocking, non-elastic bands that encircle the leg and are held together by hook-and-loop fasteners.
Perforator ligation involves tying off the blood vessels that link the deep and superficial venous systems. The one-way valves in these veins prevent flow from the deep to the superficial system. Malfunctioning perforator vessels may be responsible for increasing venous pressure in the superficial venous system, leading to ulceration.
Short-stretch bandages Minimally extensible bandages, usually made of cotton, with few or no elastomeric fibres. They are applied at near full extension to form a semirigid bandage.
Therapeutic ultrasound Application of ultrasound to a wound, using a transducer and a water-based gel. Prolonged application can lead to heating of the tissues; but, when used in wound healing, the power used is low and the transducer is constantly moved by the therapist, so that the tissue is not heated significantly.
Topical negative pressure Negative pressure (suction) applied to a wound through an open-cell dressing (e.g. foam, felt).
Unna's boot An inner layer of zinc oxide-impregnated bandage, which hardens as it dries to form a semirigid layer against which the calf muscle can contract. It is usually covered in an elastomeric bandage.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Advice to elevate leg New option for which we found no RCT evidence in people with venous leg ulcers. Categorised as Unknown effectiveness.
Advice to keep leg active New option for which we found no RCT evidence in people with venous leg ulcers; categorised as Unknown effectiveness.
Advice to modify diet New option for which we found no RCT evidence in people with venous leg ulcers; categorised as Unknown effectiveness.
Advice to stop smoking New option for which we found no RCT evidence in people with venous leg ulcers; categorised as Unknown effectiveness.
Advice to reduce weight New option for which we found no RCT evidence in people with venous leg ulcers; categorised as Unknown effectiveness.
Allogenic single-layer skin replacement One systematic review added comparing single-layer dermal replacement versus usual care. [65] The review found similar rates of healing between 12-piece, 4-piece or 1-piece dermal skin replacement and usual care. [65]
Antimicrobial agents (topical) One systematic review added comparing dressings impregnated with silver versus dressings not containing silver for venous ulcers. [42] It found no significant difference between groups in proportion of ulcers completely healed. Categorisation unchanged (Unknown effectiveness).
Foam or semi occlusive dressings: One systematic review added evaluating the effectiveness of wound dressings to treat venous leg ulcers. [35] The review included two RCTs not previously reported. The first RCT found similar rates of ulcer healing between hyaluronic dressings and paraffin gauze. [36] The second RCT compared a collagen-plus-cellulose dressing versus a modern low-adherent dressing. It found similar healing rates at 12 weeks with both treatments. [37] Categorisation unchanged (Unknown effectiveness).
Occlusive dressings One review and two subsequent RCTs added comparing occlusive dressings with simple dressing in the presence of compression, and other occlusive or semi-occlusive dressings. [35] [53] [54] The review found no significant difference in ulcer healing between hydrocolloid dressings compared with simple low-adherent dressings in the presence of compression, hydrocolloids compared with other modern dressings, or occlusive dressings compared with semi-occlusive dressings. [35] The first subsequent RCT compared a foam dressing with a silicione foam dressing (both under compression) over 24 weeks. [53] It found no significant difference between treatments for complete ulcer healing. [53] The second subsequent crossover RCT compared a foam dressing containing ibuprofen with a similar foam dressing with no ibuprofen. [54] It found that ibuprofen dressings reduced chronic pain on days 1–5 compared with non-ibuprofen dressings, but found no significant difference between groups for ulcer healing at 24 weeks. [54] Categorisation unchanged (Unlikely to be beneficial).
Pentoxifylline (oral) One systematic review updated comparing pentoxifylline (oxpentifylline) 1200 or 2400 mg daily versus placebo or versus other treatments, with or without compression. [57] It found that, in the presence of compression, pentoxifylline increased the proportion of people with healed ulcers over 8–24 weeks compared with placebo. Categorisation unchanged (Beneficial).
Skin grafting One systematic review updated, comparing different types of skin grafts. [58] It found insufficient evidence to determine whether skin grafting increased the healing of venous ulcers. Categorisation unchanged (Unknown effectiveness).
Sulodexide (oral) One RCT added comparing sulodexide versus compression alone. [63] It found that sulodexide increased healing at 30 days compared with compression alone. Categorisation unchanged (Likely to be beneficial).
Superficial vein surgery One RCT and one follow-up study added. [83] [85] The RCT compared subfascial endoscopic perforator surgery (SEPS) plus superficial venous surgery as required versus compression alone. It found no significant difference between groups in the number of ulcers healed. [83] The follow-up study compared venous

surgery (type of surgery based on duplex scan) plus compression versus compression alone, and found no difference in healing rates between groups at 3 years. [85] Categorisation unchanged (Unknown effectiveness).

Superficial vein surgery One long-term follow-up study and one RCT added. [85] [83] The long-term follow-up compared superficial vein surgery plus compression versus compression alone, and found that, after 3 years, recurrence rates were lower with surgery plus compression compared with compression alone. [85] One RCT comparing subfascial endoscopic perforating vein surgery (SEPS) plus compression versus compression alone found no significant difference in recurrence rates between groups. [83] Categorisation unchanged (Likely to be beneficial)

Topical negative pressure One RCT added comparing vacuum-assisted closure (VAC) versus conventional wound care techniques. [49] It found that VAC reduced time to complete healing compared with conventional therapy, but did not lengthen time to recurrence. The RCT reported no significant difference in adverse effects between groups, apart from an increased risk of cutaneous damage secondary to therapy in the VAC group. [49] Categorisation unchanged (Unknown effectiveness).

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Disclaimer

TABLE GRADE evaluation of interventions for venous leg ulcers

Important outcomes	Healing rates, recurrence rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of standard treatments for venous leg ulcers?									
7 (467) [8] [9]	Healing rates	Compression bandages and stockings *v* no compression	4	0	0	0	0	High	
2 (299) [14] [15]	Healing rates	Compression stockings *v* short-stretch bandages	4	–2	–1	–2	0	Very low	Quality point deducted for incomplete reporting of results and for methodological flaws. Consistency point deducted for conflicting results. Directness points deducted for inclusion of people with different severities of ulcers and for differences in treatment regimens in both groups affecting generalisability of results
6 (679) [8] [16] [17] [18]	Healing rates	Multilayer elastomeric high-compression regimens *v* each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of multiple interventions in comparison
4 (280) [8]	Healing rates	Multilayer elastomeric high-compression regimens *v* single-layer bandage	4	0	0	0	0	High	
9 (908) [8] [19] [20] [21] [22]	Healing rates	Multilayer elastomeric high-compression bandages *v* short-stretch bandages or Unna's boot	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
4 (385) [8] [24]	Healing rates	Multilayer elastomeric high-compression bandages *v* non-elastmeric high-compression bandages	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (24) [25]	Healing rates	Single-layer non-elastic system *v* multilayer elastic system	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about generalisability of results in people with different conditions
1 (38) [26]	Healing rates	Single-layer non-elastic system *v* multilayer non-elastic system	4	–2	0	0	0	Low	Quality points deduced for sparse data and incomplete reporting of results
1 (60) [27]	Healing rates	Peri-ulcer injection of granulocyte-macrophage colony-stimulating factor *v* placebo	4	–1	0	0	+1	High	Quality points deduced for sparse data. Effect-size point added for RR less than 5
8 (883) [33] [34] [35]	Healing rates	Semi-occlusive dressings *v* simple low-adherent dressings	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (89) [33]	Healing rates	Alginate dressings *v* zinc oxide dressings	4	–1	–1	0	0	Low	Quality point deduced for sparse data. Consistency point deducted for conflicting results
5 RCTs (at least 115 people) [28] [29]	Healing rates	Intermittent pneumatic compression plus compression stockings *v* compression stockings or bandages alone	4	–1	–1	0	0	Low	Quality points deduced for sparse data. Consistency point deducted for conflicting results

Important outcomes	Healing rates, recurrence rates, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
19 (at least 263 people) [41] [42] [43] [44]	Healing rates	Topical antimicrobial agents *v* placebo or usual care	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcome in one study
1 (66) [45]	Healing rates	Calcitonin gene-related peptide (topical) plus vasoactive intestinal polypeptide *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [46]	Healing rates	Topical mesoglycan *v* plant-based extract	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (60) [49]	Healing rates	Topical negative pressure *v* usual care	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for inclusion of people with non-venous ulcers and for uncertainty about generalisability of results outside a hospital setting
1 (94) [50]	Healing rates	Topical recombinant human keratinocyte growth factor 2 plus compression *v* compression	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (135) [51]	Healing rates	Platelet-derived growth factor *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 27 RCTs (at least 792 people) [33] [34] [35]	Healing rates	Hydrocolloid (occlusive) dressings *v* simple dressings in the presence of compression	4	0	0	0	0	High	
5 (351) [35]	Healing rates	Hydrocolloids *v* other occlusive or semi-occlusive dressings	4	0	0	0	0	High	
3 (388) [52] [53]	Healing rates	Different occlusive or semi-occlusive dressing (excluding hydrocollids) *v* each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (86) [55]	Healing rates	Topically applied autologous platelet lysate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (200) [56]	Healing rates	Topically applied freeze-dried keratinocyte lysate *v* vehicle or usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of adjuvant treatments for venous leg ulcers?									
8 (682) [57]	Healing rates	Oral pentoxifylline *v* placebo	4	0	0	0	0	High	
2 (345) [58]	Healing rates	Cultured allogenic bilayer skin replacement *v* non-adherent dressing	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (723) [59]	Healing rates	Flavonoids plus compression *v* compression alone	4	–1	–1	0	+1	Moderate	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Effect-size point added for RR/OR greater than 2 but less than 5
4 (488) [60] [61] [62] [63]	Healing rates	Oral sulodexide plus compression *v* compression alone	4	0	0	0	0	High	

Important outcomes	Healing rates, recurrence rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (183) [64]	Healing rates	Systemic mesoglycan plus compression *v* placebo plus compression	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (70) [65]	Healing rates	Cultured allogenic single-layer dermal replacement *v* usual care	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (87) [66]	Healing rates	Intravenous prostaglandin E1 *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and for methodological flaws
8 (420) [68] [69] [70] [71] [72] [73]	Healing rates	Low-level laser treatment *v* sham treatment	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and for differences in length of follow-up. Consistency point deducted for conflicting results. Directness points deducted for treatment inconsistencies between groups and for assessing different measures of healing
1 (reported as 'small') [74]	Healing rates	Oral aspirin *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data and for methodological weaknesses
2 (115) [75] [76]	Healing rates	Oral rutosides *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (165) [77]	Healing rates	Oral thromboxane alpha$_2$ antagonists *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
12 (888) [58] [79]	Healing rates	Different types of skin grafts *v* other treatments for leg ulcers	4	–1	0	–1	0	Low	Quality point deducted for poor studies and insufficient evidence. Directness point deducted for generalisability of results
1 (47) [81]	Healing rates	Perforator ligation *v* no surgery or *v* surgery plus skin grafting	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no intention-to-treat analysis
2 (215) [82] [83]	Healing rates	Minimally invasive surgery *v* compression bandages or usual care	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (341) [84]	Healing rates	Venous surgery (based on duplex scan) plus compression *v* compression alone	4	0	0	0	0	High	
1 (39) [86]	Healing rates	Open perforator surgery *v* subfascial endoscopic perforator surgery	4	–2	0	0	0	Low	Quality points deducted for sparse data, and incomplete reporting of results
1 (39) [86]	Adverse effects	Open perforator surgery *v* subfascial endoscopic perforator surgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of organisational interventions for venous leg ulcers?									
2 (at least 33 people) [92] [93]	Healing rates	Leg ulcer clinics *v* usual care	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for differences in treatments received by both groups and uncertainty about generalisability of results
What are the effects of advice about self-help interventions in people receiving usual care for venous leg ulcers?									

Important outcomes	Healing rates, recurrence rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
No systematic review or RCTs found									
What are the effects of interventions to prevent recurrence of venous leg ulcers?									
1 (153) [95]	Recurrence rates	Compression stockings *v* no compression	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR less than 0.5
2 (466) [94]	Recurrence rates	Compression stockings *v* other forms of compression	4	0	0	–1	0	Moderate	Directness point deducted for change over from higher to lower class
4 (673) [96] [82] [84] [83]	Recurrence rates	Surgery plus compression *v* compression alone	4	–1	0	0	0	Moderate	Quality point deducted for methodological flaws
1 RCT and 1 report (39) [86] [97]	Recurrence rates	Open *v* endoscopic surgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (139) [96]	Recurrence rates	Oral rutoside *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (48) [96]	Recurrence rates	Oral stanozolol *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and uncertainty about duration of follow-up

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio