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 advice about self-help interventions in people receiving usual care 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 June 2011 (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 101 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, self-help (advice to elevate leg, to keep leg active, to modify diet, to stop smoking, to reduce weight), short-stretch bandages, single-layer non-elastic system, skin grafting, superficial vein surgery, systemic mesoglycan, therapeutic ultrasound, 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 are beneficial, as we found few trials.
- Oral pentoxifylline increases ulcer healing in people receiving compression, and oral flavonoids, sulodexide, and mesoglycan may also be effective.

  We don't know whether therapeutic ultrasound, oral aspirin, rutosides, thromboxane alpha$_2$ antagonists, zinc, debriding agents, intravenous prostaglandin E1, superficial vein surgery, skin grafting, topical antimicrobial agents, leg ulcer clinics, 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.

  Larval therapy is not likely to be beneficial as it has no impact on healing and is painful.

- 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 >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

Healing rates: ulcer area, number of people who are ulcer-free, number of ulcers healed, number of ulcer-free limbs, time to complete ulcer healing. **Recurrence rates:** recurrence rates, number of new ulcer episodes, number of ulcer-free weeks or months, frequency of dressing/bandage changes, quality of life. **Adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal June 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2011, Embase 1980 to June 2011, and The Cochrane Database of Systematic Reviews, June 2011 [online] (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We included all studies described as "open", "open label", or not blinded. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 70). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

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

OPTION COMPRESSION BANDAGES AND STOCKINGS VERSUS NO COMPRESSION

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Compression bandages and stockings heal more ulcers compared with no compression.
- 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.

Benefits and harms

Compression bandages and stockings versus no compression:

We found one systematic review (search date 2008, 7 RCTs) comparing 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. See comment for further general information and observational data about harms of compression.

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[8] Systematic review	50 people Data from 1 RCT	**Proportion of ulcers healed** 19/27 (70%) with compression 6/23 (26%) with no compression	RR 2.70 95% CI 1.30 to 5.60	●●○	compression
[8] Systematic review	34 people Data from 1 RCT	**Healing** 9/17 (53%) with compression 7/17 (41%) with no compression	RR 1.29 95% CI 0.62 to 2.65	⟷	Not significant
[8] Systematic review	69 people Data from 1 RCT	**Proportion of ulcers healed** 21/30 (70%) with compression 15/39 (38%) with no compression	RR 1.82 95% CI 1.15 to 2.89	●○○	compression
[8] Systematic review	36 people Data from 1 RCT	**Healing** 18/19 (95%) with compression 7/17 (41%) with no compression	RR 2.30 95% CI 1.29 to 4.10	●●○	compression
[8] Systematic review	42 people Data from 1 RCT	**Healing** 17/21 (81%) with compression 15/21 (71%) with no compression	RR 1.13 95% CI 0.81 to 1.59	⟷	Not significant
[8] Systematic review	36 people Data from 1 RCT	**Healing** 12/18 (67%) with compression 4/18 (22%) with no compression	RR 3.00 95% CI 1.19 to 7.56	●●○	compression
[8] Systematic review	200 people Data from 1 RCT	**Proportion of ulcers healed , over 12 weeks** 54% with 4-layer elastomeric high-compression bandaging 34% with no compression Absolute numbers not reported	P <0.001	○○○	compression

Recurrence rates

Compression bandages and stockings compared with no compression We don't know whether compression is more effective at reducing recurrence rates in people with venous leg ulcers at 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[8] Systematic review	140 people Data from 1 RCT	**Recurrence rate , 12 months** 27/78 (35%) with compression 14/62 (22%) with no compression	RR 1.53 95% CI 0.88 to 2.66 P = 0.13	⟷	Not significant
[8] Systematic review	140 people Data from 1 RCT	**Mean ulcer-free weeks , 12 months** 20.1 weeks with compression 14.2 weeks with no compression	Difference: 5.9 weeks 95% CI 1.2 weeks to 10.5 weeks	○○○	compression

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] Systematic review	36 people Data from 1 RCT	**Withdrawal rate** 12 ulcers with compression 6 ulcers with no compression (hydrocolloid dressing) None of the people receiving compression discontinued treatment because of adverse effects; 9 people in the dressings group withdrew due to adverse effects including cellulitis and wound exudate	Not reported		

Further information on studies

[8] Many RCTs used a cut-off of 0.9 for the precise ankle/brachial pressure index below which compression is contraindicated (which is higher than the often-quoted value of 0.8; see comment).

Comment: 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. [9] One observational study (194 people) found that 4-layer compression bandaging for several months was associated with toe ulceration in 12 (6%) people. [10]

People thought to be suitable for high-compression treatments (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 included in the review 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. [11] 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 COMPRESSION BANDAGES

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Although we know compression increases healing rates in people with leg ulcers, we don't know which compression technique is most effective.

Benefits and harms

Compression stockings or tubular garments versus compression bandages:

We found two systematic reviews (search dates 2008, 8 RCTs, 688 people) [8] [12] and three subsequent RCTs [13] [14] [15] comparing compression stockings or tubular garments versus compression bandages. The two reviews included the same RCTs; however, the second review [12] included a meta-analysis for this comparison, therefore we have reported the pooled data here. One RCT [16] is included in both reviews; however, the reviews do not report recurrence for this comparison, therefore data on recurrence are reported from this individual RCT.

Healing rates

Compression stockings compared with compression bandages Compression stockings may be more effective at increasing healing rates and reducing mean time to healing in people with venous leg ulcers (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[12] Systematic review	688 people 8 RCTs in this analysis 1 RCT included in the pooled data had a crossover design	**Complete ulcer healing** 222/342 (65%) with compression stockings 161/346 (47%) with compression bandages	OR 0.44 95% CI 0.32 to 0.61 P <0.00001 The review reported significant heterogeneity between trials, P = 0.02	●●○	compression stockings
[12] Systematic review	535 people 7 RCTs in this analysis	**Mean time to healing** 11.63 weeks with compression stockings 14.77 weeks with compression bandages	SMD –0.33 95% CI –0.50 to –0.16 P <0.0001 The review reported significant heterogeneity among trials, P = 0.03	○○○	compression stockings
[13] RCT	80 people with venous leg ulcers	**Complete ulcer healing , 2 months** 15/40 (38%) with compression stockings plus drug therapy 5/40 (13%) with 2-layer short-stretch bandaging plus drug therapy All participants received drug therapy including micronised flavonoid fraction (diosmin 450 mg , hesperidin 50 mg), 2 tablets of 500 mg once daily (MPFF, Detralex)	P = 0.01	○○○	compression stockings
[14] RCT	55 people with recurrent, large (mean 13 cm^2), and long-lasting (mean 27 months) venous leg ulcers	**Ulcer healing , 90 to 180 days** 22% with compression stockings 5% with compression bandages Absolute numbers not reported	P = 0.40	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] RCT	55 people with recurrent, large (mean 13 cm^2), and long-lasting (mean 27 months) venous leg ulcers	**Mean time to healing , 180 days** 56 days with compression stockings 60 days with compression bandages	P = 0.94	⟷	Not significant
[15] RCT **3-armed trial**	46 people	**Percentage of ulcers healed , 12 weeks** 53% with compression stockings 63% with ProGuide 2-layered bandage system 60% with Profore 4-layered bandage system Absolute numbers not reported This RCT may have been underpowered for this comparison	P >0.05	⟷	Not significant

Recurrence rates

Compared with compression bandages alone Compression bandages plus tubulcus are more effective at reducing recurrence rates at 12 months in people with extensive venous leg ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[16] RCT	138 people with extensive venous leg ulceration (ulceration surface 20–210 cm^2, duration 7 months to 28 years)	**Recurrence rate , 12 months** 16/67 (24%) with multilayer bandaging system plus tubulcus 18/34 (53%) with multilayer bandaging system with elastic bandages only Tubulcus: a heel-less open-toed elastic compression device knitted in tubular form	P <0.05	○○○	multilayer bandaging system plus tubulcus

No data from the following reference on this outcome. [8] [12] [13] [14] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	134 people In review [12]	**Adverse effects** with stocking with short-stretch bandages Suspected causal relationship reported between treatments and 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	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[18] RCT	188 people randomised; 178 analysed In review [12]	**Pain caused by treatment** 14% with stocking 0% with short-stretch bandage Those affected complained of pain, and were subsequently given a larger stocking	Significance not assessed		
[12] Systematic review	53 people	**Mean pain scores at bandaging** 1.88 with compression stockings 3.69 with compression bandages Pain score range: 0 to 10; lower score = less pain 1 treatment-related adverse effect was reported in the group receiving the stocking; there were no further details relating to the nature of the adverse effect	P <0.0001	○○○	compression bandages
[12] Systematic review	53 people Data from 1 RCT	**Withdrawal rate** 4 with compression stocking 3 with compression bandage 1 person in the compression bandage group had a severe reaction to the dressing	P value not reported		
[12] Systematic review	56 people Data from 1 RCT	**Ulcer pain because of treatment** with compression stocking with compression bandage Absolute results not reported	P = 0.017	○○○	compression stocking
[12] Systematic review	56 people Data from 1 RCT	**Withdrawal rate** 38% with compression stocking 15% with compression bandage Absolute numbers not reported 1 withdrawal was deemed potentially related to compression (bullous dermatitis) in compression stocking group	P value not reported		

No data from the following reference on this outcome. [8] [13] [14] [15]

Further information on studies

Comment: See comment in option on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

OPTION MULTILAYER ELASTOMERIC HIGH-COMPRESSION REGIMENS VERSUS OTHER LAYERED REGIMENS

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .

- Although we know that compression bandages increase healing rates in people with leg ulcers, we don't know which compression bandaging technique is most effective.

Benefits and harms

Multilayer elastomeric high-compression regimens versus other layered regimens:

We found one systematic review (search date 2008, 7 RCTs, 449 people), [8] one additional RCT, [19] and one subsequent RCT. [20]

Healing rates

Multilayer elastomeric high-compression regimens compared with each other Four-layer compression bandages and other multilayer high-compression bandages may be equally effective at increasing healing rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[8] Systematic review	285 people 3 RCTs in this analysis	**Proportion of people healed** 99/142 (70%) with Charing Cross 4-layer bandages 98/143 (68%) with high-compression multilayer bandages	RR 1.02 95% CI 0.87 to 1.18 P = 0.85	⟷	Not significant
[8] Systematic review	164 people 4 RCTs in this analysis	**Complete healing** 37/83 (45%) with multilayer high compression system 33/81 (41%) with inelastic compression	RR 1.10 95% CI 0.78 to 1.53 P = 0.59	⟷	Not significant
[19] RCT	149 people	**Healing rates , at 20 weeks** 87% with original Charing Cross 4-layer bandage 84% and 83% with 2 commercial kits making a 4-layer bandage Absolute numbers not reported	P = 0.56	⟷	Not significant
[20] RCT **Crossover design**	81 people	**Wounds healed , 4 weeks** 6/39 (15%) with 2-layer compression 3/42 (7%) with 4-layer bandage	P = 0.30	⟷	Not significant
[20] RCT **Crossover design**	81 people	**Wound area reduction , 4 weeks** with 2-layer compression with 4-layer bandage Absolute results not reported	P = 0.88	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [8] [19] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	112 people In review [8]	**Number of people with at least 1 device-related adverse effect** 15/54 (28%) with 2-layer system 5/54 (9%) with 4-layer bandage Adverse effects included irritation, pain/discomfort, slippage, tissue breakdown, and excessive pressure	P = 0.01	○○○	4-layer bandage
[20] RCT **Crossover design**	81 people	**Adverse effects , 4 weeks** 67/135 (49.6%) with 2-layer compression 68/135 (50.4%) with 4-layer bandage Adverse effects included redness, eczema, folliculitis, wound infection, and pain	P value not reported		

No data from the following reference on this outcome. [19]

Further information on studies

Comment: See comment on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Although we know that compression bandages increase healing rates in people with leg ulcers, we don't know which compression bandaging technique is most effective.

Benefits and harms

Multilayer high-compression bandages versus single-layer bandage:

We found one systematic review (search date 2008, 4 RCTs, 280 people), which compared multilayer high-compression bandages versus a single layer of bandage. [8]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[8] Systematic review	280 people 4 RCTs in this analysis	**Proportion of people whose reference ulcer healed** 82/139 (59%) with multilayer compression bandages	RR 1.41 95% CI 1.12 to 1.77 P = 0.003	●○○	multilayer compression bandages

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		59/141 (42%) with single-layer bandages			

Recurrence rates

No data from the following reference on this outcome. [8]

Adverse effects

No data from the following reference on this outcome. [8]

Further information on studies

Comment: See comment on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

OPTION MULTILAYER ELASTOMERIC HIGH-COMPRESSION BANDAGES VERSUS SHORT-STRETCH BANDAGES OR UNNA'S BOOT/PASTE-BASED SYSTEMS

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Although we know compression bandages increase healing rates in people with leg ulcers, we don't know which compression bandaging technique is most effective.

Benefits and harms

Multilayer elastomeric high-compression bandages versus short-stretch bandages or Unna's boot:

We found two systematic reviews (search date 2008, 4 RCTs, 638 people [8] and search date 2008, 7 RCTs, 887 people [22]). The second review was an individual patient data meta-analysis. [22] The second review included two additional trials, so both reviews are reported here.

Healing rates

Multilayer elastomeric high-compression bandages compared with short-stretch bandages Multilayer elastomeric high-compression bandages seem no more effective than short-stretch bandages at increasing healing rates, but may reduce time to healing (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[8] Systematic review	638 people 4 RCTs in this analysis	**Healing rate** 164/317 (52%) with multilayer elastomeric bandages 149/321 (46%) with short-stretch bandages or Unna's boot	RR 1.07 95% CI 0.85 to 1.36 P = 0.57	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] Systematic review	797 people 5 RCTs in this analysis 3 RCTs included in the first review [8]	**Time to healing** with 4-layered bandage with short-stretch bandage Absolute results not reported	HR 1.31 95% CI 1.09 to 1.58	●○○	4-layered bandage

Recurrence rates

No data from the following reference on this outcome. [8] [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT	116 people In review [8]	**Withdrawal because of adverse effects** 1 with 4-layer compression bandages 1 with short-stretch bandages The RCT did not report the type of adverse effect	Significance not assessed		
[24] RCT	89 people In review [8]	**Withdrawal attributable to pain** 0 with elastomeric multilayer compression bandages 1 with short-stretch bandages	Significance not assessed		
[25] RCT	156 people In review [22]	**Adverse effects that were definitely bandage related** 12 with 4-layer bandages 9 with cohesive short-stretch bandages Adverse events included tissue damage/new ulcer, eczema/reaction to bandage, pain, and maceration	Significance not assessed		
[26] RCT	387 people In review [8]	**Adverse effects possibly related to compression treatment** 255 adverse effects (76 people) with 4-layer bandage 337 adverse effects (91 people) with short-stretch bandage 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	Significance not assessed		

Further information on studies

Comment: See comment on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Although we know compression bandages increase healing rates in people with leg ulcers, we don't know which compression bandaging technique is most effective.

Benefits and harms

Single-layer non-elastic system versus multilayer elastic system:

We found one RCT (12 people, 24 limbs). [27] The RCT compared a non-elastic compression device versus a 4-layer elastic bandage.

Healing rates

Single-layer non-elastic system compared with multilayer elastic system Non-elastic systems may be more effective than elastic systems 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[27] RCT	12 people, 24 limbs	**Complete healing of ulcers , at 12 weeks** 4/12 (33%) with non-elastic compression device 4/12 (33%) with 4-layer elastic bandage	Significance not assessed		
[27] RCT	12 people, 24 limbs	**Ulcer-area reduction , at 12 weeks** with non-elastic compression device with 4-layer elastic bandage Absolute results not reported	HR 0.56 95% CI 0.33 to 0.96	●○○	non-elastic system

Recurrence rates

No data from the following reference on this outcome. [27]

Adverse effects

No data from the following reference on this outcome. [27]

Further information on studies

Comment: See comment on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Although we know compression bandages increase healing rates in people with leg ulcers, we don't know which compression bandaging technique is most effective.

Benefits and harms

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). [28]

Healing rates

Single-layer compared with multilayer non-elastic system We don't know how single-layer and multilayer non-elastic systems compare at increasing healing rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[28] RCT	38 people	**Healing rates** 17/19 (89%) with non-elastic legging system 11/19 (58%) with Unna's boot	Significance not assessed		

Recurrence rates

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	38 people	**People withdrawing from study** 2 with non-elastic legging system 5 with Unna's boot Reasons for withdrawal: from non-elastic legging system: ulcer not healing and the person being referred for surgery; from Unna's boot (multilayer): allergy, weeping dermatitis, and increasing ulcer size	Significance not assessed		

Further information on studies

Comment: See comment on compression bandages and stockings versus no compression, p 4 for information regarding risks of high levels of compression.

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Peri-ulcer injections of granulocyte-macrophage colony-stimulating factor may increase healing.

Benefits and harms

Peri-ulcer injection of granulocyte-macrophage colony-stimulating factor:

We found one RCT, which compared a 4-week course of injections of recombinant human granulocyte-macrophage colony-stimulating factor (rHuGM-CSF) 200 micrograms or 400 micrograms around the ulcer, versus placebo. [29]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[29] RCT	60 people	**Proportion of people whose ulcers had completely healed , after 13 weeks' treatment** 23/39 (59%) with rHuGM-CSF (200 micrograms or 400 micrograms around the ulcer) 4/21 (19%) with placebo	RR (combined for rHuGM-CSF 200 micrograms and 400 micrograms) 3.21 95% CI 1.23 to 8.34 NNT for 13 weeks' treatment 2 95% CI 1 to 7	●●○	rHuGM-CSF

Recurrence rates

No data from the following reference on this outcome. [29]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT **3-armed trial**	60 people	**Proportion of people reporting adverse effects** 8/21 (38%) with rHuGM-CSF 200 micrograms 5/18 (26%) with rHuGM-CSF 400 micrograms 2/21 (9%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		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			

Further information on studies

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

OPTION COMPRESSION BANDAGES OR STOCKINGS VERSUS INTERMITTENT PNEUMATIC COMPRESSION

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether intermittent pneumatic compression is beneficial compared with compression bandages or stockings, as we found no trials.

Benefits and harms

Compression bandages or stockings versus intermittent pneumatic compression:

We found two systematic reviews (search dates 2001 [30] and 2010 [31]), which identified the same RCT (16 people). However, the number of people in this trial is below *Clinical Evidence* inclusion criteria, and is too small to draw a reliable conclusion (see comment).

Further information on studies

Comment: The RCT identified by the reviews found no significant difference in the proportion of people with healed ulcers over 2 to 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). The RCT is too small to draw a reliable conclusion.

OPTION DEBRIDING AGENTS

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We found no clinically important results from RCTs about the effects of debriding agents in people with venous leg ulcers.

Benefits and harms

Debriding agents versus usual care or versus each other:

We found two systematic reviews (search date 1997, 23 RCTs [32] and search date 2008, 8 RCTs [33]), which compared debriding agents versus traditional dressing in people with chronic non-healing wounds. The reviews did not perform meta-analysis in people with venous leg ulcers. Six RCTs (277 people) identified by first the review [32] 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 that we cannot draw any firm conclusions from these trials. The second review [33] reported on two small trials in venous ulcers; the first RCT compared collagenase with placebo ointment (30 people), the second RCT compared collagenase with a papain-urea ointment (26 people). The first RCT did not report any outcome of interest to this review and the second RCT found no significant difference between groups for change in wound size. Seven RCTs (451 people) identified by the first review compared cadexomer iodine versus traditional dressings, but only three RCTs reported complete ulcer healing. The incomplete reporting of healing rates means that we cannot draw any firm conclusions from these trials. Two RCTs identified by the first review compared enzymatic preparations versus traditional dressings (52 ulcers) and found no evidence of a difference in ulcer healing rates. See further information on studies and comment for information about adverse effects.

Further information on studies

[32] The review reported adverse effects such as pain, allergy, bacterial infection, and wound-size increase.

Comment: Preparations containing iodine may affect thyroid function if used over large surface areas for extended periods. [34] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [35]

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether semi-occlusive dressings are beneficial.

Benefits and harms

Semi-occlusive dressings (foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate) versus simple low-adherent dressings, in the presence of compression:

We found 5 systematic reviews (search date 1997, 6 RCTs; [36] search date 2003, 7 RCTs; [37] search date 2006, 2 RCTs; [38] search date 2005; [39] and search date 2009, 1 RCT, 183 people [40]). The first review identified 6 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. [36] The second review identified these 6 RCTs plus one other RCT, which compared a collagen dressing versus a non-adherent dressing. The third review identified two RCTs. [38] The first RCT included in the third review compared hyaluronic dressings versus paraffin gauze but did not fulfil *Clinical Evidence* criteria. [41] The second RCT included in the third review compared a collagen-plus-cellulose dressing versus a modern low-adherent dressing. [42] The fourth review [39] did not report trials with this comparison, so is not discussed further here. The RCT included in the fifth review [40] compared ibuprofen slow-release foam dressing versus local best practice, but only reported pain as an outcome.

Healing rates

Compared with simple low-adherent dressings Semi-occlusive dressings (foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate) may be no more effective than simple low-adherent dressings (such as paraffin-tulle or knitted viscose dressings) at increasing wound healing rates in the presence of compression (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[36] Systematic review	71 people Data from 1 RCT	**Wound healing** 11/36 (31%) with film 8/35 (23%) with saline-soaked gauze	OR 1.48 95% CI 0.5 to 4.3	⟷	Not significant
[36] Systematic review	132 people Data from 1 RCT	**Wound healing** 31/66 (47%) with foam 23/66 (35%) with knitted viscose	OR 1.67 95% CI 0.80 to 3.30	⟷	Not significant
[36] Systematic review	48 people Data from 1 RCT	**Mean change in wound area** –66% with foam compress +78% with sterile gauze compress	Mean difference between treatments: 144% 95% CI 49% to 239%	○○○	foam compress
[36] Systematic review	60 people Data from 1 RCT	**Wound healing** 26/30 (87%) with alginate dressing 24/30 (80%) with knitted viscose dressing	OR 1.62 95% CI 0.40 to 6.50	⟷	Not significant
[37] Systematic review	75 people Data from 1 RCT	**Proportion of ulcer healed** with collagen dressing with non-adherent dressing Absolute results not reported	RR 1.33 95% CI 0.71 to 2.49	⟷	Not significant
[42] RCT	73 people In review [38]	**Healing rates , at 12 weeks** 18/37 (49%) with collagen-plus-cellulose dressing 12/36 (33%) with modern low-adherent dressing	Risk difference: +0.16 95% CI –0.07 to +0.38	⟷	Not significant

No data from the following reference on this outcome. [40]

Recurrence rates

No data from the following reference on this outcome. [36] [37] [38] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[40] Systematic review	60 people with venous leg ulcers Data from 1 RCT Subgroup analysis	**Pain scores on evening of first application** with slow-release ibuprofen foam dressing with local best practice Absolute results not reported	RR for pain relief 1.08 95% CI 0.96 to 1.21	⟷	Not significant

No data from the following reference on this outcome. [36] [37] [38]

Alginate dressings versus zinc oxide dressings:

We found one systematic review (search date 1997), which identified one RCT. [36]

Healing rates

Alginate dressings compared with zinc oxide dressings We don't know how alginate dressings and zinc oxide dressings compare at increasing ulcer healing (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing rate					
[36] Systematic review **3-armed trial**	113 people, 133 ulcerated limbs Data from 1 RCT Remaining arm evaluated zinc oxide stocking	**Proportion of ulcers healed** 25/43 (58%) with zinc oxide bandage 16/46 (35%) with alginate dressings	OR 2.6 95% CI 1.1 to 6.1	●●○	zinc oxide bandage
[36] Systematic review **3-armed trial**	113 people, 133 ulcerated limbs Data from 1 RCT Remaining arm evaluated zinc oxide bandage	**Proportion of ulcers healed** 19/44 (43%) with zinc oxide stocking 16/46 (35%) with alginate dressings	OR 1.42 95% CI 0.61 to 3.34	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [36]

Adverse effects

No data from the following reference on this outcome. [36]

Comparisons between different occlusive or semi-occlusive dressings:

See option on hydrocolloid (occlusive) dressings in the presence of compression, p 29 .

Further information on studies

[36] [37] [38] The reviews reported adverse effects such as pain, infection, allergy, leakage, eczema, and odour.

[36] [37] [38] The RCTs identified by the reviews may have been too small to detect anything but a large difference in effectiveness.

Comment: 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. [34] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [35]

Simple primary dressings maintain a moist environment beneath compression bandages by preventing loss of moisture from the wound. [43]

OPTION INTERMITTENT PNEUMATIC COMPRESSION

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know how intermittent pneumatic compression alone compares with compression bandages, as no trials were found.
- We also found insufficient evidence to assess whether adding compression to bandages confers additional benefit over bandages alone.

Benefits and harms

Intermittent pneumatic compression versus compression bandages:

See option on compression bandages or stockings versus intermittent pneumatic compression, p 16 .

Intermittent pneumatic compression plus compression stockings versus compression stockings or bandages alone:

We found two systematic reviews (search date 2010, 4 RCTs, 163 people; [31] search date 2001, 2 RCTs, 99 people [30]). Two RCTs were included in both systematic reviews; therefore, only the most recent review is reported here. The first review pooled data for three RCTs, excluding one trial in a sensitivity analysis due to heterogeneity. See further information on studies and comment for more information about adverse effects.

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[31] Systematic review	123 people 3 RCTs in this analysis	**Number healed** 52/63 (83%) with intermittent pneumatic compression plus compression 46/60 (77%) with compression alone	RR 1.09 95% CI 0.91 to 1.30 P = 0.36	⟷	Not significant
[31] Systematic review	45 people Data from 1 RCT	**Proportion of people with healed ulcers , at 3 months** 10/21 (48%) with intermittent pneumatic compression plus graduated compression stockings 1/24 (4%) with graduated compression stockings alone	RR 11.4 95% CI 1.6 to 82.0	●●●	intermittent pneumatic compression plus graduated compression stockings

Recurrence rates

No data from the following reference on this outcome. [31]

Adverse effects

No data from the following reference on this outcome. [31]

Further information on studies

[31] One RCT identified by the review reported an adverse reaction to Unna's boot.

Comment: Peroneal neuropathy and compartment syndrome have been associated with the use of intermittent pneumatic compression to prevent deep vein thrombosis during surgery. [44]

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 to 4 hours daily. Treatment requires resting for 1 to 4 hours daily, which may reduce quality of life.

OPTION ANTIMICROBIAL AGENTS (TOPICAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether antimicrobial agents are beneficial, as we found few trials that assessed outcomes specifically in people with venous leg ulcers.

Benefits and harms

Topical antimicrobial agents versus placebo or usual care:

We found three systematic reviews (search date 1997, 14 RCTs; [45] search date 2006, 9 RCTs, 6 RCTs included in the first review; [46] and search date 2008, 10 RCTs [47]), two additional RCTs, [48] [49] and one subsequent RCT, [50] 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, and it is therefore not reported further here. [45] The third review included RCTs with mixed populations including people with arterial ulcers, diabetic foot ulcers, and pressure ulcers as well as venous leg ulcers; the review did not include a subgroup for venous leg ulcers. [47]

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 (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[46] Systematic review	147 people 2 RCTs in this analysis	**Proportion of ulcers completely healed** with dressings impregnated with silver with dressings not containing silver Absolute results not reported	RR 1.66 95% CI 0.68 to 4.05 P = 0.27	⟷	Not significant
[48] RCT	251 people	**Proportion of responders (defined as people with a >20% reduction in ulcer area) , at 28 days**	P <0.0001	○○○	ethacridine lactate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		104/129 (81%) with ethacridine lactate (0.1% solution) twice daily 69/122 (57%) with placebo			
[49] RCT	119 people	**Proportion of people with completely healed ulcers** 21/62 (34%) with 10% pale sulphonated shale oil 13/57 (23%) with vehicle (non-ionic gel)	P = 0.177	⟷	Not significant
[49] RCT	119 people	**Reduction in ulcer area** 72% with 10% pale sulphonated shale oil 19% with vehicle (non-ionic gel) Absolute numbers not reported	P <0.001	○○○	pale sulphonated shale oil
[47] Systematic review	1188 people with leg wounds and ulcers 7 RCTs in this analysis Population included people with surgical wounds, traumatic wounds, arterial ulcers, diabetic foot ulcers, and pressure ulcers as well as venous leg ulcers	**Complete wound healing** 68/574 (12%) with silver impregnated dressing 52/544 (10%) with non-silver dressing	Risk difference for healing: +0.02 95% CI –0.01 to +0.06 P = 0.18	⟷	Not significant
[50] RCT	213 people with venous leg ulcers	**Ulcers healed , 12 months** 95/107 (89%) with silver-donating dressings 90/106 (85%) with non-silver low-adherence dressings Intention-to-treat analysis	RR 1.03 95% CI 0.51 to 2.08	⟷	Not significant

Recurrence rates

Topical antimicrobial agents compared with placebo or usual care We don't know whether silver-donating dressings are more effective at reducing recurrence rates in people with venous leg ulcers at 12 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[50] RCT	213 people with healed venous leg ulcers	**Recurrence , 12 months** 11/107 (10%) with silver-donating dressings 13/106 (12%) with non-silver low-adherence dressings	P value not reported		

No data from the following reference on this outcome. [46] [47] [48] [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] RCT	119 people	**Adverse effects** 12% with 10% pale sulphonated shale oil 11% with vehicle (non-ionic gel) Absolute numbers not reported	Significance not assessed		
[49] RCT	119 people	**Eczema and pruritus** 2/62 (3%) with 10% pale sulphonated shale oil 2/57 (4%) with vehicle (non-ionic gel) Absolute results not reported	P value not reported		

No data from the following reference on this outcome. [46] [47] [48] [50]

Further information on studies

[45] The review reported adverse events such as erythema, pruritus, and severe irritation.

[48] Ulcer healing was not reported.

Comment: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [35]

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)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether calcitonin gene-related peptide is beneficial, as we found few trials.

Benefits and harms

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. [51]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[51] Systematic review	66 people	**Proportion of people with healed ulcers , after 12 weeks** 11/33 (33%) with calcitonin (salcatonin) gene-related peptide	RR 1.83 95% CI 0.77 to 4.38	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		plus vasoactive intestinal polypeptide 6/33 (18%) with placebo	The RCT may have been too small to detect a clinically important difference between groups		

Recurrence rates

No data from the following reference on this outcome. [51]

Adverse effects

No data from the following reference on this outcome. [51]

Further information on studies

Comment: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [35]

OPTION MESOGLYCAN (TOPICAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether mesoglycan is beneficial, as we found few trials.

Benefits and harms

Topical mesoglycan versus a plant-based extract:

We found one RCT, which compared topically applied mesoglycan, a profibrinolytic agent, and a plant-based extract. [52]

Healing rates

Compared with plant-based extract We don't know how topical mesoglycan (a profibrinolytic agent) and plant-based extract compare at increasing ulcer healing at 2 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[52] RCT	40 people	**Cure rates , 2 months** 19/20 (95%) with topical mesoglycan 16/20 (80%) with plant extract	Significance not assessed		

Recurrence rates

No data from the following reference on this outcome. [52]

Adverse effects

No data from the following reference on this outcome. [52]

Further information on studies

Comment: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [35]

OPTION TOPICAL NEGATIVE PRESSURE

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether topical negative pressure is beneficial, as we found few trials.

Benefits and harms

Topical negative pressure versus usual care:

We found two systematic reviews (search dates 2002 [53] and 2004 [54]) and one subsequent RCT. [55] Both reviews identified one RCT (24 people), which compared topical negative pressure versus simple dressings. [53] [54] 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; therefore, it is not reported further here.

Healing rates

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 arteriovenous ulcers of at least 6 months' duration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Time to complete healing** 29 days with topical negative pressure vacuum-assisted closure (VAC) 45 days with control (conventional wound care techniques)	P = 0.001	○○○	VAC

Recurrence rates

Compared with usual care Topical negative pressure (vacuum-assisted closure [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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Median length of time to recurrence** 4 months with topical negative pressure vacuum-assisted closure (VAC) 2 months with control (conventional wound care techniques)	P = 0.47	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] Systematic review	18 people Data from 1 RCT	**Adverse effects** 3/18 (17%) wounds with topical negative pressure No data with usual care Adverse effects included osteomyelitis, calcaneal features, or both 2 people suffered calcaneal features while ambulating on the topical negative pressure dressing (against medical advice). Both people eventually required amputation	Significance not assessed		
[53] Systematic review	24 people Data from 1 RCT	**Pain** with topical negative pressure with simple foam dressing Pain in some people with topical negative pressure with initial collapse, foam dressing removal, or both	Significance not assessed		
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Erysipelas** 1 with topical negative pressure vacuum-assisted closure (VAC) 0 with control (conventional wound care techniques)	Reported as not significant P value not reported	⟷	Not significant
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Pain** 3 with topical negative pressure VAC 1 with control (conventional wound care techniques)	P value not reported		
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Wound infection** 0 with topical negative pressure VAC 1 with control (conventional wound care techniques)	P value not reported		
[55] RCT	60 people with venous or arteriovenous ulcers of at	**Postoperative bleeding at donor site** 0 with topical negative pressure VAC	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	least 6 months' duration	2 with control (conventional wound care techniques)			
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Non-healing ulcers** 1 with topical negative pressure VAC 1 with control (conventional wound care techniques)	P value not reported		
[55] RCT	60 people with venous or arteriovenous ulcers of at least 6 months' duration	**Cutaneous damage secondary to treatment** 7 with topical negative pressure VAC 2 with control (conventional wound care techniques)	P <0.05	○○○	control

Further information on studies

[54] One review reported that one of the 10 RCTs of topical negative therapy underway includes venous leg ulcers.

[55] In the RCT, all the included people had chronic ulcers (>6 months' duration) and were hospitalised throughout. This limits the applicability of this evidence, as most ulcers are treated outside hospital, which reduces cost.

Comment: None.

OPTION RECOMBINANT KERATINOCYTE GROWTH FACTOR 2 (TOPICAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether topical recombinant keratinocyte growth factor 2 is beneficial, as we found few trials.

Benefits and harms

Topical recombinant human keratinocyte growth factor 2 plus compression versus placebo plus compression:

We found one RCT, which compared topically applied recombinant human keratinocyte growth factor 2 (repifermin 20 micrograms/cm^2 or 60 micrograms/cm^2) in people receiving compression versus placebo plus compression. [56]

Healing rates

Topical recombinant human keratinocyte growth factor 2 plus compression compared with placebo plus compression

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[56] RCT **3-armed trial**	94 people	**Rate of complete ulcer healing, after 12 weeks** 32% with repifermin 20 micrograms/cm^2 38% with repifermin 60 micrograms/cm^2 29% with placebo Absolute numbers not reported	P = 0.57 for all doses of human keratinocyte growth factor 2 *v* placebo	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [56]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] RCT **3-armed trial**	94 people	**Adverse effects** with repifermin (at either dose) with placebo Absolute results not reported Adverse effects included leg pain, pruritus, skin ulcers, rash abrasion, and reopening of venous leg ulcers	Reported as not significant The RCT may have lacked power to detect a clinically important difference between groups	⟷	Not significant

Further information on studies

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)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether topical platelet-derived growth factor is beneficial, as we found few trials.

Benefits and harms

Platelet-derived growth factor versus placebo:

We found two RCTs in one publication, comparing platelet-derived growth factor versus placebo gel. [57]

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[57]	71 people Data from 1 RCT	**Healing rates** 12/35 (36%) with platelet-derived growth factor 12/36 (34%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[57]	64 people Data from 1 RCT	**Healing rates** 18/32 (56%) with platelet-derived growth factor 14/32 (44%) with placebo	Significance not assessed		

Recurrence rates

No data from the following reference on this outcome. [57]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[57]	71 people Data from 1 RCT	**Proportion of people with at least 1 treatment-related, wound-related adverse effect** 11/35 (31%) with platelet-derived growth factor 14/36 (39%) with placebo	Significance not assessed		
[57]	64 people Data from 1 RCT	**Proportion of people with at least 1 treatment-related, wound-related adverse effect** 17/32 (53%) with platelet-derived growth factor 11/32 (34%) with placebo	Significance not assessed		

Further information on studies

Comment: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [35]

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/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116909.htm).

OPTION HYDROCOLLOID (OCCLUSIVE) DRESSINGS IN THE PRESENCE OF COMPRESSION

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- 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.

Benefits and harms

Hydrocolloid (occlusive) dressings versus simple dressings in the presence of compression:

We found three systematic reviews (search date 1997, 16 RCTs; [36] search date 2003, 15 RCTs; [37] and search date 2006, 27 RCTs [38]). The first systematic review identified 9 RCTs, the second review identified 8 RCTs, and the third review identified 9 RCTs comparing hydrocolloid dressings versus simple dressings in the presence of compression. Five RCTs were included in both the first and second reviews. [36] [37]

Healing rates

Compared with simple dressings Hydrocolloid dressings are no more effective than simple low-adherent dressings at increasing ulcer healing rates in people receiving compression (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[36] Systematic review	714 people 7 RCTs in this analysis	**Rates of ulcer healing** 158/358 (44%) with hydrocolloid dressing 140/356 (39%) with simple low-adherent dressing	OR 1.45 95% CI 0.83 to 2.54	⟷	Not significant
[37] Systematic review	782 people 8 RCTs in this analysis	**Ulcer healing** 172/397 (43%) with hydrocolloid dressing 168/385 (44%) with simple low-adherent dressing	RR 0.99 95% CI 0.85 to 1.15	⟷	Not significant
[38] Systematic review	792 people 8 RCTs in this analysis	**Ulcer healing** 190/397 (48%) with hydrocolloid dressing 170/395 (45%) with simple low-adherent dressing	RR 1.09 95% CI 0.89 to 1.34	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [36] [37] [38]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] [37] [38] Systematic review	Number of people not reported	**Adverse effects** with hydrocolloid dressing with simple low-adherent dressing Reported adverse effects included wound infection, cellulitis, increase in ulcer size, and dermatitis of peri-ulcer skin	Significance not assessed		

Hydrocolloids versus other occlusive or semi-occlusive dressings:

We found three systematic reviews (search date 1997, 6 RCTs; [36] search date 2003, 6 RCTs; [37] and search date 2006, 9 RCTs [38]), 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.

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[38] Systematic review	311 people 4 RCTs in this analysis	**Proportion of ulcers healed , between 12 and 16 weeks** 85/171 (50%) with hydrocolloid 69/140 (49%) with foam	RR 0.98 95% CI 0.79 to 1.22 P = 0.9	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [38]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] [38] Systematic review	Number of people not reported 4 RCTs in this analysis	**Adverse effects** with hydrocolloid with foam Absolute results not reported Reported adverse events included pain, wound infection, allergy, dressing leakage, peri-wound eczema, injury/intolerance of peri-ulcer skin, and extensive exudates and odour leakage	Significance not assessed		

Different occlusive or semi-occlusive dressings (excluding hydrocolloids) versus each other:

We found two systematic reviews (search date 1997, 1 small RCT; [36] and search date 2006, 8 RCTs [38]), and three subsequent RCTs, [58] [59] [60] 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; therefore, they are not reported further here. [36] [38]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[58] RCT	107 people	**Healing rates , at 12 weeks** 39% with foam dressing 36% with foam composite Absolute numbers not reported	Significance not assessed		
[59] RCT	159 people	**Complete ulcer healing , over 24 weeks** 50/81 (62%) with foam dressing 50/75 (67%) with silicone foam dressing Both interventions under compression	HR for healing 1.48 95% CI 0.87 to 2.54 P = 0.15	⟷	Not significant
[60] RCT **Crossover design**	122 people with chronic venous leg ulcers of >8 weeks' duration 8 RCTs in this analysis The groups were assessed in 1 treatment on days 1 to 5, and then subsequently crossed over to the other treatment and were assessed at days 43 to 47	**Ulcer healing , at 24 weeks** 11.2 cm^2 to 7.9 cm^2 with ibuprofen 7.2 cm^2 to 3.8 cm^2 with non-ibuprofen 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 to 5 and days 43 to 47 when pain was assessed	Reported as not significant P value not reported	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [58] [59] [60]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[58] RCT	107 people	**Adverse effects** with foam dressing with foam composite Absolute results not reported The most common adverse effect with foam dressing was maceration (6 people). The most common adverse effect with foam composite was new wound development in different anatomical locations (6 people)	Significance not assessed		
[59] RCT	159 people	**Adverse effects definitely related to the dressing** 11 with foam dressing 11 with silicone foam dressing	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[60] RCT **Crossover design**	122 people with chronic venous leg ulcers of >8 weeks' duration 8 RCTs in this analysis The groups were assessed in 1 treatment on days 1 to 5, and then subsequently crossed over to the other treatment and were assessed at days 43 to 47	**Proportion of people with adverse effects (number of adverse effects)** 12 people (21 adverse effects) with ibuprofen 7 people (10 adverse effects) with non-ibuprofen 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 to 5 and days 43 to 47 when pain was assessed	Significance not assessed P value not reported		

Further information on studies

[60] People were randomised to the ibuprofen group (62 people) and non-ibuprofen group (60 people).

[60] The RCT also assessed chronic (persistent) and dressing change-related (temporary) pain on days 1 to 5 and on days 43 to 47 (after crossover). 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). It found that ibuprofen dressings significantly reduced chronic pain on days 1 to 5 compared with non-ibuprofen dressings (46/62 [74%] with ibuprofen *v* 35/60 [58%] with non-ibuprofen dressings, P = 0.0003). Ibuprofen dressings reduced pain intensity from 6.8 to 4.1, while non-ibuprofen dressings 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.

Comment: 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. [34] Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives, perfumes, or dyes. [35]

Simple primary dressings maintain a moist environment beneath compression bandages as the layers of dressings and bandages prevent loss of moisture from the wound. [43] 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. [60]

OPTION AUTOLOGOUS PLATELET LYSATE (TOPICALLY APPLIED)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Autologous platelet lysate (topically applied) does not seem to be beneficial, but we found few trials.

Benefits and harms

Topically applied autologous platelet lysate versus placebo:

We found one RCT, comparing topical autologous platelet lysate versus placebo. [61]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[61] RCT	86 people	**Proportion of people healed , at 9 months** 33/42 (78%) with topical autologous platelet lysate 34/44 (77%) with placebo	RR 1.05 95% CI 0.80 to 1.30	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [61]

Adverse effects

No data from the following reference on this outcome. [61]

Further information on studies

[61] The RCT reported that there was no evidence of any adverse effects specifically related to the application of the lysate solution.

Comment: Many people (50–85%) with venous leg ulcers have contact sensitivity to preservatives. [35]

OPTION FREEZE-DRIED KERATINOCYTE LYSATE (TOPICALLY APPLIED)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Freeze-dried keratinocyte lysate (topically applied) does not seem to be beneficial, but we found few trials.

Benefits and harms

Topically applied freeze-dried keratinocyte lysate versus vehicle or usual care:

We found one RCT, which compared three interventions: keratinocyte lysate plus usual care, placebo (vehicle) plus usual care, and usual care alone. [62]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[62] RCT **3-armed trial**	200 people RCT examined usual care plus lysate, usual care	**Healing , 24 weeks** 37% with keratinocyte lysate plus usual care 27% with vehicle plus usual care or usual care alone	P = 0.14	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	plus vehicle, and usual care alone				

Recurrence rates

No data from the following reference on this outcome. [62]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[62] RCT **3-armed trial**	200 people	**Proportion of people who had at least 1 general adverse effect , during the treatment phase** 25% with keratinocyte lysate plus usual care 25% with vehicle plus usual care 22% with usual care alone Absolute numbers not reported 24% in total	Reported as not significant	⟷	Not significant
[62] RCT **3-armed trial**	200 people	**Proportion of people who had at least 1 general adverse effect , during follow-up period** 16% with keratinocyte lysate plus usual care 17% with vehicle plus usual care 12% with usual care alone Absolute numbers not reported 15% in total	Reported as not significant	⟷	Not significant

Further information on studies

Comment: None.

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

OPTION PENTOXIFYLLINE (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Oral pentoxifylline increases ulcer healing in people receiving compression.

Benefits and harms

Oral pentoxifylline versus placebo:

We found one systematic review (search date 2007, 12 RCTs). [63] The systematic review compared pentoxifylline (oxpentifylline) 1200 or 2400 mg daily versus placebo or versus other treatments, with or without compression. [63]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[63] Systematic review	659 people receiving compression 7 RCTs in this analysis	**Proportion of people with healed ulcers , over 8 to 24 weeks** 221/348 (64%) with pentoxifylline (1200 or 2400 mg/day) 126/311 (40%) with placebo	RR 1.51 95% CI 1.3 to 1.76	●○○	pentoxifylline

Recurrence rates

No data from the following reference on this outcome. [63]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] Systematic review	549 people receiving compression Number of trials not reported	**Adverse effects** 55/297 (18%) with pentoxifylline 33/252 (13%) with placebo Nearly half the adverse effects were gastrointestinal (dyspepsia, vomiting, or diarrhoea)	RR 1.27 95% CI 0.89 to 1.83	⟷	Not significant

Further information on studies

[63] 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).

Comment: None.

OPTION CULTURED ALLOGENIC BILAYER SKIN REPLACEMENT

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Cultured allogenic bilayer skin replacement (containing both epidermal and dermal components) increases healing in people with venous leg ulcers receiving compression.

Benefits and harms

Cultured allogenic bilayer skin replacement versus non-adherent dressing:

We found two systematic reviews (search date 2004, 17 RCTs; [64] and search date 2009, 2 RCTs [65]). The first review included 6 RCTs comparing cultured allogenic skin replacement compared with control; however, the review did not report data for individual trials, and did not report pooled data for a subgroup of people with venous leg ulcers, so is not discussed further here. [64]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[65] Systematic review	345 people receiving compression 2 RCTs in this analysis	**Proportion of ulcers healed completely , 6 months** with cultured allogenic bilayer skin replacement, containing both epidermal and dermal components with a simple non-adherent dressing Absolute results not reported	RR 1.51 95% CI 1.22 to 1.88 calculated using fixed-effect model	●○○	cultured allogenic bilayer skin replacement

Recurrence rates

No data from the following reference on this outcome. [65]

Adverse effects

No data from the following reference on this outcome. [65]

Further information on studies

Comment: We found no evidence of harm from tissue-engineered skin. [65]

OPTION FLAVONOIDS (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Oral flavonoids may be effective at increasing ulcer healing in people receiving compression.

Benefits and harms

Flavonoids plus compression versus compression alone:

We found one systematic review reported in two publications (search date 2003, 5 RCTs, 723 people). [66] [67] The first publication reported healing at 2 months, [66] and the second publication reported healing at 6 months. [67]

However, the review excluded two unpublished RCTs 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. Therefore, we have reported the results of the meta-analysis and the individual RCTs because of uncertainty about the meta-analysis (see further information on studies for additional information about adverse effects).

Healing rates

Compared with compression alone We don't know whether flavonoids plus compression are more effective than compression alone at increasing ulcer healing rates (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[66] Systematic review	452 people 3 RCTs in this analysis	**Ulcer healing , 2 months** with flavonoids with compression plus placebo or compression alone Absolute results not reported	HR 1.38 95% CI 1.11 to 1.70 See further information on studies	●○○	flavonoids
[67] Systematic review	616 people 5 RCTs in this analysis	**Proportion of ulcers healed , 6 months** 61% with daflon 500 mg 48% with control Absolute numbers not reported Control included: placebo plus elastic compression or 2-layer inelastic compression, or compression alone	RRR 32% 95% CI 3% to 70% P = 0.03 Significant heterogeneity P = 0.014	○○○	daflon
[66] Systematic review	107 people Data from 1 RCT	**Cure rates , at 2 months** 14/53 (26%) with flavonoids 6/52 (11%) with placebo	RR 2.29 95% CI 0.99 to 5.43	⟷	Not significant
[66] Systematic review	107 people Data from 1 RCT	**Time to healing of ulcers <10 cm^2 , at 2 months** with flavonoids with placebo Absolute results not reported	P = 0.037	○○○	flavonoids
[66] Systematic review	202 people (previously unpublished) Data from 1 RCT	**Cure rates , 2 months** 21/103 (20%) with flavonoids plus compression 25/99 (25%) with compression plus placebo	Significance not assessed		
[66] Systematic review	140 people Data from 1 RCT	**Cure rates , at 6 months** 33/71 (47%) with flavonoids 19/69 (28%) with compression alone	OR 2.3 95% CI 1.1 to 4.6	●○○	flavonoids
[66] Systematic review	150 people Data from 1 RCT	**Cure rates , at 2 months** 10/71 (14%) with flavonoids 6/69 (9%) with compression alone	Significance not assessed		
[66] Systematic review	124 people (previously unpublished) Data from 1 RCT	**Proportion of people healing , 2 months** 25/62 (40%) with flavonoids plus compression 13/62 (21%) with compression alone	Significance not assessed		

Recurrence rates

No data from the following reference on this outcome. [66] [67]

Adverse effects

No data from the following reference on this outcome. [66] [67]

Further information on studies

[66] The findings of the meta-analysis 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%).

[66] The review reported adverse effects of flavonoids, such as gastrointestinal disturbance, in 10% of people.

Comment: None.

OPTION SULODEXIDE (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Sulodexide may be effective at increasing ulcer healing in people receiving compression.

Benefits and harms

Oral sulodexide plus compression versus compression alone:

We found 4 RCTs (488 people). [68] [69] [70] [71]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[68] RCT	235 people	**Cure rates , 3 months** 63/121 (52%) with adding sulodexide to compression 36/114 (32%) with placebo	RR 1.65 95% CI 1.28 to 18.54	●○○	sulodexide
[69] RCT	95 people	**Cure rates , at 2 months** 30/52 (58%) with adding sulodexide to compression 15/43 (35%) with compression alone	RR 1.65 95% CI 1.06 to 2.7 NNT for 3 months' treatment 4 95% CI 3 to 9	●○○	sulodexide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[70] RCT	44 people	**Healing rates , 7 weeks** 16/23 (70%) with adding intramuscular and then oral sulodexide to a compression regimen 7/21 (35%) with control	P <0.05	○○○	sulodexide
[71] RCT	114 people	**Healing , at 30 days** 32/61 (52%) with oral sulodexide 17/53 (32%) with compression alone	P <0.05	○○○	sulodexide

Recurrence rates

No data from the following reference on this outcome. [68] [69] [70] [71]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[68] RCT	235 people	**Proportion of people with adverse effects** 23 (19%) with sulodexide 17 (15%) with placebo 4 adverse events in the treatment group (1 cutaneous rash, 1 diarrhoea, 1 epigastric pain, and 1 headache) were considered treatment-related	Significance not assessed		
[71] RCT	114 people	**Adverse effects** with oral sulodexide with compression alone No severe adverse effects in the people included in the RCT	Significance not assessed		

No data from the following reference on this outcome. [69] [70]

Further information on studies

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

OPTION MESOGLYCAN (SYSTEMIC)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .

- Mesoglycan may be effective at increasing ulcer healing in people receiving compression.

Benefits and harms

Systemic mesoglycan plus compression versus placebo plus compression:

We found one RCT comparing systemic mesoglycan plus compression versus placebo plus compression. [72]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[72] RCT	183 people	**Proportion of people with healed ulcers , after 24 weeks** 82/92 (89%) with systemic mesoglycan 69/91 (76%) with placebo Mesoglycan given intramuscularly daily for 21 days and then orally for 21 weeks	RR 1.17 95% CI 1.03 to 1.35	●○○	mesoglycan

Recurrence rates

No data from the following reference on this outcome. [72]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[72] RCT	183 people	**Adverse-event incidence , after 24 weeks** 7/92 (8%) with mesoglycan 6/91 (7%) with placebo 2 serious (non-fatal) events in each group; 2 people withdrew from mesoglycan treatment (road accident trauma and congestive heart failure), and 4 from placebo (skin rash, cerebral stroke, ischaemia, and rectal bleeding). Most of the events were considered unrelated to treatment	Significance not assessed		

Further information on studies

Comment: None.

OPTION CULTURED ALLOGENIC SINGLE-LAYER DERMAL REPLACEMENT

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether single-layer dermal skin replacements are effective at increasing ulcer healing rates.

Benefits and harms

Cultured allogenic single-layer dermal replacement versus usual care:

We found one systematic review (search date 2009, 2 RCTs, 71 people), which compared single-layer 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 4-piece regimen versus usual care.

Healing rates

Cultured allogenic single-layer dermal replacement 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 to 11 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[65] Systematic review	71 people 2 RCTs in this analysis	**Rates of healing , at baseline, 1, 4, 8 weeks** with 4-piece dermal skin replacement with usual care Absolute results not reported	RR 3.04 95% CI 0.95 to 9.68 P = 0.06	⟷	Not significant
[65] Systematic review	26 people Data from 1 RCT	**Rates of healing , at 11 weeks** with 12-piece dermal skin replacement with usual care Absolute results not reported	RR 2.5 95% CI 0.59 to 10.64 P = 0.2	⟷	Not significant
[65] Systematic review	26 people Data from 1 RCT	**Rates of healing , at 11 weeks** with 1-piece dermal skin replacement with usual care Absolute results not reported	RR 0.46 95% CI 0.05 to 4.53 P = 0.05	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [65]

Adverse effects

No data from the following reference on this outcome. [65]

Further information on studies

[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 4-piece regimen versus usual care.

Comment: 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. [65]

OPTION PROSTAGLANDIN E1 (INTRAVENOUS)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether intravenous prostaglandin E1 increases healing of ulcers in people treated with elastic bandaging and local treatment.

Benefits and harms

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. [73] Participants received infusions as outpatients and stayed in hospital for 6 hours. Both groups were also treated with elastic bandaging and local treatment.

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[73] RCT	87 people	**Proportion of ulcers healed , at 120 days** 40/44 (91%) with prostaglandin E1 (PGE1; 60 mg/day infused over 2 hours) 32/43 (74%) with placebo	P <0.05	○○○	PGE1

Recurrence rates

No data from the following reference on this outcome. [73]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[73] RCT	87 people	**Adverse effects** 5/44 (11%) with PGE1 (60 mg/day infused over 2 hours) 2/43 (5%) with placebo Adverse effects included headache, nausea, hypotension, diarrhoea, and vomiting	Significance not assessed		

Further information on studies

[73] The RCT did not include an analysis that was adjusted for effects of bandages and local treatment.

Comment: Prostaglandin E1 (PGE1) improves local ischaemia, and so could be effective in the treatment of venous leg ulcers.

OPTION LARVAL THERAPY

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Larval therapy is not likely to be beneficial as it has no impact on healing and is painful.

Benefits and harms

Larval therapy versus usual care:

We found one systematic review (search date 2008, 1 RCT, 12 people) on larval therapy in the healing of venous leg ulcers [74] and one subsequent RCT. [75] The RCT included in the review on venous leg ulcers only included 12 people, which does not fulfil *Clinical Evidence* criteria so it will not be discussed further here. [74] The subsequent RCT (267 people) compared loose larvae or bagged larvae with hydrogel. [75] However, the RCT reported no difference between the two larvae groups for time to ulcer healing; therefore, data are presented for overall larvae (loose and bagged) versus hydrogel.

Healing rates

Compared with hydrogel We don't know whether larval therapy is more effective at improving time to ulcer healing in people with venous leg ulcers (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[75] RCT	267 people with venous leg ulcers (sloughy)	**Time to ulcer healing** with larval therapy with hydrogel Absolute results not reported	HR 1.13 95% CI 0.76 to 1.68 P = 0.54	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [75]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[75] Systematic review	267 people with venous leg ulcers	**Adverse effects** 52% with larval therapy 48% with hydrogel Absolute numbers not reported	P = 0.10	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[75] RCT	267 people with venous leg ulcers	**Pain caused by treatment** with larval therapy with hydrogel Absolute results not reported	P <0.001	○○○	hydrogel

Further information on studies

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 ulceration. [76]

OPTION LASER TREATMENT (LOW-LEVEL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether laser treatment increases healing of ulcers in people treated with compression.

Benefits and harms

Low-level laser treatment versus sham treatment:

We found two systematic reviews (search date 2001, 4 RCTs; [77] and search date 1999, 5 RCTs [78]) and 4 subsequent RCTs (5 publications). [79] [80] [81] [82] [83] The second review [78] identified, but did not describe fully, the 4 RCTs identified by the first review, and did not perform a meta-analysis.

Healing rates

Compared with sham or control 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[77] Systematic review	88 people 2 RCTs in this analysis	**Healing rates , over 12 weeks** 17/44 (39%) with low-level laser treatment 14/44 (32%) with sham treatment	RR 1.21 95% CI 0.73 to 2.03	⟷	Not significant
[77] Systematic review **3-armed trial**	30 people Data from 1 RCT The remaining arm evaluated low-level laser treatment	**Proportion of ulcers healed , after 9 months' treatment** 12/15 (80%) with laser plus infrared light 5/15 (33%) with non-coherent, unpolarised red light	RR 2.40 95% CI 1.12 to 5.13	●●○	laser plus infrared light
[79] RCT **3-armed trial**	65 people receiving compression and drug treatment Unclear if the "no additional treatment" was established by randomisation	**Reduction in area of ulceration** 4.25 cm^2 (27%) with laser 5.21 cm^2 (39%) with sham laser 2.98 cm^2 (18%) with no treatment	Reported as not significant P value not reported The RCT may have lacked power to detect clinically important differences	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[80] [81] RCT **3-armed trial**	44 people	**Reduction in ulcer size** with compression plus low-level laser with compression plus placebo laser with compression alone Absolute results not reported	The RCT reported within-group rather than between-group differences Reported as not significant The RCT may have lacked power to detect clinically important differences	⟷	Not significant
[82] RCT **4-armed trial**	83 people The remaining arms assessed surgery (22 people), and surgery plus laser (20 people)	**Complete healing** 3/21 (14%) with low-level laser therapy plus conservative treatment 3/20 (15%) with conservative treatment alone	P value not reported Reported as not significant	⟷	Not significant
[83] RCT	34 people with venous leg ulcers	**Complete healing , 9 weeks** 3/18 (17%) with low-level laser therapy 4/16 (25%) with hydrocellular dressing	P = 0.62	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [77] [78] [79] [80] [81] [82] [83]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[80] [81] RCT **3-armed trial**	44 people The remaining arm included compression alone.	**Proportion of people with increase in ulcer area** 28% with compression plus low-level laser 11% with compression plus placebo laser Absolute numbers not reported	Significance not assessed		

No data from the following reference on this outcome. [77] [78] [79] [82] [83]

Further information on studies

[77] [78] [79] [80] [81] [82] [83] The laser power, wavelength, frequency, duration, and follow-up of treatment were different for all of the trials.

[78] The review did not assess complete ulcer healing.

Comment: Eye protection is required when using some types of laser, as the high-energy beam may damage the retina.

OPTION ASPIRIN (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether oral aspirin increases healing of ulcers in people treated with compression.

Benefits and harms

Oral aspirin versus placebo:

We found one small RCT comparing aspirin versus placebo. [84]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[84] RCT	Number of people reported as "small"	**Ulcer healing rates** 38% with aspirin (300 mg/day, enteric-coated) 0% with placebo Absolute numbers not reported	P <0.007 The RCT had several methodological weaknesses, so the result should be treated with caution	○○○	aspirin

Recurrence rates

No data from the following reference on this outcome. [84]

Adverse effects

No data from the following reference on this outcome. [84]

Further information on studies

Comment: None.

OPTION RUTOSIDES (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether oral rutosides increase healing of ulcers in people treated with or without compression.

Benefits and harms

Oral rutosides versus placebo:

We found two reports of three RCTs. [85] [86] The two RCTs (119 people) reported in one publication compared two different doses of oral hydroxyethyl rutosides (500 mg and 1000 mg twice daily) versus placebo. [85] The third RCT compared oral rutosides 500 mg twice daily plus compression versus compression alone. [86]

Healing rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[85] Systematic review	55 people, 48 analysed Data from 1 RCT	**Rates of complete ulcer healing** 12/23 (52%) with rutoside 1 g daily 7/25 (28%) with placebo	P = 0.087 The RCT may have been too small to detect a clinically important difference (between groups)	⟷	Not significant
[85] Systematic review	64 people Data from 1 RCT	**Rates of complete ulcer healing , 12 weeks** with rutoside 500 mg twice daily with placebo Absolute results not reported	Reported as not significant P value not reported The RCT may have been too small to detect a clinically important difference (between groups)	⟷	Not significant
[86] RCT	107 people	**Healing rates , 6 weeks** 10/55 (18%) with rutoside 500 mg twice daily plus compression 12/52 (23%) with compression alone	Significance not assessed The RCT may have been too small to detect a clinically important difference (between groups)		

Recurrence rates

No data from the following reference on this outcome. [85] [86]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[85] Systematic review	119 people 2 RCTs in this analysis	**Adverse effects** with rutosides with placebo Absolute results not reported	Reported as not significant P value not reported The RCT may have been too small to detect a clinically important difference	⟷	Not significant

No data from the following reference on this outcome. [86]

Further information on studies

Comment: None.

OPTION THROMBOXANE ALPHA2 ANTAGONISTS (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether thromboxane alpha$_2$ antagonists increase healing of ulcers in people treated with compression.

Benefits and harms

Oral thromboxane alpha$_2$ antagonists versus placebo:

We found one RCT comparing an oral thromboxane alpha$_2$ antagonist versus placebo. [87]

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[87] RCT	165 people	**Proportion of ulcers healed** 55% with thromboxane alpha$_2$ antagonist 54% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [87]

Adverse effects

No data from the following reference on this outcome. [87]

Further information on studies

Comment: None.

OPTION ZINC (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether zinc increases healing of ulcers in people treated with compression.
- We found no clinically important results about the effects of oral zinc in people with venous leg ulcers.

Benefits and harms

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. [88] The review found no evidence of benefit for oral zinc in people with venous leg ulcers (significance not assessed).

Healing rates

No data from the following reference on this outcome. [88]

Recurrence rates

No data from the following reference on this outcome. [88]

Adverse effects

No data from the following reference on this outcome. [88]

Further information on studies

Comment: None.

OPTION SKIN GRAFTING

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether skin grafting increases healing of ulcers in people treated with compression.

Benefits and harms

Skin grafts versus usual care or versus each other:

We found one systematic review (search date 2009, 17 RCTs, 931 people) [65] of skin grafts (autografts, allografts, or xerografts) for venous leg ulcers. In 12 RCTs identified by the review, people also received compression bandaging; two of these trials (102 people) compared a dressing with an autograft, two trials (45 people) compared fresh allografts with dressings, three RCTs (80 people) compared frozen allografts with dressings, and 4 trials (442 people) evaluated tissue-engineered products (summarised above). 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. One trial (10 people) compared an autograft delivered on porcine pads with an autograft delivered on porcine gelatin microbeads, and one trial (92 people) compared a meshed graft with a cultured keratinocyte autograft. [65] 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; therefore, no further data are reported here. We also found one subsequent RCT, reported below. [89]

Healing rates

Different types of skin grafts compared with other treatments for leg ulcers We don't know how different types of skin grafts and other treatments for leg ulcers compare at increasing healing of venous ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[89] RCT	120 people with compression	**Proportion of people healed , at 12 weeks** 55% with porcine extracellular matrix graft 34% with usual care Absolute numbers not reported	RR 1.59 95% CI 1.06 to 2.42 RR reported for healing with matrix	●○○	matrix graft

Recurrence rates

No data from the following reference on this outcome. [89]

Adverse effects

No data from the following reference on this outcome. [89]

Further information on studies

[65] The review reported that there was no evidence of harm from tissue-engineered skin.

Comment: Porcine-derived products may not be acceptable to some patient groups. [90]

OPTION SUPERFICIAL VEIN SURGERY TO TREAT VENOUS LEG ULCERS

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether superficial vein surgery increases healing of ulcers in people treated with compression.

Benefits and harms

Perforator ligation versus no surgery or versus surgery plus skin grafting in the presence of compression:
We found one RCT (47 people) comparing perforator ligation versus no surgery or surgery plus skin grafting. [91] All participants were also treated with a compression bandage.

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[91] RCT **3-armed trial**	47 people with compression	**Proportion of ulcers healed , after 1 year** with perforator ligation with no surgery with surgery plus skin grafting Absolute results not reported	P >0.05 The RCT did not perform an intention-to-treat analysis (ITT), and 7/47 (15%) people withdrew from the trial. It is likely to have been underpowered to detect a clinically important difference among groups	⟷	Not significant
[91] RCT **3-armed trial**	47 people with compression	**Time to complete ulcer healing** with perforator ligation with no surgery with surgery plus skin grafting Absolute results not reported	P >0.05 The RCT did not perform an ITT 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	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [91]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[91] RCT **3-armed trial**	47 people	**Postoperative complications** 0 with perforator ligation 0 with no surgery 0 with surgery plus skin grafting The RCT did not perform an intention-to-treat analysis, and 7/47 (15%) people withdrew from the trial.The RCT may have been too small to detect clinically important adverse effects	Significance not assessed		

Minimally invasive surgery versus compression bandages or usual care:

We found two RCTs (215 people), which compared minimally invasive surgery versus compression bandages. [92] [93] In the first RCT, people randomised to surgery were treated with a compression bandage before surgery, [92] whereas in the second RCT they wore compression until ulcer healing. [93] The second RCT compared subfascial endoscopic perforator surgery (SEPS) plus superficial venous surgery as required versus compression alone. [93]

Healing rates

Minimally invasive surgery compared with compression bandages or usual care We don't know how minimally invasive surgery and compression bandages or usual care compare for reducing time to complete healing and increasing ulcer healing rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[92] RCT	45 people	**Healing rates** 100% with surgery 96% with compression Absolute numbers not reported	Significance not assessed The RCT randomised legs rather than people		
[92] RCT	45 people	**Median time to complete healing** 31 days with surgery 63 days with compression	P <0.005 The RCT randomised legs rather than people	○○○	surgery
[93] RCT	170 people with venous leg ulcers	**Proportion of ulcers healed** 83% with subfacial endoscopic perforator surgery (SEPS) plus superficial venous surgery as required 73% with compression alone Absolute numbers not reported	P = 0.24	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [92] [93]

Adverse effects

No data from the following reference on this outcome. [92] [93]

Venous surgery (based on duplex scan) plus compression versus compression alone:

We found one systematic review (search date 2000–2007 only, 5 RCTs, 896 people) comparing superficial venous surgery versus compression therapy. [94]

Healing rates

Venous surgery (based on duplex scan) plus compression compared with compression alone Performing venous surgery (based on duplex scan) in people receiving compression is no more effective than compression alone at increasing healing rates at 24 weeks and at 3 years (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[95] RCT	341 people In review [94]	**Healing rates , at 24 weeks** 65% with surgery plus compression 65% with compression alone Absolute numbers not reported	HR for healing: 0.84 95% CI 0.77 to 1.24	⟷	Not significant
[96] RCT	341 people Further report of reference [95]	**Healing rates , at 3 years** 93% with surgery plus compression	P = 0.73	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		89% with compression alone Absolute numbers not reported			
[94] Systematic review	76 legs Data from 1 RCT	**Healed ulcers** 68% with superficial venous surgery 64% with compression therapy Absolute numbers not reported	P value not reported Reported as not significant	⟷	Not significant
[94] Systematic review	45 people Data from 1 RCT	**Healed ulcers** 100% with superficial venous surgery 96% with compression therapy Absolute numbers not reported	P value not reported Reported as significant	○○○	superficial venous surgery
[94] Systematic review	500 legs Data from 1 RCT	**Healed ulcers** 93% with superficial venous surgery 89% with compression therapy Absolute numbers not reported	P value not reported Reported as not significant	⟷	Not significant
[94] Systematic review	200 legs Data from 1 RCT	**Healed ulcers** 83% with superficial venous surgery 73% with compression therapy Absolute numbers not reported	P value not reported Reported as not significant	⟷	Not significant

Recurrence rates

Compared with compression therapy Superficial venous surgery seems more effective at reducing recurrence rates in people with venous leg ulcers (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[94] Systematic review	45 legs Data from 1 RCT	**Recurrence** 9% with superficial venous surgery 38% with compression therapy Absolute numbers not reported	Reported as significant P value not reported	○○○	superficial venous surgery
[94] Systematic review	500 legs Data from 1 RCT	**Recurrence** 31% with superficial venous surgery 56% with compression therapy Absolute numbers not reported	Reported as significant P value not reported	○○○	superficial venous surgery
[94] Systematic review	200 legs Data from 1 RCT	**Recurrence** 22% with superficial venous surgery 23% with compression therapy Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[95] RCT	341 people In review [94]	**Healing rates , at 24 weeks** with surgery plus compression with compression alone Absolute results not reported Adverse events were minimal and about equal in each group	Significance not assessed		

No data from the following reference on this outcome. [96]

Open perforator surgery versus subfascial endoscopic perforator surgery:

We found one systematic review (search date 2003, 1 RCT). [97]

Healing rates

Open perforator surgery compared with subfascial endoscopic perforator surgery We don't know how open perforator surgery and subfascial endoscopic perforator surgery compare at increasing ulcer healing rates at 4 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[97] Systematic review	39 people Data from 1 RCT	**Healing rates , at 4 months** 17/20 (85%) with subfascial endoscopic perforator surgery 17/19 (89%) with open surgery	Reported as not significant	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [97]

Adverse effects

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[97] Systematic review	39 people Data from 1 RCT	**Wound infection rates** 0% with subfascial endoscopic perforator surgery (SEPS) 53% with open surgery Absolute numbers not reported	P <0.001	○○○	SEPS
[97] Systematic review	39 people Data from 1 RCT	**Adverse effects** with SEPS with open surgery Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		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 SEPS			

Further information on studies

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 (SEPS) found that hospital stay was shorter with SEPS (4 days with SEPS *v* 7 days with open surgery). [98] About 25% of people who were offered venous surgery in one study refused it. [99]

OPTION THERAPEUTIC ULTRASOUND

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether therapeutic ultrasound is effective, as results from trials were too inconsistent to draw conclusions.

Benefits and harms

Therapeutic ultrasound versus no or sham ultrasound:

We found one systematic review (search date 2010, 8 RCTs) comparing therapeutic ultrasound versus no ultrasound or sham ultrasound for venous leg ulcers. [100] Ultrasound improved ulcer healing in all studies, but a significant difference was found in only 4 of the 8 RCTs, and heterogeneity precluded pooling the RCTs. [100] We also found one subsequent RCT (337 people) comparing low-dose, high-frequency ultrasound plus standard care versus standard care alone. [101]

Healing rates

Compared with standard care Ultrasound is no more effective than standard care at reducing time to healing at 12 weeks and increasing the proportion of people with healed ulcers at 12 months (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[101] RCT	337 people	**Time to healing , 12 weeks** with ultrasound with standard care Absolute results not reported	HR 0.99 95% CI 0.70 to 1.40 P = 0.97	⟷	Not significant
[101] RCT	337 people	**Proportion of people with healed ulcers , 12 months** 72/168 (43%) with ultrasound 78/169 (46%) with standard care	P = 0.39	⟷	Not significant

Recurrence rates

Compared with standard care Ultrasound is no more effective than standard care at reducing recurrence rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[101] RCT	337 people	**Recurrence** 17/31 (55%) with ultrasound 14/31 (45%) with standard care	P = 0.68	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [101]

Further information on studies

[100] Mild and severe erythema, local pain, and small areas of bleeding were reported in RCTs [102] [103] identified by the review.

Comment: None.

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

OPTION **LEG ULCER CLINICS**

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether leg ulcer clinics increase healing of ulcers.
- Leg ulcer clinics and leg clubs may only be suitable for mobile people.

Benefits and harms

Leg ulcer clinics versus usual care:

We found one systematic review (search date 2001, 1 RCT), [104] one additional RCT, [105] and two subsequent RCTs. [101] [106]

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Healing					
[104] Systematic review	People with leg ulcers Data from 1 RCT	**Likelihood of healing** with high-compression bandaging in a leg ulcer clinic with usual care Absolute results not reported	Cox model: ulcers 1.65 times more likely to heal when attending a leg ulcer clinic 95% CI 1.15 to 2.35	○○○	high-compression bandaging in a leg ulcer clinic
[105] RCT	33 people	**Reduction in ulcer area** with community-based "Leg Clubs"	P = 0.004	○○○	community-based "Leg Clubs"

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with usual care Absolute results not reported			
[105] RCT	33 people	**Proportion of people healed , at 12 weeks** 7/16 (44%) with community-based "Leg Clubs" 4/17 (24%) with usual care	Reported as not significant P value not reported	⟷	Not significant
[101] RCT	120 people	**Healing , 3 months** 35/60 (58%) with clinic group 34/60 (57%) with home group	P = 0.5	⟷	Not significant
[106] RCT	126 mobile people with leg ulcers	**Healing rate , 3 months** 58% with clinic care 57% with home care Absolute numbers not reported Care was given by trained nurses in both groups.	P = 0.5	⟷	Not significant

Recurrence rates

Compared with home care We don't know whether leg ulcer clinics are more effective at reducing recurrence rates in people with venous leg ulcers (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[101] RCT	120 people	**Recurrence , 12 months** 15/60 (25%) with clinic group 14/60 (22%) with home group	P = 0.42	⟷	Not significant
[106] RCT	126 mobile people with leg ulcers	**Recurrence , 1 year** 25% with clinic care 22% with home care Absolute numbers not reported Care was given by trained nurses in both groups.	P = 0.42	⟷	Not significant

No data from the following reference on this outcome. [104] [105]

Adverse effects

No data from the following reference on this outcome. [104] [105] [101] [106]

Further information on studies

[104] 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.

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**

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We found no RCT evidence about advice to elevate legs, although the intervention makes sense as venous insufficiency is corrected if the leg is elevated above the heart.
- Many people with venous leg ulcers have mobility and joint problems, which may make this intervention impractical.

Benefits and harms

Advice to elevate leg versus standard care alone:

We found no systematic review or RCTs.

Further information on studies

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 that mitigate against their being able to elevate their legs for long periods.

OPTION **ADVICE TO KEEP LEG ACTIVE**

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- 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.
- Many people with venous disease have joint or other mobility problems that may mitigate against increasing their activity levels.

Benefits and harms

Advice to keep leg active versus standard care alone:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Potential advantages of activity may include reduced leg oedema and increasing venous return.

OPTION ADVICE TO MODIFY DIET

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether advice to change diet increases healing of ulcers in people treated with compression.

Benefits and harms

Advice to modify diet versus standard care alone:

We found no systematic review or RCTs.

Further information on studies

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether advice to give up smoking increases healing of ulcers in people treated with compression.

Benefits and harms

Advice to stop smoking versus standard care alone:

We found no systematic review or RCTs.

Further information on studies

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether advice to lose weight increases healing of ulcers in people treated with compression.

Benefits and harms

Advice to reduce weight versus standard care alone:

We found no systematic review or RCTs.

Further information on studies

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

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- Compression bandages and stockings reduce recurrence of ulcers compared with no compression, and should ideally be worn for life.

Benefits and harms

Compression stockings versus no compression:

We found one systematic review (search date 2000), [107] which found no RCTs comparing compression stockings versus no compression, and one subsequent RCT. [108]

Recurrence rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[108] RCT	153 people	**Recurrence , at 6 months** 21% with compression stockings 46% with no compression stockings Absolute numbers not reported	RR 0.46 95% CI 0.28 to 0.76 NNT for 6 months' treatment 2 95% CI 2 to 5	●●○	compression stockings

Adverse effects

No data from the following reference on this outcome. [108]

Compression stockings versus other forms of compression:

We found one systematic review (search date 2000, 2 RCTs). [107] The first RCT identified by the review compared two brands of UK class 2 stockings. The second RCT identified by the review compared class 2 and class 3 stockings (see comment).

Recurrence rates

Compression stockings compared with other forms of compression High-compression stockings (UK class 3) seem no more effective than moderate-compression stockings (UK class 2) at reducing recurrence at 5 years (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[107] Systematic review	166 people Data from 1 RCT	**Recurrence , after 18 months** 22/92 (24%) with Medi stockings 27/74 (36%) with Scholl stockings	RR 0.82 95% CI 0.61 to 1.12	⟷	Not significant
[107] Systematic review	300 people Data from 1 RCT	**Recurrence , after 5 years** 59/151 (39%) with class 2 elastic compression 48/149 (32%) with class 3 compression Intention-to-treat analysis This analysis may underestimate the effectiveness of class 3 stockings, as a significant proportion of people changed from class 3 to class 2	RR 0.74 95% CI 0.45 to 1.20	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [107]

Further information on studies

[107] Both RCTs found that non-compliance with compression stockings was associated with recurrence.

Comment: The application of high compression to limbs with reduced arterial supply may result in ischaemic tissue damage and, at worst, amputation. [63]

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 mmHg to 24 mmHg pressure and class 3 are capable of applying 25 mmHg to 35 mmHg 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 59).

OPTION SUPERFICIAL VEIN SURGERY TO PREVENT RECURRENCE

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .

- Superficial vein surgery may reduce recurrence.
- Endoscopic surgery may be more effective than open surgery.

Benefits and harms

Surgery plus compression versus compression alone:

We found one systematic review (search date 1997, 1 RCT), [109] three subsequent RCTs, [92] [95] [93] and one long-term follow-up report. [96]

Recurrence rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[109] Systematic review	30 people Data from 1 RCT	**Recurrence , after 18 months** 5% with surgery plus compression stockings 24% with compression stockings alone Absolute numbers not reported	RR 0.21 95% CI 0.03 to 0.80 The RCT was poorly controlled, and its results should be interpreted with caution	●●○	surgery plus compression stockings
[92] RCT	45 people	**Recurrence rates , over 3 years** 2/21 (10%) with minimally invasive surgery 9/24 (38%) with compression bandages People randomised to surgery wore compression stockings immediately after surgery, and people randomised to compression wore compression stockings after ulcer healing was achieved	P <0.05 The RCT randomised legs rather than people	○○○	surgery
[95] RCT	428 people	**Recurrence rates , after 12 months** 12% with superficial vein surgery plus compression 28% with compression alone Absolute numbers not reported	HR –2.76 95% CI –4.27 to –1.78	○○○	surgery plus compression
[96] RCT	People with leg ulcers Further report of reference [95]	**Recurrence rates , 3 years** 31% with superficial vein surgery plus compression 56% with compression alone Absolute numbers not reported	Reported as significant P <0.01	○○○	surgery plus compression
[93] RCT	170 people	**Recurrence rates , 27 months** 22% with subfascial endoscopic perforator surgery plus compression 23% with compression alone Absolute results reported graphically	Reported as not significant	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [109] [92] [95] [93] [96]

Open versus endoscopic surgery:

We found one systematic review (search date 2003, 1 RCT), [97] which compared open surgery versus subfascial endoscopic perforator surgery (SEPS), and a subsequent long-term follow-up report [110] of the RCT identified by the review. We found one RCT that gave information on adverse effects. [98]

Recurrence rates

Open compared with endoscopic surgery Open surgery may be less effective than endoscopic surgery at reducing ulcer recurrences at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[110] RCT	39 people Further report of reference [97]	**Recurrences , at 12 months** 4 (22%) with open surgery 2 (12%) with subfascial endoscopic perforator surgery (SEPS)	P = 0.044	○○○	SEPS

No data from the following reference on this outcome. [98]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[110] RCT	39 people Further report of reference [97]	**Adverse effects** with open surgery with subfascial endoscopic perforator surgery (SEPS) Absolute numbers not reported 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	Significance not assessed		
[98] RCT	People with leg ulcers	**Wound infection rates** 53% with open surgery 0% with SEPS Absolute numbers not reported	P <0.001	○○○	SEPS

Further information on studies

Comment: Vein surgery has the usual risks of surgery and anaesthesia.

OPTION RUTOSIDE (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether oral rutosides are effective at reducing recurrence.

Benefits and harms

Oral rutoside versus placebo:

We found one systematic review (search date 1997, 1 RCT). [109] See comment for further information on adverse effects in people with obstructive arm lymphoedema.

Recurrence rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[109] Systematic review	139 people Data from 1 RCT	**Recurrences , at 18 months** 32% with rutoside 34% with placebo Absolute numbers not reported	P = 0.93	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [109]

Further information on studies

Comment: One RCT (31 people with obstructive arm lymphoedema) found that rutoside was associated with headache, flushing, rashes, and mild gastrointestinal disturbances. [111]

OPTION STANOZOLOL (ORAL)

- For GRADE evaluation of interventions for Venous leg ulcers, see table, p 70 .
- We don't know whether oral stanozolol is effective at reducing recurrence.

Benefits and harms

Oral stanozolol versus placebo:

We found one systematic review (search date 1997, 1 RCT), comparing 6 months' treatment with stanozolol versus placebo. [109] See comment for general information about adverse effects.

Recurrence rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[109] Systematic review	60 people	**Ulcer recurrence** 7/25 (28%) legs with stanozolol 4/23 (17%) legs with placebo 6 months' treatment, length of follow-up not reported	RR 1.61 95% CI 0.54 to 4.79	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [109]

Further information on studies

Comment: Stanozolol is an anabolic steroid; adverse effects include acne, hirsutism, amenorrhoea, oedema, headache, dyspepsia, rash, hair loss, depression, jaundice, and changes in liver enzymes.

GLOSSARY

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.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Intermittent pneumatic compression External compression applied by inflatable leggings or boots 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.

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.

Perforator ligation A procedure that 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.

Subfascial endoscopic perforator surgery A minimally invasive endoscopic procedure that 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.

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

Antimicrobial agents (topical) New evidence added. [47] [50] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the effects of antimicrobial agents in people with venous leg ulcers.

Compression bandages and stockings versus no compression One systematic review updated. [8] Categorisation unchanged (Beneficial).

Cultured allogenic bilayer skin replacement One systematic review updated. [65] New evidence added. [64] Categorisation unchanged (Likely to be beneficial).

Debriding agents New evidence added. [33] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of debriding agents in people with venous leg ulcers.

Flavonoids (oral) New evidence added. [67] Categorisation unchanged (Likely to be beneficial).

Foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate (semi-occlusive) dressings New evidence added. [39] [40] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of semi-occlusive dressings in people with venous leg ulcers.

Intermittent pneumatic compression One systematic review updated. [31] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of intermittent pneumatic compression in people with venous leg ulcers.

Larval therapy New evidence added. [74] [75] Categorisation unchanged (Unlikely to be beneficial).

Laser treatment (low-level) One systematic review updated, no new evidence added. [77] New evidence added. [82] [83] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the effects of low-level laser therapy in people with venous leg ulcers.

Leg ulcer clinics New evidence added. [106] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess leg ulcer clinics for people with venous leg ulcers.

Multilayer elastomeric high-compression bandages versus short-stretch bandages or Unna's boot One systematic review updated. [8] New evidence added. [22] Categorisation unchanged (Beneficial).

Multilayer elastomeric high-compression regimens versus other layered regimens One systematic review updated. [8] New evidence added. [20] Categorisation unchanged (Beneficial).

Skin grafting One systematic review updated. [65] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of skin grafting for people with venous leg ulcers.

Superficial vein surgery New evidence added. [94] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the use of superficial vein surgery to treat venous leg ulcers.

Therapeutic ultrasound New evidence added. [101] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of ultrasound in people with venous leg ulcers.

Compression stockings versus compression bandages New evidence added. [8] [12] [13] [14] [15] [16] Categorisation changed (from Beneficial to Likely to be beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Venous leg ulcers.**

Important outcomes			Adverse effects, Healing rates, Recurrence rates						
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]	Healing rates	Compression bandages and stockings versus no compression	4	0	0	0	0	High	
1 (140) [8]	Recurrence rates	Compression bandages and stockings versus no compression	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
11 (869) [12] [13] [14] [15]	Healing rates	Compression stockings or tubular garments versus compression bandages	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of data and methodological flaws. 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
1 (138) [16]	Recurrence rates	Compression stockings or tubular garments versus compression bandages	4	0	0	0	0	High	
9 (679) [8] [19] [20]	Healing rates	Multilayer elastomeric high-compression regimens versus other layered regimens	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 high-compression bandages versus single-layer bandage	4	0	0	0	0	High	
6 (850) [8] [22]	Healing rates	Multilayer elastomeric high-compression bandages versus short-stretch bandages or Unna's boot	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (24) [27]	Healing rates	Single-layer non-elastic system versus 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) [28]	Healing rates	Single-layer non-elastic system versus multilayer non-elastic system	4	–2	0	0	0	Low	Quality points deduced for sparse data and incomplete reporting of results
1 (60) [29]	Healing rates	Peri-ulcer injection of granulocyte-macrophage colony-stimulating factor	4	–1	0	0	+1	High	Quality points deduced for sparse data. Effect-size point added for RR <5
6 (459) [36] [37] [38]	Healing rates	Semi-occlusive dressings (foam, film, hyaluronic acid-derived dressings, collagen, cellulose, or alginate) versus simple low-adherent dressings, in the presence of compression	4	–1	–1	0	0	Low	Quality point deducted for spare data. Consistency point deducted for conflicting results
1 (113) [36]	Healing rates	Alginate dressings versus zinc oxide dressings	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results

Important outcomes			Adverse effects, Healing rates, Recurrence rates						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
4 (168) [31]	Healing rates	Intermittent pneumatic compression plus compression stockings versus compression stockings or bandages alone	4	–1	–1	0	0	Low	Quality point deduced for sparse data. Consistency point deducted for conflicting results
27 studies at most (1401 at most) [46] [47] [48] [49] [50]	Healing rates	Topical antimicrobial agents versus placebo or usual care	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for assessing different outcome in 1 study and the inclusion of a mixed population in 1 review
1 (213) [50]	Recurrence rates	Topical antimicrobial agents versus placebo or usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data
1 (66) [51]	Healing rates	Topical calcitonin gene-related peptide plus vasoactive intestinal polypeptide versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [52]	Healing rates	Topical mesoglycan versus a plant-based extract	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (60) [55]	Healing rates	Topical negative pressure versus 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 (60) [55]	Recurrence rates	Topical negative pressure versus 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) [56]	Healing rates	Topical recombinant human keratinocyte growth factor 2 plus compression versus placebo plus compression	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (135) [57]	Healing rates	Platelet-derived growth factor versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
at least 22 (at least 792) [36] [37] [38]	Healing rates	Hydrocolloid (occlusive) dressings versus simple dressings in the presence of compression	4	0	0	0	0	High	
4 (311) [38]	Healing rates	Hydrocolloids versus other occlusive or semi-occlusive dressings	4	0	0	0	0	High	
3 (388) [58] [59] [60]	Healing rates	Different occlusive or semi-occlusive dressings (excluding hydrocolloids) versus each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (86) [61]	Healing rates	Topically applied autologous platelet lysate versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (200) [62]	Healing rates	Topically applied freeze-dried keratinocyte lysate versus vehicle or usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes			Adverse effects, Healing rates, Recurrence rates						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of adjuvant treatments for venous leg ulcers?									
7 (659) [63]	Healing rates	Oral pentoxifylline versus placebo	4	0	0	0	0	High	
2 (345) [65]	Healing rates	Cultured allogenic bilayer skin replacement versus non-adherent dressing	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (723) [66] [67]	Healing rates	Flavonoids plus compression versus 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 >2 but <5
4 (488) [68] [69] [70] [71]	Healing rates	Oral sulodexide plus compression versus compression alone	4	0	0	0	0	High	
1 (183) [72]	Healing rates	Systemic mesoglycan plus compression versus placebo plus compression	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (71) [65]	Healing rates	Cultured allogenic single-layer dermal replacement versus usual care	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (87) [73]	Healing rates	Intravenous prostaglandin E1 versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological flaws
1 (267) [75]	Healing rates	Larval therapy versus usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (301) [77] [79] [80] [81] [82] [83]	Healing rates	Low-level laser treatment versus 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. Directness points deducted for treatment inconsistencies between groups and for assessing different measures of healing
1 (reported as "small") [84]	Healing rates	Oral aspirin versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data and for methodological weaknesses
1 (reported as "small") [85] [86]	Healing rates	Oral rutosides versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (165) [87]	Healing rates	Oral thromboxane alpha$_2$ antagonists versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (120) [89]	Healing rates	Skin grafts versus usual care or versus each other	4	–1	0	–1	0	Low	Quality point deducted for poor studies and insufficient evidence. Directness point deducted for generalisability of results
1 (47) [91]	Healing rates	Perforator ligation versus no surgery or versus surgery plus skin grafting in the presence of compression	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) [92] [93]	Healing rates	Minimally invasive surgery versus 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
5 (at least 341 people) [94]	Healing rates	Venous surgery (based on duplex scan) plus compression versus compression alone	4	0	0	0	0	High	

Important outcomes			Adverse effects, Healing rates, Recurrence rates						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
3 (745 legs) [94]	Recurrence rates	Venous surgery (based on duplex scan) plus compression versus compression alone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (39) [97]	Healing rates	Open perforator surgery versus subfascial endoscopic perforator surgery	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (39) [97]	Adverse effects	Open perforator surgery versus subfascial endoscopic perforator surgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (337) [101]	Healing rates	Therapeutic ultrasound versus no or sham ultrasound	4	0	0	0	0	High	
1 (337) [101]	Recurrence rates	Therapeutic ultrasound versus no or sham ultrasound	4	0	0	0	0	High	
What are the effects of organisational interventions for venous leg ulcers?									
4 (at least 279 people) [104] [105] [101]	Healing rates	Leg ulcer clinics versus 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
2 (246) [101] [106]	Recurrence rates	Leg ulcer clinics versus usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data.
What are the effects of interventions to prevent recurrence of venous leg ulcers?									
1 (153) [108]	Recurrence rates	Compression stockings versus no compression	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR <0.5
2 (466) [107]	Recurrence rates	Compression stockings versus other forms of compression	4	0	0	–1	0	Moderate	Directness point deducted for change-over
4 (673) [109] [92] [95] [93] [96]	Recurrence rates	Surgery plus compression versus compression alone	4	–1	0	0	0	Moderate	Quality point deducted for methodological flaws
1 (39) [97] [110]	Recurrence rates	Open versus endoscopic surgery	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (139) [109]	Recurrence rates	Oral rutoside versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (48) [109]	Recurrence rates	Oral stanozolol versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and weak methods (unit of randomisation and unit of assessment differed)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.