Effective Health Care Program

Comparative Effectiveness Review
Number 127

Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Erratum

In the original version of this report, Tables A and 1 incorrectly listed "Cryopreserved human skin allograft (TheraSkin®)" as an acellular biological dressing. TheraSkin should be listed as a cellular biological dressing.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities

Structured Abstract

Objectives. To systematically review whether the use of advanced wound dressings, systemic antibiotics, or venous surgery enhanced the healing of venous ulcers over the use of adequate venous compression.

Data sources. MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) from January 1980 through July 2012.

Review methods. We included studies of patients with venous leg ulcers lasting 6 or more weeks coincident with signs of preexisting venous disease. We excluded patients with arterial ulcers, pressure ulcers, postsurgical ulcers, and neuropathic ulcers. To select articles for analysis, teams of two independent investigators reviewed titles, abstracts, and articles. Conflicts between investigators regarding inclusion were negotiated. We found insufficient data for meta-analysis but qualitatively summarized studies not amenable to pooling.

Results. Our search retrieved over 10,000 articles. We included 60 studies (62 publications). Most of the studies of advanced wound dressings that regulate moisture, facilitate debridement, include antimicrobial activity, or incorporate putative wound healing accelerants did not demonstrate a statistically higher percentage of wounds healed compared with adequate compression with simple dressings. However, the newer biological dressings containing living cells such as the cellular human skin equivalents showed more rapid healing of venous ulcers (moderate strength of evidence).We could not draw definitive conclusions regarding the effectiveness of advanced wound dressings in terms of intermediate and other final outcomes, including quality of life and pain measures. We found insufficient evidence evaluating the benefits and harms of the routine use of antibiotics. Most venous surgery may not increase the proportion of ulcers healed (low to high strength of evidence), although there was a trend toward greater durability of healing.

Conclusions. These findings do not mean that the interventions do not have value. Rather, the risk of bias and lack of adequate sample size prevented us from establishing statistically valid conclusions. Many of the studies did not report statistical analyses beyond simple healing rates, stratification or adjustment to account for potential confounding variables, or sample size calculations. Many of the studies reviewed were small and therefore had limited power. The absence of these critical design elements limited our ability to draw conclusions. We suggest that there be consensus to frame a series of commonly agreed-upon definitions, develop model clinical research approaches, consider mutually agreed-upon schemes to classify patients, quantify healing parameters, and consider the development of research wound healing networks to collect sufficient number of patients to produce valid conclusions.

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Executive Summary

Background

Venous leg ulcers are extremely common in the United States. They affect between 500,000 and 2 million people annually, and are responsible for over 50 percent of all lower extremity ulcers.[1] Elevated venous pressure, turbulent flow, and inadequate venous return are the common causes of venous leg ulcers. Risk factors for chronic venous disease include underlying conditions associated with poor venous return (such as congestive heart failure and obesity) and primary destruction of the venous system (such as prior deep venous thrombosis, recreational injected drug use, phlebitis, and venous valvular dysfunction). Clinicians diagnose venous ulcers on the basis of anatomic location, morphology, and characteristic skin changes. Clinicians confirm this diagnosis by assessing the functionality of the venous system, most commonly by venous duplex ultrasound.[2]

The current standard clinical approach to therapy includes aggressive compression of the lower limb with debridement of the ulcer, which heals 50 to 60 percent of venous leg ulcers.[2] Clinicians must consider other therapies for the large number of patients for whom compression therapy and debridement fail, but no consensus exists about which second-line treatments work best. These additional therapies commonly include wound dressings with active components (defined here as advanced wound dressings), local or systemic antimicrobials, and venous surgery.

Advanced Wound Dressings

Wound healing requires a moist wound environment to produce growth factors and promote cellular proliferation. Advanced wound dressings regulate or donate moisture in the wound surface by moisture retention or exudate absorption, thereby protecting the wound base and periwound tissue. Some advanced wound dressings also include antiseptics, antimicrobials, cleansing agents, or autolytic debriding agents. The goal is to both improve healing and minimize patient discomfort before, during, and after dressing changes. The U.S. Food and Drug Administration classifies dressings as devices and has had a mixed approach to their regulation. Living cellular constructs have had extensive premarket evaluation and study protocol evaluation; however, premarketing testing for safety and efficacy is not as rigorous as it is for the approval of new drugs. This has clearly impacted the quality of potential efficacy data.

Antibiotics

Clinicians commonly use antibiotics to treat venous ulcers. However, the indications for the use of systemic or topical antibiotics are not well defined for chronic venous leg ulcers. Clinicians often use empiric therapy or "culture-based treatment" for wounds that are not healing, even when there are no clinical signs of infection. Overuse of antimicrobials is an emergent public health problem, and it is linked to the development of resistant organisms and iatrogenic disease, such as *Clostridium difficile* colitis, and increased health care costs.

Surgical Interventions

Most patients with venous ulcers have significant reflux and valvular incompetence in the major veins of the lower extremity, typically detected by duplex ultrasound. The current surgical practice is to repair documented reflux in patients with chronic venous ulcers that failed a 3-month period of compression dressing, debridement, and antibiotics. Clinicians increasingly use the minimally invasive endovenous approach instead of vein stripping. However, each underlying vascular pathology has different surgical treatment options, and there is no consensus about which approach is the safest and most effective for healing ulcers. In addition, there are no standardized indications for surgery.

Scope and Key Questions

Our objective was to systematically review the literature on the effectiveness and safety of advanced wound dressings, systemic antibiotics, and surgical interventions, when compared with either compression systems or each other, among patients with chronic venous leg ulcers (Figure A). We addressed the following Key Questions (KQs) in this review:

KQ 1. For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components in conjunction with compression systems when compared with using solely compression systems?

We reviewed all types of wound dressings with or without active chemical, enzymatic, biologic, or antimicrobial components, categorizing them by function (see Table A). We defined these dressings as those with biological activity, debridement activity, antimicrobial activity, or enhanced absorptive/barrier properties. We also analyzed the data on biological dressings, which are derived from human or animal skin and may contain living human or animal cells as a constituent.

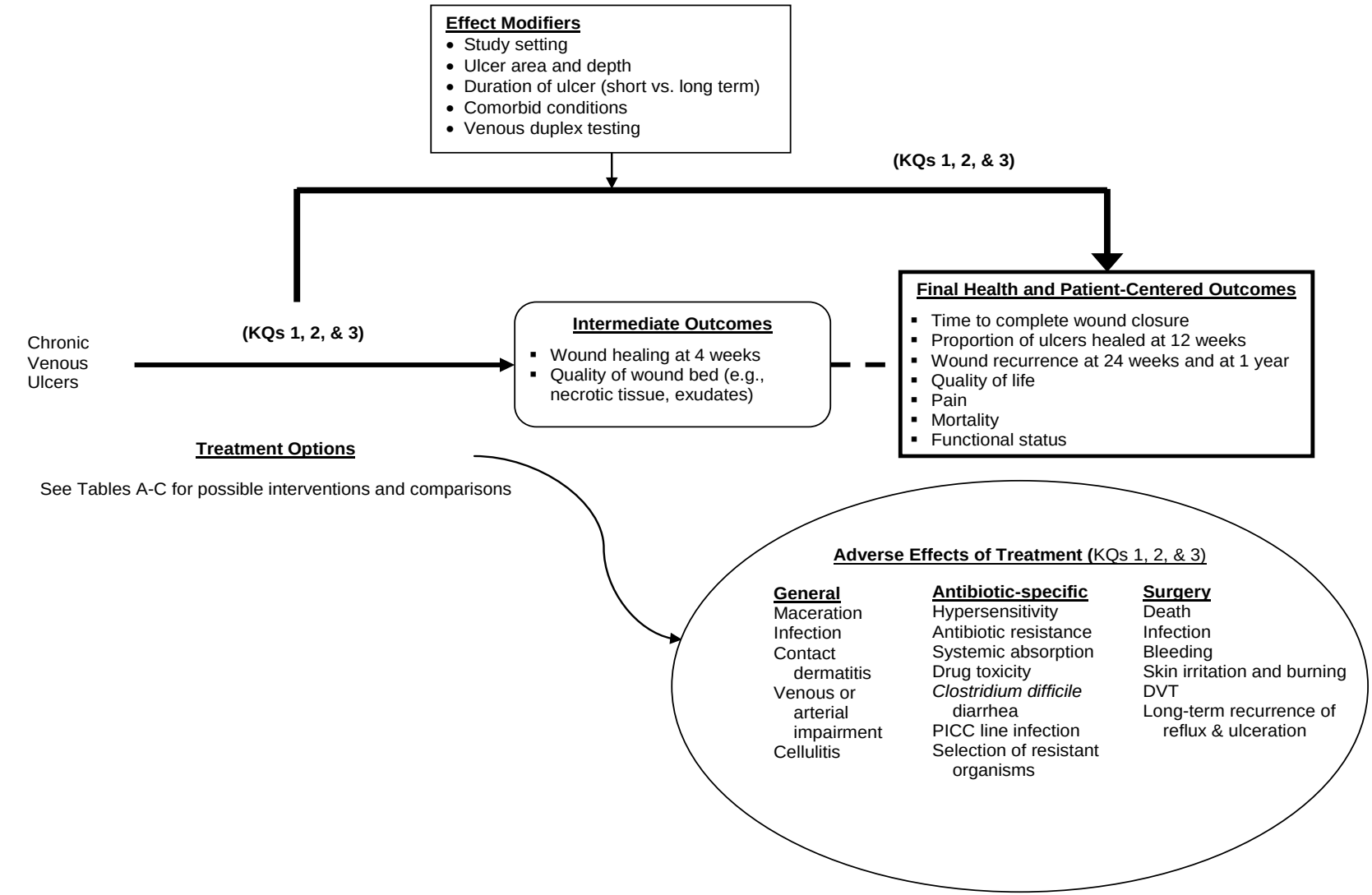
KQ 2a. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

KQ 2b. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components, what are the benefits and harms of using systemic antibiotics when compared with using dressings alone?

KQ 3a. For patients with chronic venous leg ulcers, what are the benefits and harms of surgical procedures aimed at the underlying venous abnormalities when compared with using solely compression systems?

KQ 3b. For patients with chronic venous leg ulcers, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

Figure A. Analytic framework for the treatment of chronic venous leg ulcers



DVT = deep vein thrombosis; KQ = Key Question; PICC = peripherally inserted central catheter

We used the standard definition of a chronic venous leg ulcer, which is the presence of an active ulcer for 6 weeks or more with evidence of earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema. We included studies of patients with or without other major comorbidity. Tables A–C list the advanced wound dressings, antibiotics, and surgical interventions of interest. For KQs 1, 2a, and 3a, the comparator of interest was compression therapy that includes debridement of necrotic tissue and at least moderate compression described either qualitatively or quantitatively (greater than 20 mm Hg), so that the leg does not swell significantly during the day. Although some experts recommend a higher pressure for compression therapy, we did not want to exclude too many studies and therefore used 20 mm Hg as the minimum pressure based on the results of a previous systematic review conducted by the Cochrane Collaboration.[3] For KQ 2b, the comparator of interest was advanced wound dressings. For KQ 3b, the comparators of interest were other surgical interventions for a given type of venous reflux and obstruction. We evaluated the literature for data on wound healing, recurrence rates, and intermediate outcomes, which included intermediate wound healing rates. We included pain and quality of life outcome measures in our evaluation. Finally, we attempted to evaluate the durability of healing of an ulcer over time. We required at least a 4-week duration of followup. We did not include cost as an outcome in this systematic review, but rather focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program.

Table A. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, biologic, or antimicrobial components

Functional Category	Classification	Characteristics	HCPS Classification
Dressings to enhance moisture retention	Hydrocolloids	• Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet • Polymers form a gel on contact with wound exudate: allows for wound hydration and autolytic debridement	• Hydrocolloid dressing, wound cover, sterile
	Transparent films	• Transparent sheets of polyurethane coated with an adhesive • Act as a "blister roof" to provide a moist wound-healing environment, promotes autolysis, and protects the wound and periwound tissues from external trauma	• Transparent film, sterile
Exudate management	Alginates	• Derived from seaweed and spun into a rope or sheet dressing • Fibrous and highly absorbent and can become gel-like when coming into contact with exudate to maintain a moist wound-healing environment	• Alginate or other fiber gelling dressing, wound cover • Alginate or other fiber gelling dressing, wound filler
	Foams	• Sterile, nonlinting, absorptive dressing made of open-cell, medical-grade expanded polymer • It is nonadherent	• Foam dressing, wound cover, sterile (with/without adhesive border) • Foam dressing, wound filler, sterile
	Composites	• Combine physically distinct components into a single dressing that provides multiple functions: (1) bacterial barrier; (2) absorptive layer other than an alginate, foam, hydrocolloid, or hydrogel; (3) either semiadherent or nonadherent property; and (4) adhesive border	• Composite dressing, sterile with adhesive border
	Special absorptive dressings	• Unitized, multilayer dressings that provide either a semiadherent quality or nonadherent layer and highly absorptive layers of fibers such as absorbent cellulose, cotton, or rayon	• Special absorptive dressing, wound cover, sterile with/without adhesive border
Wound bed protection	Contact layer	• Thin, nonadherent sheets placed directly on an open wound bed to protect the tissue from direct contact with other agents or dressings	• Contact layer, sterile
Dressings to enhance hydration	Hydrogels	• A polymer gel composed mostly of water in a complex network of fibers • Water is released to keep the wound moist • Can be hydrophilic	• Hydrogel dressing, wound cover, sterile with/without adhesive border • Hydrogel dressing, wound filler
Collagen dressings	Sheets, wound filler gels or powder	• Freeze-dried bovine, porcine, or equine collagen • Can contain cellulose or alginate for absorption • Porcine small intestine submucosa extracellular matrix (Oasis®)	• Collagen-based wound filler, dry form • Collagen-based wound filler, gel/paste • Collagen dressing, sterile, pad

Table A. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, or antimicrobial components (continued)

Functional Category	Classification	Characteristics	HCPCS Classification
Biological dressings	Acellular	• Extracellular matrixes that support new tissue growth • Cryopreserved human skin allograft (TheraSkin®) • Three-dimensional porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan (Integra™)	• Skin substitute
	Cellular	• Bioengineered, bilayered, living cell–based skin substitute (Apligraf®) • Cryopreserved human fibroblast–derived dermal substitute (Dermagraft®)	• Skin substitute
Antimicrobial effect	Alginates, foams, hydrocolloids, hydrogels, transparent films, absorptive specialty dressings, collagens	• See individual dressing characteristics • Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, manuka honey, gentian violet, polyvinyl alcohol with methylene blue, cadexomer iodine, and chlorhexidine	• HCPCS classifications as listed above
Gauzes	Impregnated	• Made of woven and nonwoven fibers of cotton, polyester, or a combination in which substances have been added such as: iodinated agents, petrolatum, zinc compounds, crystalline sodium chloride, chlorhexidine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents	• Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad • Gauze, impregnated, water or normal saline, sterile, pad • Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad
Enhance further debridement	Biologic enzymatic debriding agent (collagenase Santyl®)	• Derived from fermentation by *Clostridium histolyticum* • Sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP and that is able to digest collagen in necrotic tissue	

HCPS = Healthcare Common Procedure Coding System; USP = United States Pharmacopeias

Table B. Antibiotic treatments for chronic venous ulcers

Class	Indications	Drug Names	Benefits	Disadvantages
Oral antimicrobials (used primarily for Gram-positive activity)	Susceptible Staph (MSSA) and streptococci	cephalosporins (e.g., cephalexin); amoxicillin/clavulanate; dicloxacillin	Inexpensive	Usually require multiple doses/day; major adverse events include rash, intolerance, allergy
	MRSA	clindamycin	Also can treat anaerobes; allergy is rare; good bone and tissue penetration	Effective against only 50% of MRSA; requires multiple daily dosing; GI intolerance
		trimethoprim/sulfamethoxazole	Inexpensive; good bone and tissue penetration	Interacts with warfarin; not effective against streptococci; high rate of allergy for sulfamethoxazole
		linezolid	Effective against enterococci and streptococci; high bioavailability	Multiple contraindications (e.g., patients taking an SSRI); expensive; high rate of symptomatic side effects; thrombocytopenia
Oral drugs used for Gram-negative activity	Gram-negative organisms	quinolones (ciprofloxacin, levofloxacin, moxifloxacin)	Effective against most community acquired GNRs and *Pseudomonas*; rarely anaphylactoid reaction; can dose once daily; high bioavailability	GI intolerance; increased risk for *C. diff*; prolonged exposure can result in resistance
		beta lactams (amoxicillin/clavulanate, cefixime, cefpodoxime)	Usually effective first round for community-acquired organisms	Requires multiple dosing
Intravenous antibiotic regimens	Gram-positive sensitive Staph (MSSA)	cefazolin, ampicillin/sulbactam		Requires multiple dosing; requires prolonged IV access (usually PICC line); requires weekly monitoring
		ceftriaxone	Can be dosed once daily	Requires prolonged IV access (usually PICC line); requires weekly monitoring
	Gram-positive organisms (MRSA)	vancomycin	Inexpensive; effective against MRSA; can be dosed post-dialysis	Requires weekly monitoring for drug toxicity; requires frequent adjustment of dosing
		daptomycin	Used when intolerant to vancomycin; dosed once daily; can be dosed post-dialysis	Expensive; toxicity is myositis; requires weekly CK monitoring
	Gram-negative organisms (B-lactams)	ertapenem	Can be dosed once daily; broad spectrum for enteric gram-negative bacteria and anaerobes; requires minimal monitoring	Not effective for *Pseudomonas* or many MDR organisms
		ceftriaxone		No anaerobic activity
	Pseudomonas	piperacillin/tazobactam, cefipime	Minimal toxicity profile	Requires multiple daily doses
	Aminoglycosides	gentamicin, tobramycin, amikacin	Can be dosed once daily	Major renal toxicity; requires close monitoring of dose, drug levels, renal function

C. diff = *Clostridium difficile*; CK = creatine kinase; GI = gastrointestinal; GNR = Gram-negative rods; IV = intravenous; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PICC = peripherally inserted central catheter; Staph = *Staphylococcus*; SSRI = selective serotonin reuptake inhibitor

Table C. Surgical treatments for chronic venous ulcers

Pathology	Treatment	Description
Superficial venous system	Ligation	• Sapheno-femoral junction/high saphenous ligation involves the ligation and division of the great saphenous vein at the junction with femoral vein. • Sapheno-popliteal junction ligation involves the ligation and division of small saphenous vein at its junction with popliteal vein. • Ligation of tributaries
	Stripping	• Saphenous vein stripping involves the ligation and division of the sapheno-femoral junction, followed by stripping a segment of the great saphenous vein to just below the knee using an invagination or inversion catheter.
	Stab/micro phlebectomy	• Stab phlebectomy or micro phlebectomy of tributaries to great or lesser saphenous vein
	Ablation	• Thermal ablation involves the closing of the great or small saphenous veins using high temperature generated by laser light (endovenous laser treatment) or radiofrequency energy (radiofrequency ablation). • Chemical ablation (sclerotherapy) involves injecting an irritant agent (such as sodium tetradecyl sulfate mixed with air or carbon dioxide) into the vein, which results in endothelial damage. Foam preparations increase the potency of sclerosing drug by increasing its surface area.
Perforator venous system	Ligation	• Perforator vein is directly ligated using ultrasound guidance.
	Subfascial endoscopic perforator surgery	• Although rarely performed, this minimally invasive surgical procedure involves use of an endoscope through the unaffected area of skin and fascia. An elastic wrap is used to empty the leg veins of blood then a tourniquet is placed at the thigh. Clinicians insufflate the subfascial space with carbon dioxide. This creates a space for the endoscope to identify and ligate the Cockett's perforating veins in the lower calf.
	Ablation	• Thermal ablation of perforator veins (radiofrequency ablation) • Chemical ablation (sclerotherapy) of perforator veins
	Hach procedure	• This procedure involves paratibial fasciotomy and dissection of the posterior perforator veins.
Deep venous system	Obstructive	• This involves bypassing the obstructive segment of deep vein using autogenous vein or polytetrafluoroethylene synthetic graft • This involves balloon angioplasty with or without stenting of the stenotic area of the deep vein
	Reflux	• Valve replacement (transposition or transplant) involves the replacement of the affected deep venous valve with an autogenous vein valve from the upper extremity. • Valvuloplasty involves repairing or reconstructing valves in the deep venous system of the lower limb.

Methods

Literature Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) from January 1980 through October 2011 and updated in July 2012. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text words of key articles identified a priori. We adapted the MEDLINE strategy for the other databases. Additionally, we reviewed the reference lists of included articles and any relevant review articles. We reviewed the Scientific Information Packets that wound dressing and pharmaceutical manufacturers submitted. We also searched ClinicalTrials.gov to identify any relevant ongoing trials.

Study Selection

Two independent reviewers evaluated each title, abstract, and full article. We included studies that evaluated advanced wound dressings, systemic antibiotics, or surgical interventions among patients with chronic venous leg ulcers in terms of any of the outcomes of interest. Patients must have had an active ulcer for at least 6 weeks. We excluded studies that had a mixed population of patients with chronic wounds, unless the study presented a separate analysis of patients with chronic venous ulcers. We included studies that concurrently compared an intervention of interest with adequate compression therapy (i.e., at least two layers of compression) or with another intervention. We did not have any restrictions based on language or sample size for the studies with a comparison group. We included studies with at least 4 weeks of followup. We resolved differences between investigators regarding eligibility through consensus adjudication.

For surgical interventions, we included studies without a concurrent comparison group if the study (1) included at least 30 patients with chronic venous leg ulcers for at least 6 weeks, (2) described the sampling frame, (3) provided demographic and baseline characteristics for the patients with chronic venous ulcers, and (4) assessed ulcer healing rates. We decided to include noncomparative studies evaluating surgical interventions because we anticipated finding few, if any, comparative studies. We decided to include only studies in which adequate compression therapy had failed patients for at least 6 weeks because we felt that these studies would provide useful information about the effects of surgery on healing-related outcomes despite the potential bias from not having a concurrent comparison group.

Data Abstraction

We created and pilot-tested standardized forms for data abstraction. Two investigators performed data abstraction on each article. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs that included personnel with both clinical and methodological expertise.

The reviewers extracted information on general study characteristics (e.g., study design, study period, followup), study participants (e.g., age, sex, duration of ulcer, smoking status, diabetes status, other systemic diseases, concomitant use of immunosuppressives or steroids, other treatment), interventions (e.g., usual care/placebo, compression types [two-layer, short

stretch, long stretch, multilayer, Unna boot], debridement types, advanced wound dressings, antimicrobials, surgical interventions, duration of treatment), comparisons, and outcome measures (e.g., definitions, results, measures of variability). We collected data on subgroups of interest (e.g., age, presence of comorbid conditions [diabetes, obesity], setting).

Quality Assessment

Two reviewers used the Downs and Black quality assessment tool to independently assess the quality of all included studies.[4] We supplemented this tool with additional quality-assessment questions based on recommendations in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (hereafter Methods Guide).[5] Our quality assessment tool included items on study reporting, internal validity, statistical power, and conflicts of interest.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population (e.g., age, duration of ulcer, comorbidity), interventions (e.g., treatment, cointerventions, duration of treatment), outcomes, and settings (e.g., nursing home, wound care center, primary care, hospital/inpatient) are typical for the treatment of individuals with chronic venous leg ulcers.

Data Synthesis

We planned to conduct meta-analyses when at least three studies were available and were sufficiently homogenous with respect to key variables (e.g., population characteristics, study duration, comparisons). We qualitatively summarized studies not amenable to pooling. Whenever possible, we calculated the risk difference and relative risk for the individual studies for the outcomes of proportion of ulcers healed and wound recurrence. We commented on relevant subgroup analyses that the studies reported, but we did not conduct any additional sensitivity analyses.

Strength of the Body of Evidence

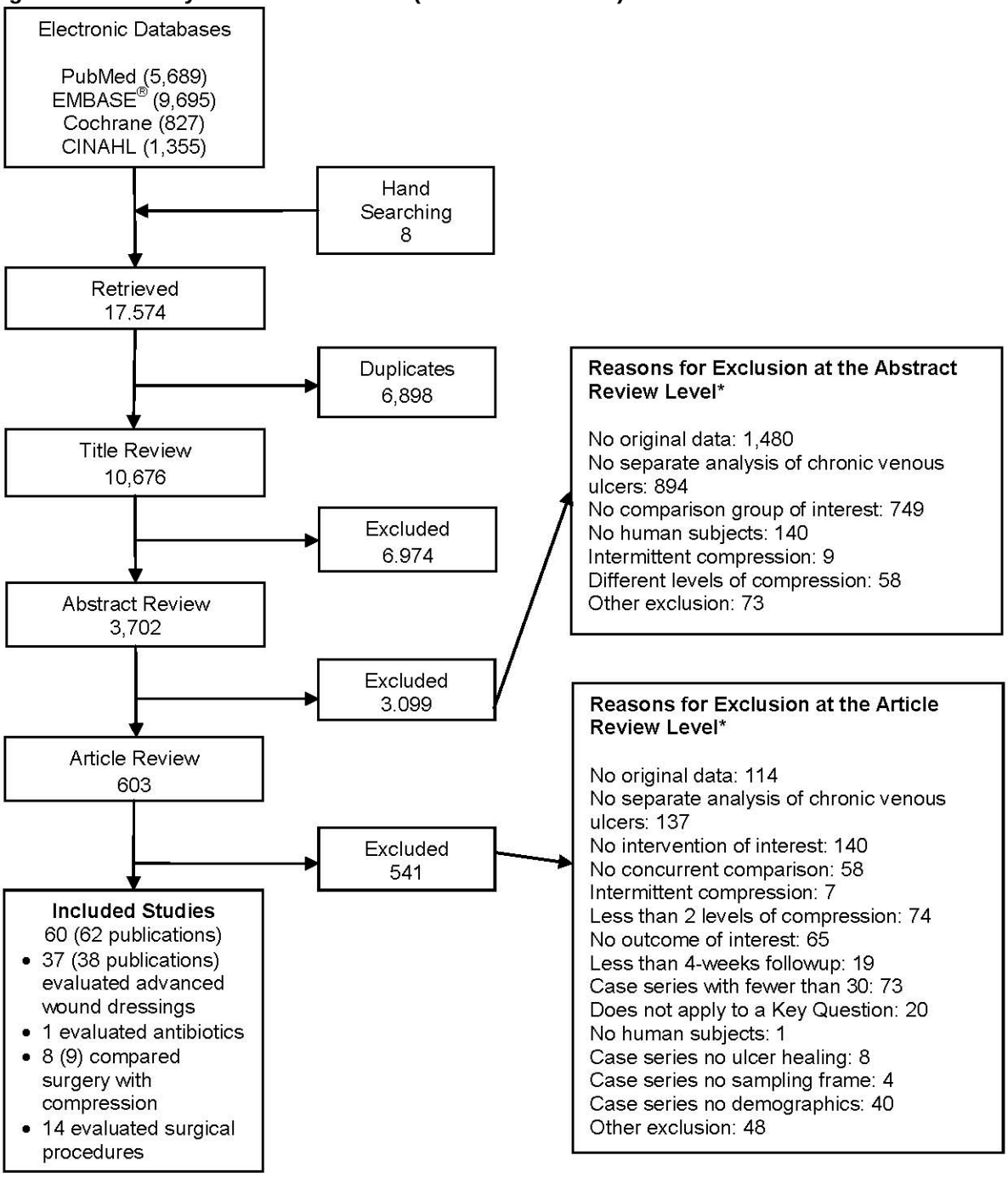
We graded the strength of evidence (SOE) addressing KQs 1, 2, and 3 by applying evidence grades to the bodies of evidence about each intervention class comparison for the outcome of wound healing (i.e., proportion of ulcers healed). We included evidence from intermediate outcomes if this was the only data available. We followed the evidence grading scheme recommended in the Methods Guide.[6] We classified evidence pertaining to the KQs into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Results

Search Results

Figure B describes our search process. We retrieved 10,088 unique citations from our search. After reviewing the titles, abstracts, and full text, we included a total of 60 studies (62 publications). We found 37 studies (38 publications) evaluating advanced wound dressings,[7-43] 1 study evaluating antibiotics,[44] 8 studies (nine publications) comparing a surgical intervention with compression systems,[45-53] 3 studies comparing at least 2 different surgical interventions,[54-56] and 11 studies evaluating a surgical intervention with no concurrent comparison group.[57-67] In most studies, the mean or median age was greater than 60 years.

Figure B. Summary of literature search (number of articles)



CINAHL = Cumulative Index of Nursing and Allied Health Literature
* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

Key Question 1. Benefits and Harms of Advanced Wound Dressings: Impact on Wound Healing, Pain, and Quality of Life

For KQ 1, three randomized controlled trials (RCTs) including 361 patients, compared a **hydrocolloid dressing** with at least two layers of compression in terms of the proportion of ulcers healed. One study showed a shorter healing time with hydrocolloid dressings, but overall wound healing across the three studies was not significantly different (SOE: Low).[37] Four studies with a total 420 subjects compared hydrocolloid dressings with other dressings. These four studies had a high risk of bias and presented inconsistent results, limiting our abilities to draw firm conclusions about the effectiveness of hydrocolloid dressings compared with other dressings (SOE: Insufficient). A small study found improved rates in terms of area healed and overall healing rates compared with impregnated gauze.[26] Another trial found more rapid healing rates but no difference in ultimate full wound healing.[35] Two studies demonstrated no differences.[37, 40] One study compared alginate dressings compared with simple gauze under adequate compression; it found no difference in the proportion of ulcers healed (SOE: Insufficient).

We found no studies that compared compression therapy with the **foam dressings** clinicians often use to manage exudates. However, three studies compared the proportion of ulcers healed between different foam products. We were unable to draw conclusions regarding these studies because they had a high risk of bias, evaluated a variety of interventions, and had imprecise results (SOE: Insufficient). Studies which evaluated additives to dressings, such as shale oil, tenuiflora bark, and human keratinocyte lysate, found no statistically significant difference.

One RCT (N=120) compared a **collagen dressing** plus compression with compression alone in terms of the proportion of ulcers healed.[19] After 12 weeks, a significantly higher proportion of ulcers were healed with the collagen dressing than with compression alone (SOE: Low). However, collagen dressings did not significantly affect the wound recurrence rate.

We were unable to draw a conclusion about the effectiveness of **antimicrobial dressings** compared with compression alone or with other antimicrobial dressings (SOE: Insufficient). Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with other types of dressings (SOE: Moderate). Three RCTs found significantly faster wound healing rates with antimicrobial dressings compared with other dressings.[11, 24, 43] However, silver dressings did not improve wound healing as compared with nonsilver dressings. One RCT comparing silver dressings with nonsilver dressings did not show any improvement in terms of the wound healing rate.[7]

Three studies evaluated **acellular human skin equivalents**.[17, 19, 32] These studies had a high risk of bias, evaluated a variety of interventions, and reported imprecise results, limiting our ability to draw conclusions (SOE: Insufficient). One study of freeze-dried pig intestinal mucosa showed improved healing in well-selected patients compared with compression. The other two studies did not show any difference in wound healing.

Four studies (five publications) evaluated **biological or cellular dressings**.[13, 21, 25, 34, 38] We graded the strength of the evidence separately for cryo-preserved human fibroblast derived dermal substitutes, allogenic bilayered human skin equivalents, and autologous keratinocytes in a fibrin sealant. Studies of a biodegradable mesh containing fibroblasts (Dermagraft®) were limited in their sample size, limiting our ability to draw conclusions (SOE: Insufficient). One of the studies demonstrated a statistically significant improvement in ulcer healing as measured by total ulcer area, but another study with limited power showed no difference. One study, evaluating

allogenic bilayered human skin equivalents, showed improvement in wound healing, especially in patients with ulcers lasting more than 1 month that had previously failed conservative treatment with ACE™ bandages and compression (SOE: Moderate). However, recurrence rates were not different between intervention and control groups. The fourth study reported a greater proportion of ulcers healed with the addition of autologous living keratinocytes than with compression alone (SOE: Low).

Table D summarizes our conclusions on the comparative benefits of wound dressings in terms of wound healing.

We could not draw any definitive conclusions about the effects of advanced wound dressings on pain and quality of life outcomes because the studies did not evaluate these outcomes in a consistent manner. When studies reported mortality rates, they were generally rare (occurring in less than 5 percent of the study population), and did not differ between intervention groups. Evidence was lacking on the effects of advanced wound dressings on maceration, infection, contact dermatitis, venous or arterial impairment, and cellulitis. Compared with compression, patients receiving hydrocolloid dressings and cellular products for chronic venous ulcers experienced similar rates of infection.

Key Question 2a. Benefits and Harms of Systemic Antibiotics Compared With Compression Systems

For KQ 2, only one RCT examined the value of adding systemic antimicrobial use to compression therapy.[44] This study of 36 patients reported a slightly higher healing rate at 16 weeks with ciprofloxacin (42 percent) than with trimethoprim (33 percent) or placebo (30 percent), but the differences were not statistically significant.

Key Question 2b. Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

We did not find any studies addressing this KQ.

Table D. Summary of the comparative benefits of advanced wound dressings in terms of wound healing

Comparison (Number of Included Studies)*	Strength of Evidence†	Conclusions
Hydrocolloids vs. compression (3)	Low	Hydrocolloid dressings were not more effective than compression therapy alone in terms of the proportion of chronic venous ulcers healed. The results from the three studies addressing this comparison were imprecise and subject to some bias.
Hydrocolloids vs. other dressings (4)	Insufficient	We were unable to draw a conclusion.
Transparent films vs. compression (1)	Insufficient	We were unable to draw a conclusion.
Transparent films vs. other dressings (1)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. compression (1)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. alginate dressings (2)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. other dressings (1)	Insufficient	We were unable to draw a conclusion.
Foam dressings vs. foam dressings (3)	Insufficient	We were unable to draw a conclusion.
Collagen dressings vs. compression (1)	Low	Collagen dressings healed a greater proportion of ulcers than compression alone.
Acellular human skin equivalent dressings vs. compression (3)	Insufficient	We were unable to draw a conclusion.
Cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression (2)	Insufficient	We are unable to draw a conclusion.
Cellular human skin equivalents (allogenic bilayered cultured HSE) vs. compression (1)	Moderate	Studies of cellular human skin equivalent dressings in patients with chronic venous ulcers showed a higher proportion of ulcers healed and more rapid healing, especially those that had failed previous therapy and were present for over 1 year.
Cellular (autologous keratinocytes in a fibrin sealant) vs. compression (1)	Low	Autologous keratinocytes in fibrin sealant healed a greater proportion of ulcers and achieved a shorter median time to complete wound closure versus compression.
Cellular human skin equivalent dressings vs. other dressings (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial dressings vs. compression (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial dressings vs. antimicrobial dressings (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial containing dressings vs. other types of dressings (4)	Moderate	Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with other nonantimicrobial dressings. However, silver dressings did not improve wound healing as compared with nonsilver dressings.

* The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

† We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Key Question 3a. Benefits and Harms of Surgical Interventions Compared With Compression

We identified eight unique studies (nine publications) meeting our inclusion criteria that compared a surgical intervention with two or more layers of compression.[45-53] We did not identify any studies that compared the effectiveness of compression therapy alone with the effectiveness of deep vein surgery or radiofrequency ablation, endovenous laser therapy, or vein stripping to treat superficial vein reflux. Table E summarizes the results on wound healing and recurrence.

Surgical Procedures Targeting Superficial Vein Reflux

Two studies, one an RCT and the other a prospective cohort study, reported similar rates of complete healing for **superficial vein surgery** and compression alone over 36 to 48 months of followup (SOE: Moderate). Notably, 19 percent of participants in the surgery arm did not receive surgery during the RCT.[46] Ulcer recurrence rates at 3 years were significantly lower after surgery in these studies (31 vs. 56% in the RCT, [$P<0.01$] and 26 vs. 44 percent in the cohort study [$P=0.03$]) (SOE: Moderate).[46, 47, 49]

Surgical Procedures Targeting Perforator Vein Reflux

Four RCTs compared compression therapy with **surgical procedures to address perforator vein reflux**, and reported similar rates of complete ulcer healing in their respective surgical and control arms.[48, 51, 52, 68] The surgical interventions in these studies included minimally invasive ligation of insufficient saphenous vein tributaries (conservative hemodynamic treatment of insufficiency of the venous system in an ambulatory setting [CHIVA]) (SOE: Low),[48] subfascial endoscopic perforator surgery (SEPS) (SOE: High),[51, 52] and sclerotherapy (SOE: Insufficient).[45] The study of CHIVA reported a faster time-to-healing with surgery than with compression alone (median of 31 vs. 63 days).[48]

Two of these RCTs reported on ulcer recurrence rates. The ulcer recurrence rate was higher in the compression arm than in the CHIVA arm (38 vs. 9%; $P<0.05$) in Zamboni, et al. (SOE: Low).[48] An RCT evaluating SEPS reported similar ulcer recurrence rates in the intervention and control arms (SOE: High).[52]

Another study compared the effectiveness of sclerotherapy with compression alone and found that the complete healing rate was 85 percent with surgery and 62 percent with compression ($P=0.06$) with a faster time-to-healing in the surgery arm (mean of 8 vs. 20 weeks).[50] The method of allocation was unclear in this study.[50] An additional retrospective study showed a similar proportion of venous ulcers healed when comparing sclerotherapy with compression.[53]

Quality of Life

Two studies reported on quality-of-life outcomes. A single study found that Short Form-36 scores were better after receiving CHIVA than after receiving compression alone.[48] The other study found that SEPS did not perform better than compression alone when researchers measured quality of life with the Charing Cross Venous Ulcer Questionnaire.[51]

Mortality

The six studies that reported on mortality did not find substantial differences between surgical interventions and compression alone.

Adverse Events

The six studies that reported on adverse events did not find substantial differences between surgical interventions and compression alone.

Table E. Summary of the comparative benefits of surgical interventions compared with compression in terms of wound healing

Comparison (Number of Included Studies)*	Strength of Evidence†	Conclusions
Superficial vein surgery vs. compression alone (1 RCT, 1 cohort)	Moderate	Adding superficial vein surgery to compression therapy does not improve healing of chronic venous leg ulcers, but there may be a lower risk of recurrence.
CHIVA vs. compression alone (1 RCT)	Low	Adding minimally invasive surgical hemodynamic correction of reflux to compression therapy does not significantly affect the proportion of ulcers healed, but it may lower the risk of recurrence.
SEPS vs. compression alone (2 RCTs)	High	SEPS with superficial vein surgery does not improve the rate of healing or the risk of recurrence of chronic venous leg ulcers in comparison with compression alone.
Sclerotherapy vs. compression alone (1 RCT, 2 cohorts)	Insufficient	We were unable to draw a conclusion.
RFA vs. compression alone (0) EVLT vs. compression alone (0) Deep venous surgery vs. compression alone (0)	Insufficient	We were unable to draw a conclusion.

CHIVA = conservative hemodynamic treatment of insufficiency of the venous system in an ambulatory setting; EVLT = endovenous laser therapy; RCT = randomized controlled trial; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery

* The strength of evidence for all comparisons not listed here were graded as inconsistent because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

† We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Key Question 3b. Benefits and Harms of Surgical Interventions Compared With Other Surgical Interventions

We divided the data for KQ 3b into two parts. Part 1 includes studies that compared two surgical interventions with each other, without a medical arm of compression treatment. Part 2 includes studies with no surgical or medical comparison at all. These were mostly case series. We included studies without a comparison group because we anticipated finding few comparative studies.

Three studies compared two surgical techniques (Table F).[54-56] We also included 11 studies that evaluated a surgical procedure without a concurrent comparison group.[57-67] Five of these were case series.[57, 61-63, 65] Five studies were cohorts,[58, 59, 64, 66, 67] and one had an unclear study design.[60] The studies evaluated a variety of interventions including venous valve surgery,[59, 60, 63] radiofrequency ablation,[61, 65] SEPS,[66, 67] saphenous vein stripping and/or ligation,[58, 62] sclerotherapy,[57] and angioplasty/stenting.[64] We did not find any studies evaluating surgical procedures for chronic venous leg ulcers associated with deep venous occlusion.

One non-RCT of 46 patients compared **perforator ligation plus saphenous vein stripping (PLSVS)** versus PLSVS plus valvular surgery.[54] The study reported wound healing rates of 44 percent for PLSVS alone and 80 percent for PLSVS plus valvuloplasty, vein transposition, or valve transplantation. Wound recurrence was 56 percent for PLSVS, 20 percent for PLSVS plus valvuloplasty, 21 percent for PLSVS plus vein transposition, and 25 percent for PLSVS plus valve transplantation. The difference was not significant between the four groups because of the small sample sizes. The SOE on this comparison was insufficient because the study had a high risk of bias and did not provide a precise effect estimate.

One cohort study compared **isolated sapheno-femoral junction ligation** with vein stripping and found that the ligation group had a significantly higher healing rate (85 vs. 70 percent; $P<0.05$). This study had a high risk for bias with an imprecise effect estimate, and therefore, we considered the SOE to be insufficient.[55]

One nonrandomized retrospective cohort study included subjects from a single author's clinical experience,[56] and evaluated four groups, each of which received a different mix of surgical interventions. The study found **sclerotherapy** produced more rapid wound healing. The study design was complex, but more important, the cases came from a single author's practice with substantial potential for selection and reporting bias. Sclerotherapy had the shortest time-to-healing with 95 percent of venous ulcers healed. The time-to-heal was significantly longer when clinicians documented femoral and popliteal vein insufficiency. In the group of patients with the shortest time-to-heal (up to 8 weeks), clinicians documented popliteal vein involvement in 55 percent of patients. The group that required more than 12 weeks to heal had 94 percent popliteal vein involvement. We considered the SOE from this study to be insufficient because of the high risk of bias and the imprecise effect estimates.

From the 11 studies included in Part 2 of our review of KQ 3b,[57-67] we concluded that the evidence was insufficient to determine the comparative benefits and harms of the interventions. The studies were all limited by sample size issues, selection bias, data heterogeneities, and lack of control for confounders or interactions. The studies did not measure quality of life, functional status, or pain.

Table F. Summary of the comparative benefits of surgical interventions compared with other surgical interventions in terms of wound healing

Comparison (Number of included studies)*	Strength of evidence†	Conclusions
PLSVS vs. PLSVS + valvuloplasty vs. PLSVS + vein transposition vs. PLSVS + valve transplantation (1)	Insufficient	We are unable to draw a conclusion.
Isolated sapheno-femoral junction ligation vs. vein stripping (1)	Insufficient	We are unable to draw a conclusion.
Sclerotherapy vs. valvular surgery (1)	Insufficient	We are unable to draw a conclusion.

PLSVS = perforator ligation and saphenous vein stripping

* The strength of evidence for all comparisons not listed here were graded as inconsistent because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

† We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Discussion

Key Findings and Strength of Evidence

Overall, the study team was struck by the paucity of evidence to guide decisions related to all of the KQs. For Each KQ, the available evidence was compromised by study designs that were often underpowered, and by a lack of standardized definitions or protocols for the wound interventions. The studies also lacked evidence on pain and quality of life assessments.

In terms of balancing benefit and harms, for KQ 1, the major issue is whether the intervention results in benefit, as the dressings have minimal systemic or local toxicity (minimal harm). The lack of known benefit for many of these dressings is complicated by the wide price range of these interventions, which impacts both patients and payors. For KQ 2, there are harms for both patient and society from antibiotic overuse, with few data to guide providers. For the surgical options explored in KQ 3, there are both potential benefits and substantial harms related to the risk of surgery. Understanding the efficacy of surgical approaches is complicated by the lack of prospective clinical trial designs, and continued technical innovation. Technical innovation has led to less invasive and endovascular techniques.

Besides the efficacy questions, our review could not answer many of the practical aspects of caring for wounds, including the rapidity in return to function and the impact on family members, and aspects related to the delivery of care. For example, the impact of specific interventions may be altered if the care is delivered by a multidisciplinary wound clinic or a primary practice office. The studies did not compare the venues for delivery of care, yet this could be a major confounder.

Key Question 1. Benefits and Harms of Advanced Wound Dressings

Minimal data existed to suggest that hydrocolloid dressings had no advantage over compression alone in healing rates and in ultimate wound healing (SOE: Low). Many studies had nonsignificant results. Collagen dressings may improve the proportion of ulcers healed compared with compression alone (SOE: Low). Antimicrobial dressings, such as those that contained cadexomer iodine, provided advantages in improved healing (SOE: Moderate), but silver dressings had no advantage over nonsilver dressings (SOE: Moderate).

For acellular skin equivalents, the SOE was insufficient to support the use of freeze-dried intestinal pig mucosa. Allogenic bilayared human skin equivalents may promote more rapid healing, particularly among patients with longstanding ulcers. However, there was no effect on post-treatment recurrence, indicating the importance of treating the underlying disease and the necessity of continuing post-treatment compression.

For none of the advanced wound dressings was there a systematic assessment of harms or adverse events.

Key Question 2a. Benefits and Harms of Systemic Antibiotics Compared With Compression Systems

We found only one study that addressed this question, and it provided insufficient evidence to determine the benefits of systemic antibiotics compared with compression. There was no

assessment of potential harms of this intervention in promoting the development of antimicrobial resistant organisms.

Key Question 2b. Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

We did not find any studies that addressed this question.

Key Question 3a. Benefits and Harms of Surgical Interventions Compared With Compression

We found low SOE that minimally invasive surgical hemodynamic correction of reflux may decrease the time-to-healing of chronic venous leg ulcers compared with compression therapy alone, but it does not increase the proportion of ulcers healed. For other surgical interventions for chronic venous leg ulcers, the SOE was moderate to high that healing was not improved, but there could be a lower risk of recurrence when compared with compression alone. We found insufficient evidence about the benefits and harms of sclerotherapy, vein stripping, radiofrequency ablation, or endovenous laser therapy for superficial vein reflux or surgery for deep vein disease in patients with chronic venous leg ulcers.

Key Question 3b. Benefits and Harms of Surgical Interventions Compared With Other Surgical Interventions

The evidence was insufficient to determine the comparative benefits and harms of different surgical procedures for chronic venous leg ulcers associated with a given type of venous reflux due to the small number, small size, and poor quality of studies.

Applicability

Studies generally did not report on the representativeness of their study populations. In most cases, we could not determine if the care received by study patients was similar to that received by other patients. The RCTs tended to include elderly patients similar in age to the population of patients with chronic venous leg ulcers, and most studies included at least a substantial minority of men. When studies reported the baseline mean duration of chronic venous ulcers, it was typically more than 12 months, and thus study results are more applicable to ulcers that are recalcitrant to prior treatment. Studies of advanced wound dressings were of short duration (4 months or less) and thus, the long-term effects are unclear.

Findings in Relationship to What is Already Known

Our findings are in concert with previous published large reviews and evidence-based practice guidelines. Previous reviews (less comprehensive than the one performed here) found a paucity of randomized or controlled clinical trials to support the use of any of the interventions described.

Key Question 1. Benefits and Harms of Advanced Wound Dressings

Cochrane Collaboration reviews[69] have addressed the use of wound dressings and have found no data to support superiority of specific dressings. Our review of cadexomer iodine-containing

dressings is consistent with that described in the Cochrane review, which indicated modest improvements in wound healing. The data on cellular equivalents are from recent well-controlled clinical trials.

Key Questions 2a and 2b. Benefits and Harms of Systemic Antibiotics Compared With Compression Systems, and Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

There have been no previous comparative effectiveness reviews of the impact of systemic antibiotics on chronic venous leg ulcers. However, the limited findings of our review are in concert with the Infectious Diseases Society of America's policy statements on wound care.

Key Questions 3a and 3b. Benefits and Harms of Surgical Interventions Compared With Compression, and Benefits and Harms of Surgical Interventions Compared With Other Surgical Interventions

There have been no evidence-based reviews of studies with control groups to evaluate surgical outcomes in patients with chronic venous leg ulcers. However, our review identified critical research needs that are in concert with a 2011 evaluation from the Center for Medical Technology Policy, which concluded that there was a paucity of evidence in wound care.[70] Their major recommendations included developing an evidence base using randomized multicenter clinical trials, blinding the assessment of patient-reported outcomes to intervention, developing a consistent standard of care arm, standardizing protocols and protocol adherence, and standardizing outcome measures.

Limitations

We reviewed the titles and abstracts of more than 10,000 published articles, but found few well-designed RCTs that addressed the comparative effectiveness of treatments for chronic venous leg ulcers. The RCTs generally did not report on allocation concealment, and did not mask patients or outcome assessors to treatment assignment. We expanded our review to include observational studies, but these studies were largely limited to convenience populations that, by definition, carry with them a substantial risk of bias. Overall, the studies that addressed the topic were very heterogeneous and had major problems that limited our ability to make firm conclusions about the effectiveness and safety of treatments for chronic venous leg ulcers. Major limitations of the published data threatened both internal and external validity. These limitations included the lack of standard definitions of chronic venous leg ulcers, inconsistent outcome measures, suboptimal comparison groups, and inconsistent duration of interventions. Studies often had large losses to followup or did not report on this. Many of the studies also did not report statistical analyses beyond simple healing rates, stratification or adjustment to account for potential confounding variables, or sample size calculations. Most studies were very small and therefore had limited statistical power.

Implications for Clinical Practice and Policy

Our findings have substantial implications for clinical practice and policies related to the care of chronic venous leg ulcers. With the exception of a few surgical interventions and the use of human skin equivalents under defined conditions, most interventions used in the management of

chronic venous leg ulcers lack supporting evidence that they add any benefits to compression therapy alone. This negative finding does not necessarily mean that the interventions are ineffective, but rather that we need better studies to demonstrate their clinical impact.

These findings therefore have impact on policy, especially for agencies and payers that provide reimbursement, and identify critical research needs. Since the prevalence of chronic venous stasis disease is increasing,[71] and will likely increase for the foreseeable future, health care payers, regulatory agencies, and other policymakers require strong evidence on outcomes that can better guide the treatment of patients with chronic venous leg ulcers. We need high-quality data on the comparative effectiveness of the treatment options to develop efficient algorithms for guiding therapy, and to better understand which therapeutic interventions have value to ensure appropriate reimbursement in an increasingly constrained health care environment.

Research Gaps

Our research identified several areas to consider for future research. We were unable to make strong conclusions regarding the efficacy of most interventions because of a lack of high-quality RCTs. Areas to consider for future research include cellular human skin equivalents, collagen dressings, dressings that enhance debridement, antibiotic treatments, and surgical techniques. The results from a recent phase 2 RCT are promising and warrant future research on a spray cell therapy containing growth arrested allogeneic neonatal keratinocytes and fibroblasts plus a foam dressing.[72]

Few studies addressed quality of life measures, and no studies assessed quality of life using standard or validated scales. Since chronic wounds have substantial impact on the patient and his/her family, quality of life measures are critical in evaluating overall wound treatment efficacy. Studies also did not adequately address or describe potential harms in interventions. This substantially differs from the studies of regulated pharmaceuticals, which carefully record adverse events.

Need for Harmonization

Our review demonstrated that studies of interventions for chronic venous leg ulcers take place in many different practice and cultural settings involving a variety of disciplines, including nursing, dermatology, vascular surgery, and internal medicine. This heterogeneity was associated with the excessive variety of methods we saw in these studies.

To adequately address this problem, clinical researchers, government regulators, payers, and other stakeholders from academic and clinical communities and industry should establish a consensus about how to harmonize studies in this area. The objective would be to develop better standards for disease definition, interventions, comparison groups, and outcome measures, including intermediate outcomes, pain, and quality of life. These experts could create templates for study designs that better demonstrate efficacy. Similar recommendations were made in a report published by the Center for Medical Technology and Policy, "Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds."[70]

One of the major issues to address is the limitation in study design. The nature of the interventions and the difficulty in many cases of developing placebo or sham conditions, makes implementing traditional double-blinded, or even single-blinded randomized trials difficult, if not impossible. We believe that implementation of appropriate, well-designed clinical trials will

require substantial clinical patient management and recruitment resources. Furthermore, the trials must be large enough to have sufficient statistical power for determining the comparative effectiveness and safety of the therapeutic options. Since future research is likely to depend on funding from a number of different sources, including manufacturers of products and devices, investigators will need to develop appropriate policies for managing potential conflict-of-interest issues. We suggest that a long-term solution to this would be the development and implementation of a clinical trials network or a patient registry that would have a broad recruiting base, specialized centers that adhere to case definitions, and a commitment to long-term followup.

Conclusions

Chronic wounds due to venous hypertension are emerging as a major clinical care and public health challenge, with rapidly increasing costs and morbidity. Following an iterative process, and consulting with the Agency for Healthcare Research and Quality and stakeholders, we developed three KQs to help guide our review of the effectiveness of treatment options for chronic venous leg ulcers. Among the studies we identified, we found a general lack of well-designed, well-controlled studies, as well as lack of a standard case definition, or approaches to managing confounders and interactions. For advanced wound dressings, we found that there was no impact on wound healing when compared with compression therapy alone, with the exception of the use of cellular skin equivalents on venous ulcers that had failed previous conservative management. The general lack of data hampered our evaluation of systemic and local antimicrobial therapy, and we found no evidence to support antimicrobial therapy for chronic venous leg ulcers in the absence of symptoms or signs of infection. Although substantial literature exists on venous surgical approaches, the vast majority of studies are uncontrolled case series or studies that did not measure ulcer outcomes. We found minimal, if any, benefit for surgical interventions for disease management. However, more recent data suggest that surgical interventions may impact recurrence rates, and therefore there is a need to validate these findings.

For clinicians and payers, this report shows that little evidence exists to support the majority of interventions used for treatment of chronic venous leg ulcers. The lack of strong evidence may impact reimbursement for various modalities.

For the clinical research community, this report has identified important systematic issues in the definition and design of clinical trials. We need to standardize case definitions, clarify clinical trial study outcomes, and develop a network of centers that have the capacity to implement high quality clinical effectiveness research for this condition.

We need to resolve these issues in order to develop a strong evidence base so clinicians can make informed therapy recommendations and better evaluate the efficacy and effectiveness of current and newly developed products and interventions.

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Introduction

Background

Venous leg ulcers constitute a majority of all ulcers seen in United States, affecting between 500,000 to 2 million people annually.[1] Individuals with venous leg ulcers tend to be older (over 60 years of age) and female. In the United Kingdom, where more comprehensive information is available, a 1987 study showed that the mean duration of ulcers was 9 months, 20 percent of ulcers had not healed within 2 years, and 66 percent of patients had a history of ulcerations lasting longer than 5 years.[2] According to a 2006 study by Bergan et al., "chronic venous disease has been estimated to account for 1 to 3 percent of total health care budgets in countries with developed health care systems."[3]

The factors that cause venous leg ulcers are elevated venous pressure, turbulent flow, and inadequate venous return. The latter can be due to venous occlusion or venous reflux. Risk factors for chronic venous disease include underlying illnesses where there is poor venous return (such as congestive heart failure and obesity), primary destruction of the venous system (such as prior history of deep venous thrombosis), recreational injected drug use (skin poppers), phlebitis, and venous valvular dysfunction.

Clinicians diagnose venous ulcers on the basis of anatomic location, morphology, and a series of characteristic skin changes. Clinicians confirm diagnosis using appropriate laboratory studies, which should include a functional assessment of the venous system. The "gold standard" for diagnosing venous disease is venography, however clinicians rarely use it because of expense, morbidity, and the availability of noninvasive tests. Today, clinicians most often use venous duplex ultrasound to diagnose venous abnormalities.[4]

The current standard clinical approach to therapy includes lower limb compression and debridement, which heals 40 to 60 percent of venous leg ulcers.[3] O'Meara, in a 2009 Cochrane review, evaluated a total of 39 randomized controlled trials and concluded that there was reasonable evidence that compression healed venous ulcers more rapidly.[5] Furthermore this review concluded that a minimum of two layers of compression, one being an elastic component, were necessary for effective therapy. Increasing the number of layers seemed to be more effective but comparisons between different compression systems was difficult. Clinicians must consider other therapies for the large number of patients for whom compression therapy and debridement fail. However, no consensus exists about which second-line treatment works best.

To evaluate the healing of venous leg ulcers with different therapies, investigators can use well-defined final health outcomes (see Figure 1), such as percentage of wounds healed based on intent to treat, and durability of healing over specified periods of time. These parameters have become the gold standards of evaluation, having gained acceptance by organizations such as the U.S. Food and Drug Administration and the Centers for Medicare and Medicaid Services.[6, 7] More recently, researchers have proposed a valuable set of surrogates for complete healing. The most notable and best-confirmed surrogate is the rate of wound healing over a 4-week period of time.[8] Clinicians can gauge the healing rate by tracing the wound margins and/or by using digital photography. This method mainly uses epithelialization (area reduction) to determine the healing rate. Clinicians can also determine healing rates using granulation (depth reduction) or vascularization. Other outcomes of interest include quality of life, pain, and cost-effectiveness.

Below is an overview of the three major types of interventions that clinicians currently use to manage chronic venous leg ulcers.

Advanced Wound Dressings

Over the past 20 years, studies have generated much evidence to support the premise that a moist wound environment is essential for wound healing.[9-11] This has caused a proliferation of expensive new wound dressings (see Figure 2 and Table 1), and has left wound care providers confused about when it is appropriate to use these expensive dressings.

Advanced wound dressings regulate moisture found at the wound surface through moisture retention or exudate absorption, thereby protecting the wound base and tissue surrounding the wound. Additionally, maintaining a good moisture balance minimizes patient discomfort before, during, and after dressing changes. Many dressings inherently support autolytic debridement by providing added moisture, while others supply enzymatic debriding agents to rid the wound of necrotic tissue. Choice of dressings may change during the course of therapy concomitant with the changing nature of the wound base and exudate. Therefore, the selection of particular dressings requires training and expertise in wound care. Evaluating the efficacy of dressings in treating venous ulcer disease may have high relevance to morphologically similar ulcers found in patients with diabetes, arterial disease, pressure ulcers, postsurgical chronic wound ulcers, and ulcers consequent to internal diseases.

Antibiotics

All chronic wounds become contaminated or colonized with bacteria, meaning that bacteria is present in the wound but not causing tissue damage.[12] Infection occurs when the bacteria start to invade the tissue. Signs of infection include pain, redness, swelling, cellulitis, presence of exudates, and odor.

Antibiotic use is widely prevalent in the management of venous ulcers. Some experts believe that clinicians should only use antibiotics in patients that have symptoms or signs of an infected ulcer or adjacent cellulitis. However, many patients with chronic venous leg ulcers receive antibiotics in the absence of clinical symptoms or signs of infection. As shown in Figure 3 and Table 2, clinicians have many different options for adding antibiotic treatment to the management of venous ulcers. However, there is no clear guidance for the use of systemic or topical antibiotics. Clinicians must keep in mind that antibiotics have profound side effects including the development of resistant organisms, the growth of undesirable organisms, and iatrogenic disease. In addition, clinicians who use peripherally inserted central catheters to administer antibiotics for long periods of time, may put patients at risk for secondary infection complications. Furthermore, intravenous antibiotics are very costly (over $100 per day).

Surgical Interventions

Most patients with venous ulcers have significant reflux on duplex ultrasound. Clinicians define reflux as retrograde blood flow lasting greater than 0.5 seconds with the Valsalva maneuver in superficial, deep, or perforator veins. The superficial veins include the great or lesser saphenous veins while the deep veins include the femoral and popliteal veins. Obstructive venous disease is a less common cause of venous ulceration. If clinicians are considering surgery, they need duplex ultrasound (now routine in most vascular laboratories) to classify the underlying pathophysiology of a venous ulcer (see Figure 4). Clinicians perform invasive venography or measure ambulatory venous pressure when clinical and duplex ultrasound findings are insufficient to confirm the underlying pathophysiology.

The current surgical practice is to eliminate documented reflux or obstruction in patients with chronic venous ulceration that have failed a 3-month period of compression dressing, debridement, and antibiotics.[13, 14] As shown in Figure 4 and Table 3, the surgical options depend on the underlying type of reflux or obstruction. However, the indications for surgery are not standardized, and there is no consensus about which surgical option is the safest and most effective in healing the ulcer.

Scope of Review and Key Questions

The overall purpose of this evidence report is to provide a systematic review of the comparative effectiveness of the above described therapeutic approaches to the management of chronic venous leg ulcers. The scope of our report is more inclusive than previously published reviews,[15, 16] and we plan to compare classes of therapeutic agents, as opposed to drawing distinctions between individual therapeutic agents. Figures 1–4 graphically depict the Key Questions (KQs) that we listed below. Tables 1–3 describe our classification schemes for the three major types of intervention: wound dressings, antibiotics, and vascular surgery.

Key Question 1. For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components in conjunction with compression systems when compared with using solely compression systems?

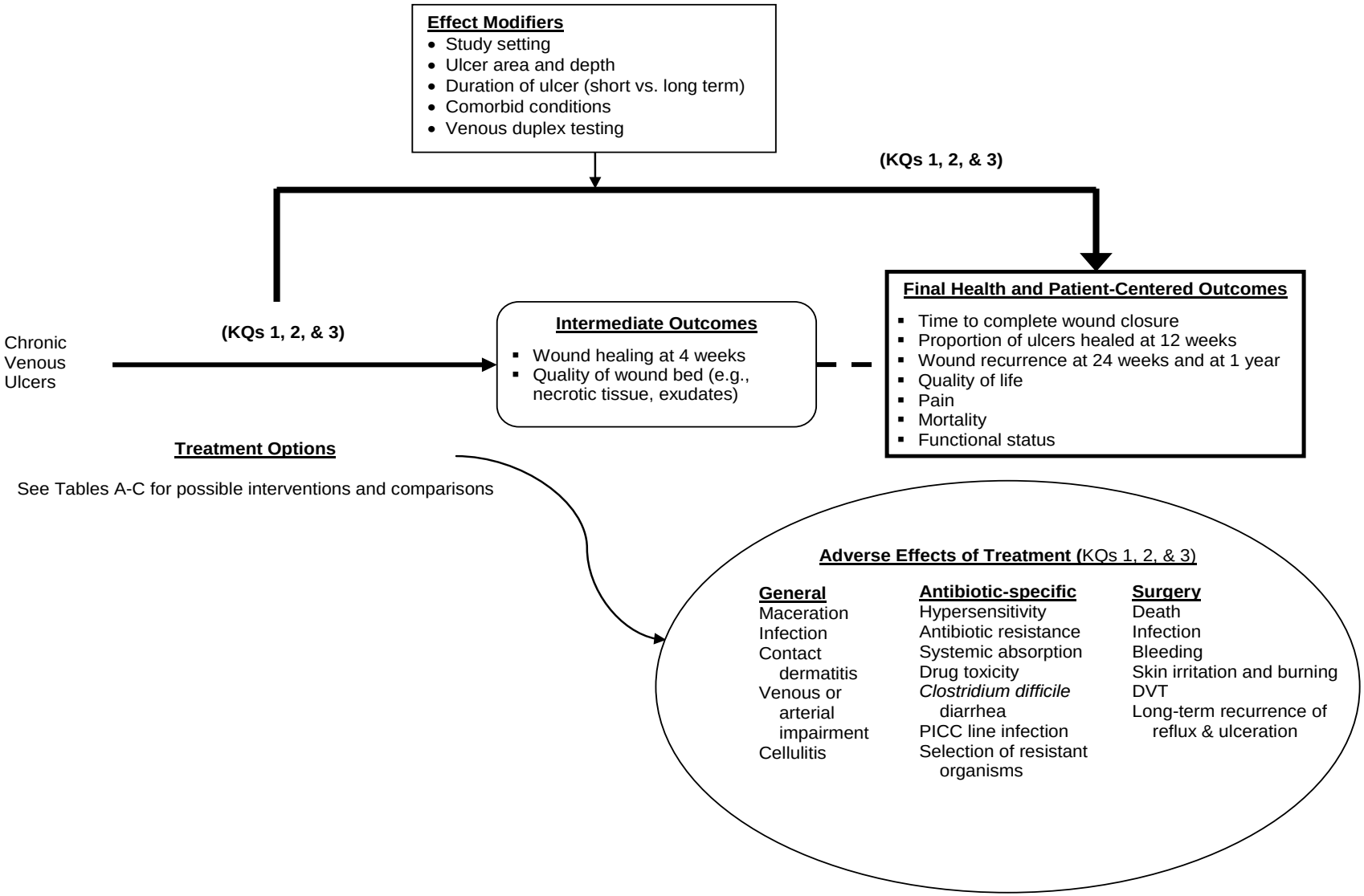
Key Question 2a. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

Key Question 2b. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components, what are the benefits and harms of using systemic antibiotics when compared with using dressings alone?

Key Question 3a. For patients with chronic venous leg ulcers, what are the benefits and harms of surgical procedures aimed at the underlying venous abnormalities when compared with using solely compression systems?

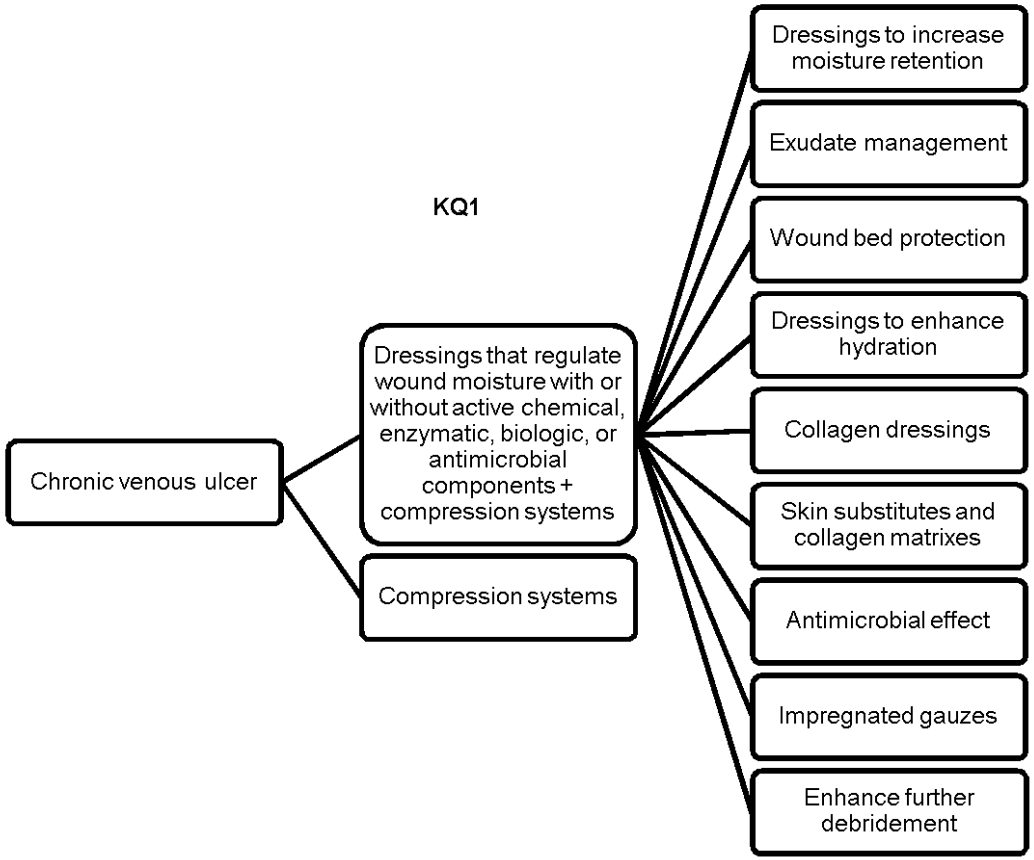
Key Question 3b. For patients with chronic venous leg ulcers, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

Figure 1. Analytic framework for the treatment of chronic venous leg ulcers



Abbreviations: DVT = deep vein thrombosis; KQ = Key Question; PICC = peripherally inserted central catheter

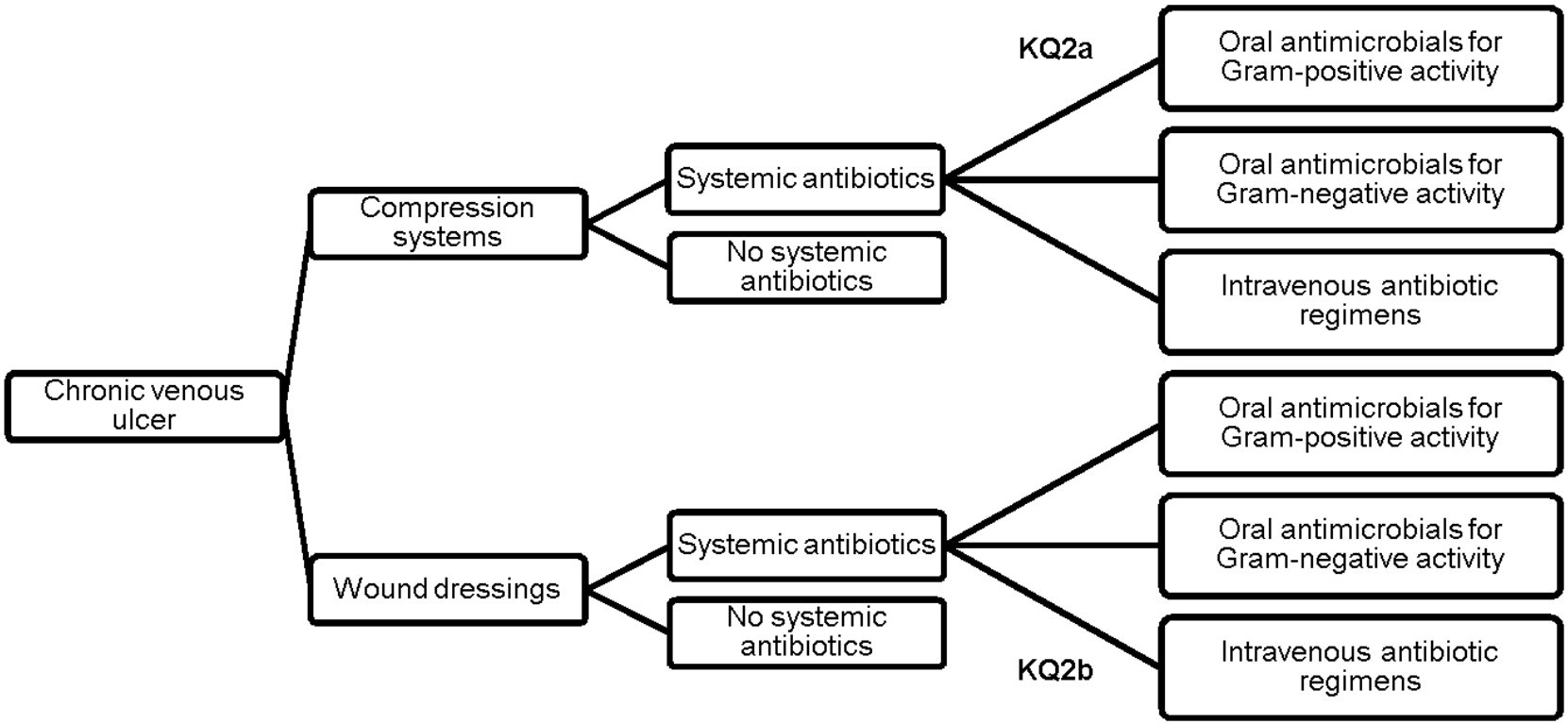
Figure 2. Potential options for wound dressings with active chemical, enzymatic, or antimicrobial components for the treatment of chronic venous leg ulcers



Compression systems include the following elements:

- Debridement of necrotic tissue that may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement that leads to a clean wound base. Debridement will be classified, when possible, into wound bed debridement and excisional debridement.
- Simple dressings containing nonactive components such as moisturizers.
- At least moderate compression described either qualitatively or quantitatively (>20 mm), so that the leg does not swell significantly during the day.

Figure 3. Potential systemic antibiotic treatment options for chronic venous leg ulcers

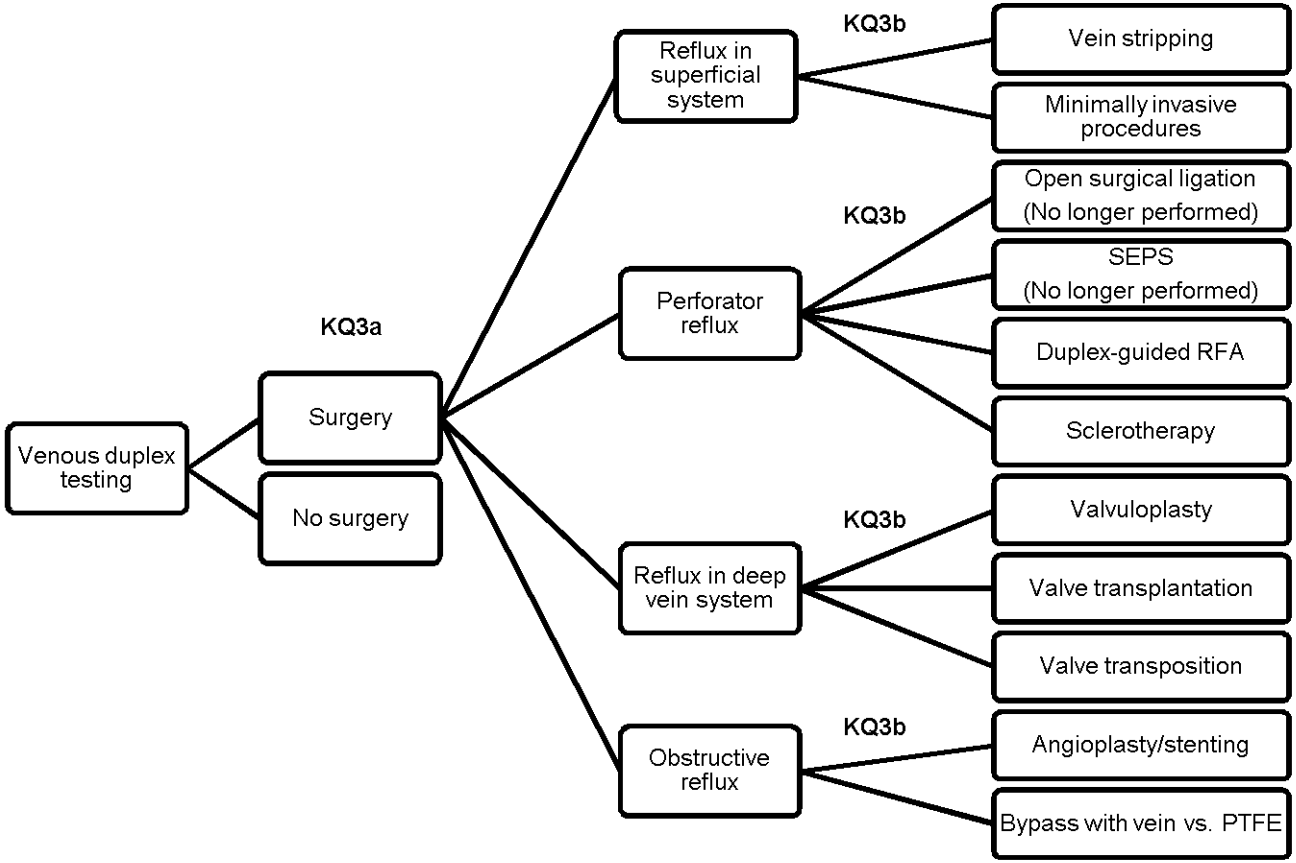


See Table 2 for a list of antibiotics.

Compression systems include the following elements:

- Debridement of necrotic tissue that may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement that leads to a clean wound base. Debridement will be classified, when possible, into wound bed debridement and excisional debridement.
- Simple dressings containing nonactive components such as moisturizers.
- At least moderate compression described either qualitatively or quantitatively (>20 mm), so that the leg does not swell significantly during the day.

Figure 4. Potential surgical treatment options for chronic venous leg ulcers



Abbreviations: KQ = Key Question; PTFE = polytetrafluoroethylene; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery

Table 1. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, biologic, or antimicrobial components

Functional Category	Classification	Characteristics	HCPS Classification
Dressings to enhance moisture retention	Hydrocolloids	• Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet • Polymers form a gel on contact with wound exudate: allows for wound hydration and autolytic debridement	• Hydrocolloid dressing, wound cover, sterile
	Transparent films	• Transparent sheets of polyurethane coated with an adhesive • Act as a "blister roof" to provide a moist wound-healing environment, promotes autolysis, and protects the wound and peri-wound tissues from external trauma	• Transparent film, sterile
Exudate management	Alginates	• Derived from seaweed and spun into a rope or sheet dressing • Fibrous and highly absorbent and can become gel-like when coming into contact with exudate to maintain a moist wound-healing environment	• Alginate or other fiber gelling dressing, wound cover • Alginate or other fiber gelling dressing, wound filler
	Foams	• Sterile, nonlinting, absorptive dressing made of open-cell, medical-grade expanded polymer • It is nonadherent	• Foam dressing, wound cover, sterile (with/without adhesive border) • Foam dressing, wound filler, sterile
	Composites	• Combine physically distinct components into a single dressing that provides multiple functions: (1) bacterial barrier; (2) absorptive layer other than an alginate, foam, hydrocolloid, or hydrogel; (3) either semi-adherent or nonadherent property; and (4) adhesive border	• Composite dressing, sterile with adhesive border
	Special absorptive dressings	• Unitized, multilayer dressings that provide either a semiadherent quality or nonadherent layer and highly absorptive layers of fibers such as absorbent cellulose, cotton, or rayon	• Special absorptive dressing, wound cover, sterile with/without adhesive border
Wound bed protection	Contact layer	• Thin, nonadherent sheets placed directly on an open wound bed to protect the tissue from direct contact with other agents or dressings	• Contact layer, sterile
Dressings to enhance hydration	Hydrogels	• A polymer gel composed mostly of water in a complex network of fibers • Water is released to keep the wound moist • Can be hydrophilic	• Hydrogel dressing, wound cover, sterile with/without adhesive border • Hydrogel dressing, wound filler
Collagen dressings	Sheets, wound filler gels or powder	• Freeze-dried bovine, porcine, or equine collagen • Can contain cellulose or alginate for absorption • Porcine small intestine submucosa extracellular matrix (Oasis®)	• Collagen-based wound filler, dry form • Collagen-based wound filler, gel/paste • Collagen dressing, sterile, pad

Table 1. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, or antimicrobial components (continued)

Functional Category	Classification	Characteristics	HCPCS Classification
Biological dressings	Acellular	• Extracellular matrixes that support new tissue growth • Cryopreserved human skin allograft (TheraSkin®) • Three-dimensional porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan (Integra™)	• Skin substitute
	Cellular	• Bioengineered, bi-layered, living cell-based skin substitute (Apligraf®) • Cryopreserved human fibroblast-derived dermal substitute (Dermagraft®)	• Skin substitute
Antimicrobial effect	Alginates, foams, hydrocolloids, hydrogels, transparent films, absorptive specialty dressings, collagens	• See individual dressing characteristics • Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, manuka honey, gentian violet, polyvinyl alcohol with methylene blue, cadexomer iodine, and chlorhexidine	• HCPCS classifications as listed above
Gauzes	Impregnated	• Made of woven and nonwoven fibers of cotton, polyester, or a combination in which substances have been added such as: iodinated agents, petrolatum, zinc compounds, crystalline sodium chloride, chlorhexidine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents	• Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad • Gauze, impregnated, water or normal saline, sterile, pad • Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad
Enhance further debridement	Biologic enzymatic debriding agent (collagenase Santyl®)	• Derived from fermentation by *Clostridium histolyticum* • Sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP and that is able to digest collagen in necrotic tissue	

Abbreviations: HCPCS = Healthcare Common Procedure Coding System; USP = United States Pharmacopeias

Table 2. Antibiotic treatments for chronic venous leg ulcers

Class	Indications	Drug Names	Benefits	Disadvantages
Oral antimicrobials (used primarily for Gram-positive activity)	Susceptible Staph (MSSA) and streptococci	cephalosporins (e.g., cephalexin); amoxicillin/clavulanate; dicloxacillin	Inexpensive	Usually require multiple doses/day; major adverse events include rash, intolerance, allergy
	MRSA	clindamycin	Also can treat anaerobes; allergy is rare; good bone and tissue penetration	Effective against only 50% of MRSA; requires multiple daily dosing; GI intolerance
		trimethoprim/sulfamethoxazole	Inexpensive; good bone and tissue penetration	Interacts with warfarin; not effective against streptococci; high rate of allergy for sulfamethoxazole
		linezolid	Effective against enterococci and streptococci; high bioavailability	Multiple contraindications (e.g., patients taking an SSRI); expensive; high rate of symptomatic side effects; thrombocytopenia
Oral drugs used for Gram-negative activity	Gram-negative organisms	quinolones (ciprofloxacin, levofloxacin, moxifloxacin)	Effective against most community acquired GNRs and Pseudomonas; rarely anaphylactoid reaction; can dose once daily; high bioavailability	GI intolerance; increased risk for C. diff; prolonged exposure can result in resistance
		beta lactams (amoxicillin/clavulanate, cefixime, cefpodoxime)	Usually effective first-round for community-acquired organisms	Requires multiple dosing
Intravenous antibiotic regimens	Gram-positive sensitive Staph (MSSA)	cefazolin, ampicillin/sulbactam		Requires multiple dosing; requires prolonged IV access (usually PICC line); requires weekly monitoring
		ceftriaxone	Can be dosed once daily	Requires prolonged IV access (usually PICC line); requires weekly monitoring
	Gram-positive organisms (MRSA)	vancomycin	Inexpensive; effective against MRSA; can be dosed post-dialysis	Requires weekly monitoring for drug toxicity; requires frequent adjustment of dosing
		daptomycin	Used when intolerant to vancomycin; dosed once daily; can be dosed post-dialysis	Expensive; toxicity is myositis; requires weekly CK monitoring
	Gram-negative organisms (B-lactams)	ertapenem	Can be dosed once daily; broad spectrum for enteric Gram-negative bacteria and anaerobes; requires minimal monitoring	Not effective for Pseudomonas or many MDR organisms
		ceftriaxone		No anaerobic activity
	Pseudomonas	piperacillin/tazobactam, cefipime	Minimal toxicity profile	Requires multiple daily doses
	Aminoglycosides	gentamicin, tobramycin, amikacin	Can be dosed once daily	Major renal toxicity; requires close monitoring of dose, drug levels, renal function

Abbreviations: C. diff = *Clostridium difficile*; CK = creatine kinase; GI = gastrointestinal; GNR = Gram-negative rods; IV = intravenous; MDR = multidrug resistant; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; PICC = peripherally inserted central catheter; Staph = Staphylococcus; SSRI = selective serotonin reuptake inhibitor

Table 3. Surgical treatments for chronic venous leg ulcers

Pathology	Treatment	Description
Superficial venous system	Ligation	• Sapheno-femoral junction/High saphenous ligation involves the ligation and division of the great saphenous vein at the junction with femoral vein. • Sapheno-popliteal junction ligation involves the ligation and division of small saphenous vein at its junction with popliteal vein. • Ligation of tributaries
	Stripping	• Saphenous vein stripping involves the ligation and division of the sapheno-femoral junction, followed by stripping a segment of the great saphenous vein to just below the knee using an invagination or inversion catheter.
	Stab / Micro phlebectomy	• Stab phlebectomy or micro phlebectomy of tributaries to great or lesser saphenous vein
	Ablation	• Thermal ablation involves the closing of the great or small saphenous veins using high temperature generated by laser light (endovenous laser treatment [EVLT]) or radiofrequency energy (radiofrequency ablation [RFA]). • Chemical ablation (sclerotherapy) involves injecting an irritant agent (such as sodium tetradecyl sulfate mixed with air or carbon dioxide) into the vein, which results in endothelial damage. Foam preparations increase the potency of sclerosing drug by increasing its surface area.
Perforator venous system	Ligation	• Perforator vein is directly ligated using ultrasound guidance.
	Subfascial endoscopic perforator surgery (SEPS)	• Although rarely performed, this minimally invasive surgical procedure involves use of an endoscope through the unaffected area of skin and fascia. An elastic wrap is used to empty the leg veins of blood then a tourniquet is placed at the thigh. Clinicians insufflate the subfascial space with carbon dioxide. This creates a space for the endoscope to identify and ligate the Cockett's perforating veins in the lower calf.
	Ablation	• Thermal ablation of perforator veins (radio frequency ablation) • Chemical ablation (sclerotherapy) of perforator veins
	Hach procedure	• This procedure involves paratibial fasciotomy and dissection of the posterior perforator veins.
Deep venous system	Obstructive	• This involves bypassing the obstructive segment of deep vein using autogenous vein or polytetrafluoroethylene synthetic graft • This involves balloon angioplasty with or without stenting of the stenotic area of the deep vein
	Reflux	• Valve replacement (transposition or transplant) involves the replacement of the affected deep venous valve with an autogenous vein valve from the upper extremity. • Valvuloplasty involves repairing or reconstructing valves in the deep venous system of the lower limb.

EVLT = endovenous laser therapy; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery

Methods

This topic was nominated via the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program's Web site. Our Evidence-based Practice Center established a team and a protocol to develop the evidence report. The project involved formulating and refining the questions, developing a protocol with input from selected technical experts, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Refinement

We recruited a panel of Key Informants to provide input on the selection and refinement of the questions to be examined. The Key Informants included a variety of wound care experts, including dermatologists, vascular surgeons, nurses, geriatricians, and a patient. A wound care organization recommended the patient to us because he has had chronic venous ulcers for several years and is very knowledgeable about his condition and treatment. We posted our draft Key Questions (KQs) on the AHRQ Effective Health Care Program's Web site in October 2011 for public comment.

With input from the Key Informants, representatives of AHRQ, and public comments, we developed the KQs that we presented in the Scope of Review and Key Questions section of the Introduction. The KQs focus on the effectiveness and safety of three major types of interventions in the management of chronic venous ulcers, including: (a) dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components; (b) the use of systemic antibiotics; and (c) the utility of surgical procedures when compared with adequate compression or other surgical techniques.

Technical Expert Panel

We recruited a Technical Expert Panel (TEP) to review a draft of the protocol for preparing this evidence report. The TEP included a variety of wound care experts, including dermatologists, vascular surgeons, nurses, and geriatricians. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the KQs. With the feedback from the TEP and AHRQ representatives, we finalized the protocol and posted it on AHRQ Effective Health Care Program's Web site.

Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature® from January 1980 through October 2011 and updated in July 2012. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text from key articles we identified a priori (Appendix A). Additionally, we reviewed the reference lists of included articles and any relevant review articles.

We downloaded the results of the searches and imported them into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in ProCite. We uploaded the articles from ProCite to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. We used this database to track the search results at the levels of title review, abstract review, and article inclusion/exclusion.

To identify additional studies, the Evidence-based Practice Center Program's Scientific Resource Center submitted requests to the wound dressing and pharmaceutical manufacturers for any published or unpublished randomized controlled trials or observational studies. We reviewed the materials submitted by 3M™, Akorn, Inc.©, Alcorn©, Baxter Healthcare, Convatec, Inc., Fagron, Healthpoint® Biotherapeutics, and Systagenix. We searched ClinicalTrials.gov to identify any relevant on-going trials.

Study Selection

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers must indicate that the study was ineligible. If the reviewers disagreed, we advanced the article to the next level (Appendix B, Title Review Form).

We designed the abstract review phase to identify studies reporting the effects of treatment options for chronic venous leg ulcers. Two investigators independently reviewed abstracts and excluded them if both investigators agreed that the article met one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 4 and Appendix B, Abstract Review Form). We tracked and resolved differences between investigators regarding the inclusion or exclusion of abstracts through consensus adjudication.

Two independent investigators reviewed articles that we promoted on the basis of the abstract review to determine if they should be included in the final systematic review. We tracked and resolved the differences regarding article inclusion through consensus adjudication. For articles that were not in English, we tried to find at least two people (either an investigator or a person with a medical or public health background) who could read the language to review the article.

We included studies that used any of the outcomes of interest to evaluate advanced wound dressings, systemic antibiotics, or surgical interventions among patients with chronic venous leg ulcers. Patients must have had an active ulcer for at least 6 weeks. We excluded studies that had a mixed population of patients with chronic wounds, unless the study presented a separate analysis of patients with chronic venous ulcers. We included studies that concurrently compared an intervention of interest with compression therapy or with another intervention. Based on the findings from a previous systematic review,[5] we required that subjects in both the experimental and control groups received at least two layers of compression therapy. We did not have any restrictions based on language or sample size for the studies with a comparison group. We included studies with at least 4 weeks of followup. We resolved differences between investigators regarding eligibility through consensus adjudication.

For surgical interventions, we included studies without a concurrent comparison group if the study (1) included at least 30 patients with chronic venous leg ulcers for at least 6 weeks, (2) described the sampling frame, (3) provided demographic and baseline characteristics for the patients with chronic venous ulcers, and (4) assessed ulcer healing rates. We decided to include noncomparative studies evaluating surgical interventions because we anticipated finding few, if any, comparative studies. We felt that including only studies where adequate compression therapy had failed patients for at least 6 weeks would provide useful information about the effects of surgery on healing-related outcomes, despite the potential bias from not having a concurrent comparison group. By including noncomparative studies and assessing their quality, we hope to inform decisionmakers about the type of evidence available and to guide future research.

Table 4. Inclusion and exclusion criteria

Population and condition of interest	• All studies included only human subjects. • We included studies of patients with chronic venous leg ulcers. We used the standard definition of a chronic venous ulcer: o Presence of an active ulcer for 6 weeks or more with evidence of earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema • We included studies of patients with or without other comorbidity. • We excluded arterial ulcers (defined by ankle brachial index less than 0.6 or toe brachial index less than 0.5 or other clinical criteria), pressure ulcers, post-surgical ulcers, and neuropathic ulcers including those with diabetic neuropathy. • We excluded the following less common types of venous ulcers: genetically determined ulcers (e.g., congenital venous disease, sickle cell disease, and inherited thrombophilias); ulcers resulting from trauma in patients without signs of previous venous disease; ulcers in the setting of collagen vascular disease or inflammatory bowel disease; ulcers occurring in atypical locations (e.g., soles, toes, above mid-calf); and ulcers complicated by active infection (e.g., cellulitis, fasciitis). • We excluded studies that had a mixed population of patients with chronic wounds (i.e., not all patients have chronic venous ulcers) unless the study presented a subgroup analysis of patients with chronic venous ulcers.
Interventions	• We included studies that evaluated wound dressings, systemic antibiotics, or surgical procedures. o We included all types of wound dressings, including those with debridement activity, antimicrobial activity, enhanced absorptive/barrier properties, and so-called biological dressings with or without viable human cells (Table 1). o We included systemic antibiotics that clinicians used to manage chronic wounds. The antimicrobials of interest included oral antimicrobials (primarily for Gram-positive activity), oral drugs (for Gram-negative activity), and intravenous antibiotic regimens (Table 2). o We included surgical interventions, including interventions for superficial reflux, perforator reflux, and reflux in the deep venous system (Table 3).
Comparisons of interest	• We included studies that compared the interventions with conservative care or if possible with each other. Conservative care included: o Debridement of necrotic tissue by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement (which lead to a clean wound base) o Simple dressings containing nonactive components such as moisturizers o At least moderate compression described either qualitatively or quantitatively (<20mm), so the leg does not swell significantly during the day • We excluded studies that evaluated wound dressings or systemic antibiotics and did not have a concurrent comparison group. For surgical interventions, we included studies without a comparison group if the study (1) included at least 30 patients with chronic venous ulcers for at least 6 weeks, (2) described the sampling frame, (3) provided demographic and baseline characteristics for the patients with chronic venous ulcers, and (4) assessed ulcer healing rates. • We excluded studies that use pneumatic intermittent compression as a comparison group.

Table 4. Inclusion and exclusion criteria (continued)

Outcomes	• We included studies that evaluated one of the following outcomes: o Intermediate outcomes (wound healing rates for a minimum of 4 weeks time, pain, quality of the wound bed, relationship of intermediate healing rates to complete healing) o Final outcomes (time to achieve complete wound closure, proportion of ulcers healed at 16 weeks, rate of wound recurrence after 1 year, development of new wounds at different anatomical locations, quality of life [general, disease-specific], mortality, functional status) o Adverse events – For topical antibiotics contained in dressings: hypersensitivity, contact dermatitis, sensitization, and systemic absorption – For systemic antibiotics: allergic and hypersensitivity reactions, drug toxicity, Clostridium difficile diarrhea, promotion of antibiotic resistance, and selection of resistant organisms – For intravenous antibiotics: peripherally inserted central catheter line and access infections • For surgical interventions: surgical site infection, bleeding, skin irritation and burn, deep vein thrombosis, and long-term recurrent reflux and ulceration • We did not include costs as an outcome in this systematic review, but rather focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program.
Type of study	• We excluded articles with no original data (reviews, editorials, and commentaries). • We excluded conference abstracts. • We included randomized controlled trials and observational studies with a concurrent comparison group. For surgical interventions, we included studies without a comparison group if the study met the criteria listed above. • We did not place any restrictions based on sample size for studies with a comparison group or language. • We excluded studies published before 1980 because most interventions were not available prior to 1980.
Timing and setting	• We included studies with at least 4 weeks of followup. • We included all study settings.

Abbreviations: FDA = U.S. Food and Drug Administration

Data Abstraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created standardized forms for data extraction (Appendix B, Study Design Form, Population Characteristics Form, Interventions Form, and Outcomes Form), which we pilot tested. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

The study investigators double-reviewed each article for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs to include personnel with both clinical and methodological expertise. We did not mask reviewers to the authors of the articles, their respective institutions, nor the journals that published the articles.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, duration of ulcer, smoking status, diabetes status, other systemic diseases, concomitant use of immunosuppressants or steroids, other treatment), interventions (compression types and debridement types, advanced wound dressings, antimicrobial use, surgical interventions, duration of treatment), comparisons (including type of compression used [e.g., two-layer, short stretch, long stretch, multilayer, or Unna boot]), outcome measures, definitions, and the results of each outcome, including measures of variability. We collected data on subgroups of interest, including age, presence of comorbid conditions (e.g., diabetes, obesity), and setting.

The individual completing the review entered all information from the article review process into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada). Reviewers entered comments into the system whenever applicable. We used the DistillerSR database to maintain the data and to create detailed evidence tables and summary tables.

Quality Assessment

Two reviewers independently assessed study quality. We used the Downs and Black quality assessment tool to assess the quality of all included studies.[17] We supplemented this tool with additional quality-assessment questions based on recommendations in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide).[18] Our quality assessment tool included items on the reporting, internal validity, power, and conflicts of interest (Appendix B, Study Quality Form). The reporting questions evaluated clear descriptions of the objectives, main outcomes, subject characteristics, interventions of interest, distribution of principal confounders, main findings, estimates of random variability, adverse events, characteristics of subjects lost to followup, and actual p-values. Internal validity questions assessed the blinding of the study subjects and outcome assessors, a priori specification of the results, adjustment for different lengths of followup, appropriateness of the statistical tests, compliance of the interventions, accuracy of the main outcome measures, selection of patients in the different intervention groups, randomization, allocation concealment, adequate adjustment for confounding, and accounting for loss to followup.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population (age, duration of ulcer, comorbidities), interventions (treatment, cointerventions, duration of treatment), outcomes, and settings (nursing home, wound care center, primary care, hospital/inpatient) are typical for the treatment of individuals with chronic venous leg ulcers who are receiving treatment. For example, if the study included a very old population in nursing homes, then it may have limited applicability to patients in other settings.

Data Analysis and Synthesis

We had planned to conduct meta-analyses when there was sufficient data (at least three studies on a given outcome for a specific comparison) and studies were sufficiently homogenous. We qualitatively assessed the homogeneity of the studies with respect to key variables (population characteristics, study duration, and comparisons). We qualitatively summarized studies not amenable to pooling. Where possible for the outcomes of proportion of ulcers healed and wound recurrence, we calculated the risk difference and relative risk for the individual studies. We commented on relevant subgroup analyses that the studies reported, but we lacked sufficient data to conduct any additional sensitivity analyses.

Data Entry and Quality Control

A second reviewer checked the data that had been entered into DistillerSR. Second reviewers were generally more experienced members of the research team. We discussed any problems with a reviewer's data abstraction at a meeting with the reviewers.

Rating the Strength of the Body of Evidence

At the completion of our review, at least two reviewers independently rated the strength of the body of evidence on each of the comparisons of classes of interventions. We graded the strength of evidence addressing KQs 1, 2, and 3 by adapting an evidence grading scheme recommended in the Methods Guide.[19] We applied evidence grades to the bodies of evidence about each class comparison for the outcome of wound healing (i.e., proportion of ulcers healed) and wound recurrence (for surgical studies). We included evidence from intermediate outcomes if this was the only data available. We assessed the risk of bias of individual studies according to internal validity measures described in the Quality Assessment section. We rated the body of evidence as "consistent" if most of the studies showed the same direction of effect. We rated the consistency of a single study as "not applicable," without downgrading the strength of evidence. We rated the body of the evidence as "direct" if most of the studies evaluated the proportion of ulcers healed and "indirect" if most of the studies only evaluated intermediate outcomes, such as wound healing rates. We based our rating of precision on the width of the confidence intervals of the risk difference. If the width of the confidence interval was less than or equal to 30 percent, then we considered the body of evidence to be "precise." When we were unable to calculate a risk difference, we used our judgment based on the data available.

We classified the strength of evidence pertaining to the KQs into four basic grades: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Peer Review and Public Commentary

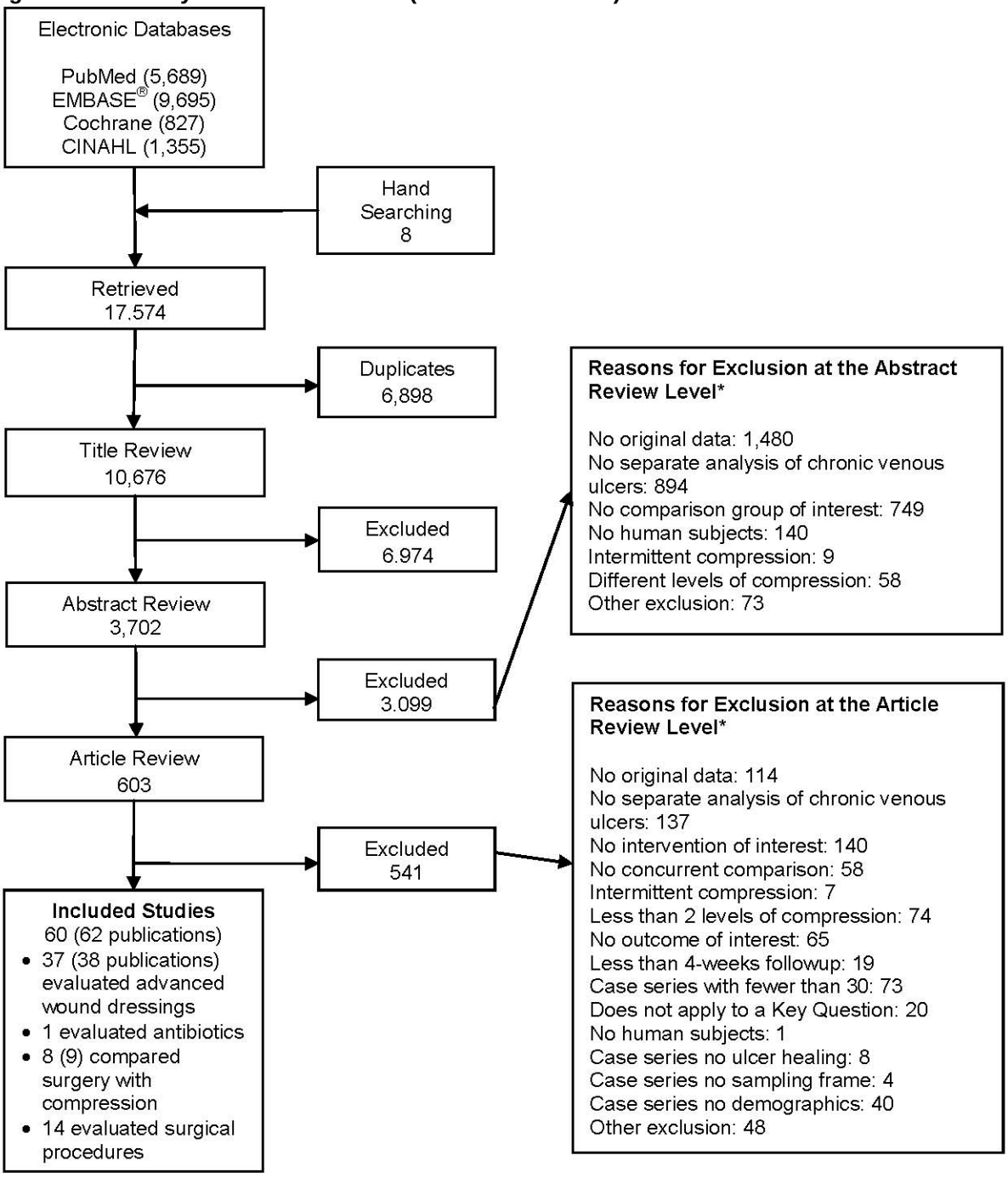
Experts in wound care, including dermatologists, vascular surgeons, nurses, and geriatricians, and individuals representing stakeholder and user communities were invited to provide external peer review of this Comparative Effectiveness Review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Effective Health Care Program's Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a "disposition of comments report" that will be made available 3 months after the Agency posts the final Comparative Effectiveness Review on the AHRQ Effective Health Care Program Web site.

Results

Search Results

Figure 5 describes our search process. We retrieved 10,088 unique citations from our search. After reviewing the titles, abstracts, and full text, we included a total of 60 studies (62 publications). We found 37 studies (38 publications) evaluating advanced wound dressings,[20-56] 1 study evaluating antibiotics,[57] 8 studies (nine publications) comparing a surgical intervention with compression systems,[58-66] 3 studies comparing at least 2 different surgical interventions,[67-69] and 11 evaluating a surgical intervention with no concurrent comparison group.[14, 70-79] In most studies, the mean or median age was greater than 60 years. Twenty-two studies received industry support.[20, 21, 23, 25, 27, 28, 30-33, 36-39, 43, 44, 47, 49-51, 53, 54]

Figure 5. Summary of literature search (number of articles)



Key Question 1. For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components in conjunction with compression systems when compared with using solely compression systems?

Key Points

Wound Healing

- The randomized controlled trials (RCTs) that evaluated the most advanced wound dressings (transparent films, alginate, acellular human skin equivalents, cryo-preserved human fibroblast-derived dermal substitutes, and antimicrobial dressings vs. compression; hydrocolloid, transparent films, alginates, and cellular human skin equivalents vs. other types of dressings; and head-to-head comparisons of different types of alginate, foam, and antimicrobial dressings) did not find a statistically significant difference between the comparison and study groups in terms of the proportion of ulcers healed. We could not draw definitive conclusions about the comparative effectiveness of most advanced wound dressings due to limitations in study quality, imprecise estimates, and the heterogeneity in study designs. (Insufficient strength of evidence)
- Hydrocolloid dressings were not more effective than compression therapy alone in terms of the proportion of chronic venous ulcers healed. The results from the three studies addressing this comparison were imprecise and subject to some bias. (Low strength of evidence)
- Collagen dressings healed a greater proportion of ulcers than compression alone. (Low strength of evidence)
- The cellular human skin equivalent dressing, Apligraf®, healed a greater proportion of ulcers and provided as much as 3 times more rapid healing of chronic venous ulcers than compression alone, especially for ulcers that had failed therapy and were present for over 1 year. (Moderate strength of evidence)
- Autologous keratinocytes in fibrin sealant healed a greater proportion of ulcers and achieved a shorter median time to complete wound closure versus compression. (Low strength of evidence)
- Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with other nonantimicrobial dressings. However, silver dressings did not improve wound healing as compared with nonsilver dressings. (Moderate strength of evidence)

Mortality

- When reported, mortality rates were generally rare (occurring in less than 5 percent of the study population), and did not differ between intervention groups.

Pain and Quality of Life

- We were unable to draw conclusions about the effects of advanced wound dressings on pain or quality of life (QOL) due to the inconsistent manner of reporting these outcomes.

Condition of the Wound Bed

- Due to the heterogeneity in study design and the inconsistency of evaluating and reporting on the condition of the wound bed, we were unable to draw conclusions about the effect of advanced wound dressings on the condition of the wound bed.

Adverse Events

- Evidence was lacking on the effects of advanced wound dressings on maceration, contact dermatitis, venous or arterial impairment, and cellulitis.
- Compared with compression, patients receiving hydrocolloid dressings and cellular products for chronic venous ulcers experienced similar infection rates.

Study Design Characteristics

We included 37 studies (38 publications) for review (Appendix D, Tables 1 and 2).[20-56] These studies enrolled a total of 4,062 patients with chronic venous ulcers (median, 79; range, 18 to 309). All, except one,[46] of the studies were RCTs. Two of the RCTs had a factorial design.[28, 29] Most of the studies were of short duration; the length of followup ranged between 4 weeks and 1 year (median, 12 weeks).

Most (59 percent) of the studies took place in Europe.[20-24, 26, 28-30, 32-34, 36, 37, 39, 40, 44, 46-50, 53, 54] Five took place exclusively in the United States,[35, 38, 42, 51, 52] one took place in the United States, Canada, and the United Kingdom,[32] and one was conducted in the United States and the United Kingdom.[39] One took place in Canada and Europe.[27] One study each took place in Canada, the United Kingdom,[47] Brazil,[45] and Mexico.[56]

Thirteen studies did not report the location from where the study recruited patients.[20, 21, 25-27, 30, 34, 39, 45, 51, 52, 54, 55] Most of the other studies reported recruiting patients from some type of outpatient center: five recruited from dermatology clinics,[22, 32, 37, 40, 41] 11 from wound centers,[24, 29, 31-33, 35, 36, 43, 49, 53, 56] and two from vascular clinics.[24, 32] Three studies recruited patients from a hospital setting.[24, 28, 48] None of the studies recruited patients from a nursing home or long-term care facility.

Most studies (80 percent) did not report the number of patients screened.[20, 21, 23, 26-28, 30, 32, 34-46, 48, 49, 51-56] Among the studies that did report the number of patients screened, the percent they enrolled ranged from 38 to 94 percent.[22, 24, 25, 29, 31, 33, 47, 50]

Study Population Characteristics

The majority of studies we included for final analysis had similar profiles for the patient populations evaluated (Appendix D, Table 3). The median age of patients was between 60 and 70 years with a female preponderance. Most studies excluded patients under the age of 18 to minimize enrollment of patients with genetic or clotting abnormalities. Patients tended to be overweight in studies that reported weight. Almost all studies excluded patients with insulin dependent diabetes, but did include patients with elevated blood sugars. Studies uniformly evaluated patients for their arterial blood flow competence by obtaining ankle brachial indices; studies excluded patients with ankle brachial index ratios of below 0.8. Less than 50 percent of the studies used venous ultrasound or the equivalent. When reported, patients most often had abnormal venous function, usually of the reflux type.

All studies that we included used venous compression of at least two layers or, where measured, 20 mm Hg. Compliance with the interventions was rarely reported.

Wound Healing, Including Proportion of Ulcers Healed, Time to Wound Healing, Wound Healing Rates, and Wound Recurrence

Hydrocolloid Dressings

Hydrocolloid Dressings Plus Compression Versus Compression Systems Alone

Three RCTs (total N=361) compared hydrocolloid dressings with compressions systems alone (Table 5 and Appendix D, Table 4a).[29, 43, 49] One trial was a factorial design that compared pentoxiphylline, knitted viscose, and hydrocolloid with single-layer and four-layer wraps.[29] The data the studies extracted focused on the comparison of hydrocolloid with knitted viscose under the four-layer compression. Results showed decreased time-to-healing in the hydrocolloid group (median 99 days vs. 127 days knitted viscose), but healing rates were not significantly different between groups, 20 of 33 (60 percent) healed in the hydrocolloid group versus 17 of 27 (63 percent) in the knitted viscose group (the hazard ratio for healing with hydrocolloid compared with knitted viscose was 1.1, 95% confidence interval [CI], 0.8 to 1.6).[29] The other two RCTs evaluated percent healing over time as well as percent ulcers healed.[43, 49] After 12 weeks in one trial, 13 of 30 (43 percent) ulcers healed in the hydrocolloid group, compared with only seven of 30 (23 percent) in the compression group, but the difference was not statistically significant ($P > 0.05$).[49] Cumulative healing rates in this second trial were 46 percent in the hydrocolloid group and 17 percent in the compression group over 12 weeks (relative risk [RR], 2.25; 95% CI, 0.88 to 5.75).[49] The third trial evaluated the percentage of ulcer area healed each week and percentage of ulcers healed after 12 weeks and found no clinically important difference between groups.[43] Hydrocolloids healed 18.0 percent and compression dressings healed 20.5 percent of the original ulcer size per week.[43] After 12 weeks, 21 (75 percent) of the hydrocolloid group and 22 (78 percent) of the compression group healed completely ($P > 0.05$).[43]

Table 5. Summary of wound healing measures* among patients with chronic venous ulcers comparing hydrocolloid dressings with compression systems alone

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, n / N (%)	Time-to-Healing	Wound Healing Rates
Moffatt, 1992[49]	G1: Nonadherent, 30 G2: Hydrocolloid (Comfeel, Coloplast), 30	4-layer	12 weeks	G1: 7 / 30 patients (23) G2: 13 / 30 patients (43)	G1: Ref G2: RR, 2.25 (CI, 0.88 to 5.75); *P* = 0.077	NR
Nelson, 2007[29]	G1: Knitted viscose, 27 G2: Hydrocolloid, 33	4-layer	24 weeks	G1: 17 / 27 patients (63) G2: 20 / 33 (60)	G1: 127 days - median G2: 99 days - median; *P* > 0.05	NR
Backhouse, 1987[43]	G1: Compression, 28 G2: Hydrocolloid, 28	Multilayer	12 weeks	G1: 22 / 28 patients (78) G2: 21 / 28 patients (75); *P* > 0.05	NR	G1: 20.5%/ week G2: 18% / week; *P* > 0.05

*The studies did not report wound recurrence.
CI = 95% confidence interval; G = group; NR = not reported; Ref = reference group; RR = relative risk

Hydrocolloid Dressings Versus Other Types of Dressings

Four RCTs (total N=420) compared hydrocolloids with other types of dressings (Table 6).[39, 48, 50, 53] Two of the trials measured percent changes in ulcer area over time and two trials measured area change per day. One trial that compared a hydrocolloid with impregnated gauze (with paraffin in the United States or Betadine® in the United Kingdom) evaluated the number of ulcers healed but did not specifically report the number of ulcers in each group or the number of ulcers per patient.[39] The mean percent reduction in ulcer area over 10 weeks was 71 percent (standard deviation [SD], 4.3) for the hydrocolloid versus 43 percent (SD, 7.1) for impregnated gauze (P>0.05 for this small study with a total of 70 patients).[39] Complete healing occurred in 11 ulcers among 35 patients in the hydrocolloid group versus 14 ulcers among 35 patients in the impregnated gauze group (P>0.05).[39] Another trial that compared hydrocolloids with impregnated gauze (magnesium sulfate paste and Vaseline® with gauze) found a clinically important difference in mean healing rates per day (32 mm^2 per day for hydrocolloids vs. 21 mm^2 per day for impregnated gauze) (P=0.0001).[48] The trial measured the followup period by the number of dressing changes, one through 10, and not over time.[48] Ulcer healing occurred in three of 55 (5 percent) patients in the hydrocolloid group versus zero of 55 patients in the impregnated gauze group over the 10 dressing changes.[48] Another small trial did not find much of a difference in healing rates when comparing hydrocolloids with alginates over 6 weeks.[53] Two of 20 (10 percent) patients healed in the hydrocolloid group versus six of 20 (30 percent) patients healed in the alginate group.[53] Lastly, a trial that compared hydrocolloids with Betadine® and a contact layer over 4 months, taking into account the ulcer size at baseline, found no clinically important difference in healing rates (RR, 1.16, 95% CI, 0.8 to 1.8).[50] However, a trial that evaluated the proportion of ulcers healed among ulcers with an initial measurement of greater than 4 cm saw a clinically important and statistically significant difference (12 of 35 [34 percent] patients healed in the hydrocolloid group vs. four of 39 [10 percent] patients healed in the Betadine® plus contact layer group; P=0.02).[50]

Table 6. Summary of wound healing measures among patients with chronic venous ulcers comparing hydrocolloid dressings with other types of dressings

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, n / N (%)	Time-to-Healing	Wound Healing Rates
Arnold, 1994	G1: Impregnated gauze; paraffin in U.S., saline/ Betadine® in U.K., 35 G2: Hydrocolloid, 35	Unna boot gradient and zinc oxide paste	10 weeks	G1: 14 ulcers G2: 11 ulcer, *P*>0.05	G1: 8.2 (0.4) mean weeks (SE) G2: 7.09 (0.2) mean weeks (SE); *P*>0.05	G1: 43% (7.1) mean decrease in area of ulcer (SD) G2: 71% (4.3) mean decrease in area of ulcer (SD); *P*>0.05
Greguric, 1994[48]	G1: Impregnated gauze, 55 G2: Hydrocolloid, 55	2-layer compression	NR	G1: 0 (0) G2: 3 (5)	G1: 22 mm^2 /day G2: 32 mm^2 /day; *P*=0.0001	G1: 21 mm^2 /day (mean) G2: 32 mm^2/ day (mean) (*P*=0.0001)
Scurr, 1994 [53]	G1: Alginates, 20 G2: Hydrocolloid, 20	Graduated elastic compression stocking	6 weeks	G1: 6 (30) G2: 2 (10)	NR	G1: ≥ 40% increase in area: 2 / 20 (10%) ≥ 40% decrease in area: 14 / 20 (70%) G2: ≥ 40% increase in area: 8 / 20 (40%) ≥ 40% decrease in area: 9 / 20 (45%); *P*=0.258
Smith, 1992 Among those with initial ulcer size of 2-4 cm	G1: Betadine® and contact layer, 62 G2: Hydrocolloid, 64	2-layer compression, linear, graduated	4 months	G1: 43 / 62 patients (69) G2: 38 / 64 patients (59); *P*=0.27	G1: Reference G2: RR† for time to complete healing, 1.16 (CI, 0.77 to 1.77) Treatment and ulcer area interaction, *P*=0.37	G1: 0.062 cm^2 per day (median) G2: 0.056 cm^2 per day (median); *P*=0.40
Smith, 1992 Among those with initial ulcer size of > 4 cm	G1: Betadine® and contact layer, 39 G2: Hydrocolloid, 35	2-layer compression, linear, graduated	4 months	G1:4 / 39 patients (10) G2:12 / 35 patients (34); *P*=0.02	See above	G1: 0.017 cm^2 per day (median) G2: 0.184 cm^2 per day (median); *P*=0.09

† Reported for the entire sample

CI = 95% confidence interval; cm = centimeter; G = group; mm = millimeter; NR = not reported; RR = relative risk; SD = standard deviation; SE = standard error; U.K. = United Kingdom; U.S. = United States

Transparent Film Dressings

Transparent Film Dressings Plus Compression Versus Compression Systems Alone

Kucharzewski[46] compared adequate compression under an Unna boot with adequate compression over a cellulose film in carefully selected venous ulcers (see Table 7). The compression was about 20 mmHg for both groups, though the mean of compression for each group was different. Healing rates at 11 weeks were 18 out of 27 patients (67 percent) treated with the film versus nine out of 27 patients (33 percent) treated with compression alone. All of the ulcers treated with the film were healed by 14 weeks, and all of the ulcers treated with compression alone were healed by 20 weeks. The study did not present data regarding healing rates in healed ulcers. Since the means of compression were quite different in the two treatment groups, it would have been impossible to avoid bias since the modes of therapy were so different to the patients and observers.

Table 7. Summary of the wound healing measures among patients with chronic venous ulcers comparing transparent film dressings with compression systems alone

Author,Year	Intervention	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, N / N (%)	Time-to-Healing
Kucharzewski, 2003[46]	G1: Unna boot G2: (Bioprocess) Cellulose membrane	Unspecified compression	11 weeks	G1: 9 / 27 patients (33) G2: 18 / 27 patients (67); *P*<0.05; RR, 0.5 (CI, 0.3 to 0.9) RD, -33% (CI, -58% to -8%)	G1: Time at complete closure in weeks, 20 G2: Time at complete closure in weeks, 14

CI = 95% confidence interval; G = group; RD = risk difference; RR = relative risk

Transparent Film Dressings Versus Other Types of Dressings

One small non-RCT trial (N=20) compared a transparent film with a foam as a secondary dressing over an alginate over 6 weeks.[54] The study found that 80 percent of the ulcers treated with transparent film and 70 percent of the ulcers treated with foam had a 30 percent or more decrease in wound size at final evaluation, but this was not a statistically significant finding.

Alginate Dressings

Alginate Dressings Versus Other Alginate Dressings

Two RCTs compared different alginate dressings (Table 8).[21, 35] In one small trial (N=19), Tegagen™ HG reduced wound area by 34 percent over 6 weeks compared with Sorbsan® topical wound dressing that reduced wound area by 30 percent.[35] This was not a statistically significant difference in healing rates (*P*=0.88).[35] The other trial (N=82) compared Vulnamin®, an alginate with glycine, leucine, proline, lysine, and sodium hyaluronate, with another alginate without additives over 70 days and found a difference in healing rates.[21] When clinicians treated ulcers with Vulnamin® there was a mean decrease in area from 13.95 (SD, 4.5) cm^2 to 3.04 (SD, 0.8) cm^2.[21] This is significant when compared with the other alginate without glycine, leucine,

proline, lysine, and sodium hyaluronate, which resulted in a mean reduction in ulcer area from 15.14 (SD, 4.7) cm^2 to 10.96 (SD, 3.8) cm^2 (P<0.05).[21]

Table 8. Summary of the wound healing measures* among patients with chronic venous ulcers comparing alginate dressings with other alginate dressings

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, N / N (%)	Wound Healing Rate
Limova, 2003	G1: Alginate (3M Tegagen™ HG), 10 G2: Alginate (Sorbsan Topical Wound Dressing), 9	2-layer compression	6 weeks	G1: 0 / 10 (0%) G2: 2 / 9 (22%)	G1: 33.7% wound area reduction G2: 29.6% wound area reduction (P=0.88)
Maggio, 2011	G1: Alginate, 26 G2: Alginate (Vulnamin®), 26	Multilayer	70 days	G1: 7 / 26 (27%) G2: 16 / 26 (61%); P = 0.01	G1: 15.14 (SD, 4.7) cm^2 to 10.96 (SD, 3.8) cm^2 (mean) G2: 13.95 (SD, 4.5) cm^2 to 3.04 (SD, 0.8) cm^2 (mean); P<0.05

* None of the studies reported on time-to-healing or wound recurrence.
cm = centimeter; SD = standard deviation

Alginate Dressings Versus Other Types of Dressings

One prospective RCT of 113 patients compared a hydropolymer dressing with an alginate plus a secondary dressing of transparent film on moderate to heavily exuding wounds over 4 weeks.[36] However, part way through the trial, the investigators changed the transparent film to a cotton gauze pad believing that the transparent film over the alginate was causing maceration or erythema. Therefore, the study evaluated three treatment groups: Hydropolymer, alginate plus transparent film, and alginate plus cotton gauze pads. The mean rate of reduction in ulcer area was 0.17 (SD, 0.31), 0.05 (SD, 0.29), and 0.00 (SD, 0.45) cm^2 per day for the hydropolymer, alginate plus film, and alginate plus cotton gauze pad respectively. The difference between groups was not statistically significant.[36] The proportion of ulcers healed did not differ between the groups.[36]

Foam Dressings

Foam Dressings Versus Other Foam Dressings

A foam dressing that released 112.5 mg of ibuprofen over 7 days in the presence of exudate was compared with the same foam dressing without ibuprofen.[23] The difference in the average reduction in ulcer area over 42 days was not statistically significant between the groups (P=0.26) nor was the proportion of ulcers healed (15 percent healed in the foam dressing with ibuprofen vs. 17 percent in the foam dressing without ibuprofen, P>0.05) (Table 9).[23] Preliminary results of another small, ongoing trial (N=18) found a greater reduction in average ulcer size over 16 weeks in the slightly adhesive hydroactive foam, Cutinova™, as compared with the nonadhesive foam dressing, Allevyn™; however, there was no formal statistical comparisons between groups.[52] Franks[28] noticed no difference in healing rates between two established foam products under appropriate aggressive compression (Table 9). This trial of 156 patients reported a 64 percent healing rate over 24 weeks.

Table 9. Summary of the wound healing measures* among patients with chronic venous ulcers comparing foam dressings with other foam dressings

Author, Year	Intervention	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, N / N (%)	Time-to-Healing	Wound Healing Rates
Franks, 2007[28]	G1: Foam (Allevyn™) G2: Foam (Mepilex®)	Short stretch or multilayer	24 weeks	G1: 50 / 81 patients (62) G2: 50 / 75 patients (67); *P*>0.05 RR, 0.9 (CI, 0.7 to 1.2) RD, -4% (CI, -20% to 10%)	NR	NR
Gottrup, 2008[23]	G1: Foam (Biatain® Non-Adhesive, Coloplast A/S) G2: Foam, with ibuprofen (Biatain-Ibu® Non-Adhesive, Coloplast A/S)	Kept a constant circumference at the ankle	47 days	G1: 10/ 60 patients (16) G2: 9 / 62 patients (15); *P*>0.05 RR, 1.15 (CI, 0.5 to 2.6) RD, 2% (CI, -10% to 15%)	NR	G1: Average area reduction from 7.2 to 3.8 cm^2 G2: Average area reduction from 11.2 to 7.9 cm^2 (*P*=0.26)
Weiss, 1996[52]	G1: Foam (Cutinova™ foam) G2:Foam (Allevyn™)	Jobst® UlcerCare stocking	16 weeks	G1: 8 / 10 patients (80) G2: 4 / 8 patients (50); *P*>0.05 RR, 1.6 (CI, 0.75 to 3.4) RD, 30% (CI, -13% to 72%)	G1: Mean weeks, 5.6 G2: Mean weeks, 6.5	NR

* Wound recurrence was not reported.
CI = 95% confidence interval; G = group; NR = not reported; RD = risk difference; RR = relative risk

Collagen Dressings

Collagen Dressings Plus Compression Versus Compression Systems Alone

One multicenter U.S. trial examined small intestinal freeze-dried pig submucosa (OASIS® Wound Matrix) as a therapy of venous ulcers (Table 10).[32] Fifty-five percent (34 out of 62 patients) of venous ulcer patients who received small intestinal submucosa healed, compared with 34 percent (20 out of 58 patients) of patients who received standard compression therapy (*P*=0.02).[32] Furthermore, after adjusting for baseline ulcer size, ulcers that received the test intervention were 3 times more likely to heal than those treated with standard compression (*P*=0.01). If clinicians performed an aggressive debridement before beginning therapy, the odds ratio for healing rose to 4. A Cox proportional hazards model estimated the probability of healing with the test material dressing was 64 percent and the probability of healing with standard therapy was 40 percent (*P*=0.02). At the end of the study, 54 patients had healed. Twenty-six out of 29 patients receiving the test material remained healed in contrast with seven out of 10 patients with standard therapy (*P*>0.05).[32]

Table 10. Summary of the wound healing measures* among patients with chronic venous ulcers comparing collagen dressings with compression systems alone

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion Ulcers Healed, N / N (%)	Wound Recurrence (%)
Mostow, 2005[32]	G1: Standard compression therapy G2: Composite acellular or ECM	Multilayer Debridement	6 months	G1: 20 / 58 (34) G2: 34 / 62 (55); *P*=0.02 G2: aOR†, 3.0; *P*=0.01	G1: 3 / 10 (30) G2: 0 / 19 (0)

* The study did not report time to healing and wound healing rates.
† Adjusted for baseline ulcer size
Abbreviations: aOR = adjusted odds ratio; ECM = extracellular matrix

Acellular Human Skin Equivalent Dressings

Acellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

Preliminary results from a small nonrandomized trial of 24 patients evaluated the effect of fibrin sealant derived from snake venom plus essential fatty acids and compression versus a control group that received essential fatty acids plus compression over 8 weeks (Table 11).[45] Patients in the fibrin sealant group had a higher percentage of deep wounds and cavities but five of the participants healed. However, there were no formal statistical comparisons.[45] In a single-blinded RCT of 123 patients, there was no difference in healing rates between Amelogenin protein 30 milligrams per milliliter solution (Xelma® extracellular matrix [ECM]) plus a soft silicone dressing versus control, 7 percent polypropylene glycol alginate plus soft silicone dressing over 12 weeks.[30]

Table 11. Summary of the wound healing measures among patients with chronic venous ulcers comparing acellular human skin equivalent dressings with other types of dressings

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion of Ulcers Healed, N / N (%)	Wound Healing Rates
Gatti, 2011[45]	G1: Fatty acids plus compression, 11 G2: Fibrin sealant derived from snake venom, fatty acids, compression, 13	Unna boot	8 weeks	G1: 5 / 11 (45%) G2: 7 / 13 (54%)	NR*
Vowden, 2008[30]	G1: Amelogenin proteins (Xelmat) G2: Alginate	High-compression	12 weeks	No difference	G1: 33.8% median percentage reduction in wound area G2: 25.6% median percentage reduction in wound area

*No studies reported on time-to-healing or wound recurrence.

Biological or Cellular Dressings

Biological or Cellular Dressings Plus Compression Versus Compression Systems Alone and Versus Cellular Skin Replacements

Dermagraft® is a biodegradable mesh containing viable fibroblasts that produce growth factors. A study subjected a carefully selected group of 53 patients with venous ulcers (average age over 70, more females than males, and no extraneous complications), to a 2-week run-in period to eliminate patients who might heal on adequate compression alone (Table 12).[47] The study randomized patients to four groups of 13. The first group received 12 weekly applications of Dermagraft®; the second, four applications over the 12 weeks; the third, one application at the beginning of the trial; and the fourth, only compression. Forty-seven patients completed the study and investigators analyzed the results by intention-to-treat. The authors reported having insufficient power to draw statistical conclusions from the trial. Ulcer healing occurred in five out of 13 patients (38 percent) receiving 12 applications, five out of 13 patients (38 percent) receiving four applications, one out of 13 patients (8 percent) receiving one application, and two out of 13 patients (15 percent) receiving only compression. A statistical analysis of healing rates as measured by percent of ulcer resurfaced by epithelium at 12 weeks showed no differences between groups.

Another small prospective RCT of 18 patients compared healing rates of patients receiving human fibroblast derived dermal replacement, Dermagraft®, or compression alone over 12 weeks.[34] The treatment group (N=10) received one piece of Dermagraft® on day 0 and weeks 1, 4, and 8. The Dermagraft® group had a significantly greater mean total ulcer area rate of healing than the compression group (0.82 cm^2 per week vs. 0.15 cm^2 per week respectively) (P=0.001) and a greater mean linear rate of healing than the compression group (0.14 cm per week vs. 0.033 cm per week) (P = 0.006).[34] The reduction in wound surface area was greater in the Dermagraft® group than in the compression-alone group (P=0.02).[34]

Another prospective, parallel group comparative trial (N=293) compared allogeneic cultured human skin equivalent with compression alone over 6 months in ulcers with a duration greater than 1 month that had not adequately responded to conventional therapy.[38] Both groups received adequate compression. Patients received no more than five applications of human skin equivalent, and received no human skin equivalent after week 3. Human skin equivalent was

more effective than compression therapy in median time to complete wound closure (61 vs. 181 days; *P*=0.003, log rank test) and median time to 75 percent wound closure (30 vs. 50 days, *P*=0.001).[38] Human skin equivalent was more effective in healing than compression alone among the study population (*P*=0.02), large ulcers of over 1,000 mm surface area (*P*=0.02), deeper ulcers (*P*=0.003), and ulcers older than 6 months (*P*=0.001, log rank test). Researchers confirmed this throughout the treatment period by observing statistically significant decreases in days needed for healing of 50 percent (*P*=0.02) and 75 percent (*P*=0.01) in ulcer area. The human skin equivalent healed the ulcers with a similar recurrence rate of ulcers between the groups. In a subgroup analysis on hard-to-heal ulcers (those older than 1 year) over 6 months (N=120), 34 out of 72 (47 percent) patients in the human skin equivalent group achieved complete wound closure at 6 months versus nine out of 48 (19 percent) patients with compression alone (*P*<0.005).[51] The median time to complete closure for human skin equivalent was significantly faster than the control group (*P*=0.005). Human skin equivalent had a 60 percent advantage over rates of wound closure in the comparison group (*P*=0.01). Recurrence rates did not differ between ulcers healed with human skin equivalent and ulcers healed with standard therapy).[51]

Addition of autologous living keratinocytes to nonhealing venous ulcers is a novel therapeutic approach. Vanscheidt et al.[26] performed an open label RCT of 226 carefully selected patients.[26] Autologous keratinocytes healed 38 percent of the ulcers compared with 22 percent of ulcers in the group of patients that received adequate compression alone (*P*=0.01). Furthermore, time-to-healing in the keratinocyte group was 176 days, compared with 201 days in the comparison group (*P*=0.0001). The experimental design included a 4-week run-in period with optimal conservative care and adequate compression, thereby maximizing selection of recalcitrant ulcers.[26]

Table 12. Summary of the wound healing measures* among patients with chronic venous ulcers comparing biological or cellular dressings with compression alone

Author, Year	Intervention, N	Compression Used in Both Groups	Followup Time	Proportion Of Ulcers Healed, N / N (%)	Wound Healing Rate	Wound Recurrence
Krishnamoorthy, 2003[47]	G1: Cellular skin substitute or ECM Dermagraft 12 pcs G2: Cellular skin substitute or ECM Dermagraft 4pc G3: Cellular skin substitute or ECM Dermagraft 1pc G4: Compression only	Multilayer Profore	12 weeks	G1: 5 / 13 (38) G2: 5 / 13 (38) G3: 1 / 13 (8) G4: 2 / 13 (15); *P*>0.05	NR	NR
Omar, 2004[34]	G1: Compression only G2: human fibroblast derived dermal replacement, Dermagraft®	4-layer	12 weeks	NR	G1: 0.15 cm^2 per week G2: 0.82 cm^2 per week; *P* = 0.001	NR
Falanga, 1998 [38]	G1: Compression, 129 G2: Cellular skin substitute or ECM, 146	Unna boot	6 months	G1: 63 / 129 patients (49) G2: 92 / 146 patients (63); *P*=0.02	G1: Median days, 181 (Range, 10 to 232) G2: Median days, 61 (Range, 9 to 233) RH of wound closure per unit time, 1.5 (CI, 1.3 to 1.9)	G1: 10 / 63 (16) G2: 11 / 92 (12); *P*=0.48
Vanscheidt, 2007[26]	G1: Contact layer, 109 G2: Contact layer + cellular skin substitute or ECM, 116	Short stretch	182 days	G1: 24 / 109 patients (22) G2: 44 / 116 patients (38); *P*=0.0106	G1: Median days, > 201 (CI, 201 to ∞) G2: Median days, 176 (CI, 114 to 184); *P* < 0.0001	NR
Falanga,1999[51] [Subgroup analysis from Falanga, 1998[38] on ulcers > 1 year duration]	G1: Compression G2: Cellular skin substitute or ECM	Unna boot	24 weeks	G1: 9 / 48 (19) G2: 34 / 72 (47) *P*<0.005	G1: closure not attained G2: 181 days (*P*<0.005)	G1: 4 / 54 (7) at 6 months 12 / 54 (22) at 12 months G2: 6 / 72 (8) at 6 months 13 / 72 (18) at 12 months

* None of the studies reported on time-to-healing.
CI = 95% confidence interval; cm = centimeter; ECM = extracellular matrix; G = group; NR = not reported; RH = relative hazard

Cellular Skin Replacement Dressings Versus Other Types of Dressings

Two RCTs compared the healing rates of cellular human skin equivalents with the healing rates of hydrocolloid dressings.[33, 40] One trial (N=47) had an almost significant difference in ulcer size between the groups at baseline (*P*=0.07) and a significant number of withdrawals (N=9).[40] Also, this trial treated patients for 6 weeks and then crossed over any unhealed ulcers to the alternate treatment.[40] We evaluated data from the first 6 weeks of the trial. The other trial (N=178) evaluated a lyophilized human keratinocyte lysate added to a hydrocolloid preparation versus the hydrocolloid vehicle itself over 6 weeks.[33] These investigators noted that ulcers that were increasing in size at the start of the trial demonstrated a statistically improved healing rate with the epidermal lysate (30 vs. 11 percent; *P*=0.02) which was even more marked in smaller ulcers (*P*=0.008). The study did not report data on recurrence.[33]

Antimicrobial Dressings

Antimicrobial Dressings Plus Compression Versus Compression Systems Alone

One crossover RCT (N=75) compared cadexomer iodine with saline wet to dry gauze dressings over 24 weeks (Table 13).[42] Patients performed their own daily dressing cleaning and changes. Many patients withdrew or dropped out of the study (25 out of 75 patients) and the study only included 54 out of 75 patients in the statistical analysis.[42] Additionally, baseline characteristics differed between the treatment and control groups. The cadexomer iodine group showed significantly greater mean ulcer area reduction per week than the gauze dressing group (0.95; standard error [SE], 0.12 cm^2 per week versus 0.41; SE, 0.13 cm^2 per week; *P*=0.003). After 12 weeks, the patients with unhealed ulcers had the opportunity to change to the alternate therapy.[42] All 12 switched from the control group to the cadexomer iodine group. Five of these patients did not benefit, but seven of them showed healing of their ulcers. The trial did not conduct a formal statistical evaluation of this outcome.[42]

Another observer-blinded, multicenter RCT (N=119) showed a relative reduction in ulcer area with pale sulfonated shale oil 10 percent plus Jelonet™ compared with vehicle plus Jelonet™ over 20 weeks (-72 vs. -19 percent; *P*<0.0001).[31]

Table 13. Summary of the wound healing measures* among patients with chronic venous ulcers comparing antimicrobial dressings with compression alone

Author, year	Intervention	Compression used in both groups	Followup time	Wound healing rate
Holloway, 1989[42]	G1: Wet to dry saline gauze G2: Cadexomer iodine	Toe to knee elastic compression	24 weeks	G1: Mean, 0.41 (SE, 0.13) cm^2/week G2: Mean, 0.95 (SE, 0.12) cm^2/week; *P*=0.0025
Beckert, 2005[31]	G1: Vehicle + Jelonet™ G2: Pale sulfonated shale oil 10% + Jelonet™	Short stretch	20 weeks	G1: Relative mean change in ulcer area, -18.7% (SD, 68.1) G2: Relative mean change in ulcer area, -72.0% (SD, 37.2); *P*<0.0001

* Neither study reported on the proportion of ulcers healed, time-to-healing, or wound recurrence.
cm = centimeter; SD = standard deviation; SE = standard error

Antimicrobial Dressings Versus Other Antimicrobial Dressings

One RCT (N=281) compared Urgotul® Silver with Aquacel® Ag over 4 weeks (Table 14).[20] The study randomized 145 patients to the Aquacel® Ag group followed by Aquacel® for another 4 weeks. The study randomized 136 patients to Urgotul® Silver for 4 weeks then switched to Urgotul® for another 4 weeks. This analysis included data over the first 4 weeks of the trial. The study found no significant difference in healing rates between groups.[20]

A randomized optional crossover trial compared cadexomer iodine with gentian violet and Polyfax ointment (standard treatment) over 24 weeks among 61 outpatients.[44] However, the data discussed here pertains to the period prior to the cross-over at 12 weeks. At 12 weeks, the cadexomer iodine group healed at a rate of 0.89 cm^2 per week versus 0.46 cm^2 per week in standard treatment ($P < 0.001$).[44]

Table 14. Summary of wound healing measures* among patients with chronic venous ulcers comparing antimicrobial dressings with other antimicrobial dressings

Author, year	Intervention	Compression used in both groups	Followup time	Wound healing rate
Harding, 2011[20]	G1: Aquacel Ag G2: Urgotul Silver	Class III compression	4 weeks	G1: Relative mean wound area reduction, 38.24% (SD, 40.63) G2: Relative mean wound area reduction, 32.47% (SD, 48.93)
Ormiston, 1985[44] Ormiston, 1983[55]: interim data	G1: Gentian violet and Polyfax G2: Cadexomer iodine	Crepe then cotton crepe compression bandage	12 weeks	G1: Mean, 0.46 (SEM, 0.1) cm^2/week G2: Mean, 0.89 (SEM, 0.1) cm^2/week; *P*=0.0001

* Neither study reported on the proportion of ulcers healed, time-to-healing, or wound recurrence.
cm = centimeter; SD = standard deviation; SEM = standard error of the mean

Antimicrobial Dressings Versus Other Types of Dressings

A large RCT recruited 213 patients to prospectively analyze healing rates at 12 weeks, 6 months, and 1 year, and time-to-healing between silver antimicrobial dressings (foams, specialty absorptives, alginates, and contact layers) and any nonantimicrobial dressing (including knitted viscose, foams, contact layers, and low adherent tulle) (Table 15).[22] Investigators and nurses caring for patients could change the frequency of dressing changes. The choice of silver-donating dressings was up to the clinician. Likewise, the dressing choice for the nonsilver dressings was clinician-guided based on wound characteristics. The overall median time-to-healing was 67 (95% CI, 54 to 80) days for the antimicrobial dressings and 58 (95% CI, 43 to 73) days for the other dressings. This was not statistically significant (*P*=0.41). Large ulcers, those above 3 cm, healed significantly more slowly than small ulcers, those up to 3 cm. Significant predictors of healing at 12 weeks included patient location, ulcer size, and sex of patient.[22]

Another prospective, multicenter RCT (N=108) evaluated healing rates over 4 weeks using manuka honey compared with using hydrogel.[24] The manuka honey group healed faster than the hydrogel group (34 percent reduction in median wound size vs. 13 percent reduction in wound size respectively) (*P*<0.001).[24]

A double-blind RCT of 41 patients compared hydrogel with hydrogel plus Mimosa tenuiflora (M. tenuiflora) cortex extract (MTC-2G), a substance with antiseptic properties.[56] After 8 weeks, the mean area of wound reduction was significant in the MTC-2G group and the hydrogel group at 6.29 cm^2 (95% CI, 3.28 to 9.29 cm^2, *P*=0.0001) and 5.85 cm^2 (95% CI, 3.58 to 8.12 cm^2,

P=0.0001), respectively. However, the study found no significant difference between the groups.[56]

Lastly, one RCT (N=153) compared cadexomer iodine with hydrocolloid and paraffin gauze over a duration of 12 weeks.[37] During the course of the trial, 12 patients from the cadexomer iodine group, seven from the hydrocolloid group, and nine in the paraffin gauze group withdrew and researchers excluded them from the analyses. Of the patients treated for 12 weeks (N=51), the cadexomer iodine group had a 66 percent (SD, 25.4) mean ulcer area reduction from baseline and the hydrocolloid group had an 18 percent (SD, 51.6) mean ulcer area reduction (*P*=0.01). The paraffin gauze group had a 51 percent (SD, 53.2) mean ulcer area reduction, but this was not considered significant. The mean ulcer area reduction per week was significantly greater in the cadexomer iodine group compared with the paraffin gauze group (*P*=0.04).[37]

Table 15. Summary of the wound healing measures* among patients with chronic venous ulcers comparing antimicrobial dressings versus other types of dressings

Author, year	Intervention, N	Compression used in both groups	Followup Time	Wound healing rate
Michaels, 2009[22]	G1: Any nonantimicrobial dressing G2: Silver antimicrobial dressing	Multilayer	12 months	G1: Median time-to-healing, 58 days (CI, 43 to 73) G2: Median time-to-healing, 67 days (CI, 54 to 80); *P*=0.51
Gethin, 2009[24]	G1: Hydrogel, 54 G2: Manuka honey, 54	Multilayer	4 weeks	G1: 13% reduction to wound area G2: 34% reduction to wound area; *P*<0.001
Lammoglia-Ordiales, 2011 [56]	G1: Hydrogel, 14 G2: Hydrogel plus Mimosa tenuiflora (M. tenuiflora) cortex extract, 18	2-layer compression	NR	G1: 5.85 cm^2 mean area wound reduction (CI, 3.58 to 8.12 cm^2) *P*=0.0001 G2: 6.29 cm^2 mean area wound reduction (CI, 3.28 to 9.29 cm^2), *P*=0.0001
Hansson, 1998[37]	G1: Paraffin gauze G2: Cadexomer iodine G3: Hydrocolloid	Short stretch	12 weeks	G1: Mean area reduction, 51 (SD, 53.2) G2: Mean area reduction, 66 (SD, 25.4); *P*=0.04 vs. G1 G3: Mean area reduction, 18 (SD, 51.6)

* None of the studies reported on the proportion of ulcers healed, time-to-healing, or wound recurrence.
CI = 95% confidence interval; cm = centimeter; G = group; SD = standard deviation

Other Types of Advanced Wound Dressings

We did not find any studies meeting our inclusion criteria that evaluated composite dressings, specialty absorptive dressings, contact layer dressings, hydrogel dressings, impregnated gauzes, or dressings with debriding agents in terms of wound healing.

Strength of Evidence

Because of their differing effects, we decided to grade the evidence separately for the different types of biological or cellular dressings. The three types of biological or cellular dressings are cryo-preserved human fibroblast derived dermal substitute, allogenic bilayered human skin equivalent, and autologous keratinocytes in a fibrin sealant.

Overall, we found moderate strength of evidence that allogenic bilayered cultured human skin equivalents have a moderate effect on wound healing when compared with compression systems alone (Table 16). We also found moderate strength of evidence that antimicrobial

Table 16. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence among studies comparing advanced wound dressings with either compression systems alone or other advanced wound dressings in terms of wound healing

Comparison	Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence				Magnitude of Effect SOE*
		Risk of Bias	Consistency	Directness	Precision	
Hydrocolloids vs. compression	3 (361)	Medium	Consistent	Direct	Imprecise	No effect Low SOE
Hydrocolloids vs. other dressings	4 (420)	High	Inconsistent	Direct	Precise	Unclear effect Insufficient SOE
Transparent films vs. compression	1 (54)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Transparent films vs. other dressings	1 (20)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Alginates vs. alginates	2 (101)	High	Inconsistent	Direct	Imprecise	Unclear effect Insufficient SOE
Alginates vs. other dressings	1 (113)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Foam vs. foam	3 (296)	High	Unknown - heterogeneity in interventions	Direct	Imprecise	Unclear effect Insufficient SOE
Collagen vs. compression	1 (120)	Low	NA	Direct	Imprecise	Moderate effect Low SOE
Acellular HSE vs. compression	3 (267)	High	Unknown - heterogeneity in interventions	Direct	Imprecise	Unclear effect Insufficient SOE
Cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression	2 (70)	Medium	Inconsistent	Indirect	Imprecise	Unclear effect Insufficient SOE
Cellular (allogenic bilayered cultured HSE) vs. compression	1 (275)	Low	NA	Direct	Precise	Moderate effect Moderate SOE
Cellular (autologous keratinocytes in fibrin sealant) vs. compression	1 (225)	Medium	NA	Direct	Precise	Small effect Low SOE
Cellular skin replacements vs. other dressings	2 (225)	High	Consistent	Direct	Imprecise	Unclear effect Insufficient SOE
Antimicrobial dressings vs. compression	2 (194)	High	Consistent	Direct	Imprecise	Unclear effect Insufficient SOE
Antimicrobial dressings vs. antimicrobial dressings	2 (342)	Medium	Unknown - heterogeneity in interventions	Direct	Precise	Unclear effect Insufficient SOE
Antimicrobial dressings vs. other dressings	4 (515)	Medium	Consistent	Direct	Precise	Small effect Moderate SOE

HSE = human skin equivalent; SOE = strength of evidence; vs. = versus

* We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

dressings had a small effect on wound healing rates when compared with other types of advanced wound dressings. The strength of the evidence comparing other advanced wound dressings in terms of wound healing was considered to be low or insufficient, generally due to a high risk of bias, inconsistent results, and/or imprecise estimates. These results could also be subjected to publication bias and selective outcome reporting.

Mortality

We included 11 studies that reported on mortality.[20, 22, 26, 28, 32, 33, 38, 44, 47, 49, 50] In most of these studies, deaths were rare, occurring in less than 5 percent of patients, and did not differ between intervention groups.

Quality of Life

In this report, we classified QOL measures as either general health-related QOL (nonspecific measures) or ulcer-specific QOL (QOL associated with venous ulcers). One study evaluated health-related QOL using six validated QOL assessment tools.[22] Three other studies used customized QOL assessment tools that were specific to each study and not validated.[23, 39, 48] Table 17 categorizes these QOL assessment tools into general health-related QOL and ulcer-specific QOL.

Table 17. Health-related quality of life assessment tools used in each category

Domain	Instrument	Range of Total Scores (High Scores Indication)
General health-related QOL	EuroQol 5D (EQ-5D)	-0.59 – 1 (better QOL)
	Short Form 6D (SF-6D)	0.29 – 1 (better QOL)
	Customized for study	Varies
Ulcer-specific QOL	Customized for study	Varies

QOL = quality of life

Hydrocolloid Dressings

Two studies examined the comparative effectiveness of hydrocolloid dressings versus control dressings on general and ulcer-specific QOL in adults with venous leg ulcers (Table 18).[39, 48] One study examined the comparative effectiveness of hydrocolloid dressings versus paraffin-impregnated gauze dressings using ulcer-specific QOL measures that assessed comfort, convenience, ease of use, and aesthetic appearance of the dressings.[39] This study did not find a statistically significant difference in QOL between the two intervention arms.[39] Another study examined the comparative effectiveness of hydrocolloid dressings versus conventional dressings using ulcer-specific QOL measures that assessed discomfort during dressing change (no discomfort, mild discomfort, moderate discomfort, severe discomfort, intolerable discomfort) and convenience while changing the dressing (most convenient, quite convenient, convenient, inconvenient, totally inconvenient).[48] This study found that patients favored hydrocolloid dressings over conventional dressings for ulcer-specific QOL measures related to discomfort and convenience during dressing change.[48]

Table 18. Quality of life in hydrocolloid dressings versus controls

QOL Domain	Author, Year	Comparison (N)	Population	Difference in QOL Between Comparison Groups	Group Favored for QOL Measure
Custom*	Arnold, 1994[39]	Hydrocolloid dressings (35) vs. impregnated gauze (35)	70 patients (mean age 65 years for hydrocolloid dressings and 60 years for control) with lower extremity venous ulcers	After 10 weeks of followup, 60% of the hydrocolloid-dressing group and 50% of the control group were satisfied with their treatment (score ≤ 2) based on comfort, ease of use, and aesthetics (*P*=0.3).	Neither
Custom*	Greguric, 1994[48]	Hydrocolloid dressings (55) vs. conventional dressing (55)	110 patients (mean age 61 years for both groups) with venous leg ulcers	After 10 dressing changes of followup, hydrocolloid dressing caused less discomfort than control (*P*=0.003), and hydrocolloid was significantly more convenient than control (*P*=0.004).	Hydrocolloid dressing

QOL = quality of life; vs. = versus

*Ulcer-specific QOL measure. Custom patient satisfaction questionnaire used by Arnold et al. assessed comfort, convenience, ease of use, and aesthetic appearance of the treatment modality using a 10-point scale ranging from 0 to 10, with higher scores indicating discomfort and difficulty of use. Custom patient satisfaction questionnaire used by Greguric et al. assessed discomfort during dressing change (no discomfort, mild discomfort, moderate discomfort, severe discomfort, intolerable discomfort) and convenience while changing the dressing (most convenient, quite convenient, convenient, inconvenient, totally inconvenient). Numerical translation of these ratings was not provided.

Foam Dressings

One study examined the comparative effectiveness of a foam dressing with ibuprofen versus foam dressing without ibuprofen on general QOL in adults with venous leg ulcers (Table 19).[23] The study questionnaire assessed changes in responses to four domains of the patients' activities of daily living, which included appetite, sleep, mood/feeling, and well-being.[23] This study did not find a statistically significant difference in QOL between the two intervention arms.[23]

Table 19. Quality of life in foams versus controls

QOL Domain	Author, Year	Comparison	Population	Difference in QOL Between Comparison Groups	Group Favored for QOL Measure
Custom*	Gottrup, 2008[23]	Ibuprofen-foam (62) vs. foam alone (60)	122 patients (mean age 66 years for Ibuprofen-foam, 70.0 years for control) with venous leg ulcers	After 6 weeks of followup, the two study groups had no statistically significant differences in four domains of the patients' ADL: appetite, sleep, mood/feeling, and well-being.	Neither

ADL = activities of daily living; QOL = quality of life

*General QOL measures. Custom questionnaire used by Gottrup et al. used three responses (improved, stayed the same, deteriorated) across four domains (appetite, sleep, mood/feeling, and well-being) and did not provide a standardized QOL measure on a numerical scale.

Antimicrobial Dressings

One study examined the comparative effectiveness of antibacterial dressings versus nonantibacterial control dressings on general and ulcer-specific QOL in adults with venous leg ulcers (Table 20).[22] One study examined general QOL in adults with venous leg ulcers using EuroQoL 5D, and did not show a statistically significant difference in QOL between silver-releasing antibacterial dressings and nonantibacterial dressings in this population.[22] This study also used the Short Form 6-Dimensions QOL measure, and did not find a statistically significant difference in QOL between the two intervention arms.[22]

Table 20. Quality of life in antibacterial dressings versus controls

QOL Domain	Author, Year	Comparison	Population	Difference in QOL Between Comparison Groups	Group Favored for QOL Measure
EQ-5D*	Michaels, 2009[22]	Silver (107) vs. nonsilver dressing (106)	213 patients (mean age 69 years for silver, 72 years for nonsilver) with venous leg ulcers	After 12 months of followup, mean difference between silver (0.7526) and nonsilver groups (0.6752) was -0.0774 (*P*>0.05)	Neither
SF-6D*	Michaels, 2009[22]	Silver (107) vs. nonsilver dressing (106)	213 patients (mean age 69 years for silver, 72 years for nonsilver) with venous leg ulcers	After 12 months of followup, mean difference between silver (0.7092) and nonsilver (0.6662) groups was -0.0430 (*P*>0.05)	Neither

EQ-5D = Euro Quality of Life 5-Dimensions; SF-6D = Short Form 6-Dimensions; QOL = quality of life
*General QOL measures. Total scores from EuroQol 5-Dimensions range from -0.59 to 1, with higher scores indicating better quality of life. Total scores from Short Form 6D range from 0.29 to 1, with higher scores indicating better quality of life.

Other Types of Advanced Wound Dressings

We did not find any studies that met our inclusion criteria and evaluated transparent film dressings, alginate dressings, composite dressings, specialty absorptive dressings, contact layer dressings, hydrogel dressings, collagen dressings, acellular human skin equivalent dressings, cellular human skin equivalent dressings, impregnated gauzes, and dressings with debriding agents in terms of QOL.

Pain

Hydrocolloid Dressings

Hydrocolloid Dressings Versus Other Types of Dressings

One trial compared hydrocolloids with Betadine® and a contact layer in terms of ulcer pain (moderate to severe) and dressing comfort (very to fairly comfortable) for the first month of treatment.[50] The hydrocolloid group experienced less pain than the Betadine® and contact layer group among small and large ulcers (P=0.02). Both groups experienced more pain with large ulcers (P<0.001). The treatments did not differ in their effect on dressing comfort, but large ulcers tended to be less comfortable (P=0.02).[50]

Another trial comparing hydrocolloid with impregnated gauze with magnesium sulfate and Vaseline® found that patients had no discomfort at the fifth dressing change in the hydrocolloid group, but more than 20 percent of the patients experienced discomfort by dressing change 10 of the impregnated gauze group (P=0.0003).[48]

Another trial compared hydrocolloid with impregnated gauze containing paraffin or Betadine®. Patients rated their pain on a scale of 0 (minimal pain) to 10 (maximal pain).[39] Patients in the hydrocolloid group reported less pain at followup as compared with patients in the impregnated gauze group. Additionally, 60 percent of the hydrocolloid group and 50 percent of the impregnated gauze group rated their treatment as very comfortable, but this difference was not statistically significant (P=0.3).[39]

Lastly, in the trial that compared a hydrocolloid with an alginate, the patients ranked their pain on a 4-point numeric scale as follows: 1 = painless, 2 = slight pain, 3 = painful, 4 = very painful.[53] Wounds treated with the alginate dressing were less painful at week 0 (P=0.0004) than those treated with the hydrocolloid and remained that way at week 6 (P=0.03).[53]

Although these studies suggested that patients had less pain with use of hydrocolloid dressings than with other types of dressings, the strength of evidence was insufficient to support a firm conclusion because of the marked heterogeneity of the studies.

Transparent Film Dressings

Transparent Film Dressings Versus Other Types of Dressings

The trial comparing an alginate plus transparent film with an alginate plus foam evaluated pain on a 1 to 4 scale: 1 = painless, 2 = slightly painful, 3 = sufficiently painful to require analgesia, and 4 = painful enough to interfere with lifestyle and not relieved with high levels of analgesia.[54] The alginate plus foam group experienced a 26 percent reduction of pain scores and the alginate plus transparent film group experienced an 18 percent reduction in pain scores, but the difference between groups was not statistically significant.[54]

Alginate Dressings

Alginate Dressings Versus Other Alginate Dressings

The trial comparing the alginates, Sorbsan® with Tegagen™ HG, evaluated patient comfort during wear of the dressing and comfort during removal of the dressing on a scale of 1 to 5 (1 = very good and 5 = very poor).[35] Patients in the Sorbsan alginate group experienced much more comfort during dressing wear (P=0.0005) and dressing removal (P=0.003).[35]

Specialty Absorptive Dressings

Specialty Absorptive Dressings Versus Other Types of Dressings

In a trial comparing a hydropolymer dressing with an alginate plus transparent film and an alginate plus cotton gauze pad, the investigators asked the patients to rate comfort on a scale of 1 to 5 (1 = poor comfort and 5 = good comfort).[36] Patients rated the hydropolymer dressings higher in comfort (mean comfort score, 4.27) than the alginate plus transparent film (mean comfort score, 3.37) or the alginate plus cotton gauze pad (mean comfort score, 3.74; P<0.02).[36]

Acellular Human Skin Equivalent Dressings

Acellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

One trial evaluated pain on a scale of 0 to 10 comparing Amelogenin protein 30 milligrams per milliliter solution (Xelma® ECM) plus a soft silicone dressing with a control dressing of 7 percent propylene glycol alginate.[30] The mean baseline pain score for the treatment group was 4 compared with 3 for the control. Both groups had a pain score of 1 on the final visit. The trial did not show any statistical between-group comparisons.

Antimicrobial Dressings

Antimicrobial Dressings Plus Compression Versus Compression Systems Alone

A trial comparing cadexomer iodine to saline wet to dry dressings, reported pain but did not use a specific scale, making it difficult to interpret the findings.[42] However, the investigators reported that there was no statistically significant difference in pain between the two groups.[42] In another trial that compared pale sulfonated shale oil 10 percent plus Jelonet to vehicle plus Jelonet, pain was reported on a visual analog scale of 0 (no pain) to 10 (maximal pain).[31] The investigators reported no significant difference in pain between groups.[31]

Antimicrobial Dressings Versus Other Antimicrobial Dressings

A randomized optional crossover trial compared cadexomer iodine to gentian violet and Polyfax™ ointment (standard treatment) over 24 weeks among 61 outpatients and evaluated pain on a linear scale of 0 to 100.[44] The trial compared the change in pain per week and found no statistical significance.[44]

Antimicrobial Dressings Versus Other Types of Dressings

A trial comparing cadexomer iodine to a hydrocolloid dressing and a paraffin gauze dressing reported the percentage of wounds with pain at different time points.[37] While 29 percent of the cadexomer iodine group, 57 percent of the hydrocolloid group, and 15 percent of the paraffin gauze group reported pain at week 12, the trial did not report the intensity of the pain nor did it make a statistical comparison between groups. It also did not use a specific pain scale.[37]

Other Types of Advanced Wound Dressings

We did not find any studies that evaluated how foam dressings, composite dressings, contact layer dressings, hydrogel dressings, collagen dressings, cellular human skin equivalent dressings, impregnated gauzes, or dressings with debriding agents affected pain.

Condition of the Wound Bed

Transparent Film Dressings

Transparent Film Dressings Versus Other Types of Dressings

A trial comparing a transparent film with a foam as a secondary dressing over an alginate evaluated wound appearance on a scale of 1 to 4 (1 = healed; 2 = clean and epithelializing; 3 = clean and sloughy or mildly sloughy; and 4 = infected, very sloughy and odorous).[53] While both groups started with a comparable number of wounds ranked as sloughy/infected, the transparent film group experienced a 32 percent reduction in total wound condition scores while the foam group experienced a 40 percent reduction in total wound condition scores. The trial made no statistical comparisons between groups.[53]

Alginate Dressings

Alginate Dressings Versus Other Alginate Dressings

A trial comparing the alginate dressings, Sorbsan® and Tegagen™ HG evaluated the wound-bed condition for the amount of exudate, purulent or serosanguinous exudate, necrotic tissue, foul odor, and the need for debridement over 6 weeks.[35] A medium to large amount of exudate was present in 86 percent of visits in the Sorbsan® group and 72 percent of visits in the Tegagen™ group, but this difference was not significant (P=0.18). Likewise, purulent or serosanguinous exudate was present in 72 percent of visits in the Sorbsan® group and 48 percent of visits in the Tegagen™ wounds (P=0.24). Necrotic tissue was present in 69 percent of the visits in the Sorbsan® group and 60 percent of visits in the Tegagen™ group (P=0.57). A foul odor was present for 58 percent of visits in the Sorbsan® group and 16 percent of visits in the Tegagen™ group. The trial found this significant between groups (P<0.02). Lastly, wounds in the Sorbsan® group required debridement in 41 percent of the visits while wounds in the Tegagen™ group required debridement in 19 percent of visits (P=0.18).[35]

Specialty Absorptive Dressings

Specialty Absorptive Dressings Versus Other Types of Dressings

A trial, comparing a hydropolymer dressing with an alginate plus transparent film and an alginate plus cotton gauze pad, evaluated the wound bed for odor during 4 weeks in moderately to heavily exuding wounds.[36] The investigators used a scale of 1 to 5 to evaluate odor (1 = poor odor control and 5 = good odor control). The investigators gave a higher control of odor score to the hydropolymer dressing (mean odor score, 4.24) than the alginate plus transparent film group (mean odor score, 2.95; P<0.001). The alginate plus cotton gauze pad received the same mean odor score as the hydropolymer dressing. The patients gave a higher control of odor score to the hydropolymer dressing (mean odor score 4.45) than alginate plus transparent film (mean odor score, 3.05) and the alginate plus cotton gauze pad (mean odor score, 3.96; P=0.001).[36]

Acellular Human Skin Equivalent Dressings

Acellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

An RCT, comparing amelogenin protein 30 milligrams per milliliter solution (Xelma® ECM) plus a soft silicone dressing with a control dressing of 7 percent propylene glycol alginate, analyzed the wound bed for percent of viable tissue and amount of exudate expressed over time.[30] The study extrapolated these data from figures within the published study using the software DigitizeIt 1.5 (ShareIt Inc., Koln, Germany). However, the trial made no statistical comparisons of the within- and between-group differences. The percent viable tissue in wound bed of amelogenin at baseline was 52 versus 77 percent for the comparison group. At the study end-point, the mean percentage of viable tissue in the wound bed of the amelogenin-treated group was 91 versus 92 percent for the comparison group. The study ranked 0 percent of the wounds in the amelogenin and comparison groups as having high exudate at baseline. At the final evaluation, 14 percent of the amelogenin group had high amounts of exudate versus 22 percent in the control group.[30]

Cellular Human Skin Equivalent Dressings

Cellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

A trial comparing Dermagraft® 12 pieces over 12 weeks, versus four pieces over 12 weeks, versus one piece over 12 weeks evaluated the histology of the wound bed.[47] A greater number of blood vessels formed in the wounds treated with four pieces of Dermagraft® over 12 weeks (P=0.037). High numbers of blood vessels at week 0 (P=0.06) and week 6 (P=0.04) correlated with increased numbers of healed wounds at week 12 and a significant percentage reduction in wound area by week 12 (P=0.05). While Dermagraft® had no significant influence on the number of blood vessels forming fibrin cuffs, a low percentage of blood vessels with fibrin cuffs in the granulation tissue near the ulcer surface at week 0 and 6 correlated with an increased percentage of healing at weeks 6 and 12 as well as with the number of patients healed.

Another trial, comparing the cellular human skin equivalent, Dermagraft®, with compression over 12 weeks, histologically evaluated wound beds by biopsy at the beginning of treatment and at week 6 (if the ulcer was not healed).[34] While the Dermagraft® group saw an increase in capillary count in the wound bed compared with compression, it was not statistically significant (P=0.36). Likewise, the 25 percent increase in skin blood flow by blood perfusion in the Dermagraft group versus 9 percent increase in the compression group was not statistically significant (P=0.55).[34]

Antimicrobial Dressings

Antimicrobial Dressings Plus Compression Versus Compression Systems Alone

A trial comparing cadexomer iodine with wet to dry saline gauze under compression over 24 weeks found no significant difference when the study evaluated wound beds for granulation tissue (P=0.16), exudate (P=0.96), and pus/debris (P=0.55).[42] Likewise, a trial comparing pale sulfonated shale oil 10 percent plus Jelonet™ to vehicle plus Jelonet™ over 20 weeks, found no

significant difference between groups when evaluating wound beds for fibrinous discharge and necrotic tissue.[31]

Antimicrobial Dressings Versus Other Types of Dressings

One trial compared cadexomer iodine versus hydrocolloid versus paraffin gauze over 12 weeks.[37] Cadexomer iodine treatment resulted in less slough at 4 and 8 weeks than the paraffin gauze treatment group ($P<0.05$) and the hydrocolloid group had significantly less slough than the paraffin gauze group at week 4 only ($P<0.05$).[37]

Another trial that enrolled 32 patients compared hydrogel with hydrogel plus *M. tenuiflora* extract (MTC-2G), a substance with alleged antiseptic properties.[56] The study evaluated the percentage of granulation tissue, fibrin, maceration, wound exudates, and necrosis and found no significant difference in the clinical condition of the wound beds after 8 weeks. However, the presence of epithelial islands was greater in the MTC-2G group (58 percent) than in the hydrogel only group (39 percent; $P=0.02$). Investigators took biopsies at the beginning and end of the trial to evaluate the wounds for necrosis, perivascular fibrosis, presence and type of inflammatory infiltrates, granulation tissue, and new vessel formation. Both groups had five patients with necrosis present in the biopsies taken at the beginning of the trial, but on final biopsy, the MTC-2G group had one patient versus four in the hydrogel group ($P=0.035$) that showed residual necrosis in the biopsy. In the end, the study only biopsied 21 patients as it was deemed unethical to obtain biopsies from patients with healed wounds or wounds that decreased to less than 5 millimeters. The study saw no difference between initial and final biopsies concerning fibrosis, vascular proliferation, granulation tissue, or perivascular fibrosis. However, the density of the lymphocytic and neutrophilic inflammatory infiltrates decreased in both groups on final biopsy. Moreover, the density of neutrophils decreased in the MTC-2G group compared with the hydrogel group after treatment ($P=0.05$).[56] Measuring the density of inflammatory infiltrates by histological analysis is extremely difficult because of sampling variability.

Antimicrobial Dressings Versus Other Antimicrobial Dressings

A randomized optional crossover trial compared cadexomer iodine with gentian violet and Polyfax ointment (standard treatment) over 24 weeks among 61 outpatients and evaluated the condition of the wound bed based on the presence of granulation tissue, exudate pus, and debris.[44] The study found no significant differences between the treatment groups.[44]

Other Types of Advanced Wound Dressings

We did not find any studies evaluating how hydrocolloid dressings, foam dressings, composite dressings, contact layer dressings, hydrogel dressings, collagen dressings, impregnated gauzes, or dressings with debriding agents affected the condition of the ulcer bed.

Maceration

No study meeting our specified selection criteria evaluated the effect of the following dressings on maceration: hydrocolloid dressings, transparent films, alginates, foams, composites, specialty absorptive dressings, contact layer, hydrogels, collagen dressings, acellular human skin equivalents or extracellular matrices, cellular human skin equivalents or extracellular matrices, antibacterial dressings, impregnated gauzes, or biologic debriding agents.

Infection

Hydrocolloid Dressings

Hydrocolloid Dressings Plus Compression Versus Compression Systems Alone

Four RCTs (that analyzed a total of 463 participants at 3 to 4 months of followup) compared a hydrocolloid dressing with a standard dressing in terms of the effects on wound infection rates.[37, 43, 48, 50] Infection rates were similar across arms for all studies[43, 48, 50] with the exception of the subgroup of participants with baseline ulcer size greater than 4 cm in Smith, 1992 et al.[50] In this study, those receiving a hydrocolloid dressing (Biofilm powder plus Biofilm dressing) developed fewer infections at 4 months (one out of 35 patients; 3 percent) compared with the control group which received a Betadine®/Jelonet™ dressing (11 out of 39, 28 percent; *P*=0.004).[50] Infection rates were similar in the participants with a baseline ulcer size of 2 to 4 cm regardless of study arm.[50] Two studies did not provide definitions of infection,[37, 43] and the two others used different definitions ("acute infection[50]" and "erysipelas[48]") (Tables 21 and 22).

Table 21. Summary of infection rates as an adverse event among patients with chronic venous ulcers comparing hydrocolloid dressings with a standard dressing and compression system

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Infection Rate in Group 1, N / N (%)	Infection Rate in Group 2, N / N (%)
Backhouse, 1987[43]	Nonadherent, nonocclusive dressing	Hydrocolloid - Granuflex (occlusive hydrocolloid)	Multilayer	12 weeks	3 / 28 (11)	4 / 28 (14)
Greguric, 1994[48]	Magnesium sulfate paste + Vaseline + gauze	Hydrocolloid - Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam)	2-layer	NR	0 / 55 (0)	1 / 55 (2)
Smith, 1992[50] Among those with initial ulcer size of 2–4 cm	Betadine/ Jelonet	Hydrocolloid Biofilm powder + Biofilm dressing	2-layer compression linear, graduated (Tubigrip or Venosan 2002)	4 months	1 / 62 (2)	0 / 64 (0)
Smith, 1992[50] Among those with initial ulcer size of > 4 cm	Betadine/ Jelonet	Hydrocolloid Biofilm powder + Biofilm dressing	2-layer compression linear, graduated (Tubigrip or Venosan 2002)	4 months	11 / 39 (28)	1 / 35 (3); *P*=0.004
Hansson, 1998 [37]	Jelonet paraffin gauze	Hydrocolloid Duoderm E	Comprilan short-stretch	12 weeks	4 / 49 (8)	5 / 48 (10)

cm = centimeters; NR = not reported

Table 22. Definitions of wound infection reported in included studies

Author, year	Infection Definition
Gottrup, 2008[23]	Coexistent presence of the classical signs of clinical infection: pain, erythema, edema, heat, and purulence
Mostow, 2005[32]	Not further specified

Hansson, 1998[37]	Not further specified
Falanga, 1998[38]	Not further specified
Backhouse, 1987[43]	Not further specified
Krishnamoorthy, 2003[47]	Characterized as: local wound infection, cellulitis, or osteomyelitis
Greguric, 1994[48]	Erysipelas cruis
Smith, 1992[50]	Acute infection

Foam Dressings

Foam Dressings Versus Other Foam Dressings

In a single, multicenter European RCT of 122 patients with chronic venous ulcers comparing two types of foam dressings, infection rates were similar across arms.[23] Two of 60 (3 percent) patients developed an infection in the foam without ibuprofen arm, and three of 62 (5 percent) patients developed an infection in the foam with ibuprofen arm.[23] Both study arms used compression, and patients were likely followed for 42 days, although the study did not explicitly state this.[23] The average duration of chronic venous ulcers was 20 to 23 months at baseline.[23] Three of 60 participants (5 percent) withdrew consent in the foam without ibuprofen arm while seven of 62 participants (11 percent) withdrew (withdrew consent or investigators withdrew them from the study because of adverse events or protocol violations) from the foam plus ibuprofen arm.[23] The study defined infection by the presence of several typical signs (Table 23).

Table 23. Summary of infection as an adverse event among patients with chronic venous ulcers comparing foam dressings to one another

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Infection* Rate in Group 1, N / N (%)	Infection* Rate in Group 2, N / N (%)
Gottrup, 2008[23]	Foam WITHOUT ibuprofen (Biatain Non-Adhesive, Coloplast A/S)	Foam + ibuprofen (Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S)	Not specified; kept constant circumference at ankle	42 days†	2 / 60 (3)	3 / 62 (5)

* Definition included eczema, blisters, bullae, and urticaria.
† Presumed followup time but unclear

Acellular Human Skin Equivalent Dressings

Acellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

A single, multicenter RCT of 120 participants compared an extracellular matrix dressing with multilayer compression and reported five wound infections in the control arm and one in the active intervention arm at 12 weeks (P=0.10).[32] The study did not provide a definition of infection (Table 24).

Table 24. Summary of wound infection as an adverse event among patients with chronic venous ulcers comparing acellular human skin equivalent dressings with compression systems alone

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Infection Rate in Group 1, N / N (%)	Infection Rate in Group 2, N / N (%)

Mostow, 2005[32]	None	Composite acellular or extracellular matrix	Multilayer Debridement	12 weeks	5 events / 58 patients	1 event / 62 patients; *P*=0.10

Biological Dressings

Cellular Human Skin Equivalent Dressings Plus Compression Versus Compression Systems Alone

Two RCTs (N=328) compared a cellular human skin equivalent with compression alone.[38, 47] Wound infection rates were similar across cellular human skin equivalent and compression arms (Table 25).[38, 47] Infection rates were very low in a study lasting 12 weeks with only a single infection occurring in one study arm.[47] Similarly, infections occurred in 8 percent of participants in the RCT lasting 12 months.[38] In this larger study of longer duration, dropout rates were substantial but similar across study arms (26 and 20 percent in the compression and intervention arms, respectively).[38] One study included local wound infection, cellulitis, or osteomyelitis in its definition of infection[47] while the other did not specify a definition.[38]

Table 25. Summary of wound infection as an adverse event among patients with chronic venous ulcers comparing cellular human skin equivalent dressings with compression systems alone

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Infection Rate in Group 1, N / N (%)	Infection Rate in Group 2, N / N (%)
Krishnamoorthy, 2003[47]	None	Cellular human skin equivalent Dermagraft 12 pcs	Multilayer Profore	12 weeks	0 / 13 (0)	0 / 13 (0)
Krishnamoorthy, 2003[47]	None	Cellular human skin equivalent Dermagraft 4 pcs	Multilayer Profore	12 weeks	0 / 13 (0)	1 / 13 (8)
Krishnamoorthy, 2003[47]	None	Cellular human skin equivalent Dermagraft 1 pc	Multilayer Profore	12 weeks	0 / 13 (0)	0 / 14 (0)
Falanga, 1998[38]	None	Cellular human skin equivalent	Unna boot	12 months	10 / 129 (8)	12 / 146 (8)

Antimicrobial Dressings

Antimicrobial Dressings Plus Compression Versus Compression Systems Alone

A single, multicenter RCT analyzing 105 participants compared a cadexomer iodine dressing with a paraffin gauze dressing plus compression and reported four wound infections in the control arm and one in the active intervention arm at 12 weeks.[32] Participants in a third arm received a hydrocolloid dressing and five of 48 participants (10 percent) developed an infection (Table 26).[37] The study did not provide a definition of infection (Table 22).

Table 26. Summary of infection as an adverse event among patients with chronic venous ulcers comparing antimicrobial dressings with standard dressings plus compression systems

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Infection Rate in Group 1, N / N (%)	Infection Rate in Group 2, N / N (%)
Hansson, 1998 [37]	Jelonet paraffin gauze	Cadexomer iodine	Comprilan short-stretch	12 weeks	4 / 49 (8%)	1 / 56 (2%)

Other Types of Advanced Wound Dressings

No study meeting our specified selection criteria evaluated the effect of the following dressings on wound infection rates: transparent films, alginates, composites, specialty absorptive dressings, contact layer, hydrogels, collagen dressings, impregnated gauzes, or biologic debriding agents.

Contact Dermatitis

Hydrocolloid Dressings

Hydrocolloid Dressings Plus Compression Versus Compression Systems Alone

A single RCT of 110 patients with chronic venous ulcers in Croatia compared a standard dressing (gauze with magnesium sulfate paste and Vaseline®) with hydrocolloid Varihesive E® (hydrocolloid in an adhesive elastomeric polymer matrix and coated with polyurethane foam). Both arms used two-layer compression (Table 27).[48] No participant developed a contact dermatitis reaction in the control arm (zero out of 55, 0 percent), and a single participant developed contact dermatitis in the active intervention arm (one out of 55, 2 percent).[48] The number of dressing changes required for complete wound healing dictated the maximum followup time with a maximum of 10 dressing changes allowed.[48] The study anticipated dressing changes would occur every 5 days in the intervention arm and nearly daily in the control arm.[48] The authors did not report followup time explicitly.[48] On average, participants had chronic venous ulcers for 5 years at baseline.[48]

Table 27. Summary of contact dermatitis as an adverse event among patients with chronic venous ulcers comparing hydrocolloid dressings with a standard dressings and compression

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Contact Dermatitis Rate in Group 1*, N / N (%)	Contact Dermatitis Rate in Group 2*, N / N (%)
Greguric, 1994[48]	Magnesium sulfate paste + Vaseline + gauze	Hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated with polyurethane foam)	2-layer	NR†	0 / 55 (0)	1 / 55 (2)

NR = not reported
*Defined as "bullous/erythematous reaction."
†Maximum duration of followup was time to 10 dressings. Participants could have fewer than 10 dressings, and the time between dressings changes varied across participants and intervention arms.

Foams

Foam Dressings Versus Other Foam Dressings

In a single, multicenter European RCT of 122 patients with chronic venous ulcers comparing two types of foam dressings, rates of contact dermatitis were similar across study arms (Table 28).[23] Four of 60 (7 percent) patients developed contact dermatitis in the foam without ibuprofen arm, and five of 62 (8 percent) patients developed contact dermatitis in the foam with ibuprofen arm.[23] Both arms used compression, and likely followed patients for 42 days, although the study did not explicitly indicate the followup time.[23] The average duration of chronic venous ulcers under study was 20 to 23 months at baseline.[23] Three of 60 participants (5 percent) withdrew consent in the foam without ibuprofen arm while seven of 62 participants (11 percent) withdrew (withdrew consent or investigators withdrew them because of adverse events or protocol violations) from the foam plus ibuprofen arm.[23]

Table 28. Summary of contact dermatitis as an adverse event among patients with chronic venous ulcers comparing foam dressings to one another

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used in Both Groups	Followup Time	Contact Dermatitis Rate in Group 1*, N / N (%)	Contact Dermatitis Rate in Group 2*, N / N (%)
Gottrup, 2008[23]	Foam WITHOUT ibuprofen (Biatain Non-Adhesive, Coloplast A/S)	Foam + ibuprofen (Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S)	Not specified, kept constant circumference at ankle	42 days†	4 / 60 (7)	5 / 62 (8)

*Definition included eczema, blisters, bullae, and urticaria.
†Presumed followup time but unclear

Other Types of Advanced Wound Dressings

No study meeting our specified selection criteria evaluated the effect of the following dressings on contact dermatitis: transparent films, alginates, composites, specialty absorptive dressings, contact layer, hydrogels, collagen dressings, acellular human skin equivalents or extracellular matrices, cellular human skin equivalents or extracellular matrices, antibacterial dressings, impregnated gauzes, or biologic debriding agents.

Venous or Arterial Impairment

No study meeting our specified selection criteria evaluated the effect of the dressings of interest on venous or arterial impairment.

Cellulitis

No study meeting our specified selection criteria evaluated the effect of dressings on cellulitis.

Study Quality

The RCTs overall were at moderate risk of bias (Appendix D, Table 5). Studies tended to account for different lengths of followup and used appropriate statistical tests. Since dressing changes tended to occur in a clinical setting in most studies, we assumed reliable adherence to randomized interventions. We found numerous potential threats to internal validity in the RCTs evaluating the effect of advanced wound dressings. Many studies did not report on allocation concealment. Studies either did not attempt to mask or did not report on masking of outcome assessors. Also, studies did not report on prespecified analyses, and thus, selective reporting of results is a possibility. Most studies either did not account for or had substantial losses to followup. Finally, most studies did not provide specific definitions or details on ascertainment of adverse events.

Key Question 2a. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

Key Question 2b. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components, what are the benefits and harms of using systemic antibiotics when compared with using dressings alone?

Summary of Findings

Despite the widespread use of both local and systemic antimicrobials to treat nonhealing lower extremity ulcers in the setting of chronic venous stasis disease, we found only one RCT that addressed KQ 2a.[57] This small study evaluated systemic oral antimicrobials, took place in Finland, and was published 18 years ago. The Finnish study[57] enrolled 36 outpatients with chronic venous leg ulcers and randomized them to three treatment groups. The treatment groups were oral ciprofloxacin, trimethoprim, or placebo. All groups received adequate compression. The treatment assignment was double-blind, and the treatment period was 12 weeks. Final assessment for outcomes was at 16 weeks. The groups had similar ulcer size at baseline. After 16 weeks, the healing rate was 42 percent in the ciprofloxacin group, 33 percent in the trimethoprim group, and 30 percent in the placebo group. The differences in this underpowered study were not statistically significant. In patients treated with the antibiotics, emergence of resistant organisms was common and occurred in two-thirds of subjects treated with either ciprofloxacin or trimethoprim. This study did not report on the time to complete healing, wound recurrence, quality of life, pain, mortality, functional status, quality of the wound bed, and adverse events other than the emergence of resistant organisms.

Strength of Evidence

The study that addressed KQ 2 had a high risk of bias, the most important being ascertainment bias. This study evaluated the microbiology of ulcers using methods that are now known to be inaccurate (swab culture) in a small number of subjects in a referral center. Furthermore, the sensitivity of culture technique was likely lower, as the study infrequently reported anaerobes. We cannot determine consistency since there was only one study. The study measured a direct effect. The results were imprecise, and were limited by both sample size and study design issues. These results could also be subjected to publication bias and selective outcome reporting. Thus, the strength of evidence addressing the effects of systemic antibiotics when compared with compression systems alone is insufficient.

The strength of the evidence evaluating the effects of systemic antibiotics when compared with advanced wound dressings (KQ 2b) is insufficient, as we did not find any studies addressing this comparison.

Key Question 3a. For patients with chronic venous leg ulcers, what are the benefits and harms of surgical procedures aimed at the underlying venous abnormalities when compared with using solely compression systems?

Key Points

- Adding superficial vein surgery to compression therapy does not improve healing of chronic venous leg ulcers, but there may be a lower risk of recurrence. (Moderate strength of evidence)
- Adding minimally invasive surgical hemodynamic correction of reflux to compression therapy does not significantly affect the proportion of ulcers healed, but it may lower the risk of recurrence. (Low strength of evidence)
- Subfascial endoscopic perforator surgery (SEPS) with superficial vein surgery does not improve the rate of healing or the risk of recurrence of chronic venous leg ulcers in comparison with compression alone. (High strength of evidence)
- We were unable to draw a conclusion if sclerotherapy can improve the healing of chronic venous leg ulcers or lower the risk of occurrence when compared with compression therapy alone. (Insufficient strength of evidence)
- Insufficient evidence exists to determine whether the healing of chronic venous leg ulcers improves with the addition of radiofrequency ablation (RFA), endovenous laser therapy (EVLT), or deep venous surgery to compression therapy.

Study Design Characteristics

We reviewed eight studies (nine publications) (Appendix D, Table 1).[58-66] Two publications[59, 60] reported on the same trial (Effect of Surgery and Compression on Healing and Recurrence [ESCHAR]). Barwell et al.[60] reported the short-term results and Gohel et al.[59] reported the long-term results.

These studies enrolled a total of 1,841 (range, 40 to 500) patients with chronic venous leg ulcers between 1988 and 2008. The studies screened an average of 596 patients, and enrolled an average of 145 patients. The enrollment rate was 13 to 93 percent, with an average of 33 percent. Six of the eight studies were RCTs,[58-62, 64, 65] one was a cohort study,[62] one was a retrospective cohort study,[66] and one a non-RCT.[63] The studies had 1 to 5 years of reported followup.

Four of the studies took place in the United Kingdom,[58-60, 62, 64] one in Italy,[61] one in the Netherlands,[65] one in Italy,[66] and one in Mexico.[63] The clinic setting also varied; two studies recruited from specialist nurse-led venous ulcer clinics,[58-60] one recruited from 12 centers across the Netherlands,[65] one from an outpatient community base clinic,[62] and four studies did not describe the source of the study population.[61-64]

All of these studies had at least one surgical arm: superficial vein surgery,[59-62] SEPS,[64, 65] and sclerotherapy[58, 63, 66] (Appendix D, Table 2). All of the surgical patients had multilayer compression therapy. The comparison groups in these studies received compression therapy alone.

Study Population Characteristics

Seven of the eight studies reported age with a median of 69 years[58-60, 62-66] (Appendix D, Table 3). In studies that reported gender,[59, 60, 62-66] most patients were female. The studies varied

in how they factored diabetes into the study design. Diabetes was an exclusion criterion in three studies.[61, 62, 64] One study[58] excluded only patients with poorly controlled diabetes. The other three studies[59, 60, 62, 65] included patients with diabetes, which was more prevalent in the compression group. Two studies[63, 66] did not report diabetes status of the subjects.

For all patients, investigators conducted vascular evaluations using venous duplex ultrasound and arterial evaluations using the ankle brachial index. Investigators excluded patients with arterial insufficiency, defined in most studies by an ankle brachial index less than 0.8, except for two studies that used an ankle brachial index less than 0.85,[59, 60, 62] and one study that used an ankle brachial index less than 0.9.[61] None of the eight studies reported smoking status. Most of the publications did not describe the presence of other systemic diseases;[58, 59, 61-66] only two publications reported on the prevalence of rheumatoid arthritis.[60, 62]

Wound Healing

Superficial Vein Surgery Plus Compression Versus Compression

One RCT[59, 60] and one prospective cohort study[62] compared superficial vein surgery with compression alone, and reported on wound healing (Table 29 and Appendix D, Table 4). These two studies were too different to be combined in a meta-analysis.

Gohel et al.[59] reported the short-term results, and Barwell et al.[60] reported the long-term results of the ESCHAR trial, which compared compression alone with superficial vein surgery in addition to compression. ESCHAR was an RCT that enrolled 500 patients. It included 242 patients in the surgical intervention group and 258 patients in the compression-only group. Contamination of the defined groups after randomization limited the study--three patients in the comparison group requested surgery, and 47 patients in the surgical group refused surgery. The study performed analysis on an intention-to-treat basis. The study included patients with either a currently open ulcer (N=341) or recently healed ulcer (N=159). The average ulcer size was 2 cm^2 (range, 1 to 5 cm^2) and was similar in both groups. The chronicity of the ulcer was also similar in both groups, averaging 5 months (range, 3 to 11 months). All patients received arterial and venous ultrasound, and the study excluded them if they had arterial insufficiency (ankle brachial index less than 0.8) or deep venous obstruction. All randomized patients received multilayer compression dressings with graduated pressure of 40 mm Hg at the ankle to 17-20 mm Hg at the calf. The surgical arm patients underwent a surgical procedure tailored to their underlying level of superficial venous insufficiency as dictated by the venous duplex (disconnection of the saphenofemoral or sphenopopliteal junction and/or long saphenous vein striping plus varicosity avulsion if needed). The followup period was 4 years. The ulcer-healing rate was 89 percent in the compression group versus 93 percent in the surgical group (P =0.73).

The prospective nonrandomized cohort study took place in an outpatient clinic setting in England.[62] Over a 4-year period (1995 to 1999), the study evaluated 669 patients (766 legs) with chronic venous leg ulcers. The study measured the ankle brachial index for all patients, and excluded 120 legs that had measured less than 0.85. All patients received 4-layer compression therapy and underwent venous duplex. The study excluded 410 legs with deep or mixed venous reflux. Only 236 legs (39 percent) had isolated superficial venous reflux and the study only offered those patients surgery. Only 56 percent of those patients accepted and underwent surgery (131 legs). The study compared the proportion of ulcers healed between the surgical group (131 legs) and the group with isolated superficial vein reflux that refused surgery (105 legs). Patient characteristics were similar in both groups, except for slightly older age and less mobility in the

compression group. This study did not exclude patients with diabetes mellitus or rheumatoid arthritis. The study performed surgery on the long saphenous vein in 97 legs (74 percent), the short saphenous vein in 18 legs (14 percent), both the long and short saphenous veins in 12 legs (9 percent), and perforator veins in four legs (3 percent). Two patients received SEPS. Forty-four legs had concomitant perforator and saphenous reflux, but the study did not perform SEPS on these patients. The healing rate of ulcers was similar in both groups (72 percent in the surgical group compared with 74 percent in the medical group, P=0.67). The statistical analysis was limited in that the study treated each leg as an independent unit without adjusting for the fact that some patients had more than one ulcer in the study. Furthermore, the analysis did not account for the baseline differences between the surgical intervention and comparison groups, even though healthier and younger patients may have been biased toward having surgical intervention.

Table 29. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing superficial vein surgery with compression alone

Author, Year Study Design	Group 1	Group 2	Compression Used	Followup Period	Ulcer Healing in Group 1, N / N (%)	Ulcer Healing in Group 2, N / N (%)	Relative Risk Risk Difference
Gohel, 2007[59] RCT	Compression alone	Superficial vein surgery plus compression	Multilayer	48 months	165 / 185 patients (89%)	145 / 156 patients (93%); *P*=0.73	RR, 0.96 (CI, 0.90 to 1.02) RD, -4% (CI, -10 to 2%)
Barwell, 2003[60] RCT	Compression alone	Superficial vein surgery plus compression	Multilayer	12 weeks	141 / 185 patients (76%)	128 / 156 patients (82%); *P*=0.85	RR, 0.93 (CI, 0.83 to 1.04) RD, -6% (CI, -14% to 3%)
Barwell, 2000[62] Prospective cohort	Compression alone	Superficial vein surgery plus compression	4-layer	24 weeks	74% of limbs	72% of limbs; *P*=0.67	RR or RD not calculable

CI = 95% confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

Minimally Invasive Ligation of Insufficient Saphenous Vein Tributaries Plus Compression Versus Compression Alone

Zamboni et al.[61] compared compression alone with minimally invasive surgical hemodynamic correction of reflux (CHIVA) in addition to compression (Table 30). This was a randomized nonblinded trial that screened 80 patients and included 24 patients (with 24 ulcers) in the compression group and 21 patients (with 23 ulcers) in the surgical group. This study excluded patients if they were over the age of 80, were taking intravenous antibiotics, were nonambulatory, or had diabetes mellitus, a history of deep vein thrombosis, congenital angiodysplasia, or ankle brachial index less than 0.9. The study performed venous duplex ultrasound on all patients and excluded those with deep venous obstruction. The median ulcer size was similar in both groups (11 cm^2 (range, 3 to 12 cm^2) in the compression group vs. 10 cm^2 (range, 2.6 to 11.8 cm^2) in the surgical group). The study excluded patients with ulcers less than 2 or greater than 12 cm^2. This study did not report on age, gender, duration of ulcer, smoking status, or other co-morbidity. Clinical management varied across groups. Although all patients received 20 to 30 mm Hg compression dressings, some patients received additional foam or antibiotic dressings at the discretion of the treating physician. The principle of the surgical approach was to use intra-operative venous duplex ultrasound to identify and ligate (under local anesthesia) the insufficient saphenous tributaries that drain into the perforator veins. The mean followup was 3 years. The ulcer-healing rate was 96 percent in the compression group versus 100 percent in the surgical group ($P>0.05$).

Table 30. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing CHIVA with compression therapy alone

Author, Year Study Design	Group 1	Group 2	Compression Used	Followup Time	Ulcer Healing in Group 1, N / N (%)	Ulcer Healing in Group 2, N / N (%)	Relative Risk, Risk Difference
Zamboni, 2003[61] RCT	Compression + foam dressing	CHIVA	20-30 mmHg elastic stocking	36 months	23 / 24 patients (96%)	23 / 23 patients (100%); *P*>0.05	RR, 0.96 (0.88 to 1.04) RD, -4% (-12% to 4%)

CHIVA = Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting; CI = 95% confidence interval; mmHg = millimeters of mercury; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

Subfascial Endoscopic Perforator Surgery and Superficial Vein Surgery Plus Compression Versus Compression

Two studies included patients undergoing SEPS (Table 31).[64, 65] Both studies were prospective RCTs.[64, 65] The followup duration in these two studies was 24 weeks and 36 months. We did not perform a meta-analysis because of the differences between the two studies in their design, length of followup, and comparisons reported. One study used four layers of compression,[64] and the other used two layers of compression.[65] One study[64] reported results per patient while the other[65] reported results per limb.

One RCT screened 121 patients with chronic venous leg ulcers.[64] The study excluded patients without superficial venous reflux or patients with diabetes mellitus, rheumatoid arthritis, vasculitis, arterial insufficiency (ankle brachial index less than 0.8), skin cancer, or trauma, and patients who were not appropriate for surgery. The study randomized 76 patients; 39 received four-layer compression and 37 patients received surgery in addition to compression. The mean duration of ulcer was similar in both groups (6 months). The median ulcer size was also similar in the groups: 10 cm^2 in the compression group and 11 cm^2 in the surgical group. All patients underwent venous duplex ultrasound, and all included patients had superficial venous reflux. In addition, several patients had concomitant deep venous or perforator reflux. The study tailored the surgical procedure to the underlying venous pathology (24 patients had long saphenous vein ligation and stripping, 13 had sequential avulsion, four had short saphenous vein ligation, and 24 had perforator surgery SEPS or ligation). The ulcer-healing rate at 26 weeks was 64 percent in the compression group compared with 68 percent in the surgical group (P=0.75).

Another RCT included 200 chronic venous leg ulcers in 170 patients in 12 centers in the Netherlands.[65] Exclusion criteria included: ankle brachial index less than 0.8, partial or complete occlusion of a deep vein, prior SEPS procedure, and immobility. The randomization process allocated 97 ulcers to surgery in addition to two-layer compression, and 103 ulcers to two-layer compression alone. Patients had similar baseline characteristics except for diabetes mellitus, which was more prevalent in the compression group. All patients underwent venous duplex ultrasound, which helped determine the surgical procedure type: 40 patients had SEPS only (29 of them had prior superficial vein surgery), and 51 patients (59 percent) had SEPS and concomitant superficial vein surgery (ligation of long and/or short saphenous veins and stripping). The study lost four patients to followup (three in the surgical group prior to the procedure). Three patients did not undergo surgery after randomization (one due to a deep vein thrombosis, one due to a myocardial infarction, and one due to unrelated pathology). The ulcer-healing rate was 83 percent in the surgical group compared with 73 percent in the compression group (P=0.24). However, in a post hoc subgroup analysis, patients with a medial ulcer or ulcer greater than 2.5 cm^2 had a greater proportion of healed ulcers with surgery than with compression therapy alone (P=0.04 for medial ulcer, P=0.01 for larger ulcers).

Table 31. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing SEPS with compression systems alone

Author, Year Study Design	Group 1	Group 2	Compression Used	Followup Time	Ulcer Healing in Group 1, N / N (%)	Ulcer Healing in Group 2, N / N (%)	Relative Risk, Risk Difference
Guest, 2003[64] RCT	Compression alone	SEPS + compression	4-layer	26 weeks	25 / 39 patients (64%)	25 / 37 patients (68%); *P*=0.75	RR, 0.95 (CI, 0.69 to 1.31) RD, -3% (CI, -25% to 18%)
Van Gent, 2006[65] RCT	Compression alone	SEPS + compression	2-layer	36 months	74 / 102 limbs (73%)	78 / 94 limbs (83%); *P*=0.24	RR or RD not calculable*

CI = 95% confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SEPS = subfascial endoscopic perforator surgery

*Unable to calculate RR or RD because of lack of independency giving that some patients had two limbs included

Sclerotherapy of Saphenous and Perforator Veins Plus Compression Versus Compression

Three studies compared sclerotherapy with compression in patients with chronic venous leg ulcers (Table 32).[58, 63, 66] These three studies were too different to be combined in a meta-analysis.

One was a prospective RCT that took place in a nurse-led clinic.[58] The trial included 315 new patients and 11 followup patients. Inclusion criteria included patients with chronic venous leg ulcers with documented superficial venous incompetence without total deep vein incompetence on venous duplex. The study excluded patients with an ankle brachial index less than 0.8, poorly controlled diabetes mellitus, rheumatoid arthritis, malignancy, immobility, deep vein thrombosis, pulmonary embolism, or an inability to provide informed consent. The study randomized 40 patients. Twenty-two patients were in the four-layer compression group, and 18 patients were in the four-layer compression in addition to foam sclerotherapy group. Four patients withdrew and two patients in the sclerotherapy group did not meet inclusion criteria after randomization. One unrelated death occurred in the compression group (the study did not report the cause).The sclerotherapy was limited to the greater saphenous vein and its tributaries and did not address incompetent perforators. The followup at 24 weeks showed the healing rate of venous ulcers to be 85 percent in the compression group compared with 92 percent in the sclerotherapy group (P=0.72).

The second study compared sclerotherapy of saphenous and perforator veins with compression alone.[63] The study measured ankle brachial index and performed venous ultrasound. Investigators excluded patients with an ankle brachial index less than 0.8. Thirty-seven patients were in the compression group and received compression at 20 to 30 mm Hg. Thirty-three patients were in the sclerotherapy group and received treatment to the saphenous vein as well as perforator veins if needed. The study did not describe how they allocated patients to the treatment groups or if randomization occurred. At 21 weeks of followup, the ulcer-healing rate was 62 percent in the compression group and 85 percent in the sclerotherapy group (P=0.06).

The third study, a retrospective study, compared sclerotherapy of the saphenous and perforator veins with compression alone.[66] The study included patients from dermatology and vascular clinics. Forty-six patients received compression alone and 72 received sclerotherapy. All patients in both groups had ulcers that healed. The study lost one patient in the sclerotherapy group to followup.

Table 32. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing sclerotherapy with compression systems alone

Author, Year Study Design	Group 1	Group 2	Compression Used	Followup Time	Ulcer Healing in Group 1, N / N (%)	Ulcer Healing in Group 2, N / N (%)	Relative Risk, Risk Difference
O'Hare, 2010[58] RCT	Compression	Sclerotherapy - saphenous vein	Multilayer	24 weeks	17 / 20 (85%)	12 / 13 (92%); *P*=0.72	RR, 0.92 (CI, 0.72 to 1.17) RD, -7% (CI, -29% to 14%)
Rojas, 2009[63] Unclear	Compression	Sclerotherapy - saphenous vein + perforator	Multilayer + Unna boot, 20-30 mmHg	21 weeks	23 / 37 (62%)	28 / 33 (85%); *P*=0.06	RR, 0.73 (CI, 0.55 to 0.98) RD, -23% (CI, -43% to -3%)
Galimberti, 1988[66] Retrospective cohort	Compression	Sclerotherapy- saphenous vein + perforator	Class 3, 40-50 mm Hg	40 months	46 / 46 (100%)	72 / 72(100%)	RR, 1 RD, 0

CI = confidence interval; mmHg = millimeters of mercury; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

Other Surgical Interventions Plus Compression Versus Compression

We did not find any data comparing RFA, EVLT, or deep venous surgery with compression therapy in terms of the healing of chronic venous leg ulcers.

Time to Complete Ulcer Healing

Minimally Invasive Ligation of Insufficient Saphenous Vein Tributaries Plus Compression Versus Compression Alone

In addition to reporting on ulcer healing rates as indicated above, Zamboni et al. reported a median time to ulcer healing of 31 days (range, 17 to 53 days) in the CHIVA group versus 63 days (range, 21 to 180 days) in the compression group.[61]

Subfascial Endoscopic Perforator Surgery and Superficial Vein Surgery Plus Compression Versus Compression

In addition to reporting on ulcer-healing rates as indicated above, Guest et al.[64] reported no statistically significant difference between the time-to-healing in the two treatment groups (P=0.41). The median time-to-healing was 83 days for surgery versus 98 days for compression. Even after adjusting for ulcer size and duration and prior history of deep vein thrombosis, the treatment groups did not differ in time-to-healing (adjusted hazard ratio [HR], 0.79, 95% CI, 0.45 to 1.39).

In addition to reporting on ulcer healing rates as indicated above, van Gent et al.[65] reported a mean time to complete ulcer healing of 4.2 months for the surgical patients versus 5.7 months for the patients treated with compression. The median time was 11 and 15 months, respectively. This difference was not statistically significant.

Sclerotherapy of Saphenous and Perforator Veins Plus Compression Versus Compression

In addition to reporting on ulcer healing rates as indicated above, Rojas et al.[63] reported a median of 8 weeks to complete wound healing in the surgical group compared with 20 weeks among patients in the control group.

In the Galimberti et al.[66] study mentioned above, the time-to-healing for the compression-only group was a mean of 20 weeks, and for the sclerotherapy group a mean of 23 weeks.

Other Surgical Interventions Plus Compression Versus Compression

We did not find any data comparing RFA, EVLT, or deep venous surgery with compression therapy in terms of the time-to-healing.

Ulcer Recurrence

Superficial Vein Surgery Plus Compression Versus Compression

The ESCHAR study mentioned above also evaluated ulcer recurrence in short-term[59] and long-term followup (Table 33).[60] As above, the study randomized 500 patients with either recently healed ulcers or chronic ulcers (average ulcer duration, 5 months; range, 3 to 11 months). For patients with healed ulcers at recruitment (73 in compression group, 86 in surgical

group), or patients who healed their ulcers during the followup period (185 in compression group, 156 in surgical group), the recurrence rate varied base on the level of concomitant deep venous reflux involvement. For isolated superficial reflux, the 4-year recurrence rate was 51 percent in the compression group versus 27 percent in the surgical group (P<0.01). For patients with superficial and segmental deep venous reflux, the 3-year recurrence rate was 52 percent in the compression group versus 24 percent in the surgical group (P=0.04). For patients with superficial and total deep venous reflux, the 3-year recurrence rate was 46 percent in the compression group versus 32 percent in the surgical group (P=0.33). The proportion of ulcer-free time at 3-year followup was greater in the surgical group compared with the compression group (78 vs. 71 percent, P=0.007).

As mentioned in the previous section on wound healing, a prospective nonrandomized cohort study included 131 patients receiving superficial vein surgery and 105 patients receiving compression alone.[62] In the surgical group, 23 patients had recently healed ulcers and 25 patients healed their ulcer while waiting for surgery. The recurrence rate at 3-year followup was better in the surgical group (26 percent) than in the compression group (44 percent; P=0.03). This was also seen at 1- and 2-year followup (14 vs. 28 percent, and 20 vs. 30 percent, respectively).

These two studies were too different to be combined in a meta-analysis.

Table 33. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing superficial vein surgery with compression treatment alone

Author, Year Study Design	Followup Time	Ulcer Healing Compression Group, N / N (%)	Ulcer Healing Surgical Group, N / N (%)	Ulcer Recurrence in Compression Group (%)	Ulcer Recurrence in Surgical Group (%)
Gohel, 2007[59] RCT	48 months	165 / 185 patients (89%)	145 / 156 patients (93%); P =0.74	56%	31%; P< 0.01
Barwell, 2004[60] RCT	12 weeks	141 / 185 patients (76%)	128 / 156 patients (82%); P =0.85	28%	12%; P=0.85
Barwell, 2000[62] RCT	36 months	74% of limbs	72% of limbs; P =0.67	44%	26%; P=0.03

RCT = randomized controlled trial

Minimally Invasive Ligation of Insufficient Saphenous Vein Tributaries Plus Compression Versus Compression Alone

As reported above, one RCT[61] compared compression alone with minimally invasive surgical hemodynamic correction of reflux (CHIVA) in addition to compression (Table 34). The recurrence rate at 3 years was 38 percent in the compression group compared with 9 percent in the surgical group (P<0.05).

Table 34. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing vein CHIVA with compression systems alone

Author, Year Study Design	Followup Time	Ulcer Healing Compression Group, N / N (%)	Ulcer Healing Surgical Group, N / N (%)	Ulcer Recurrence in Compression Group (%)	Ulcer Recurrence in Surgical Group (%)
Zamboni, 2003[61] RCT	36 months	23 / 24 patients (96%)	23 / 23 patients (100%); *P*<0.02	38%	9%; *P*<0.05

CHIVA = Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting; RCT = randomized controlled trial

Subfascial Endoscopic Perforator Surgery and Superficial Vein Surgery Plus Compression Versus Compression

In the previously mentioned trial comparing SEPS with compression, the main study outcome was ulcer-free time during followup (Table 35).[65] The mean followup time was 29 months in the surgical group and 26 months in the compression group. During this period, the percent of ulcer-free time was 72 percent in the surgical group compared with 53 percent in the compression group (*P*=0.11). Subgroup analysis showed a significant difference in ulcer-free time for patients with a medial ulcer (78 percent) versus a lateral ulcer (43 percent; *P*=0.02), first time ulcer (62 percent) versus recurrent ulcer (33 percent; *P*=0.02), and ulcers less than 4 months old (85 percent) versus ulcers more than 4 months old (39 percent; $P < 0.001$).

As shown in Table 35, the recurrence rate was similar in both groups. However, patients with first-time ulcers had a lower recurrence rate than recurrent ulcers (13 vs. 29 percent; *P*=0.01) regardless of the treatment group.

Table 35. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing SEPS with compression systems alone

Author, Year Study Design	Followup Time	Ulcer Healing Compression Group, N / N (%)	Ulcer Healing Surgical Group, N / N (%)	Ulcer Recurrence in Compression Group (%)	Ulcer Recurrence in Surgical Group (%)
Van Gent, 2006[65] RCT	36 months	74 / 102 limbs (73%)	78 / 94 limbs (83%); *P*=0.24	22%	23%; *P*>0.05

RCT = randomized controlled trial

Sclerotherapy Plus Compression Versus Compression

One of the studies that evaluated this comparison reported on ulcer recurrence rates.[66] Ulcer recurrence only occurred in the compression-only group with 21 patients (29 percent) reporting an ulcer recurrence (Table 36).

Table 36. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing sclerotherapy with compression systems alone

Author, Year Study Design	Followup Time	Ulcer Healing Compression Group, N / N (%)	Ulcer Healing Surgical Group, N / N (%)	Ulcer Recurrence in Compression, N / N Group (%)	Ulcer Recurrence in Surgical Group, N / N (%)
Galimberti, 1988[66]	40 months	72 / 72 (100)	46 / 46 (100)	21 / 72 (29)	0 / 46 (0); *P*<0.05

Other Surgical Interventions Versus Compression

We could not find any data comparing RFA, EVLT, or deep venous surgery with compression therapy in terms of ulcer recurrence.

Quality of Life

Only two studies reported health-related QOL.[61, 64] Zamboni et al.[61] evaluated general health-related QOL using the Short Form-36 questionnaire with eight domains. They reported that patients who had surgery did better than patients who received compression alone ($P<0.05$). Guest et al.[64] used the ulcer-specific Charing Cross Venous Ulcer Questionnaire, which showed no significant difference between the two groups at followup. However, this study also used the Short Form-36 and found that surgical patients scored better at followup in the domains of physical functioning and general health. The compression group patients scored better at followup in the domains of bodily pain and emotional role. We need to consider these results in the context of the nonblinded design, small sample size, and other bias issues that we previously mentioned.

Mortality

None of the eight studies on KQ 3a reported any deaths related to the surgical procedure or compression therapy. During intermediate and long-term followup, several studies reported a few unrelated deaths with no difference between the treatment groups (Table 37).

Table 37. Summary of mortality rates among patients with chronic venous leg ulcers comparing surgical interventions with compression systems alone

Author, Year	Intervention, Group 1	Intervention, Group 2	Compression Used	Followup Time	Mortality Group 1, N / N (%)	Mortality Group 2, N / N (%)
Gohel, 2007[59] RCT	Compression alone	Superficial vein surgery plus compression	Multilayer	3 years	49 / 258 (19)	39 / 242 (16); *P*=0.25
Barwell, 2003[60] RCT	Compression alone	Superficial vein surgery plus compression	Multilayer	12 months	26 / 258 (10)	19 / 242 (8)
Barwell, 2000[62] Prospective cohort	Compression alone	Superficial vein surgery plus compression	4-layer	24 weeks	0*	0*
Guest, 2003[64] RCT	Compression alone	SEPS + compression	4-layer	26 weeks	0 / 39 (0)	0 / 37 (0)
van Gent, 2006[65] RCT	Compression alone	SEPS + compression	2-layer	36 months	8 / 102 legs†	17 / 94 legs†
O'Hare, 2010[58] RCT	Compression	Sclerotherapy - saphenous vein	Multilayer	24 weeks	1 / 21 (5)	0 / 13 (0)

CHIVA = Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting; RCT = randomized controlled trial; SEPS = subfascial endoscopic perforator surgery

* Sixty-one patients died during the 4-year followup, but the authors did not report in which treatment arm these deaths occurred. The authors reported no postoperative deaths. The authors did not report the number of patients randomized to each treatment group.

† A total of 23 patients died during followup. Eight patients with a leg randomized to receive compression therapy and 17 patients with a leg randomized to receive surgery died. Two patients had one leg randomized to each treatment.

Pain, Functional Status, and Quality of the Wound Bed

We did not include any studies comparing surgical techniques with compression therapy that reported on pain, functional status, or quality of the wound bed.

Adverse Events

The authors reported very few adverse events, those reported were mostly minor wound complications. In the studies that reported on adverse events, the number of adverse events did not differ much between the treatment groups.

Study Quality

Overall, the quality of the studies was fair (Appendix D, Table 5). Five of the eight studies were RCTs,[58-61, 64, 65] but only one had adequate allocation concealment.[58] None of the studies were blinded. Generally, the studies recruited intervention groups from the same population and time, and adequately reported demographic and baseline characteristics. Most studies did not report a statistical power calculation.

Strength of Evidence

The strength of evidence is moderate that adding superficial vein surgery to compression therapy does not improve healing of chronic venous leg ulcers (Table 38). This is based on one RCT (with two publications) and one prospective cohort study. The body of evidence has a medium risk of bias. The data is direct, consistent, and precise.

The strength of evidence is low that adding minimally invasive surgical hemodynamic correction of reflux (CHIVA) to compression therapy does not significantly affect the proportion of ulcers healed. This is based on one RCT with a small number of patients. Although this study had a low risk of bias, no other RCT exists that confirms the findings. The use of multiple interventions in the patients may also bias the results.

The strength of evidence was high that adding SEPS with superficial vein surgery to compression alone does not improve the healing rate of venous ulcers. This evidence came from two RCTs[64, 65] with low risk of bias. The evidence is consistent between the two studies and is direct and precise.

The strength of evidence is insufficient that sclerotherapy is beneficial when added to compression therapy in healing chronic venous ulcers. This is based primarily on one RCT[58] that failed to enroll enough patients to detect a statistically significant difference between the two groups. Power calculation called for 170 patients, but the study randomized only 40 patients. A second study was a prospective nonrandomized cohort that showed better healing rate in the sclerotherapy group compared with compression alone. The data from that study were inconsistent with the RCT and had a high risk of bias. There was one additional retrospective study that showed similar healing of venous ulcer when comparing sclerotherapy with compression.[66]

All of the above results are also subject to publication bias and selective outcome reporting.

The evidence is insufficient to determine the benefit of adding RFA, EVLT, or deep venous surgery to compression therapy to improve the healing rate of chronic venous leg ulcers.

Table 38. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence among studies comparing surgical interventions with compression systems alone in terms of wound healing or wound recurrence

Comparison / Outcome*	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence				Strength of Evidence†
		Risk of Bias	Consistency	Directness	Precision	
Superficial vein surgery vs. compression alone / wound healing	1 RCT (500); 1 cohort (669)	Medium	Consistent	Direct	Precise	No effect Moderate SOE
CHIVA vs. compression alone / wound healing	1 RCT (47)	Low	NA	Direct	Imprecise	No effect Low SOE
SEPS vs. compression alone / wound healing	2 RCTs (246)	Low	Consistent	Direct	Precise	No effect High SOE
Sclerotherapy vs. compression alone / wound healing	1 RCT (40) 2 cohorts (188)	High	Inconsistent	Direct	Imprecise	Unclear effect Insufficient SOE
Superficial vein surgery vs. compression alone / wound recurrence	1 RCT (500); 1 cohort (669)	Medium	Consistent	Direct	Precise	Small effect Moderate SOE
CHIVA vs. compression alone / wound recurrence	1 RCT (47)	Low	NA	Direct	Imprecise	Small effect Low SOE
SEPS vs. compression alone / wound recurrence	1 RCT (170)	Low	NA	Direct	Precise	No effect High SOE
Sclerotherapy vs. compression alone / wound recurrence	1 cohort (118)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE

CHIVA = Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting; EVLT = endovenous laser therapy; NA = not applicable; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery; SOE = strength of evidence; vs. = versus

*The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them. † We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Key Question 3b. For patients with chronic venous leg ulcers, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

We divided the data for KQ 3b into two parts. Part 1 includes studies that compared two surgical interventions with each other, without a medical arm of compression treatment. Part 2 includes studies with no surgical or medical comparison at all. These were mostly case series. We included studies without a comparison group to address this question indirectly because we anticipated finding few, if any, comparative studies.

Key Points

- The evidence generally is insufficient to determine the comparative benefits and harms of different surgical procedures for chronic venous leg ulcers associated with a given type of venous reflux. None of the studies provided precise estimates. We graded the evidence as insufficient because of the limited number and small size of relevant studies, and their high risk of bias.
- We did not find any studies evaluating surgical procedures for chronic venous leg ulcers associated with deep venous occlusion. (Insufficient strength of evidence)

Study Design Characteristics

To address the comparative effectiveness and safety of surgical procedures for chronic venous leg ulcers associated with a given type of venous reflux or obstruction, we included studies that compared two surgical treatments with each other as well as studies (usually case series) with neither a surgical nor a medical comparison group. We included only those studies that had patients with documented chronic venous leg ulcers, as we described in the Methods section.

We found three studies that compared two surgical techniques (Appendix D, Table 1).[67-69] Two studies were cohort studies.[68, 69] The first[68] took place in Egypt and Saudi Arabia, enrolled 36 patients, and followed them for 1 year. This cohort study compared isolated sapheno-femoral junction ligation with vein stripping. The second cohort study[69] took place in Slovakia and followed patients for 5 years. It evaluated the open ligation of incompetent perforator veins (Linton procedure) with or without stripping compared with sclerotherapy or with an anti-reflux valvular procedure on the deep veins among 793 patients. The last study[67] took place in the United States, had an unclear study design, and enrolled 46 patients with 76 treated limbs. This study compared four surgical procedures: perforator ligation plus saphenous vein stripping (PLSVS), PLSVS plus valvuloplasty, PLSVS plus vein transposition, and PLSVS plus valve transplantation.

We also found 11 studies that evaluated a surgical procedure for patients with chronic venous leg ulcers without a concurrent comparison group.[14, 70-79]

Five of these studies were case series.[14, 70, 74-76] Five were cohort studies,[71, 72, 77-79] and one had an unclear study design.[73]

Three of these studies took place in the United States,[14, 72, 74] two took place in the United Kingdom,[70, 71] two took place in Germany,[78, 79] two in Australia,[73, 77] one in Poland,[75] and one in the Slovak Republic.[76] The years of enrollment ranged from 1968 to 2010. The length of followup ranged from 1 to nearly 12 years. The median number of patients enrolled was 72 (range, 41 to 305).

Three studies evaluated venous valve surgery (Appendix D, Table 2),[72, 73, 76] two evaluated RFA,[14, 74] two evaluated SEPS,[78, 79] two evaluated saphenous vein stripping and/or ligation,[71, 75] one evaluated sclerotherapy,[70] and one evaluated angioplasty/stenting.[77]

Study Population Characteristics

None of the three studies with a comparison group[67-69] reported baseline and demographic characteristics by study group (Appendix D, Table 3). The mean age of the patients, in the two studies that reported age, was 42 years[68] and 59 years.[69] Seventy-eight percent of the participants were women. Two studies[68, 69] reported on the mean duration of ulcers at baseline, which ranged from 5 to 11 months. None of the studies reported smoking status, the percent of patients having diabetes mellitus or other systemic disease, or the percent of patients taking immunosuppressive medications.

Of the 11 studies without a comparison group, eight[14, 71, 74-79] reported the average age of the subjects, which ranged from 54 to 74 years. Most of the participants in these studies were women, ranging from 42 to 78 percent in the nine studies reporting on patient sex.[14, 70, 71, 74-79]

All 11 studies reported the average duration of the ulcer at baseline. Three studies[70, 71, 76] reported a median duration of 5 to 8 months (range, 3 to 420 months), while eight studies[14, 72-75, 77-79] reported a mean duration of 8 to 100 months (range, 2 to 432 months). One study[73] simply noted very long periods of conservative ulcer management, with 51 of 90 enrolled subjects reported as having more than 5 years of ulcer duration at baseline.

One study reported that 23 percent of the patients were smokers.[75] In three studies, the percent of patients with diabetes ranged from 18 to 21 percent.[14, 74, 79] In one study, two percent of the patients were taking immunosuppressives. None of the studies reported on the use of corticosteroids.[14]

Part 1: Evidence From Studies That Compared Two Surgical Interventions

Wound Healing, Including Time to Wound Healing and Wound Recurrence

Perforator Ligation and Saphenous Vein Stripping Versus Perforator Ligation and Saphenous Vein Stripping Plus Valvular Surgery

One nonrandomized cohort study with 46 patients with recurrent chronic venous leg ulcers evaluated four groups: PLSVS, PLSVS plus valvuloplasty, PLSVS plus vein transposition, and PLSVS plus valve transplantation.[67] The study reported wound-healing rates at 44 percent for PLSVS alone and 80 percent for PLSVS plus valvuloplasty, vein transposition, or valve transplantation (Appendix D, Table 4). In patients with incompetent deep venous valves and perforators, the disassociation of the superficial from the deep venous system (stripping) plus correction of the deep venous valvular incompetence (valvuloplasty, transposition, and valve transplant) produced superior rates of healing of chronic venous leg ulcers when compared with perforator ligation and saphenous vein stripping alone ($P<0.005$). The study did not report the time to complete wound healing. It followed patients for a mean of 37 months (range, 10 to 73 months). Wound recurrence was 56 percent for PLSVS, 20 percent for PLSVS plus

valvuloplasty, 21 percent for PLSVS plus vein transposition, and 25 percent for PLSVS plus valve transplantation. The difference was not statistically significant between the four groups.

Isolated Sapheno-Femoral Junction Ligation Versus Vein Stripping

We found one cohort study that included 36 patients with chronic venous leg ulcers divided into two groups.[68] Group I (10 patients) underwent isolated sapheno-femoral junction ligation, and group II (26 patients) underwent vein stripping. The baseline ulcer size and duration were similar in both groups. At 12-month followup, the wound healing rate was higher for group I (85 percent) than for group II (70 percent; $P<0.05$).

Sclerotherapy Versus Valvular Surgery

We included one nonrandomized retrospective cohort study that enrolled subjects from a single author's clinical experience (Table 39).[69] The study evaluated four groups. Group I received a classical Linton procedure, vein stripping, and varicose vein extirpation. Group II received Linton SPS (small incision using a hook instrument), stripping, and varicose vein extirpation. Group III received compression sclerotherapy (Sigg's and Fegan's techniques). Group IV received an antireflux operation on the deep venous system including valvuloplasty and valve interposition. Since the Linton procedure is no longer used, we will only report on Groups III and IV. Group III (sclerotherapy) had the shortest time-to-healing with 95% of venous ulcers healed. The time-to-healing was significantly longer when clinicians documented femoral and popliteal vein insufficiency. In the group of patients with the shortest time-to-heal (up to 8 weeks), clinicians documented popliteal vein involvement in 55 percent of patients. However, the group that required more than 12 weeks to heal had 94 percent popliteal vein involvement.

Table 39. Summary of the time-to-heal and recurrence rates among patients with chronic venous leg ulcers reported in one cohort study

Group	Number of Patients	LOS (Days)	Time to Heal (Days)	Ulcer Recurrence	P
III – Compression sclerotherapy	698	0	39±12	18%	NS
IV – Anti-reflux operation on deep venous system	32	7	12-120	Not reported	

LOS = hospital length of stay; NS = not significant

Mortality

None of the above three trials included under this section reported mortality rates.

Adverse Events

Isolated Sapheno-Femoral Junction Ligation Versus Vein Stripping

Patients who received isolated saphenofemoral ligation had less postoperative severe pain, hematoma, infection, and delayed wound healing, but had more limb swelling in comparison with saphenous vein stripping (Table 40).[68]

Table 40. Summary of the complication rates in patients with chronic venous leg ulcers treated with isolated sapheno-femoral junction ligation or vein stripping reported in one cohort study

Complications	Sapheno-Femoral Junction Ligation	Vein Stripping	P-Value
Severe pain	42%	70%	<0.05
Hematoma	23%	80%	<0.05
Limb swelling	77%	40%	<0.05
Wound infection	15%	30%	<0.05
Delay wound healing	19%	40%	<0.05

Sclerotherapy Versus Valvular Surgery

One cohort study reported similar complication rates (not further specified) among patients who received compression sclerotherapy compared with those who received an anti-reflux operation (Table 41).[69]

Table 41. Summary of the complication rate in patients with chronic venous leg ulcers treated with sclerotherapy or valvular surgery reported in one cohort study

Group	Number of Patients	Complication Rate	P-Value
III – Compression sclerotherapy	698	7%	NS
IV – Anti-reflux operation on deep venous system	32	6%	

Quality of Life, Pain, and Functional Status

None of the studies we reviewed reported QOL outcomes, pain measures, or functional status measures.

Intermediate Outcomes

We did not find any data on intermediate outcomes in these studies.

Part 2: Evidence From Studies Without a Comparison Group

Part 2 includes 11 studies without a surgical or medical comparison group, most of which were case series.[14, 70-79]

Wound Healing, Including Time to Wound Healing and Wound Recurrence

Valvuloplasty, Valve Transposition, Valve Transplantation

Masuda et al. evaluated the long-term results of venous valve reconstruction.[72] Forty-nine patients with chronic venous leg ulcers underwent direct femoral vein valve repair, transposition, or transplantation. Many patients had superficial and/or perforator venous insufficiency and received perforator ligation and/or saphenous vein stripping/ligation before, during, or after the primary procedure. The mean followup was 10.6 years. The 10-year cumulative clinical success rate, defined as mild or no symptoms with or without elastic compression, was 60 percent (by life-table analysis). Primary valvular insufficiency treated with valvuloplasty had far more superior clinical success than post-thrombotic valvular insufficiency treated with valve transplant or transposition (73 vs. 43 percent at 10 years, P=0.03). Significant postoperative complications included bleeding among 15 percent of patients. The recurrence rate was up to 39 percent during the followup period. Only one patient had deep vein occlusion after valve surgery at 16 years of followup.

Nash et al. reported on a retrospective analysis of 90 patients with chronic venous ulcers treated between 1979 and 1986.[73] Investigators chose surgical procedures based on underlying venous pathology. Patients with valvular incompetence confined to perforating and superficial veins (N=42) had a 100 percent healing rate of their venous leg ulcers with one recurrence. Patients with additional but limited incompetence of deep veins (N=19) also achieved 100 percent ulcer healing, but three patients developed recurrent ulcers. Patients with extensive deep vein valvular incompetence, including popliteal valve incompetence (N=29), had the lowest healing and highest recurrence rates with 12 patients either failing to heal their ulcer or having a recurrence within 18 months.

Labas el al. reported on 56 patients with a mean age of 54 years (range, 24 to 84 years).[76] Seventy-eight percent of the patients were women. These patients had venous ulceration that failed superficial vein surgery and compression therapy. Patients were treated with Fegan's technique, which consists of compression sclerotherapy combined with an anti-reflux operation (valve interposition and valvuloplasty). The healing rate was 95 percent (53 of 56 ulcers). The average time-to-healing was 39 days. The recurrence rate within 5 years was 18 percent.

Radiofrequency Ablation of Long Saphenous, Short Saphenous, and Perforator Veins

Harlander-Locke el al. evaluated the impact of radiofrequency endovenous ablation of incompetent superficial veins (long saphenous vein, small saphenous vein, posterior tibial perforator vein) on the healing rates of venous leg ulcers in patients that failed conventional compression therapy.[74] The study performed 140 consecutive endovenous ablation procedures (74 on superficial veins and 66 on perforator veins) on 110 venous ulcers in 88 limbs. The mean ulcer duration prior to ablation was 71 months. After at least 6 months following ablation, 76 of 110 ulcers (76 percent) had healed. The mean time-to-healing was 142 days (SE, 14 days). Ulcers did not completely heal in 12 patients (26 ulcers): two patients died, six patients were still actively healing, and the study lost four patients to followup. The healing rate for all healed ulcers improved from 1.0 cm^2/month (SE, 0.1 cm^2/month) prior to ablation to -4.4 cm^2/month (SE, 0.1 cm^2/month; $P<0.05$) after ablation. Six of the healed ulcers (7.1 percent) recurred within 1 year.

Lawrence el al. evaluated patients who had chronic venous leg ulcers for longer than 3 months despite compression treatment.[14] All patients underwent venous duplex ultrasound to assess incompetence of superficial, perforating, and deep veins. Patients with demonstrated perforator incompetence (greater than 3 mm) received vein ablation. All of these patients either had functional saphenous veins or had received saphenous vein ablation. The investigators first treated the perforator vein adjacent to the ulcer, and then treated additional incompetent veins if the ulcer didn't heal. They treated 45 patients with 75 ulcers and 86 associated incompetent perforating veins. The success rate was 58 percent for initial perforator vein ablation, and 90 percent for repeat ablation, for an overall success rate of 71 percent. No complications (skin necrosis, infection, or nerve injury) occurred. When perforator closure was successful, 90 percent of ulcers healed. The mean time-to-healing was 138 days (range, 60 to 365 days). On average, investigators ablated 1.5 incompetent perforator veins for ulcer healing.

Subcutaneous Paratibial Fasciotomy and SEPS

Sigala et al. described a single center study of paratibial fasciotomy and dissection of the posterior perforator veins (Hach procedure) for the treatment of patients with chronic venous leg

ulcers.[78] The study included 62 patients (65 percent women), with active venous ulcers. The center performed 67 subcutaneous paratibial fasciotomy procedures with saphenofemoral junction ligation and stripping in 43 limbs. The center used vacuum-assisted therapy in 28 ulcers for a median time of 8 days. The center performed autologous skin grafting in 22 patients with ulcers larger than 9 cm^2. The cumulative ulcer-healing rate after fasciotomy was 97 percent in 1 year. Healing time was significantly related to ulcer size ($P<0.001$).

Wolters et al. reported a prospective observational study that evaluated endoscopic subfascial dissection of perforating veins in 74 patients with a followup of 21 months. The healing rate was 77 percent at 12 and 21 months.[79]

Sclerotherapy

Pang et al. evaluated ultrasound-guided foam sclerotherapy of superficial venous reflux in 130 consecutive patients (132 limbs) with healed and open chronic venous ulcers in terms of healing and recurrence rates.[70] Eighty three of the patients had active ulcers. The study followed patients for a median of 16 months. At 1 month after the first treatment, 67 of 82 patients (82 percent) with active ulcers had healed. Among the 49 limbs with originally healed ulcers and 67 limbs that healed during the study period, five ulcers (5 percent) recurred after 2 years. This study reported a similar proportion of ulcers healed and recurrence rate as the studies that compared sclerotherapy with compression.

Superficial Vein Surgery

Bello et al. was a prospective study that examined how well superficial venous surgery heals venous leg ulcers.[71] The study offered patients with isolated superficial venous incompetence saphenofemoral and/or saphenopopliteal surgery. None of the patients underwent perforator surgery or skin grafting. The study did not use postoperative compression hosiery or bandaging. The investigators performed superficial venous surgery on 122 legs with normal deep veins. Cumulative healing rates at 6, 12, and 18 months were 57, 74, and 82 percent, respectively. The ulcers healed in a median time of 18 weeks.

Taradaj et al. selected a group of patients that opted for surgery and another group that opted out of surgery. The study then randomly assigned these groups to one of five treatment groups: high-voltage stimulation, ultrasound, low-level laser therapy, compression stockings, and drug therapy. This study does not directly address our KQs, but it included a study arm that was treated with surgery and compression therapy. The healing rate at 7 weeks in the surgery and compression group was 53 percent, and was significantly higher than the healing rates in all of the other groups (range of healing rates in other groups, 11.4 to 37.3 percent). Ulcer recurrence rates at 2 years were lower in continued compression plus surgical treatment (18.7 percent) compared with other groups (range 25.9 to 37.5 percent).

These studies reported similar proportions of ulcers healed as the studies that compared superficial vein surgery with compression.

External Valvular Stenting

Lane et al. was a prospective nonrandomized study that included 41 patients with chronic venous leg ulcers that failed 6 months of medical management.[77] To be included in this study, a patient had to have deep venous insufficiency involving the femoral and/or popliteal vein documented on venous duplex ultrasound and venography. The surgeons repaired 125 valves with external stenting in 42 limbs (2.98 valves per limb). The mean followup time was 7.9 years

(range, 5.4 to 11.9 years). At 86 months of followup, 80 percent of ulcers healed. The ulcer areas decreased from a mean preoperative area of 12.9 cm^2 to 1.2 cm^2 at the same followup period. The number of stents related to an increased number of ulcers healed.

Mortality, Quality of Life, Functional Status, Pain, Quality of the Wound Bed, and Adverse Events

The studies included in this section did not report on these measures.

Study Quality

Overall, the quality of the studies addressing KQ 3b was limited (Appendix D, Table 5). None of the studies were RCTs, and only three had a comparison group.[67-69] Among the three studies with a comparison group, it was often difficult to determine the comparability of the different intervention groups because the studies often did not report baseline and demographic characteristics separately by group. Studies did not describe adjusting for confounding. One study recruited patients from different time periods.[69] Most studies did not adequately account for loss to followup.

Strength of Evidence

Our review of the surgical treatment of chronic venous leg ulcers did not find any RCTs that assessed the comparative benefits and harms of different surgical procedures for chronic venous leg ulcers associated with a given type of venous reflux, and did not find any studies that assessed surgical procedures for chronic venous leg ulcers associated with deep venous occlusion. The only studies we found were case series, retrospective cohort studies, and non-RCTs, often from a single institution. The populations were diverse and the studies did not describe them completely. Surgical interventions in some of the studies were patient-specific, which minimized generalizability. None of these studies included a nonsurgical comparison group, which severely limited our assessment of comparative effectiveness. We also found that the studies had a high risk of selection and publication bias, did not account for confounding or interaction effects, and were inconsistent. Due to the these limitations, we concluded that the strength of evidence generally was insufficient to estimate the comparative effectiveness of the different types of surgical interventions that could be performed for patients with chronic venous leg ulcers associated with any given type of venous reflux (see Table 42).

Table 42. Numbers of studies and subjects, strength of evidence domains, and strength of evidence among studies comparing surgical interventions for chronic venous leg ulcers, in terms of wound healing

Comparison	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence				Strength of Evidence*
		Risk of Bias	Consistency	Directness	Precision	
PLSVS vs. PLSVS + valvuloplasty vs. PLSVS + vein transposition vs. PLSVS + valve transplantation	1 (46)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Isolated sapheno-femoral junction ligation vs. vein stripping	1 (36)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Sclerotherapy vs. valvular surgery	1 (826)	High	NA	Direct	Imprecise	Unclear effect Insufficient SOE
Valvuloplasty, valve transposition, valve transplantation	3 (195)	High	Consistent	Indirect	Imprecise	Unclear effect Insufficient SOE
RFA	2 (unable to determine)	High	Consistent	Indirect	Imprecise	Unclear effect Insufficient SOE
Subcutaneous paratibial fasciotomy and SEPS	2 (136)	High	Consistent	Indirect	Imprecise	Unclear effect Insufficient SOE
Sclerotherapy	1 (82)	High	NA	Indirect	Imprecise	Unclear effect Insufficient SOE
Superficial vein surgery	2 (153)	High	Unable to determine	Indirect	Imprecise	Unclear effect Insufficient SOE
External valvular stenting	1 (41)	High	NA	Indirect	Imprecise	Unclear effect Insufficient SOE

NA = not applicable; PLSVS = perforator ligation and saphenous vein stripping; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery; vs. = versus

* We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Discussion

Key Findings and Strength of Evidence

Overall, the study team was struck by the paucity of evidence to guide decisions related to all of the Key Questions. For Each KQ, the available evidence was compromised by study designs that were often underpowered, and by a lack of standardized definitions or protocols for the wound interventions. The studies also lacked evidence on pain and quality of life assessments.

In terms of balancing benefit and harms, for KQ1, the major issue is whether the intervention results in benefit, as the dressings have minimal systemic or local toxicity (minimal harm). The lack of known benefit for many of these dressings is complicated by the wide price range of these interventions, which impacts both patients and payors. For KQ2, there are harms for both patient and society from antibiotic overuse, with few data to guide providers. For the surgical options explored in KQ3, there are both potential benefits and substantial harms related to the risk of surgery. Understanding the efficacy of surgical approaches is complicated by the lack of prospective clinical trial designs, and continued technical innovation. Technical innovation has led to less invasive and endovascular techniques.

Besides the efficacy questions, our review could not answer many of the practical aspects of caring for wounds, including the rapidity in return to function and the impact on family members, and aspects related to the delivery of care. For example, the impact of specific interventions may be altered if the care is delivered by a multidisciplinary wound clinic or a primary practice office. The studies did not compare the venues for delivery of care, yet this could be a major confounder.

Key Question 1. Benefits and Harms of Advanced Wound Dressings

Minimal data existed to suggest that hydrocolloid dressings had no advantage over compression alone in the healing rates and ultimate wound healing of chronic venous leg ulcers (low strength of evidence). Many studies had nonsignificant results. Collagen dressings may improve the proportion of ulcers healed compared with compression alone (low strength of evidence). Antimicrobial dressings, such as those that contained cadexomer iodine, provided advantage in improved healing (moderate strength of evidence), but silver-based dressings had no advantage over nonsilver dressings (moderate strength of evidence).

For acellular skin equivalents, the strength of evidence was insufficient to support the use of freeze-dried intestinal pig mucosa. Allogenic bilayered human skin equivalents may promote more rapid healing, particularly among patients with long-standing ulcers (moderate strength of evidence). However, there was no effect on post-treatment recurrence, indicating the importance of treating the underlying disease and the necessity of continuing post-treatment compression. Table 43 summarizes our conclusions on the comparative benefits of advanced wound dressings in terms of wound healing.

There were minimal data on harms and quality of life measures and therefore we could not make any conclusions.

Table 43. Summary of the comparative benefits of advanced wound dressings in terms of wound healing

Comparison (Number of Included Studies)*	Strength of Evidence†	Conclusions
Hydrocolloids vs. compression (3)	Low	Hydrocolloid dressings were not more effective than compression therapy alone in terms of the proportion of chronic venous ulcers healed. The results from the three studies addressing this comparison were imprecise and subject to some bias.
Hydrocolloids vs. other dressings (4)	Insufficient	We were unable to draw a conclusion.
Transparent films vs. compression (1)	Insufficient	We were unable to draw a conclusion.
Transparent films vs. other dressings (1)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. compression (1)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. alginate dressings (2)	Insufficient	We were unable to draw a conclusion.
Alginate dressings vs. other dressings (1)	Insufficient	We were unable to draw a conclusion.
Foam dressings vs. foam dressings (3)	Insufficient	We were unable to draw a conclusion.
Collagen dressings vs. compression (1)	Low	Collagen dressings healed a greater proportion of ulcers than compression alone.
Acellular human skin equivalent dressings vs. compression (3)	Insufficient	We were unable to draw a conclusion.
Cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression (2)	Insufficient	We are unable to draw a conclusion.
Cellular human skin equivalents (allogenic bilayered cultured HSE) vs. compression (1)	Moderate	Studies of cellular human skin equivalent dressings in patients with chronic venous ulcers showed a higher proportion of ulcers healed and more rapid healing, especially those that had failed previous therapy and were present for over 1 year.
Cellular (autologous keratinocytes in a fibrin sealant) vs compressions (1)	Low	Autologous keratinocytes in fibrin sealant healed a greater proportion of ulcers and achieved a shorter median time to complete wound closure versus compression.
Cellular human skin equivalent dressings vs. other dressings (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial dressings vs. compression (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial dressings vs. antimicrobial dressings (2)	Insufficient	We were unable to draw a conclusion.
Antimicrobial containing dressings vs. other types of dressings (4)	Moderate	Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with other nonantimicrobial dressings. However, silver dressings did not improve wound healing as compared with nonsilver dressings.

***** The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

† We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Key Question 2a. Benefits and Harms of Systemic Antibiotics Compared With Compression Systems

We found only one study that addressed this question, and it provided insufficient evidence to determine the benefits of systemic antibiotics compared with compression. There was no assessment of potential harms of this intervention in promoting the development of antimicrobial resistant organisms.

Key Question 2b. Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

We did not find any studies that addressed this question.

Key Question 3a. Benefits and Harms of Surgical Interventions Compared With Compression

We found low strength of evidence that minimally invasive surgical hemodynamic correction of reflux may decrease the time-to-healing of chronic venous leg ulcers compared with compression therapy alone, but it does not increase the proportion of ulcers healed. For other surgical interventions for chronic venous leg ulcers, the strength of evidence was moderate to high that healing may not be improved, but there could be a lower risk of recurrence when compared with compression alone. We found insufficient evidence about the benefits and harms, or quality of life measures of vein stripping, radiofrequency ablation or endovenous laser therapy for superficial vein reflux, or surgery for deep vein disease in patients with chronic venous leg ulcers.

Table 44 summarizes our conclusions on the comparative benefits of surgical interventions compared with compression therapy in terms of wound healing.

Table 44. Summary of the comparative benefits of surgical interventions compared with compression in terms of wound healing

Comparison (Number of Included Studies)*	Strength of Evidence†	Conclusions
Superficial vein surgery vs. compression alone (1 RCT, 1 cohort)	Moderate	Adding superficial vein surgery to compression therapy does not improve healing of chronic venous leg ulcers,but there may be a lower risk of recurrence.
CHIVA vs. compression alone (1 RCT)	Low	Adding minimally invasive surgical hemodynamic correction of reflux to compression therapy does not significantly affect the proportion of ulcers healed, but it may lower the risk of recurrence.
SEPS vs. compression alone (2 RCTs)	High	SEPS with superficial vein surgery does not improve the rate of healing or the risk of recurrence of chronic venous leg ulcers in comparison with compression alone.
Sclerotherapy vs. compression alone (1 RCT, 2 cohorts)	Insufficient	We were unable to draw a conclusion.
RFA vs. compression alone (0) EVLT vs. compression alone (0) Deep venous surgery vs. compression alone (0)	Insufficient	We were unable to draw a conclusion.

CHIVA = conservative hemodynamic treatment of insufficiency of the venous system in an ambulatory setting; EVLT = endovenous laser therapy; RCT = randomized controlled trial; RFA = radiofrequency ablation; SEPS = subfascial endoscopic perforator surgery

*The strength of evidence for all comparisons not listed here were graded as inconsistent because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

†We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Key Question 3b. Benefits and Harms of Surgical Interventions Compared With Other Surgical Interventions

The evidence was insufficient to determine the comparative benefits and harms, or impact on quality of life of different surgical procedures for chronic venous leg ulcers associated with a given type of venous reflux, due to the small number, small size, and poor quality of studies.

Table 45 summarizes our conclusions regarding the comparative benefits of surgical interventions in terms of wound healing.

Table 45. Summary of the comparative benefits of surgical interventions compared with other surgical interventions in terms of wound healing

Comparison (Number of Included Studies)*	Strength of Evidence†	Conclusions
PLSVS vs. PLSVS + valvuloplasty vs. PLSVS + vein transposition vs. PLSVS + valve transplantation (1)	Insufficient	We are unable to draw a conclusion.
Isolated sapheno-femoral junction ligation vs. vein stripping (1)	Insufficient	We are unable to draw a conclusion.
Sclerotherapy vs. valvular surgery (1)	Insufficient	We are unable to draw a conclusion.

PLSVS = perforator ligation and saphenous vein stripping;

*The strength of evidence for all comparisons not listed here were graded as inconsistent because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

†We defined the strength of evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

Findings in Relationship to What is Already Known

Our findings are in concert with previous published large reviews and evidence-based practice guidelines. Previous reviews, albeit not as comprehensive as the one performed here, found a paucity of randomized or controlled clinical trials to support the use of any of the interventions described.

Key Question 1. Benefits and Harms of Advanced Wound Dressings

Cochrane collaboration reviews[16] have addressed the use of wound dressings and have found no data to support superiority of specific dressings. Our review of cadexomer iodine-containing dressings is consistent with that described in the Cochrane review, which indicated modest improvements in wound healing. The data on cellular equivalents are from recent well controlled clinical trials.

Key Questions 2a and 2b. Benefits and Harms of Systemic Antibiotics Compared With Compression Systems, and Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

There have been no previous comparative effectiveness reviews of the impact of systemic antibiotics on chronic venous ulcers. However, the limited findings of our review are in concert with the Infectious Diseases Society of America's policy statements on wound care.

Key Questions 3a and 3b. Benefits and Harms of Surgical Interventions Compared With Compression, and Benefits and Harms of Surgical Interventions Compared With Other Surgical Interventions

There have been no evidence-based reviews of studies with control groups to evaluate surgical outcomes in patients with chronic venous ulcers.

However, our review identified critical research needs which are in concert with a 2011 evaluation from the Center for Medical Technology Policy, which concluded that there was a paucity of evidence in wound care.[6] Their major recommendations included developing an evidence base using multicenter randomized clinical trials (RCTs), blinding patient-reported outcomes to intervention, developing a consistent standard of care arm, standardizing protocols and protocol adherence, and standardizing outcome measures.

Applicability

Studies generally did not report on the representativeness of their study populations. In most cases, we could not determine if the care received by study patients was similar to that received by other patients. The RCTs tended to include elderly patients similar in age to the population of patients with chronic venous leg ulcers, and most studies included at least a substantial minority of men. When studies reported the baseline mean duration of chronic venous ulcers, it was typically more than 12 months, and thus study results are more applicable to ulcers that are

recalcitrant to prior treatment. Studies of advanced wound dressings were of short duration (4 months or less) and thus, the long-term effects are unclear.

Limitations

Limitations of the Review Process

Our review was comprehensive in scope, including studies in any language evaluating wound dressings, antibiotics, and surgical interventions. Although we designed our search to be as comprehensive as possible, it is plausible that we missed key studies. For articles that were not published in English, we tried to find suitable reviewers who were able to read the language. However, we were unable to find a reviewer for one article.

We excluded studies that were not peer-reviewed and could have potentially missed information that was published only in abstract form. Our results could be subjected to publication bias and selective outcome reporting.

In our review, we included studies only if the participants used at least a moderate level of compression (e.g., at least 20 mm Hg of pressure), excluding studies that either did not report the level of compression used or did not use an adequate level of compression. Although some experts recommend a higher pressure for compression therapy (at least 40 mm Hg), we did not want to exclude too many studies and therefore used 20 mm Hg as the minimum pressure based on the results of a previous systematic review conducted by the Cochrane Collaboration.[3] However, we may have biased our results in favor of the advanced wound dressings and surgical procedures by including studies that allowed a lower level of compression therapy (i.e., between 20 and 40 mm Hg).

Limitations of the Evidence Base

We reviewed the titles and abstracts of more than 10,000 published articles, but found few well-designed RCTs that addressed the comparative effectiveness of treatments for chronic venous leg ulcers. The RCTs generally did not report on allocation concealment, and did not mask patients or outcome assessors to treatment assignment. We expanded our review to include observational studies, but these studies were largely limited to convenience populations, which, by definition, carry with them a substantial risk of bias. Overall, the studies that addressed the topic were very heterogeneous and had major problems that limited our ability to make firm conclusions about the effectiveness and safety of treatments for chronic venous leg ulcers. Major limitations of the published data threatened both internal and external validity. These limitations included the lack of standard definitions of chronic venous leg ulcers, inconsistent outcome measures, suboptimal comparison groups, and inconsistent duration of interventions. Studies often had large losses to followup or did not report on this. Many of the studies also did not report statistical analyses beyond simple healing rates, stratification or adjustment to account for potential confounding variables, or sample size calculations. Most studies were very small and therefore had limited statistical power. Most of the studies evaluating wound dressings received industry support, which is associated with more favorable outcomes.

Implications for Clinical Practice and Policy

Our findings have substantial implications for clinical practice and policies related to the care of chronic venous leg ulcers. With the exception of a few surgical interventions and the use of human skin equivalents under defined conditions, most interventions used in the management of chronic venous leg ulcers lack supporting evidence that they add any benefits to compression therapy alone. This negative finding does not necessarily mean that the interventions are ineffective, but rather that we need better studies to demonstrate their clinical impact.

These findings therefore have impact on policy, especially for agencies and payers in providing reimbursement and identifying critical research needs. Since the prevalence of chronic venous stasis disease is increasing,[80] and will likely continue to increase for the foreseeable future, health care payers, regulatory agencies, and other policymakers will require strong evidence on outcomes that can better guide the treatment of patients with chronic venous leg ulcers. We need high quality data on the comparative effectiveness of the treatment options to develop efficient algorithms for guiding therapy, and to better understand which therapeutic interventions have value to ensure appropriate reimbursement in an increasingly constrained health care environment.

Research Gaps

Our research identified several areas to consider for future research. We were unable to make strong conclusions regarding the efficacy of most interventions because of a lack of high quality RCTs. Promising areas to consider for future research include cellular human skin equivalents, collagen dressings, dressings that enhance debridement, antibiotic treatments, and surgical techniques. The results from a recent phase 2 RCT are promising and warrant future research on the effects of a spray cell therapy containing growth arrested allogeneic neonatal keratinocytes and fibroblasts plus a foam dressing.[81]

Few studies addressed quality of life measures, and no studies assessed quality of life using standard or validated scales. Since chronic wounds have substantial impact on the patient and his/her family, quality of life measures are critical in evaluating overall wound treatment efficacy. Studies also did not adequately address or describe potential harms in interventions. This substantially differs from the studies of regulated pharmaceuticals, which carefully record adverse events.

Need for Harmonization

Our review demonstrated that studies of interventions for chronic venous leg ulcers take place in many different practice and cultural settings involving a variety of disciplines, including nursing, dermatology, vascular surgery, and internal medicine. This heterogeneity was associated with the excessive variety of methods we saw in these studies.

To adequately address this problem, clinical researchers, government regulators, payers, and other stakeholders from academic and clinical communities and industry should establish a consensus regarding how to harmonize studies in this area. The objective would be to develop better standards for disease definition, interventions, comparison groups, and outcome measures, including intermediate outcomes, pain, and quality of life. These experts could help to develop templates for study designs that better demonstrate efficacy. Similar recommendations were made in a report published by the Center for Medical Technology and Policy, “Methodological

Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds."[6]

One of the major issues we need to address is the limitation in study design. The nature of the interventions, and the difficulty in many cases of developing placebo or sham conditions, makes implementing traditional double-blinded, or even single-blinded randomized trials difficult, if not impossible. We believe that implementation of appropriate, well-designed clinical trials will require substantial clinical patient management and recruitment resources. Furthermore, the trials must be large enough to have sufficient statistical power for determining the comparative effectiveness and safety of the therapeutic options. Since future research is likely to depend on funding from a number of different sources, including manufacturers of products and devices, investigators will need to develop appropriate policies for managing potential conflict-of-interest issues. We suggest that a long-term solution to this would be the development and implementation of a clinical trials network that would have a broad recruiting base, specialized centers that adhere to case definitions, and a commitment to long-term followup.

Conclusions

Chronic wounds due to venous hypertension are emerging as a major clinical care and public health challenge, with rapidly increasing costs and morbidity. Following an iterative process, and consulting with AHRQ and stakeholders, we developed three Key Questions to help guide our review of the effectiveness of treatment options for chronic venous leg ulcers. We performed an extensive review of the literature, and graded the evidence, which included review by content experts. We found a paucity of well-designed well-controlled studies, as well as a lack of a standard case definitions, or approaches to managing confounders and interactions. Most studies were not blinded, and the results are therefore subject to reporting and ascertainment bias. We found that advanced wound dressings had no impact on wound healing when compared with compression therapy alone, with the exception of cellular skin equivalents. We found no evidence to support antimicrobial therapy for chronic venous leg ulcers, in the absence of symptoms or signs of infection, due to a general lack of data. Although a substantial literature exists on venous surgical approaches, the vast majority of these were uncontrolled case series or studies that did not measure ulcer outcomes. We found minimal, if any, benefit for surgical interventions in managing this disease. However, more recent data suggest that surgical interventions may impact recurrence rates, and therefore there is a need to validate these findings.

Future research should focus on developing a strong evidence base to evaluate the efficacy and effectiveness of current and newly developed products and interventions. These include standardizing case definition, clarifying the study outcomes to be used in clinical trials, and developing a network of centers that have the capacity to implement clinical effectiveness research for this condition.

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Abbreviations

ABI	ankle brachial index
AHRQ	Agency for Healthcare Research and Quality
CHIVA	Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting
CVU	chronic venous ulcers
DVT	deep vein thrombosis
ECM	extracellular matrix
EPC	Evidence-based Practice Center
ESCHAR	Effect of Surgery and Compression on Healing and Recurrence
EVLT	endovenous laser therapy
HCPS	Healthcare Common Procedure Coding System
HR	hazard ratio
HSE	human skin equivalent
KQ	Key Question
Mm	millimeters
mm Hg	millimeters of mercury
MTC-2g	Mimosa tenuiflora
NOSF	nano-oligosaccharide factor lipido-colloid
PLSVS	perforator ligation plus saphenous vein stripping
QOL	quality of life
RCT	randomized controlled trial
RFA	radiofrequency ablation
SD	standard deviation
SEPS	subfascial endoscopic perforator surgery

Appendix A. Detailed Electronic Database Search Strategies

Advanced Wound Dressings PubMed Strategy

Search	String	# Hits
#1	“Leg ulcer”[mh]	15937
#2	“Varicose ulcer”[mh]	3520
#3	“chronic leg”[tiab]	738
#4	“chronic venous”[tiab]	3133
#5	“lower extremity”[tiab] OR “lower extremeties”[tiab] OR “lower limb”[tiab] OR “lower limbs”[tiab]	45746
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	110973
#7	(#3 OR #4 OR #5) AND #6	3415
#8	“leg ulcer”[tiab] OR “leg ulcers”[tiab] OR “leg ulceration”[tiab]	4576
#9	“venous ulcer”[tiab] OR “venous ulcers”[tiab] OR “venous ulceration”[tiab]	1576
#10	“venous stasis ulcer”[tiab] OR “venous stasis ulcers”[tiab] OR “venous stasis ulceration”[tiab]	181
#11	“chronic wound”[tiab] OR “chronic wounds”[tiab]	2416
#12	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11	19852
#13	Bandages[mh]	17853
#14	“Bandages, hydrocolloid”[mh]	546
#15	“Iodine compounds”[mh]	14763
#16	“Iodine/therapeutic use”[mh]	3596
#17	Iodophors[mh]	2401
#18	Collagen[mh]	90149
#19	“Skin, artificial”[mh]	1628
#20	Dressing*[tiab] or bandag*[tiab]	16767
#21	Hydrocolloid*[tiab]	1178
#22	Film*[tiab]	94974
#23	Alginate*[tiab]	8261
#24	Foam*[tiab]	15060
#25	Composite*[tiab]	69266
#26	Absorb*[tiab] OR absorpt*[tiab]	260534
#27	Gauze*[tiab]	2741
#28	Antibacterial*[tiab]	37842
#29	iodine*[tiab]	33619
#30	“silver”[tiab]	37082
#31	"polyhexamethylene biguanide"[tiab]	189
#32	"bismuth"[tiab]	5315
#33	honey[tiab]	4835
#34	collagen*[tiab]	144270
#35	oasis*[tiab]	1738

#36	"extracellular matrix"[tiab]	55940
#37	Iodosorb[tiab]	18
#38	Polyurethanes[mh]	6685
#39	Allograft*[tiab]	47819
#40	Bilayer*[tiab] OR bi-layer*[tiab]	31836
#41	Bioengineer*[tiab] OR bio-engineer*[tiab]	3100
#42	Biological*[tiab]	440724
#43	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	1266975
#44	(animal[mh] NOT human [mh])	3686454
#45	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Case Reports"[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	2699284
#46	(#12 AND #43) NOT #44 NOT #45 AND PUBLICATION DATE LIMIT OF 1980/01/01	3138

Advanced Wound Dressings EMBASE Strategy

Search	**String**	**# Hits**
#1	'Leg ulcer'/exp	12005
#2	"chronic leg":ti,ab	942
#3	"chronic venous":ti,ab	4676
#4	"lower extremity":ti,ab OR "lower extremities":ti,ab OR "lower limb":ti,ab OR "lower limbs":ti,ab	79717
#5	Ulcer:ti,ab OR ulcers:ti,ab OR ulceration:ti,ab	140840
#6	(#2 OR #3 OR #4) AND #5	5457
#7	"leg ulcer":ti,ab OR "leg ulcers":ti,ab OR "leg ulceration":ti,ab	6143
#8	"venous ulcer":ti,ab OR "venous ulcers":ti,ab OR "venous ulceration":ti,ab	2187
#9	"venous stasis ulcer":ti,ab OR "venous stasis ulcers":ti,ab OR "venous stasis ulceration":ti,ab	236
#10	"chronic wound":ti,ab OR "chronic wounds":ti,ab	3509
#11	#1 OR #6 OR #7 OR #8 OR #9 OR #10	19217
#12	'wound dressing'/exp	8225
#13	'foam dressing'/exp	205
#14	'hydrocolloid dressing'/exp	542
#15	'polyethylene derivative'/exp	3752
#16	'Polyurethane'/exp	9419

#17	'silver derivative'/exp	1870
#18	Dressing*:ti,ab or bandag*:ti,ab	21839
#19	Hydrocolloid*:ti,ab	1456
#20	Film*:ti,ab	98285
#21	Alginate*:ti,ab	11321
#22	Foam*:ti,ab	20001
#23	Composite*:ti,ab	84026
#24	Absorb*:ti,ab OR absorpt*:ti,ab	300653
#25	Gauze*:ti,ab	3594
#26	Antibacterial*:ti,ab	52023
#27	iodine*:ti,ab	41353
#28	“silver”:ti,ab	41454
#29	"polyhexamethylene biguanide":ti,ab	224
#30	"bismuth":ti,ab	6004
#31	honey:ti,ab	6301
#32	collagen*:ti,ab	178128
#33	oasis*:ti,ab	2210
#34	"extracellular matrix":ti,ab	67720
#35	Iodosorb:ti,ab	25
#36	Allograft*:ti,ab	62289
#37	Bilayer*:ti,ab OR bi-layer:ti,ab OR bi-layered:ti,ab OR bi-layers:ti,ab	34372
#38	Bioengineer*:ti,ab OR bio-engineer:ti,ab OR bio-engineered:ti,ab OR bio-engineering:ti,ab	4835
#39	Biological*:ti,ab	564888
#40	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	1504879
#41	#11 AND #40	3917
#42	([animals]/lim NOT [humans]/lim)	4592309
#43	'conference abstracts':it OR 'conference paper':it OR 'conference reviews':it OR editorial:it OR erratum:it OR letter:it OR note:it	2567814
#44	#41 NOT #42 NOT #43	3484

Advanced Wound Dressings Cochrane Strategy

Search	**String**	**# Hits**
#1	“chronic leg”:ti,ab,kw	125
#2	“chronic venous”:ti,ab,kw	491
#3	“lower extremity”:ti,ab,kw OR “lower extremities”:ti,ab,kw OR “lower limb”:ti,ab,kw OR “lower limbs”:ti,ab,kw	3950
#4	Ulcer:ti,ab,kw OR ulcers:ti,ab,kw OR ulceration:ti,ab,kw	12129
#5	(#1 OR #2 OR #3) AND #4	495
#6	“leg ulcer”:ti,ab,kw OR “leg ulcers”:ti,ab,kw OR “leg ulceration”:ti,ab,kw	1004

#7	“venous ulcer”:ti,ab,kw OR “venous ulcers”:ti,ab,kw OR “venous ulceration”:ti,ab,kw	374
#8	“venous stasis ulcer”:ti,ab,kw OR “venous stasis ulcers”:ti,ab,kw OR “venous stasis ulceration”:ti,ab,kw	26
#9	“chronic wound”:ti,ab,kw OR “chronic wounds”:ti,ab,kw	188
#10	#5 OR #6 OR #7 OR #8 OR #9	1520
#11	Dressing*:ti,ab,kw or bandag*:ti,ab,kw	3561
#12	Hydrocolloid*:ti,ab,kw	333
#13	Film*:ti,ab,kw	1937
#14	Alginate*:ti,ab,kw	356
#15	Foam*:ti,ab,kw	888
#16	Composite*:ti,ab,kw	5323
#17	Absorb*:ti,ab,kw OR absorpt*:ti,ab,kw	14289
#18	Gauze*:ti,ab,kw	445
#19	Antibacterial*:ti,ab,kw	1374
#20	iodine*:ti,ab,kw	2246
#21	“silver”:ti,ab,kw	862
#22	"polyhexamethylene biguanide":ti,ab,kw	27
#23	"bismuth":ti,ab,kw	916
#24	honey:ti,ab,kw	169
#25	collagen*:ti,ab,kw	3365
#26	oasis*:ti,ab,kw	82
#27	"extracellular matrix":ti,ab,kw	229
#28	Iodosorb:ti,ab,kw	11
#29	Allograft*:ti,ab,kw	1767
#30	Bilayer*:ti,ab,kw OR bi-layer:ti,ab,kw OR bi-layered:ti,ab,kw OR bi-layers:ti,ab,kw	73
#31	Bioengineer*:ti,ab,kw OR bio-engineer:ti,ab,kw OR bio-engineered:ti,ab,kw OR bio-engineering:ti,ab,kw	78
#32	Biological*:ti,ab,kw	17855
#33	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	49768
#34	(#10 AND #33), from 1980 to 2011	602

Advanced Wound Dressings CINAHL Strategy

Search	String	# Hits
S1	(MH "Leg Ulcer+")	7248
S2	TX “chronic leg”	462
S3	TX “chronic venous”	558
S4	TX “lower extremity” OR TX “lower extremities” OR TX “lower limb” OR TX “lower limbs”	11938
S5	TX Ulcer OR TX ulcers OR TX ulceration	18750
S6	(S2 OR S3 OR S4) AND S5	1369
S7	TX “leg ulcer” OR TX “leg ulcers” OR TX “leg ulceration”	2795
S8	TX “venous ulcer” OR TX “venous ulcers” OR TX “venous ulceration”	1845
S9	TX “venous stasis ulcer” OR TX “venous stasis ulcers” OR TX “venous stasis ulceration”	98
S10	TX “chronic wound” OR TX “chronic wounds”	2652
S11	S1 OR S6 OR S7 OR S8 OR S9 OR S10	9620
S12	(MH "Bandages and dressings+")	7737
S13	TX Dressing* OR TX bandag*	10651
S14	TX Hydrocolloid*	565
S15	TX Film*	3747
S16	TX Alginate*	597
S17	TX Foam*	1686
S18	TX Composite*	6400
S19	TX Absorb* OR TX absorpt*	9217
S20	TX Gauze*	669
S21	TX Antibacterial*	1448
S22	TX iodine*	2082
S23	TX “silver”	4274
S24	TX "polyhexamethylene biguanide"	25
S25	TX "bismuth"	139
S26	TX honey	852
S27	TX collagen*	5402
S28	TX oasis*	607
S29	TX "extracellular matrix"	1239
S30	TX Iodosorb	8
S31	TX Allograft*	3253
S32	TX Bilayer* OR TX bi-layer OR TX bi-layered OR TX bi-layers	135
S33	TX Bioengineer* OR TX bio-engineer OR TX bio-engineered OR TX bio-engineering	947
S34	TX Biological*	53531
S35	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34	97168
S36	S11 AND S35	2976
S37	Limiters - Publication Type: Abstract, Accreditation, Algorithm,	0

	Anecdote, Audiovisual, Bibliography, Biography, Book, Book Chapter, Book Review, Brief Item, Care Plan, Cartoon, Case Study, CEU, Clinical Innovations, Code of Ethics, Commentary, Computer Program, Consumer/Patient Teaching Materials, Corrected Article, Critical Path, Diagnostic Images, Directories, Doctoral Dissertation, Drugs, Editorial, Equations & Formulas, Exam Questions, Forms, Games, Glossary, Historical Material, Interview, Legal Cases, Letter, Listservs, Masters Thesis, Nurse Practice Acts, Nursing Diagnoses, Nursing Interventions, Obituary, Pamphlet, Pamphlet Chapter, Pictorial, Poetry, Practice Acts, Proceedings, Protocol, Questions and Answers, Response, Software, Standards, Statistics, Tables/Charts, Teaching Materials, Tracings, Website	
S38	S36 NOT S37	541

Antimicrobials PubMed Strategy

Search	String	# Hits
#1	“Leg ulcer”[mh: noexp]	7117
#2	“Varicose ulcer”[mh]	3580
#3	“chronic leg”[tiab]	739
#4	“chronic venous”[tiab]	3133
#5	“lower extremity”[tiab] OR “lower extremities”[tiab] OR “lower limb”[tiab] OR “lower limbs”[tiab]	59033
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	110990
#7	(#3 OR #4 OR #5) AND #6	3863
#8	“leg ulcer”[tiab] OR “leg ulcers”[tiab] OR “leg ulceration”[tiab]	4577
#9	“venous ulcer”[tiab] OR “venous ulcers”[tiab] OR “venous ulceration”[tiab]	1577
#10	“venous stasis ulcer”[tiab] OR “venous stasis ulcers”[tiab] OR “venous stasis ulceration”[tiab]	181
#11	“chronic wound”[tiab] OR “chronic wounds”[tiab]	2416
#12	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11	14928
#13	“Anti-infective agents”[mh]	455226
#14	“beta-Lactams”[mh]	102689
#15	Clindamycin[mh]	4618
#16	“Trimethoprim-Sulfamethoxazole Combination”[mh]	5341
#17	Oxazolidinones[mh]	5645
#18	Quinolones[mh]	32034
#19	Lactams[mh]	10814
#20	Vancomycin[mh]	9108
#21	Daptomycin[mh]	977
#22	Gentamicins[mh]	16315
#23	Tobramycin[mh]	3543
#24	Tetracyclines[mh]	38254
#25	Metronidazole[mh]	10154
#26	Antibiotic*[tiab] OR anti-biotic*[tiab] OR antimicrobial*[tiab] OR anti-microbial*[tiab] OR antibacterial*[tiab] OR anti-bacterial*[tiab]	291474
#27	Cephalosporin*[tiab]	16075
#28	Cephalexin*[tiab] OR Cefalexin*[tiab]	2304
#29	Amoxicillin*[tiab] OR Clavulanate*[tiab]	10002
#30	Linezolid*[tiab]	2718
#31	Dicloxacillin*[tiab]	590
#32	Clindamycin*[tiab]	7305
#33	Trimethoprim*[tiab] OR sulfamethoxazole*[tiab]	12639
#34	Quinolone*[tiab]	9509
#35	Levofloxacin*[tiab]	4079
#36	Moxifloxacin*[tiab]	2393
#37	“Beta lactam”[tiab] OR “beta lactam”[tiab] OR beta-lactam*[tiab]	27026
#38	Augmentin*[tiab]	7922

#39	Cefixime*[tiab]	1116
#40	Cefpodoxime*[tiab]	617
#41	Cefazolin*[tiab]	3101
#42	Ceftriaxone*[tiab]	6475
#43	Vancomycin*[tiab] OR Daptomycin*[tiab]	16477
#44	Ertapenem*[tiab]	604
#45	Piperacillin*[tiab] OR tazobactam*[tiab] OR cefipime*[tiab]	4608
#46	Gentamicin*[tiab] OR tobramycin*[tiab] OR amikacin*[tiab]	25125
#47	aminoglycoside*[tiab]	13881
#48	Neomycin*[tiab]	8115
#49	Tetracycline*[tiab] OR doxycycline*[tiab] OR minocycline*[tiab]	35085
#50	Metronidazole*[tiab]	10967
#51	Cefuroxime*[tiab]	3317
#52	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	745663
#53	#12 AND #52	1231
#54	(animal[mh] NOT human [mh])	3687258
#55	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR “Case Reports”[pt] OR “Classical Article”[pt] OR “Clinical Conference”[pt] OR “Collected Works”[pt] OR Comment[pt] OR Congresses[pt] OR “Consensus Development Conference”[pt] OR “Consensus Development Conference, NIH”[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR “Legal Cases”[pt] OR Legislation[pt] OR News[pt] OR “Newspaper Article”[pt] OR Portraits[pt]	2699639
#56	#53 NOT #54 NOT #55	897
#57	#56 WITH PUBLICATION DATE LIMIT OF 1980	703

Antimicrobials EMBASE Strategy

Search	**String**	**# Hits**
#1	‘Leg ulcer’/exp	11779
#2	“chronic leg”:ti,ab	920
#3	“chronic venous”:ti,ab	4552
#4	“lower extremity”:ti,ab OR “lower extremities”:ti,ab OR “lower limb”:ti,ab OR “lower limbs”:ti,ab	76614
#5	Ulcer:ti,ab OR ulcers:ti,ab OR ulceration:ti,ab	137892
#6	(#2 OR #3 OR #4) AND #5	5245
#7	“leg ulcer”:ti,ab OR “leg ulcers”:ti,ab OR “leg ulceration”:ti,ab	6018
#8	“venous ulcer”:ti,ab OR “venous ulcers”:ti,ab OR “venous ulceration”:ti,ab	2121
#9	“venous stasis ulcer”:ti,ab OR “venous stasis ulcers”:ti,ab OR “venous stasis ulceration”:ti,ab	225

#10	“chronic wound”:ti,ab OR “chronic wounds”:ti,ab	3124
#11	#1 OR #6 OR #7 OR #8 OR #9 OR #10	18595
#12	‘antiinfective agent’/exp	1990306
#13	‘beta lactam’/exp	314212
#14	‘quinolone’/exp	98780
#15	Antibiotic*:ti,ab OR “anti-biotic”:ti,ab OR antimicrobial*:ti,ab OR “anti-microbial”:ti,ab OR antibacterial*:ti,ab OR “anti-bacterial”:ti,ab	368749
#16	Cephalosporin*:ti,ab	21317
#17	Cephalexin*:ti,ab OR Cefalexin*:ti,ab	2983
#18	Amoxicillin*:ti,ab OR Clavulanate*:ti,ab	13527
#19	Linezolid*:ti,ab	3658
#20	Dicloxacillin*:ti,ab	734
#21	Clindamycin*:ti,ab	9061
#22	Trimethoprim*:ti,ab OR sulfamethoxazole*:ti,ab	15465
#23	Quinolone*:ti,ab	12843
#24	Levofloxacin*:ti,ab	5714
#25	Moxifloxacin*:ti,ab	3167
#26	“Beta lactam”:ti,ab OR “beta lactams”:ti,ab OR “beta-lactam”:ti,ab OR “beta-lactams”:ti,ab	5338
#27	Augmentin*:ti,ab	9500
#28	Cefixime*:ti,ab	1670
#29	Cefpodoxime*:ti,ab	901
#30	Cefazolin*:ti,ab	3907
#31	Ceftriaxone*:ti,ab	8687
#32	Vancomycin*:ti,ab OR Daptomycin*:ti,ab	21081
#33	Ertapenem*:ti,ab	896
#34	Piperacillin*:ti,ab OR tazobactam*:ti,ab OR cefipime*:ti,ab	6499
#35	Gentamicin*:ti,ab OR tobramycin*:ti,ab OR amikacin*:ti,ab	32032
#36	aminoglycoside*:ti,ab	17357
#37	Neomycin*:ti,ab	8829
#38	Tetracycline*:ti,ab OR doxycycline*:ti,ab OR minocycline*:ti,ab	41515
#39	Metronidazole*:ti,ab	1400
#40	Cefuroxime*:ti,ab	4442
#41	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	2107091
#42	#11 AND #41	3130
#43	([animals]/lim NOT [humans]/lim)	4415955
#44	'conference abstracts':it OR 'conference paper':it OR 'conference reviews':it OR editorial:it OR erratum:it OR letter:it OR note:it	2506412
#45	#42 NOT #43 NOT #44	2806
#46	#45 WITH PUBLICATION DATE LIMIT OF 1980	2626

Antimicrobials Cochrane Strategy

Search	String	# Hits
#1	“chronic leg”:ti,ab,kw	125
#2	“chronic venous”:ti,ab,kw	491
#3	“lower extremity”:ti,ab,kw OR “lower extremities”:ti,ab,kw OR “lower limb”:ti,ab,kw OR “lower limbs”:ti,ab,kw	3950
#4	Ulcer:ti,ab,kw OR ulcers:ti,ab,kw OR ulceration:ti,ab,kw	12129
#5	(#1 OR #2 OR #3) AND #4	68
#6	“leg ulcer”:ti,ab,kw OR “leg ulcers”:ti,ab,kw OR “leg ulceration”:ti,ab,kw	1004
#7	“venous ulcer”:ti,ab,kw OR “venous ulcers”:ti,ab,kw OR “venous ulceration”:ti,ab,kw	374
#8	“venous stasis ulcer”:ti,ab,kw OR “venous stasis ulcers”:ti,ab,kw OR “venous stasis ulceration”:ti,ab,kw	26
#9	“chronic wound”:ti,ab,kw OR “chronic wounds”:ti,ab,kw	188
#10	#5 OR #6 OR #7 OR #8 OR #9	1437
#11	Antibiotic*:ti,ab,kw OR “anti-biotic”:ti,ab,kw OR antimicrobial*:ti,ab,kw OR “anti-microbial”:ti,ab,kw OR antibacterial*:ti,ab,kw OR “anti-bacterial”:ti,ab,kw	19305
#12	Cephalosporin*:ti,ab,kw	1930
#13	Cephalexin*:ti,ab,kw OR Cefalexin*:ti,ab,kw	417
#14	Amoxicillin*:ti,ab,kw OR Clavulanate*:ti,ab,kw	3113
#15	Linezolid*:ti,ab,kw	127
#16	Dicloxacillin*:ti,ab,kw	59
#17	Clindamycin*:ti,ab,kw	1030
#18	Trimethoprim*:ti,ab,kw OR sulfamethoxazole*:ti,ab,kw	1470
#19	Quinolone*:ti,ab,kw	891
#20	Levofloxacin*:ti,ab,kw	537
#21	Moxifloxacin*:ti,ab,kw	378
#22	“Beta lactam”:ti,ab,kw OR “beta lactams”:ti,ab,kw OR “beta-lactam”:ti,ab,kw OR “beta-lactams”:ti,ab,kw	421
#23	Augmentin*:ti,ab,kw	504
#24	Cefixime*:ti,ab,kw	247
#25	Cefpodoxime*:ti,ab,kw	122
#26	Cefazolin*:ti,ab,kw	569
#27	Ceftriaxone*:ti,ab,kw	934
#28	Vancomycin*:ti,ab,kw OR Daptomycin*:ti,ab,kw	723
#29	Ertapenem*:ti,ab,kw	53
#30	Piperacillin*:ti,ab,kw OR tazobactam*:ti,ab,kw OR cefipime*:ti,ab,kw	539
#31	Gentamicin*:ti,ab,kw OR tobramycin*:ti,ab,kw OR amikacin*:ti,ab,kw	2688
#32	aminoglycoside*:ti,ab,kw	632
#33	Neomycin*:ti,ab,kw	504

#34	Tetracycline*:ti,ab,kw OR doxycycline*:ti,ab,kw OR minocycline*:ti,ab,kw	2650
#35	Metronidazole*:ti,ab,kw	2570
#36	Cefuroxime*:ti,ab,kw	713
#37	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	28126
#38	(#10 AND #37) from 1980 to 2011	70

Antimicrobials CINAHL Strategy

Search	**String**	**# Hits**
S1	(MH "Leg Ulcer+")	7248
S2	TX “chronic leg”	462
S3	TX “chronic venous”	558
S4	TX “lower extremity” OR TX “lower extremities” OR TX “lower limb” OR TX “lower limbs”	11938
S5	TX Ulcer OR TX ulcers OR TX ulceration	18750
S6	(S2 OR S3 OR S4) AND S5	1369
S7	TX “leg ulcer” OR TX “leg ulcers” OR TX “leg ulceration”	2797
S8	TX “venous ulcer” OR TX “venous ulcers” OR TX “venous ulceration”	1845
S9	TX “venous stasis ulcer” OR TX “venous stasis ulcers” OR TX “venous stasis ulceration”	98
S10	TX “chronic wound” OR TX “chronic wounds”	2652
S11	S1 OR S6 OR S7 OR S8 OR S9 OR S10	9620
S12	(MH "Antiinfective agents+”)	29109
S13	TX Antibiotic* OR TX “Anti-biotic” OR TX antimicrobial* OR TX “anti-microbial” OR TX antibacterial* OR TX “anti-bacterial”	1119
S14	TX Cephalosporin*	99
S15	TX Cephalexin* OR TX Cefalexin*	1088
S16	TX Amoxicillin* OR TX Clavulanate*	306
S17	TX Linezolid*	10
S18	TX Dicloxacillin*	620
S19	TX Clindamycin*	889
S20	TX Trimethoprim* OR TX sulfamethoxazole*	792
S21	TX Quinolone*	348
S22	TX Levofloxacin*	254
S23	TX Moxifloxacin*	411
S24	TX “Beta lactam” OR TX “beta lactams” OR TX “beta-lactam” OR TX “beta-lactams”	537
S25	TX Augmentin*	47
S26	TX Cefixime*	40

S27	TX Cefpodoxime*	198
S28	TX Cefazolin*	574
S29	TX Ceftriaxone*	2440
S30	TX Vancomycin* OR Daptomycin*	61
S31	TX Ertapenem*	235
S32	TX Piperacillin* OR TX tazobactam* OR TX cefipime*	1280
S33	TX Gentamicin* OR TX tobramycin* OR TX amikacin*	1011
S34	TX aminoglycoside*	153
S35	TX Neomycin*	1677
S36	TX Tetracycline* OR TX doxycycline* OR TX minocycline*	996
S37	TX Metronidazole*	233
S38	TX Cefuroxime*	5512
S39	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	37572
S40	S11 AND S39	801
S41	Limiters - Publication Type: Abstract, Accreditation, Algorithm, Anecdote, Audiovisual, Bibliography, Biography, Book, Book Chapter, Book Review, Brief Item, Care Plan, Cartoon, Case Study, CEU, Clinical Innovations, Code of Ethics, Commentary, Computer Program, Consumer/Patient Teaching Materials, Corrected Article, Critical Path, Diagnostic Images, Directories, Doctoral Dissertation, Drugs, Editorial, Equations & Formulas, Exam Questions, Forms, Games, Glossary, Historical Material, Interview, Legal Cases, Letter, Listservs, Masters Thesis, Nurse Practice Acts, Nursing Diagnoses, Nursing Interventions, Obituary, Pamphlet, Pamphlet Chapter, Pictorial, Poetry, Practice Acts, Proceedings, Protocol, Questions and Answers, Response, Software, Standards, Statistics, Tables/Charts, Teaching Materials, Tracings, Website	1
S42	S40 NOT S41	801
S43	S40 NOT S41 publication date limited 1980 to 2012	814

Surgical PubMed Strategy

Search	String	# Hits
#1	“Leg ulcer”[mh: noexp]	7117
#2	“Varicose ulcer”[mh]	3520
#3	“chronic leg”[tiab]	739
#4	“chronic venous”[tiab]	3133
#5	“lower extremity”[tiab] OR “lower extremities”[tiab] OR “lower limb”[tiab] OR “lower limbs”[tiab]	59033
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	110990
#7	(#3 OR #4 OR #5) AND #6	3863
#8	“leg ulcer”[tiab] OR “leg ulcers”[tiab] OR “leg ulceration”[tiab]	4577
#9	“venous ulcer”[tiab] OR “venous ulcers”[tiab] OR “venous ulceration”[tiab]	1577
#10	“venous stasis ulcer”[tiab] OR “venous stasis ulcers”[tiab] OR “venous stasis ulceration”[tiab]	181
#11	“chronic wound”[tiab] OR “chronic wounds”[tiab]	1160
#12	“Venous Insufficiency/Surgery”[mh]	15788
#13	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	231557
#14	Endoscopy[mh]	17747
#15	“Catheter ablation”[mh]	45571
#16	“Laser therapy”[mh]	45571
#17	“Balloon dilation”[mh]	57915
#18	Ligation[mh]	16709
#19	Sclerotherapy[mh]	3985
#20	Thrombectomy[mh]	2663
#21	Angioplasty[mh]	50543
#22	Endoscop*[tiab]	124799
#23	Stripping[tiab]	7623
#24	Ablat*[tiab]	59141
#25	Ligat*[tiab]	66926
#26	Laser*[tiab]	164238
#27	Valvuloplast*[tiab]	3490
#28	Valve*[tiab]	91443
#29	Sclerotherap*[tiab]	5111
#30	Thrombolys*[tiab]	15531
#31	Thrombectom*[tiab]	3962
#32	Angioplast*[tiab]	34805
#33	Stent*[tiab]	551282
#34	(Vein[tiab] OR venous[tiab]) AND (surgery[tiab] OR surgeries[tiab])	28014
#35	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	792514
#36	#13 AND #35	2013
#37	(animal[mh] NOT human [mh])	3687258

#38	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	1148100
#39	#36 NOT #37 NOT #38	1914
#40	#39 WITH PUBLICATION DATE LIMIT OF 1980.	1848

Surgical EMBASE Strategy

Search	String	# of hits
#1	'Leg ulcer'/exp	12201
#2	"chronic leg":ti,ab	963
#3	"chronic venous":ti,ab	4764
#4	"lower extremity":ti,ab OR "lower extremities":ti,ab OR "lower limb":ti,ab OR "lower limbs":ti,ab	81416
#5	Ulcer:ti,ab OR ulcers:ti,ab OR ulceration:ti,ab	143251
#6	(#2 OR #3 OR #4) AND #5	5569
#7	"leg ulcer":ti,ab OR "leg ulcers":ti,ab OR "leg ulceration":ti,ab	6253
#8	"venous ulcer":ti,ab OR "venous ulcers":ti,ab OR "venous ulceration":ti,ab	2220
#9	"venous stasis ulcer":ti,ab OR "venous stasis ulcers":ti,ab OR "venous stasis ulceration":ti,ab	238
#10	"chronic wound":ti,ab OR "chronic wounds":ti,ab	3580
#11	'vein insufficiency'/exp	8401
#12	#1 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	26150
#13	'endoscopic surgery'/exp	139183
#14	'vein surgery'/exp	10760
#15	'radiofrequency ablation'/exp OR 'sclerotherapy'/exp OR 'vein transplantation'/exp	40067
#16	Endoscop*:ti,ab	183402
#17	Stripping:ti,ab	10723
#18	Ablat*:ti,ab	84509
#19	Ligat*:ti,ab	83442
#20	Laser*:ti,ab	170434
#21	Valvuloplast*:ti,ab	4729
#22	Valve*:ti,ab	121023
#23	Sclerotherap*:ti,ab	7260
#24	Thrombolys*:ti,ab	22560
#25	Thrombectom*:ti,ab	5940
#26	Angioplast*:ti,ab	45775

#27	Stent*:ti,ab	85953
#28	(Vein:ti,ab OR venous:ti,ab) AND (surgery:ti,ab OR surgeries:ti,ab)	42433
#29	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	893507
#30	#12 AND #29	4231
#31	([animals]/lim NOT [humans]/lim)	4639462
#32	'conference abstracts':it OR 'conference paper':it OR 'conference reviews':it OR editorial:it OR erratum:it OR letter:it OR note:it	2615920
#33	#30 NOT #31 NOT #32	3726
#34	#33 AND [1980-2012]/py	3585

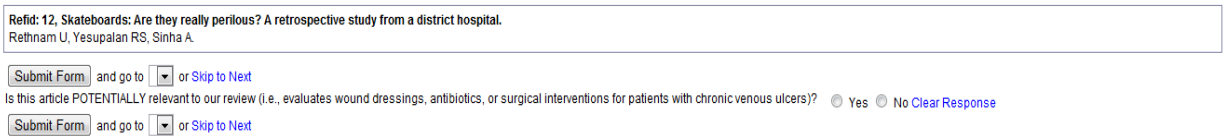
Surgical Cochrane Strategy

Search	String	# of hits
#1	“chronic leg”:ti,ab,kw	125
#2	“chronic venous”:ti,ab,kw	491
#3	“lower extremity”:ti,ab,kw OR “lower extremities”:ti,ab,kw OR “lower limb”:ti,ab,kw OR “lower limbs”:ti,ab,kw	3950
#4	Ulcer:ti,ab,kw OR ulcers:ti,ab,kw OR ulceration:ti,ab,kw	12129
#5	(#1 OR #2 OR #3) AND #4	495
#6	“leg ulcer”:ti,ab,kw OR “leg ulcers”:ti,ab,kw OR “leg ulceration”:ti,ab,kw	1004
#7	“venous ulcer”:ti,ab,kw OR “venous ulcers”:ti,ab,kw OR “venous ulceration”:ti,ab,kw	374
#8	“venous stasis ulcer”:ti,ab,kw OR “venous stasis ulcers”:ti,ab,kw OR “venous stasis ulceration”:ti,ab,kw	26
#9	“chronic wound”:ti,ab,kw OR “chronic wounds”:ti,ab,kw	188
#10	#5 OR #6 OR #7 OR #8 OR #9	1520
#11	Endoscop*:ti,ab,kw	9764
#12	Stripping:ti,ab,kw	1033
#13	Ablat*:ti,ab,kw	2470
#14	Ligat*:ti,ab,kw	1280
#15	Laser*:ti,ab,kw	7633
#16	Valvuloplast*:ti,ab,kw	67
#17	Valve*:ti,ab,kw	2786
#18	Sclerotherap*:ti,ab,kw	1031
#19	Thrombolys*:ti,ab,kw	2084
#20	Thrombectom*:ti,ab,kw	165
#21	Angioplast*:ti,ab,kw	5472
#22	Stent*:ti,ab,kw	4278
#23	(Vein:ti,ab,kw OR venous:ti,ab,kw) AND (surgery:ti,ab,kw OR	4381

	surgeries:ti,ab,kw)	
#24	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	36210
#25	#10 AND #24	169
#26	#25 – clinical trials and limit 1980-2012	155

Appendix B. Forms

Title review form



Abstract review form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Chronic Venous Ulcers Systematic Review
Abstract Review Form

1. *Exclude* article if: (check the first response that applies)

- ☐ No original data (e.g., review article, commentary, editorial)
- ☐ No subjects with chronic venous ulcers
- ☐ Does not evaluate an advanced wound dressing, antibiotics, or surgical intervention
- ☐ Does not have a comparison with an advanced wound dressing, antibiotic, surgical intervention, or conservative care **SEE BELOW IF SURGICAL INTERVENTION**
- ☐ No human subjects
- ☐ Other reason for exclusion (specify):
- ☐ Used intermittent compressoin
- ☐ Treatment and control groups did not receive same level of compression

2. *Unclear*

- ☐ Unclear- pull article for review

3. *Include*

- ☐ Include article for review
- ☐ Mark if study evaluates surgical intervention but does not have a comparison group

4. *ONLY IF are including OR it is unclear*, check this box if this article in a foreign language.

- ☐ Yes, article is written in a foreign language

5. Handsearch

- ☐ Exclude article from review, but pull for handsearching (i.e. systematic review published since 2005)

6. Comments (please limit to 250 characters):

Article review form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Treatments for Chronic Wounds
Article Review Form

1. Exclude article if: (check the first response that applies)

- ☐ No **original data** (e.g., review article, commentary, editorial)
- ☐ No subjects **with chronic venous ulcers**; if mixed population of patients with chronic wounds, then exclude if no separate analysis for patients with chronic venous ulcers
- ☐ Does not evaluate an advanced wound dressing, antibiotic, or surgical **intervention of interest**
- ☐ Evaluates an advanced wound dressing or antibiotic AND does not have a **concurrent comparison** with an advanced wound dressing, antibiotic, surgical intervention, or conservative care
- ☐ Used **intermittent compression**
- ☐ Treatment and control groups did not receive **at least 2 levels of compression**
- ☐ Does not evaluate an **outcome** of interest
- ☐ Less than **4 weeks** followup
- ☐ **Case series** of surgical intervention with **less than 30 patients with venous ulcers**
- ☐ Does not apply to **key question**
- ☐ **No human** subjects
- ☐ **Other** reason for exclusion (specify):
- ☐ **Case series** of surgical intervention **that does not assess ulcer healing**
- ☐ **Case series** of surgical intervention with **ulcers less than 6 weeks old**
- ☐ **Case series** of surgical intervention **that does not describe the sampling frame**
- ☐ **Case series** of surgical intervention that **does not provide demographic and clinical characteristics of patients with venous ulcers**

2. Include article for review (indicate the main intervention of interest):

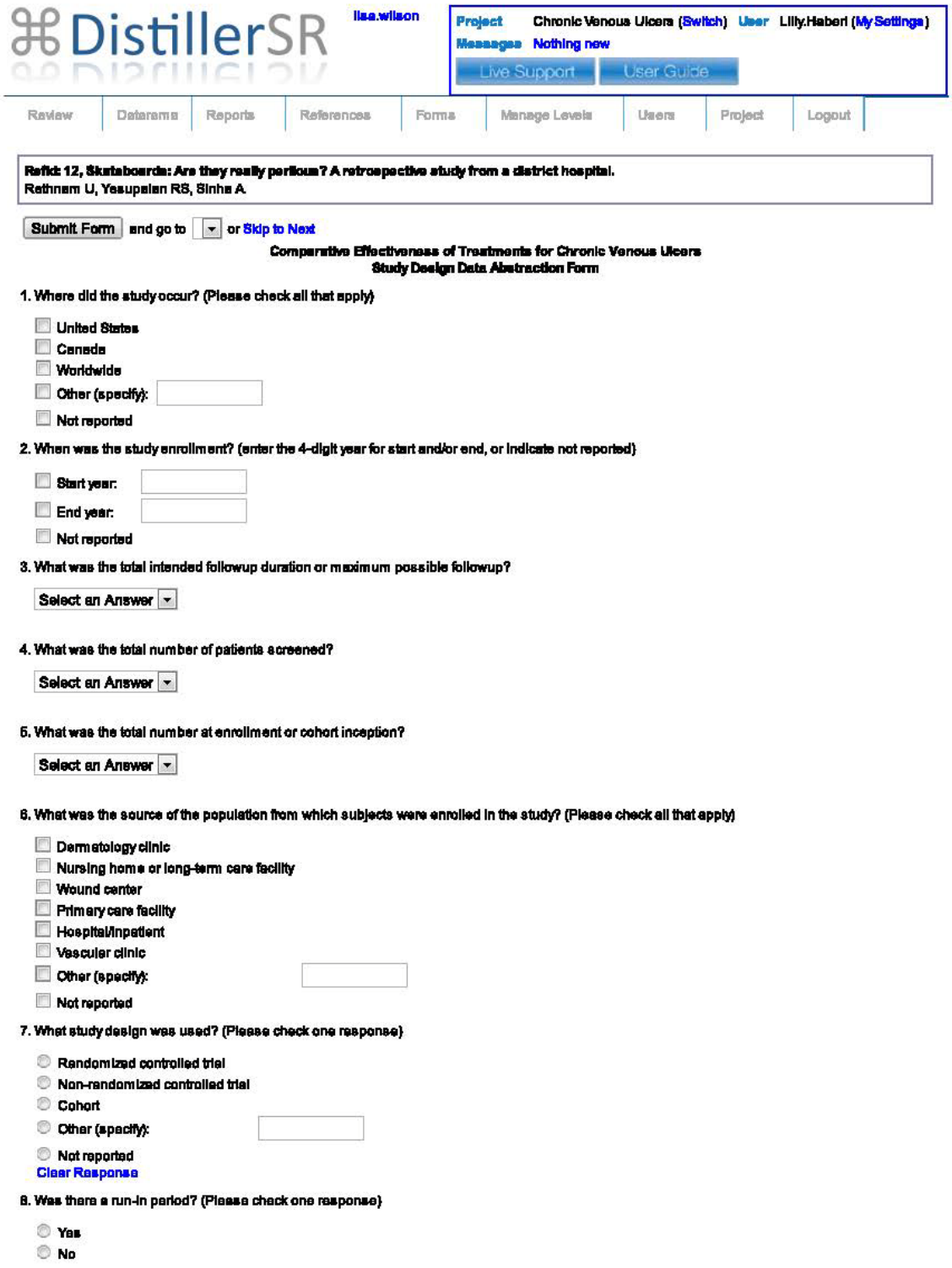
- ☐ Advanced wound dressings
- ☐ Antibiotic
- ☐ Surgical intervention

3. Handsearch

- ☐ Exclude article from review, but pull for handsearching (i.e. systematic review published since 2005)

Comments (limit 250 characters)

Study design form



- ○ Not reported

Clear Response

9. Select trial type (Please check one response)

- ○ Parallel arms
- ○ Factorial design
- ○ Crossover design
- ○ Other (specify): _____
- ○ Not applicable

Clear Response

10. If it applies (e.g. crossover), was there a washout period between therapies?

Select an Answer

11. Please specify the exclusion criteria. Any inclusion criteria should be entered as exclusion criteria (e.g., if the study included females only, then the exclusion criteria would be males).

- ☐ No patients with chronic venous ulcers
- ☐ Age < _____
- ☐ Age > _____
- ☐ Ulcer duration < (weeks) _____
- ☐ Ulcer duration > (weeks) _____
- ☐ Clinical infection
- ☐ Ankle/brachial index < _____
- ☐ Exudate level: _____
- ☐ Comorbid conditions (e.g., vasculitis, rheumatoid arthritis, severe kidney disease, heart disease)
- ☐ Patients with diabetes
- ☐ Treatment with systemic antimicrobials
- ☐ Treatment with corticosteroids
- ☐ Pain: _____
- ☐ Other (specify): _____
- ☐ Other (specify): _____
- ☐ Other (specify): _____
- ☐ Other (specify): _____

12. Did this study evaluate (Note: these outcomes will be abstracted separately):

- ☐ Pain
- ☐ Qualitative aspects of wound bed
- ☐ Size
- ☐ Quality of life
- ☐ None of the above

13. Did the study measure compliance?

- ○ Yes
- ○ No

Clear Response

14. Did the study report on the following subgroup analyses:

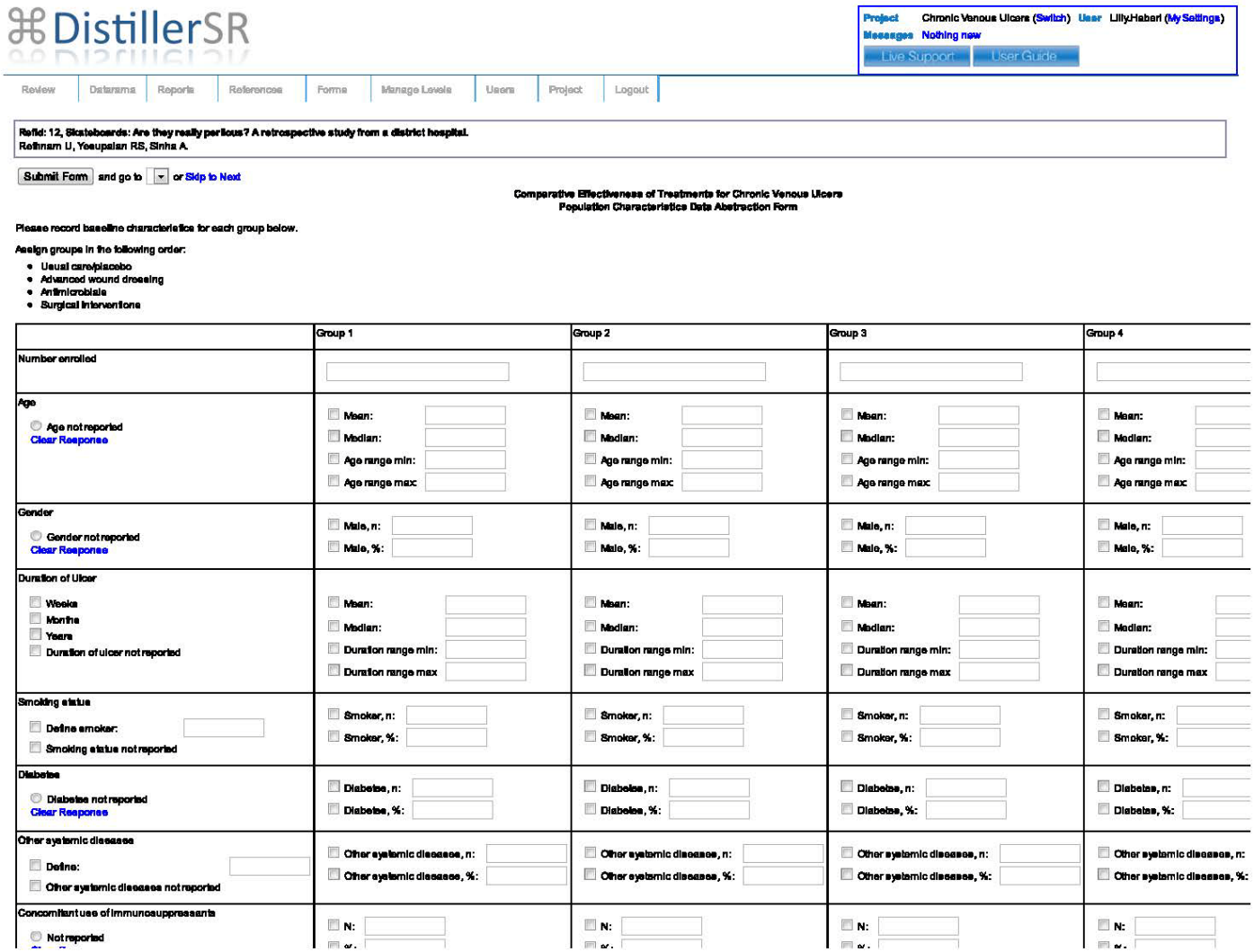
- ☐ Study setting
- ☐ Ulcer area and depth
- ☐ Duration of ulcer (short vs. long-term)
- ☐ Co-morbid conditions
- ☐ Venous duplex testing
- ☐ Other: _____
- ☐ No

Comments:

Comments:

Submit Form and go to or Skip to Next

Population Characteristics Form



DistillerSR

Project: Chronic Venous Ulcers (Switch) User: LillyHabarl (My Settings)
Messages: Nothing new
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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Reihman U, Yeaupaian RS, Sinha A.

Submit Form and go to [ ] or Skip to Next

Comparative Effectiveness of Treatments for Chronic Venous Ulcers
Population Characteristics Data Abstraction Form

Please record baseline characteristics for each group below.

Assign groups in the following order:

- Usual care/placebo
- Advanced wound dressing
- Antimicrobials
- Surgical interventions

	Group 1	Group 2	Group 3	Group 4
Number enrolled				
Age Age not reported Clear Response	Mean: Median: Age range min: Age range max:	Mean: Median: Age range min: Age range max:	Mean: Median: Age range min: Age range max:	Mean: Median: Age range min: Age range max:
Gender Gender not reported Clear Response	Male, n: Male, %:	Male, n: Male, %:	Male, n: Male, %:	Male, n: Male, %:
Duration of Ulcer Weeks Months Years Duration of ulcer not reported	Mean: Median: Duration range min: Duration range max	Mean: Median: Duration range min: Duration range max	Mean: Median: Duration range min: Duration range max	Mean: Median: Duration range min: Duration range max
Smoking status Define smoker: Smoking status not reported	Smoker, n: Smoker, %:	Smoker, n: Smoker, %:	Smoker, n: Smoker, %:	Smoker, n: Smoker, %:
Diabetes Diabetes not reported Clear Response	Diabetes, n: Diabetes, %:	Diabetes, n: Diabetes, %:	Diabetes, n: Diabetes, %:	Diabetes, n: Diabetes, %:
Other systemic diseases Define: Other systemic diseases not reported	Other systemic diseases, n: Other systemic diseases, %:	Other systemic diseases, n: Other systemic diseases, %:	Other systemic diseases, n: Other systemic diseases, %:	Other systemic diseases, n: Other systemic diseases, %:
Concomitant use of immunosuppressants Not reported	N: %:	N: %:	N: %:	N: %:

Clear Response	%:	%:	%:	%:
Concomitant use of steroids Not reported Clear Response	N: %:	N: %:	N: %:	N: %:
Receiving additional procedure/dressing (specify): Not reported	N: %:	N: %:	N: %:	N: %:
Withdrawals Not reported Total number withdrawals: Clear Response	N:	N:	N:	N:

Comments:

Comments:

Submit Form and go to or Skip to Next

Interventions Form

DistillerSR

Project Chronic Venous Ulcers (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
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Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

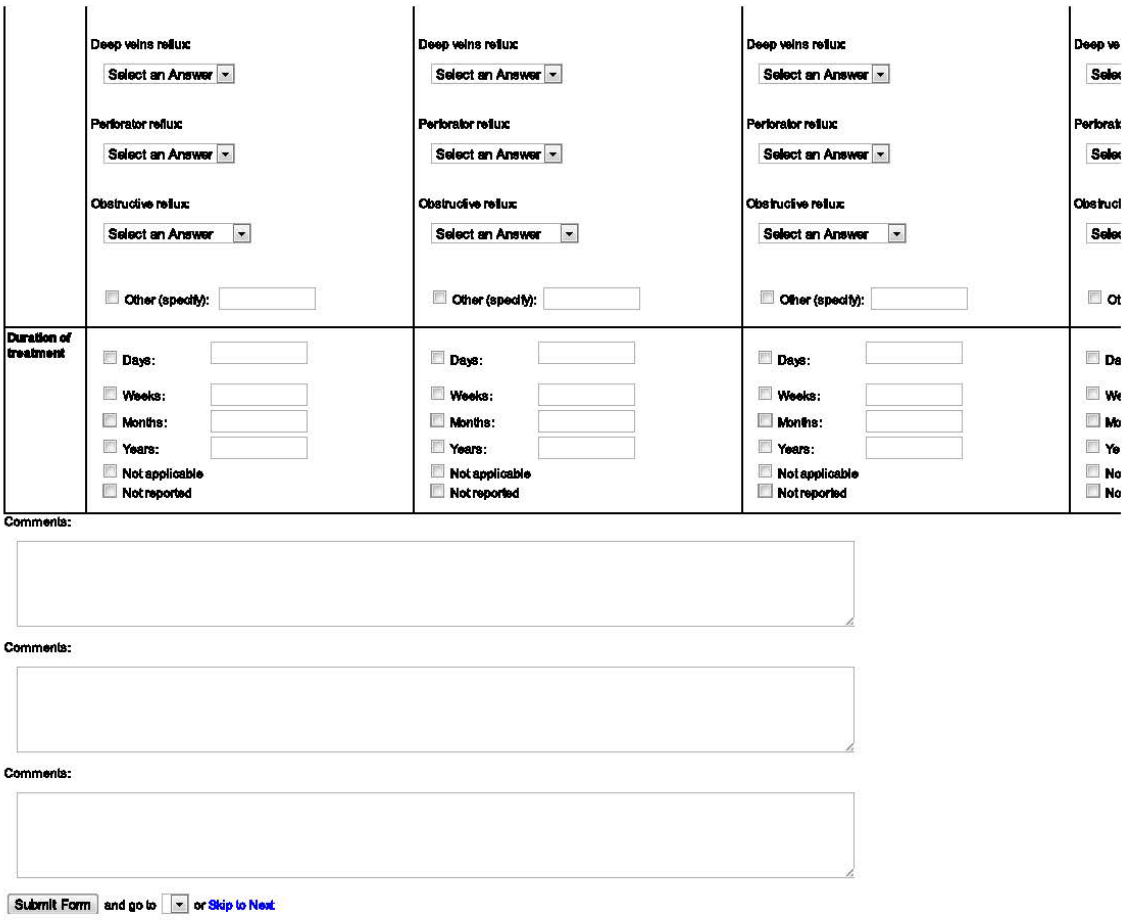
Submit Form and go to [▾] or Skip to Next

Comparative Effectiveness of Treatments for Chronic Venous Ulcers
Intervention Characteristics Data Abstraction Form

Please indicate the interventions for each group below. Assign groups in the following order:

- Usual care/placebo
- Advanced wound dressing
- Antimicrobials
- Surgical interventions

	Group 1	Group 2	Group 3	Group 4
Usual care/placebo	☐ Compression, 2-layer ☐ Compression, short stretch ☐ Compression, long stretch ☐ Compression, multi-layer ☐ Compression pump ☐ Compression, Unna boot ☐ Compression, other: [ ] ☐ Compression, unspecified ☐ Debridement (sharp) ☐ Debridement (enzymatic)	☐ Compression, 2-layer ☐ Compression, short stretch ☐ Compression, long stretch ☐ Compression, multi-layer ☐ Compression pump ☐ Compression, Unna boot ☐ Compression, other: [ ] ☐ Compression, unspecified ☐ Debridement (sharp) ☐ Debridement (enzymatic)	☐ Compression, 2-layer ☐ Compression, short stretch ☐ Compression, long stretch ☐ Compression, multi-layer ☐ Compression pump ☐ Compression, Unna boot ☐ Compression, other: [ ] ☐ Compression, unspecified ☐ Debridement (sharp) ☐ Debridement (enzymatic)	☐ Co ☐ Co ☐ Co ☐ Co ☐ Co ☐ Co ☐ Co ☐ Co ☐ De ☐ De
Advanced wound dressing	☐ Hydrocolloid ☐ Transparent film ☐ Alginate ☐ Foam ☐ Composite ☐ Specialty absorptive dressings ☐ Contact layer ☐ Hydrogel ☐ Collagen dressing ☐ Acellular skin substitute or ECM ☐ Cellular skin substitute or ECM ☐ Antibacterial dressings ☐ Impregnated gauze ☐ Biologic debriding agents ☐ Other (specify): [ ]	☐ Hydrocolloid ☐ Transparent film ☐ Alginate ☐ Foam ☐ Composite ☐ Specialty absorptive dressings ☐ Contact layer ☐ Hydrogel ☐ Collagen dressing ☐ Acellular skin substitute or ECM ☐ Cellular skin substitute or ECM ☐ Antibacterial dressings ☐ Impregnated gauze ☐ Biologic debriding agents ☐ Other (specify): [ ]	☐ Hydrocolloid ☐ Transparent film ☐ Alginate ☐ Foam ☐ Composite ☐ Specialty absorptive dressings ☐ Contact layer ☐ Hydrogel ☐ Collagen dressing ☐ Acellular skin substitute or ECM ☐ Cellular skin substitute or ECM ☐ Antibacterial dressings ☐ Impregnated gauze ☐ Biologic debriding agents ☐ Other (specify): [ ]	☐ Hy ☐ Tra ☐ Alg ☐ Fo ☐ Co ☐ Sp ☐ Co ☐ Hy ☐ Co ☐ Ac ☐ Ce ☐ An ☐ Im ☐ Bic ☐ Ot
Antimicrobial	☐ Amikacin ☐ Amoxicillin ☐ Cefazolin ☐ Cefipime ☐ Cefixime ☐ Cefpodoxime ☐ Ceftriaxone ☐ Cephalexin ☐ Ciprofloxacin ☐ Clavulanate ☐ Daptomycin ☐ Dicloxacillin ☐ Ertapenem ☐ Gentamicin ☐ Levofloxacin ☐ Linezolid ☐ Moxifloxacin ☐ Piperacillin tazobactam ☐ Tobramycin ☐ Trimethoprim/ sulfamethoxazole ☐ Unasyn ☐ Vancomycin ☐ Other systemic antibiotic [ ] ☐ Placebo	☐ Amikacin ☐ Amoxicillin ☐ Cefazolin ☐ Cefipime ☐ Cefixime ☐ Cefpodoxime ☐ Ceftriaxone ☐ Cephalexin ☐ Ciprofloxacin ☐ Clavulanate ☐ Daptomycin ☐ Dicloxacillin ☐ Ertapenem ☐ Gentamicin ☐ Levofloxacin ☐ Linezolid ☐ Moxifloxacin ☐ Piperacillin tazobactam ☐ Tobramycin ☐ Trimethoprim/ sulfamethoxazole ☐ Unasyn ☐ Vancomycin ☐ Other systemic antibiotic [ ]	☐ Amikacin ☐ Amoxicillin ☐ Cefazolin ☐ Cefipime ☐ Cefixime ☐ Cefpodoxime ☐ Ceftriaxone ☐ Cephalexin ☐ Ciprofloxacin ☐ Clavulanate ☐ Daptomycin ☐ Dicloxacillin ☐ Ertapenem ☐ Gentamicin ☐ Levofloxacin ☐ Linezolid ☐ Moxifloxacin ☐ Piperacillin tazobactam ☐ Tobramycin ☐ Trimethoprim/ sulfamethoxazole ☐ Unasyn ☐ Vancomycin ☐ Other systemic antibiotic [ ]	☐ Am ☐ Am ☐ Ce ☐ Ce ☐ Ce ☐ Ce ☐ Ce ☐ Ce ☐ Cip ☐ Cla ☐ Da ☐ Dic ☐ Ert ☐ Ge ☐ Le ☐ Lin ☐ Mo ☐ Pip ☐ To ☐ Tri ☐ Un ☐ Va ☐ Ot
Surgical interventions	Superficial veins reflux: Select an Answer ▾	Superficial veins reflux: Select an Answer ▾	Superficial veins reflux: Select an Answer ▾	Superfic Selec


Deep veins reflux:
Select an Answer
Perforator reflux:
Select an Answer
Obstructive reflux:
Select an Answer
Other (specify):
Deep veins reflux:
Select an Answer
Perforator reflux:
Select an Answer
Obstructive reflux:
Select an Answer
Other (specify):
Deep veins reflux:
Select an Answer
Perforator reflux:
Select an Answer
Obstructive reflux:
Select an Answer
Other (specify):
Duration of treatment
Days:
Weeks:
Months:
Years:
Not applicable
Not reported
Days:
Weeks:
Months:
Years:
Not applicable
Not reported
Days:
Weeks:
Months:
Years:
Not applicable
Not reported
Comments:
Comments:
Comments:
Submit Form
and go to
or Skip to Next

Outcomes Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rehman U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities
Outcomes Form

Please fill out one outcomes form for each outcome.

Select one outcome	Define outcome	Specify method of measurement
Final Outcomes ○ Proportion of ulcers healed ○ Time to achieve complete wound closure ○ Rate of wound recurrence ○ Incident chronic venous ulcer at different anatomical location(s) ○ Function status ○ Mortality Clear Response	○ Specify definition and units: ○ Not further specified Clear Response	○ Specify method of measurement ○ Not further specified Clear Response
Intermediate Outcomes ○ Wound healing rates (defined as % area reduction from baseline) as measured by planimetry (photos, etc.); YES study evaluates relationship of intermediate healing rate to complete healing ○ Wound healing rates (defined as % area reduction from baseline) as measured by planimetry (photos, etc.); NO study does NOT evaluate relationship of intermediate healing rate to complete healing ○ Quality of the wound bed Clear Response	○ Specify definition and units: ○ Not further specified Clear Response	
General Adverse Events for all KQ ○ Maceration ○ Infection ○ Contact dermatitis ○ Venous or arterial impairment Clear Response		
Adverse Events for Topical Antibiotics Contained in Dressings (KQ1) ○ Hypersensitivity, contact dermatitis, sensitization ○ Antibiotic resistance ○ Systemic absorption Clear Response		
Adverse Events for Systemic Antibiotics (KQ2) ○ Allergic and hypersensitivity reactions ○ Renal toxicity ○ Hepatic toxicity		

○ Gastrointestinal upset ○ Clostridium difficile infection ○ Catheter-associated bloodstream infections ○ Antibiotic resistance ○ Selection of resistant organisms Clear Response		
Adverse Events for Surgical Interventions (KQ3) ○ Surgical site infection ○ Bleeding ○ Skin irritation and burn ○ Deep vein thrombosis ○ Long-term recurrent reflux and ulceration Clear Response		

Followup time:

○ Days: ☐
○ Weeks: ☐
○ Months: ☐
○ Not reported
Clear Response

Table 1. Incidence of outcome

Intervention Group1	N for analysis	Outcome measure	Denominator	P-value	Reference group
		☐ # of patients with one or more events ☐ ☐ % of patients with one or more events ☐ ☐ # of events ☐ ☐ Other measure of incidence ☐ ☐ Value for other measure of incidence ☐	Select an Answer		Select an Answer
Intervention Group2	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ ☐ % of patients with one or more events ☐ ☐ # of events ☐ ☐ Other measure of incidence ☐ ☐ Value for other measure of incidence ☐	Select an Answer		Select an Answer
Intervention Group3	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ ☐ % of patients with one or more events ☐ ☐ # of events ☐ ☐ Other measure of incidence ☐ ☐ Value for other measure of incidence ☐	Select an Answer		Select an Answer

Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Group4		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ Other measure of incidence ☐ Value for other measure of incidence	Select an Answer		Select an Answer
Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Group5		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ Other measure of incidence ☐ Value for other measure of incidence	Select an Answer		Select an Answer
Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Group6		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ Other measure of incidence ☐ Value for other measure of incidence	Select an Answer		Select an Answer
Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Group7		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ Other measure of incidence ☐ Value for other measure of incidence	Select an Answer		Select an Answer
Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Group8		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events ☐ Other measure of incidence ☐ Value for other measure of incidence	Select an Answer		Select an Answer

Table 2. Measure of Association

Intervention	N for analysis	Point estimate (Select one response)	Measure of variability (Select one response)	95% CI	P-value	Reference group
		Select an Answer	Select an Answer			

Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer
Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer
Intervention Group8				☐ LL ☐ UL		Select an Answer

If a multivariable analysis, what other variables were adjusted for in the model? **(Select all that apply)**

- ☐ Matching factors
- ☐ Age
- ☐ Sex
- ☐ Race/ethnicity
- ☐ Duration of ulcer
- ☐ Size of ulcer
- ☐ Co-morbid conditions (specify):
- ☐ Other (specify):
- ☐ Other (specify):

Table 3. Mean difference from other group (e.g. Change from baseline in group 2 - Change in baseline in Group 1)

Intervention	N for analysis	Point estimate (Select one response)	Measure of variability (Select one response)	CI or IQR (Select one response)	P-value	Reference group
		Select an Answer	Select an Answer	Select an Answer		
Intervention						

Group1				LL UL		Select an Answer
Intervention Group2				LL UL		Select an Answer
Intervention Group3				LL UL		Select an Answer
Intervention Group4				LL UL		Select an Answer
Intervention Group5				LL UL		Select an Answer
Intervention Group6				LL UL		Select an Answer
Intervention Group7				LL UL		Select an Answer
Intervention Group8				LL UL		Select an Answer

Table 4. Mean difference from baseline.

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value
Intervention Group1				LL UL	
Intervention Group2				LL UL	
Intervention Group3				LL UL	

Table 6. Final measures

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value	Reference group
Intervention Group1				LL UL		Select an Answer
Intervention Group2				LL UL		Select an Answer
Intervention Group3				LL UL		Select an Answer
Intervention Group4				LL UL		Select an Answer
Intervention Group5				LL UL		Select an Answer
Intervention Group6				LL UL		Select an Answer
Intervention Group7				LL UL		Select an Answer
Intervention Group8				LL UL		Select an Answer

Comments (Limit 250 characters)

Comments (Limit 250 characters)

Comments (Limit 250 characters)

Submit Form and go to or Skip to Next

Study Quality Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A

Submit Form and go to or Skip to Next

Comparative Effectiveness of Treatments for Chronic Venous Ulcers
Downs and Black Checklist for Measuring Study Quality

REPORTING

1. Is the hypothesis/aim/objective of the study clearly described?

   Yes
   No
   Clear Response

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

   If the main outcomes are first mentioned in the Results section, the question should be answered 'no.'

   Yes
   No
   Clear Response

3. Are the characteristics of the subjects included in the study clearly described?

   In trials, inclusion and/or exclusion criteria should be given.

   Yes
   No
   Clear Response

4. Are the interventions of interest clearly described?

   Interventions and controls (where relevant) that are to be compared should be clearly described.

   Yes
   No
   Clear Response

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

   A list of principal confounders is provided.

   Yes
   No
   Clear Response

6. Are the main findings of the study clearly described?

   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

   Yes
   No
   Clear Response

7. Does the study provide estimates of the random variability in the data for the main outcomes?

   In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

   Yes
   No
   Clear Response

8. Have all important adverse events that may be a consequence of the intervention been reported?

This should be answered 'yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

- Yes
- No

Clear Response

9. Have the characteristics of subjects lost to follow-up been described?

This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.

- Yes
- No

Clear Response

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

- Yes
- No

Clear Response

EXTERNAL VALIDITY

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered 'unable to determine.'

- Yes
- No
- Unable to determine

Clear Response

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

- Yes
- No
- Unable to determine

Clear Response

13. Were the staff, places, and facilities where the subjects were treated (or where the intervention was implemented) representative of the treatment the majority of subjects receive?

For the question to be answered 'yes' the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered 'no' if, for example, the intervention was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.

- Yes
- No
- Unable to determine

Clear Response

INTERNAL VALIDITY-BIAS

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the subjects would have no way of knowing which intervention they received, this should be answered 'yes.'

- Yes
- No
- Unable to determine

Clear Response

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes
No
Unable to determine
Clear Response

16. If any of the results of the study were based on "data dredging", was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes.'

Yes
No
Unable to determine
Clear Response

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?

Where follow-up was the same for all study participants the answer should be 'yes.' If different lengths of follow-up were adjusted, for example, by survival analysis, the answer should be 'yes.' Studies where differences in follow-up are ignored should be answered 'no.'

Yes
No
Unable to determine
Clear Response

18. Were the statistical tests used to assess the main outcomes appropriate?

The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes.' If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

Yes
No
Unable to determine
Clear Response

19. Was compliance with the intervention/s reliable?

Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered 'no.' For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered 'yes.'

Yes
No
Unable to determine
Clear Response

20. Were the main outcome measures used accurate (valid and reliable)?

For studies where the outcome measures are clearly described, the question should be answered 'yes.' For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes.'

Yes
No
Unable to determine
Clear Response

INTERNAL VALIDITY- CONFOUNDING AND SELECTION BIAS

21. Were the subjects in different intervention groups (trials and cohort studies) recruited from the same population?

For example, subjects for all comparison groups should be selected from the same school. The question should be answered unable to determine for cohort where there is no information concerning the source of subjects included in the study.

Yes
No
Unable to determine
Clear Response

22. Were study subjects in different intervention groups (trials and cohort studies) recruited over the same period of time?

For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes

NR
Unable to determine
Clear Response

23. Were study subjects randomized to intervention groups?

Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes
No
Unable to determine
Clear Response

24. Was the randomized intervention assignment concealed from both subjects and those conducting the study until recruitment was complete and irrevocable?

All non-randomized studies should be answered 'no.' If assignment was concealed from patients but not from staff, it should be answered 'no.'

Yes
No
Unable to determine
Clear Response

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no.'

Yes
No
Unable to determine
Clear Response

26. Were losses of subjects to follow-up taken into account?

If the numbers of subjects lost to follow-up are not reported, the question should be answered 'unable to determine.' If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes.'

Yes
No
Unable to determine
Clear Response

POWER

27. Did they report a power calculation?

Yes
No
Clear Response

28. Was the study supported by industry?

Yes (e.g. supported financially by industry, treatment provided by industry, co-author involved with industry)
No (sources of funding provided by non-industry sponsors such as government, etc.)
Not reported
Clear Response

29. Were > 30% of the enrolled patients not analyzed? (e.g. withdrawals, losses to followup)

Yes
No
Not reported
Clear Response

Comments:

Submit Form and go to or Skip to Next

Appendix C. Excluded Articles

[Management of infections in chronic wounds: hydroactive dressing instead of antiseptics?]. Krankenpfl J. 98; 36 (11): 454. **No original data**

[UrgoClean: a new wound dressing features high absorption and uptake of fibrous deposits]. Pflege Z. 2011; 64 (11): 698. **No original data**

Controlled trial of Iodosorb in chronic venous ulcers. Br Med J (Clin Res Ed). 85; 291 (6499): 902. **No original data**

Adam, D. J., Bello, M., Hartshorne, T., and London, N. J. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. Eur J Vasc Endovasc Surg. 2003; 25 (5): 469-72. **Different levels of compression used**

Akesson, H. and Bjellerup, M. Leg ulcers: report on a multidisciplinary approach. Acta Derm Venereol. 95; 75 (2): 133-5. **No separate analysis of CVU**

Akesson, H., Brudin, L., Cwikiel, W., Ohlin, P., and Plate, G. Does the correction of insufficient superficial and perforating veins improve venous function in patients with deep venous insufficiency?. PHLEBOLOGY. 90; 5 (2): 113-123. **Case series with <10**

Alhabouni, S., Hingorani, A., Ascher, E., Marks, N., Shiferson, A., Patel, N., Gopal, K., and Jacob, T. Iliac venous stenting for lower extremity venous stasis disease. J. Vasc. Surg. 2009; 49 (5): 40S. **No separate analysis of CVU**

Alikhanov, V. P. and Keshokov, R. K. Laser therapy in the combined treatment of the trophic disorders in the postthrombophlebitis syndrome: Lazernaia terapiia v kompleksnom lechenii troficheskikh narushenii pri posttromboflebiticheskom sindrome. Med Sestra. 89; 48 (9): 24-25. **No original data; no separate analysis of CVU**

Almeida, J. I., Kaufman, J., Gockeritz, O., Chopra, P., Evans, M. T., Hoheim, D. F., Makhoul, R. G., Richards, T., Wenzel, C., and Raines, J. K. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol. 2009; 20 (6): 752-9. **No separate analysis of CVU**

Ananthakrishnan, N., Parkash, S., and Banerjee, S. N. A new technique for chronic venous ulcers of the lower limb: modified Felder-Rob procedure. Aust N Z J Surg. 89; 59 (2): 157-60. **No KQ**

Andersen KE, Franken CPM, Gad P, Larsen AM, Larsen JR, and van Neer PAFA et al A randomized, controlled study to compare the effectiveness of two foam dressings in the management of lower leg ulcers. Ostomy Wound Management. 2002; 48 (8): 34-41. **Different levels of compression used**

Askerkhanov, R. P. Some aspects of the pathology, clinical picture, and treatment of occlusive and valvular venous circulatory insufficiency in the lower extremities. KARDIOLOGIYA. 80; 20 (2): 67-71. **No intervention of interest**

Askerov, N. G., Zhukov, A. O., and Malinina, V. N. [Comparative analysis of horizontal venous reflux surgical correction by large trophic lower leg ulcers]. Khirurgiia (Mosk). 2009; (10): 29-32. **No separate analysis of CVU**

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Zuccarelli, F. [A comparative study of the hydrocellular dressing Allevyn and the hydrocolloid dressing Duoderm in the local treatment of leg ulcers]. Phlebologie. 92; 45 (4): 529-33. **Different levels of compression used**

Appendix D. Evidence Tables

Table D-1. Study design characteristics of studies evaluating treatments for chronic venous ulcers

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Alinovi, 1986[82]	RCT; parallel arms	48 (NR)	1983 to 1984 20 days	Primary care	Italy	No run-in	Ulcer duration: < 4 weeks Comorbids excluded Diabetes excluded	Ulcers with clinical signs of infection, ulcers with negative bacteriologic cultures, ulcers with non-venous main cause, arterial insufficiency
Arnold, 1994[39]	RCT; parallel arms	70 (NR)	Year NR 10 weeks	pop source NR	US, UK	No run-in No compliance	clinical infection Comorbids excluded	arterial insufficiency, dermatological conditions
Backhouse, 1987[43]	RCT; parallel arms	58 (NR)	Year NR 12 weeks	wound center	NR	NR run-in No compliance	no CVU	Ulcer size > 10cm^2 Doppler indicating arterial cause
Barwell, 2000[62]	cohort; NA	(669)	1995 to 1999 3 years	pop source NR	UK	Yes run-in No compliance	ABI: < 0.85	
Barwell, 2004[60]	RCT; parallel arms	500 (1418)	1999 to 2002 5 years	nursing home, Primary care medical specialists	UK	Yes run-in Yes compliance	Ulcer duration: <4 weeks ABI: < 0.85	Complete color duplex imaging not possible; veins completely occluded; Those unable to give informed consent; were unfit for surgery; compression was not practical; malignant ulcers
Beckert, 2006[31]	RCT; parallel arms	119 (137)	2002 to 2004 20 weeks	wound center	Europe	Yes run-in No compliance	Age: <18 ABI: < 0.8	Ulcerations due to CVI, severe cardiac , respiratory, gastrointestinal, liver, or renal disease, malignancy or signs of wound infection Pregnant women and nursing mothers, ulcer area < 3 cm
Bello, 1999[71]	cohort	111 (325)	1994 to 1997 NR	a single Venous ulcer assessment clinic	UK	No run-in No compliance	ABI: < 0.8	No venous reflux on duplex scanning
Cambal, 2008[69]	Cohort, retrospective	793 (NR)	1973 5 years	Surgery	Slovakia	No run-in	no CVU No compliance	

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
El-Hafez, 2004[68]	Cohort	36 (NR)	2000 to 2001 12 months	surgical outpatient clinic	Egypt and Saudi Arabia	No run-in	No CVU Ulcer duration: < 4 weeks ABI: < 0.9	ulcer diameter 2 to 7cm
Falanga V, 1999[51]	RCT; parallel arms	(NR)	Year NR 12 months	pop source NR	US	No run-in No compliance	no CVU Age: <18 & >85 Ulcer duration: <52 weeks Comorbids excluded Diabetes excluded	receiving immunosuppressive agents, radiation therapy or chemotherapy within 1 month of entry into study
Falanga, 1998[38]	RCT; parallel arms	309 (NR)	Year NR 12 months	outpatient setting but type not specified	US	No run-in No compliance	no CVU Age: <18 & >85 ABI: < 0.65 Comorbids excluded Diabetes excluded	receiving immunosuppressive agents, radiation therapy or chemotherapy within 1 month of entry into study cellulitis, exudation indicative of heavy bacterial contam, eschar, obvious necrotic material that could interfere with graft/healing pregnancy, lactation collagen vascular diseases
Franks, 2007[28]	RCT; factorial	156 (NR)	2002 24 weeks	Primary care hospital inpatient	United Kingdom	NR run-in No compliance	Age: <18 Ulcer duration: <2 & >52 clinical infection ABI: < 0.8 Systemic antimicrobials excluded	Pregnant, dry non-exuding wounds
Galimberti, 1988[66]	Retrospective	118 (NR)	NR 40 months	Dermatology clnic, vascular clinic	Italy	NR run-in No compliance	NR	NR
Gatti, 2011[45]	NR; parallel arms	24 (NR)	Year NR 8 weeks	pop source NR	Brazil	No run-in No compliance	no CVU Ulcer duration: >260 weeks	Unable to receive dressing once per week associated arterial disease not adhering to treatment not accepting the use of Unna's boot

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Gethin, 2009[24]	RCT; parallel arms	108 (256)	2003 to 2006 12 weeks	wound center hospital inpatient vascular clinic	Ireland	No run-in Yes compliance	no CVU Age: <18 clinical infection ABI: < 0.8 Comorbids excluded Systemic antimicrobials excluded	Having < 50% wound bed covered in slough Ulcer > 100cm^2; Pregnant women or lactating mothers; Having a cavity wound
Gohel, 2007[59]	RCT; parallel arms	500 (1418)	1999 to 2002 4 years	nursing home, Primary care hospital inpatient	UK	NR run-in No compliance	Ulcer duration: <4 weeks ABI: < 0.85	Healed ulcer >6months; Those in whom duplex scan was not possible; those unwilling or refused to give consent; Those with deep venous occlusion; Malignant ulceration; Those unfit for surgery; Multiple layered compression not practical
Gottrup, 2007[27]	RCT; parallel arms	122 (NR)	2005 to 2006 47 days	pop source NR	6 European countries, Great Britain, Lithuania, Denmark, Germany, Czech Republic, Finland	NR run-in No compliance	Age: <18 Ulcer duration: <8 weeks clinical infection Diabetes excluded Systemic antimicrobials excluded Pain: Less than moderate pain on 5-point verbal rating scale (none, slight, moderate, lots, complete)	Pregnant or lactating women; Painful ulcers resistant to analgesic treatment over past 6 months or more allergy or other contraindication to ibuprofen; Use of unscheduled additional pain medication for 3 days prior to study admission

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Gottrup, 2008[23]	RCT; parallel arms	122 (NR)	2005 to 2006 47 days	From 13 centers from 6 countries (but the centers are not defined)	6 European countries, Great Britain, Lithuania, Denmark, Germany, Czech Republic, Finland	Yes run-in No compliance	no CVU Age: <19 Ulcer duration: <8 weeks clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded Systemic antimicrobials excluded Pain: (1) Less than 'Moderate', on a 5 point Verbal Rating Score and also, (2) ulcers not resistant to analgesic treatment over the past 6 months or more	1) Wound size of <1.6cm in any direction and maximum area of 50cm^2, (2) Pregnant or lactating women (3) Local (and also clinical) infection or bacterial imbalance within or surrounding the ulcer area 1) Allergy or other contraindication to ibuprofen or related analgesics (non-steroidal anti-inflammatory agents), (2) History of asthma, rhinitis or urticaria, (3) previous participation in this study 1) use of unscheduled additional pain medication for 3 days before the study admission (except for regular concomitant pain medication), (2) Treatment with other immunosuppressant or cancer chemotherapeutic agents within 1 month before inclusion (1) Concomitant participation in other studies
Greguric, 1994[48]	RCT; parallel arms	110 (NR)	1993 to 1993	hospital inpatient outpatient	Croatia	No run-in Yes compliance	no CVU Age: <18 ABI: < 0.9 Comorbids excluded	treatment with immunodepressants, malignant ulcers, chemotx, immune def, other condition affecting wound healing Pregnancy, sensitivity to any of the tx materials; Ulcers resulting from other disease ulcers <2.5 or >5 cm
Guest, 2003[64]	RCT; parallel arms	76 (206)	NR	Primary care	UK	Yes run-in No compliance	ABI: < 0.8 Comorbids excluded Diabetes excluded	Patients unfit for surgery
Hansson, 1998[37]	RCT; parallel arms	153 (NR)	Year NR 12 weeks	derm clinic	Sweden, Denmark, the Netherlands, and the UK	No run-in Yes compliance	clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded	known sensitivity to products in trial, treatment with systemic antimicrobials patients undergoing investigation of thyroid

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Harding, 2005[33]	RCT; parallel arms	194 (259)	Year NR 14 weeks	wound center	Belgium, UK, Germany and Poland	Yes run-in No compliance	Age: < 30 & > 85 Ulcer duration: < 6 weeks clinical infection ABI: < 0.8	Previous treatments with cell derived or growth factor derived therapies within 1 month prior to screening or planned during the study History of allergy to materials used within the study DVT at the time of the screening
Harding, 2011[20]	RCT; parallel arms	281 (NR)	2010 to 2010 8 weeks	pop source NR	UK, Germany, France, Denmark, and Poland	NR run-in No compliance	Age: <18 Ulcer duration: >96 weeks clinical infection ABI: < 0.8 Systemic antimicrobials excluded	Recent DVT within last 3 months Recent venous surgery within last 3 months Progressive neoplastic lesion treated by radiotherapy or chemotherapy
Harlander-Locke, 2011[74]	Case series	72 (433)	2007 to 2011 12 months	wound center		No run-in No compliance	no CVU	Failed non-interventional venous ulcer treatment for a minimum of 5 weeks
Holloway, 1989[42]	RCT; parallel arms	75 (NR)	Year NR 24 weeks	outpatient, but not otherwise specified	US	No run-in Yes compliance	no CVU Ulcer duration: <12 weeks Comorbids excluded	ulcer < 2cm in max diam (was relaxed later in trial) Proven/suspected non-venous cause of ulcer, inability to comply with treatment regimen, iodine allergy, clinically significant arterial disease
Huovinen, 1994[57]	RCT; parallel arms	NR	Year NR 16 weeks	pop source NR	Finland	No compliance No washout	Age: < 18 years	body weight < 50 kg, allergies to antimicrobial agents used; current warfarin or theophylline treatment; antimicrobial treatment within 2 weeks of study
Krishnamoorthy, 2003[47]	RCT; parallel arms	53 (63)	Year NR 12 weeks	Undefined health centers	Can UK	Yes run-in Yes compliance	no CVU Age: <18 Ulcer duration: > 8 weeks & > 240 weeks clinical infection ABI: < 0.7 Comorbids excluded	ulcer area <3 or >25 cm^2 Severe leg edema, impaired mobility, other cause of ulcer lack of either venous reflux, h/o DVT, or clinical appearance of post-DVT limb ulcer healed >50% during 14-day run-in period with treatment with compression

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Kucharzewski, 2003[46]	non randomized; parallel arms	54 (NR)	Year NR	people who 'applied for consultation by surgery doctor'	Poland	No run-in No compliance	no CVU ABI: < 0.8 Diabetes excluded	
Labas, 2009[76]	Case series	56 (NR)	1991 to 2002 NR	pop source NR	Slovak Republic	No run-in No compliance	no CVU	Responded to sclerotherapy of the superficial system combined with compression within 6 months
Lammoglia-Ordiales, 2011[56]	RCT; parallel arms	41 (NR)	2007 to 2009	wound center	Mexico	No run-in No compliance	Age: <18 clinical infection ABI: < 0.8 Diabetes excluded	Patients who were immunosupressed or had arterial disease
Lane, 2003[77]	cohort	41 (NR)	1987 to 1991 11.9 years	pop source NR	Australia	NR run-in No compliance	Age: <18 years Ulcer duration: <4 weeks ABI: < 0.7	chronic insufficiency not cause by deep venous disease; symptoms of venous insufficiency of less than 2 years; not medically fit for surgery; history of thrombophlebitis, DVT or pregnancy within the previous year
Lawrence, 2011[14]	Case aeries	45 (208)	2007 to 2010 12.85 months	wound center		No run-in No compliance	no CVU	<3 months of treatment at wound center; no incompetent perforating veins
Limova, 2003[35]	RCT; parallel arms	20 (NR)	1997 to 1999 6 weeks	wound center	US	No run-in No compliance	Age: < 21 Ulcer duration: <4 weeks clinical infection ABI: < 0.8	Uncontrolled diabetes mellitus Allergy to materials used in the study
Maggio, 2011[21]	RCT; parallel arms	52 (NR)	Year NR 70 days	pop source NR	Italy	No run-in No compliance	Age: <18 & >70 ABI: < 0.8 Diabetes excluded	Treatment with immunosuppressive agents Treatment with cytotoxic agents History of bleeding disorders History of delayed wound healing

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Masuda, 1994[72]	cohort	48 (81)	1968 to 1990 21 years	hospital inpatient		NR run-in No compliance		less than 4 years of follow-up
Michaels, 2009[22]	RCT; parallel arms	213 (304)	2005 to 2007 12 months	derm clinic Primary care	UK	NR run-in Yes compliance	no CVU Ulcer duration: < 6 weeks ABI: < 0.8 Comorbids excluded Diabetes excluded Systemic antimicrobials excluded	refusal to give informed consent pregnancy sensitivity or specific contraindications to the use of silver leg ulcers with a maximum diameter of less than 1 cm, atypical ulcers including those with suspicion of malignancy
Moffatt, 1992[49]	RCT; parallel arms	60 (NR)	Year NR 12 weeks	wound center	UK	No run-in No compliance	no CVU Ulcer duration: <12 weeks ABI: < 0.8	previously treated and healed within 24 weeks or decreased in size decreased by 20% or more after 12 weeks known allergy or other contraindication to the product
Mostow, 2005[32]	RCT; crossover if desired	120 (NR)	Year NR	derm clinic wound center vascular clinic	United States, United Kingdom and Canada	NR run-in Yes compliance	no CVU Age: <18 Ulcer duration: <4 weeks clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded Systemic antimicrobials excluded	Previous organ transplantation; Patients with Malnutrition and sickle cell disease; History of radiotherapy to the ulcer site; Patients with exposed bone, fascia and tendon
Nash, 1991[73]	NR	90 (NR)	1979 to 1986 3 years	pop source NR	NR	NR run-in No compliance	no CVU	
Nelson, 2007[29]	RCT; factorial	245 (525)	Year NR 24 weeks	wound center	UK	No run-in Yes compliance	no CVU Age: <18 Ulcer duration: <8 weeks clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded	ulcer < 1 cm in length; Significant arterial disease; Pregnant or lactating women; Unable or unwilling to provide written, informed consent; Premenopausal women not using contraceptives; Sensitivity to methylxanthines or caffeine containing drinks; Taking warfarin, steroids, oxpentifylline, oxerutins, or naftidrofuryl; Life expectancy <6 months, immobile patients, immunosuppression

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
O'Hare, 2010[58]	RCT; parallel arms	40 (315)	2005 to 2007 24 weeks	Leg ulcer clinic	UK	No run-in No compliance	ABI: < 0.8 Comorbids excluded Diabetes excluded	<1s retrograde flow on venous duplex imaging in GSV, SSV, AASV or other large superficial vein with significant proximal deep venous connection; Previous deep vein thrombosis or pulmonary embolism; Treatment with warfarin; Immobility and unable to give informed consent
Omar, 2004[34]	RCT; parallel arms	18 (NR)	Year NR 12 weeks	pop source NR	UK	No run-in No compliance	no CVU Ulcer duration: <12 weeks ABI: < 0.9	lack of superficial reflux presence of deep venous reflux DVT non-venous causes of ulceration, area <3 or >25 cm^2
Ormiston MC, 1983[55]	RCT; parallel arms	(NR)	Year NR 24 weeks	pop source NR	NR	NR run-in No compliance	no CVU Age: <21 Ulcer duration: <13 weeks Diabetes excluded	Ulcer diameter< 2cm; patients unable to change their own dressings non-venous cause, metabolic disease, psychiatric disease, malignancy patients with travel problems, iodine sensitivity multiple ulcers, pregnancy
Ormiston, 1985[44]	RCT; Parallel but allowed optional cross-over	61 (NR)	Year NR 24 weeks	Outpatients (center not identified)	UK	No run-in No compliance	Ulcer duration: <12 weeks ABI: < 0.7	Non-venous etiology ulcers When poor compliance was anticipated (because of distance or other limitations) unable to change dressing and did not have relative/friend to change dressing
Pang, 2010[70]	Case series	83 (NR)	2005 to 2009 16 months	vascular clinic	UK	No run-in No compliance	ABI: < 0.8	patients that do not have CEAP 5-6; post thrombotic DVR and/or obstruction
Pessenhofer, 1989[41]	RCT; parallel arms	48 (NR)	Year NR 281 days	derm clinic	NR	NR run-in No compliance		Hospitalization
Rojas, 2009[63]	non randomized; parallel arms	67 (72)	2006 to 2008 NR	hospital inpatient	Mexico	No run-in No compliance	no CVU ABI: < 0.8	Pulses at all levels

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Schulze, 2001[36]	RCT; Randomised Stratified controlled open-label study	113 (NR)	Year NR 4 weeks	wound center	Germany, UK	No run-in No compliance	no CVU ABI: < 0.8	Patients who were part of another research study within the previous 30 days
Scurr JH, 1993[54]	RCT; parallel arms	(NR)	Year NR 6 weeks	pop source NR	UK	NR run-in No compliance	no CVU ABI: < 0.9 Comorbids excluded Diabetes excluded	ulcer of unclear etiology
Scurr JH, 1994[53]	RCT; parallel arms	40 (NR)	to Year NR 6 weeks	wound center	UK	No run-in Yes compliance	Diabetes excluded Systemic antimicrobials excluded	chemotherapy or radiation treatment peripheral arterial disease
Sigala, 2007[78]	cohort	62 (NR)	2001 to 2005 1 year	vascular clinic	Germany	No run-in No compliance	Ulcer duration: >12 weeks clinical infection excluded ABI: < 0.8 comorbids excluded diabetes excluded	Malignancy; no venous perforator insufficiency; no CEAP stage 6
Smith, 1992[50]	RCT; parallel arms	200 (529)	1987 to 1988 4 months	community	UK	No run-in No compliance	no CVU ABI: < 0.75 Comorbids excluded Diabetes excluded	ulcer diameter <2cm; infection requiring immediate antibiotics; lymphedema, history of iodine allergy, neurologic disease
Sottiurai, 1991[67]	NR NA	46 (NR)	1981 to 1987 73 months	pop source NR	US	NR run-in		No recurrent leg ulcer refractory to non-surgical treatment, no incompetent perforator and deep venous valve demonstrated by venography, not compliant to pre-and post-treatment protocol

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Taradaj, 2011[75]	Case series from a RCT	305 (NR)	1999 to 2008 2 years	vascular clinic	Poland	No run-in No compliance	no CVU ABI: < 1 comorbids excluded diabetes excluded corticosteroids excluded	patients with metal implants; pregnancy
Teepe, 1993[40]	RCT; parallel arms	43 (NR)	1989 to 1991 6 weeks	derm clinic	Belgium	Yes run-in NR compliance	no CVU Ulcer duration: <12 weeks	
van Gent, 2006[65]	RCT; parallel arms	170 (NR)	1997 to 2001 36 months	pop source NR	The Netherlands	NR run-in No compliance	no CVU ABI: < 0.8	Total or partial occlusion of the deep venous system; Former subfascial ligation of perforating veins; Severe neurologic or muscular pathology; Immobility
Vanscheidt, 2007[26]	RCT; parallel arms	225 (NR)	NR 182 days	pop source NR	Germany, Czech Republic, Hungary	Yes run-in No compliance	Age: <18 & >90 Ulcer duration: <12 weeks ABI: < 0.8 Comorbids excluded Diabetes excluded	Venous leg ulcers above the knee joint or on distal metatarsal part of foot; venous ulcers <2 cm^2 or > 50cm^2; Pregnant or lactating women Venous surgery or sclerotherapy in preceding 3 months; know hypersensitivity to bovine proteins or other constituents of Bioseed; Phlebitis or deep leg vein thrombosis in preceding 3 months; unable to get or apply compression therapy
Vowden, 2006[30]	RCT; parallel arms	123 (NR)	2003 to 2004 12 weeks	pop source NR	pan-Europe	No run-in No compliance	Ulcer duration: <26 weeks clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded	ulcer size between <5 and >25 cm2 patient had to have received at least 1 month of compression therapy without ulcer improvement before study entry highly exuding wounds, recent vascular surgery or overt evidence of arterial disease, severe immobility those undergoing concomitant topical therapy

Author, year	Study design	N enrolled (N screened)	Enrollment year Followup duration	Source population	Country	Run in period? Washout period? Compliance measured?	Exclusion criteria	Other exclusion criteria comments
Vowden, 2007[25]	RCT; parallel arms	83 (101)	NR 12 weeks	pop source NR	NR	Yes run-in No compliance	Age: <18 Ulcer duration: <24 weeks clinical infection ABI: < 0.8 Comorbids excluded Diabetes excluded	Ulcer area <8cm^2 or >36cm^2 Confinement to bed or wheelchair; Physical and/or mental conditions making compliance difficult; Known allergy/hypersensitivity to product components
Weiss RA, 1996[52]	RCT; parallel arms	18 (NR)	NR 16 weeks	pop source NR	US	NR run-in Yes compliance	no CVU Ulcer duration: <9 weeks	<1 or >4 cm^2 in size
Wolters, 1997[79]	cohort	74 (NR)	1992 to 1995 1 year	vascular clinic	Germany	NR run-in No compliance		no singular insufficiency of perforating veins
Zamboni, 2003[61]	RCT; parallel arms	45 (80)	3 years	pop source NR	Italy	Yes run-in NR compliance	Age: >80 ABI: < 0.9 Diabetes excluded systemic antimicrobials excluded	Ulcer size<2cm^2 & >12cm^2; Patients unable to walk; secondary or congenital venous disease; (History of DVT &/duplex evidence of deep venous reflux or obstruction; congenital angiodysplasia)

Abbreviations: AASV = antibody associated systemic vasculitis; ABI = Ankle Brachial Index; CVI = chronic venous insufficiency; CVU = cardiovascular unit; Derm clinic = dermatological clinic; Diam = diameter; DM = diabetes mellitus; DVR = double valve replacement; DVT = deep vein thrombosis; GSV = great saphenous vein; Immune def = immune deficient; NR = not reported; RCT = randomized controlled trial; SSV = short saphenous vein; kg = kilogram; CEAP = clinical severity, etiology or cause, anatomy, pathophysiology; IMM = immunosuppressants

Table D-2. Study population characteristics of studies evaluating treatments for chronic venous ulcers

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Alinovi, 1986[82]	Compression: bandages	24	46	Mean: 66.7 Range: 46 to 81	Mean: 11.7 months	smoking NR systemic disease NR	IMM NR Steroids NR Additional procedure NR	
Alinovi, 1986[82]	antibiotic used: systemic antibiotics	23	57	Mean: 69.3 Range: 46 to 85	Mean: 10.4 months	smoking NR systemic disease NR	IMM NR Steroids NR Additional procedure NR	1
Arnold, 1994[39]	Compression: Unna boot gradient and zinc oxide paste AWD used: impreg gauze paraffin in US, salin/betadine in UK	35	Gender NR	Mean: 60	Mean: 47.8	Smoking status NR Diabetes NR Systemic disease NR	IMM NR Steroids NR Additional procedure NR	7
Arnold, 1994[39]	Compression: Unna boot gradient and zinc oxide paste AWD used: hydrocolloid	35	Gender NR	Mean: 65	Mean: 46.2	Smoking status NR Diabetes NR Systemic disease NR	IMM NR Steroids NR Additional procedure NR	9
Backhouse, 1987[43]	Compression: multi layer AWD used: Non-adherence non-occlusive dressing	28	43	Mean: 67.5 Median: Range: 30 to 90	Median: 21 months Range: 84 to months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Backhouse, 1987[43]	Compression: multi layer AWD used: hydrocolloid Granuflex (occlusive hydrocolloid)	28	39	Mean: 69.9 Median: Range: 34 to 92	Median: 22 months Range: 88 to months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Barwell, 2000[62]	Compression: refused surgery	515	gender NR	Median: 77 Range: 29 to 92	Mean: weeks Median: 16 weeks Range: 4 to 260 weeks	smoking NR 1 Rheumatoid Arthritis	NR steroid NR additional procedure NR	Total: 65
Barwell, 2000[62]	surgery: vein stripping, SEPS	131	gender NR	Median: 70 Range: 27 to 97	Median: 18 weeks Range: 4 to 180 weeks	smoking NR 9 Rheumatoid Arthritis	NR steroid NR additional procedure NR	Total: 65

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Barwell, 2004[60]	Compression: multi layer	258	44	Median: 72	Median: 5 months	smoking NR 10 Rhuematoid Arthritis	NR steroid NR additional procedure NR	22 Total: 40
Barwell, 2004[60]	Compression: multi layer surgery: vein stripping	242	40	Median: 74	Median: 5 months	smoking NR 5 Rhuematoid Arthritis	NR steroid NR additional procedure NR	18 Total: 40
Beckert, 2006[31]	Compression: 2 layer compression AWD used: hydrogel mildy antimicrobial shale oil	62	32	Mean: 66.8	Mean: 24.9 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR Jelonet (Nonadherent wound dressing): 100%	9 Total: 18
Beckert, 2006[31]	Compression: 2 layer compression AWD used: hydrogel	57	33	Mean: 70.6	Mean: 17.8 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR Jelonet (Nonadherent wound dressing): 100%	9 Total: 18
Bello, 1999[71]	surgery: other surgery	111	32	Median: 72 Range: 28 to 94	Median: 32 weeks Range: 2 to 1680 weeks	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	12 Total: 12
Cambal, 2008[69]	Compression: multi layer surgery: vein stripping	39	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Cambal, 2008[69]	Compression: multi layer surgery: SEPS	56	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Cambal, 2008[69]	Compression: multi layer surgery: sclerotherapy	698	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
El-Hafez, 2004[68]	Compression: multi layer AWD used: hydrocolloid antibiotic used: surgery: vein stripping	10	gender NR	age NR	Mean: 10.7 months Range: 7 to 15 months	smoking NR diabetes NR systemic disease NR	NR steroid NR intravenous antibiotics	

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
El-Hafez, 2004[68]	Compression: multi layer AWD used: hydrocolloid surgery: ligation	26	gender NR	age NR	Mean: 11.1 months Range: 8 to 15 months	smoking NR diabetes NR systemic disease NR	NR steroid NR intravenous antibiotics	
Falanga V, 1999[51]	Compression: Unna boot	48	64.6	Mean: 57.1 Range: 31 to 83	Range: 12 to months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Falanga V, 1999[51]	Compression: Unna boot AWD used: cellular or ECM	74	58.1	Mean: 58.7 Range: 20 to 86	Range: 12 to months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Falanga, 1998[38]	Compression: Unna boot	129	50.4	Mean: 60.4 Range: 31 to 85	Duration of ulcer NR	smoking NR diabetes NR systemic disease NR	IMM NR Steroids: 0% additional procedure NR	33
Falanga, 1998[38]	Compression: Unna boot AWD used: cellular or ECM	146	53.4	Mean: 60.2 Range: 28 to 84	Duration of ulcer NR	smoking NR diabetes NR systemic disease NR	IMM NR Steroids: 0% additional procedure NR	29
Franks, 2007[28]	Compression: short stretch multi layer AWD used: foam	81	39.5	Mean: 69.3	Median: 8 weeks Range: 2 to 36 weeks	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	23 Total: 46
Franks, 2007[28]	Compression: short stretch multi layer AWD used: foam	75	38.7	Mean: 69.2	Median: 8 weeks Range: 2 to 40 weeks	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	23 Total: 46
Galimberti, 1988[66]	Compression: 2 layer AWD: hydrocolloid	72	8	Mean: 69	Mean: 23 weeks	smoking NR diabetes NR systemic disease NR	NR	0
Galimberti, 1988[66]	Compression: 2 layer AWD: hydrocolloid Sclerotherapy	46	5	Mean: 67	Mean: 20 weeks	smoking NR diabetes NR systemic disease NR	NR	0
Gatti, 2011[45]	Compression: Unna boot AWD used: Essential fatty acid	11	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Gatti, 2011[45]	Compression: Unna boot AWD used: Essential fatty acid and fibrin sealant	13	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Gethin, 2009[24]	Compression: multi layer AWD used: hydrogel	54	gender NR	Mean: 68.3	Mean: 29.93 weeks	Smoker: 15% diabetes NR Hypertension: 35	IMM NR Steroids: 0% additional procedure NR	17
Gethin, 2009[24]	Compression: multi layer AWD used: Manuka honey	54	gender NR	Mean: 68.5	Mean: 39.46 weeks	Smoker: 19% diabetes NR Hypertension: 26	IMM NR Steroids: 0% additional procedure NR	9
Gohel, 2007[59]	Compression: multi layer	258	44	Median: 72	Median: 5 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR	27 Total: 54
Gohel, 2007[59]	Compression: multi layer surgery: vein stripping	242	40	Median: 74	Median: 5 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR	27 Total: 54
Gottrup, 2007[27]	Compression: unspec compression AWD used: foam	60	38	Mean: 70	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	3
Gottrup, 2007[27]	Compression: unspec compression AWD used: foam Ibuprofen	62	31	Mean: 66	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	7
Gottrup, 2008[23]	Compression: kept a constant circumference at the ankle AWD used: foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S)	60	38	Mean: 70	Mean: 19.8 months	smoking NR Diabetes NR Systemic disease NR	IMM NR Steroids NR Additional procedure NR	

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Gottrup, 2008[23]	Compression: kept a constant circumference at the ankle AWD used: foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S	62	31	Mean: 66	Mean: 23.1 months	smoking NR Diabetes NR Systemic disease NR	IMM NR Steroids NR Additional procedure NR	13
Greguric, 1994[48]	Compression: 2 layer compression AWD used: magnesium sulfate paste + vaseline + gauze	55	44	Mean: 61	Median: 284 weeks	Smoker: 25% diabetes NR systemic disease NR	IMM: 0% Steroids: 0% Additional procedure NR	
Greguric, 1994[48]	Compression: 2 layer compression AWD used: hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam)	55	38	Mean: 61	Median: 248 weeks	Smoker: 15% diabetes NR systemic disease NR	IMM: 0% Steroids: 0% Additional procedure NR	
Guest, 2003[64]	Compression: 4-layer	37	35	Mean: 67	Median: 6 months Range: 1 to 200 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR	
Guest, 2003[64]	Compression: 4-layer surgery: vein stripping, SEPS	39	38	Mean: 68	Median: 6 months Range: 1 to 240 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR	
Hansson, 1998[37]	Compression: short stretch AWD used: paraffin gauze	40	Gender NR	Mean: 72	duration NR	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR additional procedure NR	9

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Hansson, 1998[37]	Compression: short stretch AWD used: hydrocolloid Duoderm	48	Gender NR	Mean: 74	duration NR	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR additional procedure NR	7
Hansson, 1998[37]	Compression: short stretch AWD used: antibacterial dressings cadexomer iodine paste	56	Gender NR	Mean: 74	duration NR	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR additional procedure NR	12
Harding, 2005[33]	Compression: 2 layer compression AWD used: hydrocolloid keratinocyte lysate	46	39	Median: 68 Range: 46 to 82	Median: 0.83 years Range: 0.2 to 47 years	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 16
Harding, 2005[33]	Compression: 2 layer compression AWD used: hydrocolloid	53	43	Median: 68 Range: 40 to 84	Median: 0.75 years Range: 0.1 to 20 years	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 16
Harding, 2005[33]	Compression: AWD used: cellular or ECM	95	25	Median: 67 Range: 36 to 85	Median: 0.83 years Range: 0.1 to 20 years	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 16
Harding, 2011[20]	Compression: UK Class III compression system AWD used: antibacterial dressings impreg gauze	136	33.8	Mean: 71.21 Range: 40 to 99	Mean: 0.72 years	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	16 Total: 27
Harding, 2011[20]	Compression: UK Class III compression system AWD used: specialty absorp antibacterial dressings	145	35.2	Mean: 68.72 Median: Range: 34 to 97	Mean: 0.8 years	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	11 Total: 27
Harlander-Locke, 2011[74]	Compression: multi layer surgery: RFA	72	44	Mean: 71	Mean: 71 months Range: 2 to 432 months	smoking NR 20.8 Vasculitis	NR steroid NR microphlebectomy	4

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Holloway, 1989[42]	Compression: Toe-to-knee elastic compression bandage	37	73	Mean: 61.5 Range: 31 to 84	Mean: 11.4 months Median: 4.5 months Range: 3 to 130 months	smoking NR diabetes NR Systemic disease NR	IMM NR steroid NR additional procedure NR	Not given Total: 21
Holloway, 1989[42]	Compression: Toe-to-knee elastic compression bandage AWD used: hydrocolloid antibacterial dressings	38	74	Mean: 63 Range: 34 to 93	Mean: 29.5 months Median: 7.5 months Range: 3 to 240 months	smoking NR diabetes NR Systemic disease NR	IMM NR steroid NR additional procedure NR	Not given Total: 21
Huovinen, 1994[57]	Antibiotic used: Placebo	10	Gender NR	Age NR	Mean: 29 months Range: 3 to 96 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure: comprilan elastic bandage and local therapy, zinc and varitube sock	1
Huovinen, 1994[57]	antibiotic used: Placebo trimethoprim/ sulfamethoxazole	9	Gender NR	Age NR	Mean: 67 months Range: 4 to 252 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NRcomprilan elastic bandage and local therapy, zinc and varitube sock	2
Huovinen, 1994[57]	antibiotic used: Placebo ciprofloxacin	12	Gender NR	Age NR	Mean: 72 months Range: 3 to 216 months	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NRcomprilan elastic bandage and local therapy, zinc and varitube sock	1
Huovinen, 1994[57]	antibiotic used: Placebo		Gender NR	Age NR	Duration of ulcer NR	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR; comprilan elastic bandage and local therapy, zinc and varitube sock	

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Krishnamoorthy, 2003[47]	Compression: multi layer Profore	13	46	Mean: 67.3	Median: 73.7 weeks Range: 8.7 to 260 weeks	Smoking status NR Diabetes NR Deep vein thrombosis: 38	IMM NR steroid NR Additional procedure NR	1 Total: 5
Krishnamoorthy, 2003[47]	Compression: multi layer Profore AWD used: cellular or ECM Dermagraft 4pc	13	31	Mean: 62.5	Median: 52 weeks Range: 9 to 260 weeks	Smoking status NR Diabetes NR Deep vein thrombosis: 38	IMM NR steroid NR Additional procedure NR	1 Total: 5
Krishnamoorthy, 2003[47]	Compression: multi layer Profore AWD used: Dermagraft 1pc	14	50	Mean: 72	Median: 43.3 weeks Range: 11.7 to 238.3 weeks	Smoking status NR Diabetes NR Deep vein thrombosis: 29	IMM NR steroid NR Additional procedure NR	3 Total: 5
Krishnamoorthy, 2003[47]	Compression: multi layer Profore AWD used: Dermagraft 12 pcs	13	38	Mean: 72.8	Median: 34.7 weeks Range: 13 to 260 weeks	Smoking status NR Diabetes NR Deep vein thrombosis: 31	IMM NR steroid NR Additional procedure NR	0 Total: 5
Kucharzewski, 2003[46]	Compression: Unna boot	27	37	Mean: 59.2 Range: 50 to 68	Mean: 70 months Range: 9 to 100 months	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR additional procedure NR	
Kucharzewski, 2003[46]	Compression: unspec compression AWD used: (Bioprocess) Cellulose membrane	27	44	Mean: 60.6 Range: 52 to 70	Mean: 68 months Range: 7 to 108 months	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR additional procedure NR	
Labas, 2009[76]	Compression: multi layer elastic compression for 10 days postsurgery surgery: valvuloplasty of the popliteal vein and reflux in GSV and SSV treated with compression sclerotherapy	56	22	Mean: 54 Median: Range: 27 to 79	Median: 5 months Range: 3 to 14 months	Smoking status NR Diabetes NR Systemic disease NR	IMM NR Steroids NR skin grafting	
Lammoglia-Ordiales, 2011[56]	Compression: 2 layer compression AWD used: hydrogel	19	32	Mean: 62.6	Mean: 91.89 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	5 Total: 9

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Lammoglia-Ordiales, 2011[56]	Compression: 2 layer compression AWD used: MTC-2G	22	41	Mean: 58.12	Mean: 101.9 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	4 Total: 9
Lane, 2003[77]	surgery: angioplasty stenting	41	46	Mean: 60.3 Range: 30 to 82	Mean: 8.7 months	Smoking status NR Diabetes NR Systemic disease NR	IMM NR Steroids NR Additional procedure NR	
Lawrence, 2011[14]	Compression: multi layer surgery: RFA	45	58	Mean: 74 Range: 35 to 93	Mean: 93 months Range: 1 to 300 months	smoking NR 18 systemic disease NR	2 steroid NR additional procedure NR	10
Limova, 2003[35]	Compression: 2 layer compression AWD used: alginate	10	30	Mean: 75.4 Range: 51 to 88	Mean: 6.1 months Range: 2 to 14 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Limova, 2003[35]	AWD used: alginate	9	0	Mean: 75.8 Range: 45 to 93	Mean: 9.1 months Range: 1 to 24 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Maggio, 2011[21]	Compression: multi layer AWD used: alginate	26	52.2	Mean: 57.9	Mean: 23.4	smoking NR Diabetes: 0% systemic disease NR	MM: 0% Steroids: 0% Calcium alginate: 100%	
Maggio, 2011[21]	Compression: multi layer AWD used: alginate Vulnamin- glycine, leucine, proline, lysine, sodium hyaluronate	26	53.9	Mean: 58.6	Mean: 25.4	smoking NR Diabetes: 0% systemic disease NR	IMM: 0% Steroids: 0% Calcium alginate: 100%	
Masuda, 1994[72]	Compression: elastic stocking surgery: vein stripping	48	gender NR	age NR	Mean: 8.3 years	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Michaels, 2009[22]	Compression: multi layer AWD used: antibacterial dressings	107	50.47	Mean: 68.8	duration NR	Smoker: 16.8% diabetes NR systemic disease NR	IMM NR Steroids NR additional procedure NR	3

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Michaels, 2009[22]	Compression: multi layer AWD used: seem to be matched various dressings	106	41.51	Mean: 72.4	duration NR	Smoker: 19.8% diabetes NR systemic disease NR	IMM NR Steroids NR additional procedure NR	2
Michaels, 2009[22]	Compression: enzymatic debris AWD used: hydrocolloid		Gender NR	Age NR	duration NR	Smoking status NR diabetes NR systemic disease NR	IMM NR Steroids NR additional procedure NR	
Moffatt, 1992[49]	Compression: 4-layer AWD used: Non-adherent	30	40	Mean: 71 Range: 26 to 87	duration NR	smoking NR Diabetes: 10% Hypertension: 13	IMM NR steroid NR additional procedure NR	Total: 4
Moffatt, 1992[49]	Compression: 4-layer AWD used: hydrocolloid Comfeel, Coloplast	30	50	Mean: 74 Range: 50 to 89	duration NR	smoking NR Diabetes: 0% Hypertension: 10	IMM NR steroid NR additional procedure NR	Total: 4
Mostow, 2005[32]	Compression: multi layer Unspecified Compression+ Debridementement	58	36	Mean: 65 Range: 36 to 93	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	8 Total: 17
Mostow, 2005[32]	Compression: multi layer composite acellular or ECM	62	47	Mean: 63 Range: 21 to 90	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	9 Total: 17
Nash, 1991[73]	Compression: 30-40mmHg surgery: vein stripping	42	gender NR	age NR	Duration of ulcer NR	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure NR	
Nelson, 2007[29]	Compression: multi layer AWD used: Pentoxifylline, Knitted viscose	25	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Nelson, 2007[29]	Compression: multi layer AWD used: hydrocolloid Pentoxifylline	32	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Nelson, 2007[29]	Compression: multi layer AWD used: Knitted viscose, Placebo	27	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Nelson, 2007[29]	Compression: multi layer AWD used: hydrocolloid Placebo	33	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
O'Hare, 2010[58]	Compression: multi layer	22	gender NR	Median: 69	Median: 14 weeks	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	1
O'Hare, 2010[58]	Compression: multi layer surgery: sclerotherapy	18	gender NR	Median: 69	Median: 14 weeks	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	3
Omar, 2004[34]	Compression: 4-layer	8	62	Mean: 62 Range: 54 to 77	Mean: 120 weeks Range: 24 to 288 weeks	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Omar, 2004[34]	Compression: 4-layer AWD used: cellular or ECM Dermagraft	10	60	Mean: 58 Range: 44 to 65	Mean: 118.8 weeks Range: 12 to 192 weeks	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Ormiston MC, 1983[55]	Compression: unspec compression AWD used: Cadexomer iodine	27	33.3	Mean: 65	Mean: 52 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Ormiston MC, 1983[55]	Compression: unspec compression AWD used: antibacterial dressings	27	29.6	Mean: 66	Mean: 20 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Ormiston, 1985[44]	Compression: crepe then cotton crepe compression bandage (STD) AWD used: Gentian violet and Polyfax	30	27	Mean: 70.3 Range: 44 to 92	Mean: 15.9 months Median: 6 months Range: 3 to 96 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	0 Total: 1

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Ormiston, 1985[44]	Compression: crepe then cotton crepe compression bandage (STD) AWD used: Cadexomer iodine	30	43	Mean: 67.3 Range: 49 to 86	Mean: 45.9 months Median: 8.5 months Range: 3 to 517 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	1 Total: 1
Pang, 2010[70]	Compression: 2 layer compression surgery: sclerotherapy	83	45	age NR	Median: 8 weeks	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Pessenhofer, 1989[41]	Compression: Unna boot	25	16	Mean: 65.7	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR Additional procedure; Fibrolan ointment	1 Total: 7
Pessenhofer, 1989[41]	Compression: Unna boot AWD used: foam	23	13	Mean: 66.7	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR Additional procedure; Fibrolan ointment	6 Total: 7
Rojas, 2009[63]	Compression: Unna boot	37	8	Mean: 53	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	Total: 2
Rojas, 2009[63]	Compression: Unna boot surgery: sclerotherapy, ultrasound guided	33	12	Mean: 58	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	Total: 2
Schulze, 2001[36]	AWD used: Specialty absorp	54	30	Mean: 73.6 Range: 34 to 95	Mean: 49.5 months Range: 0.5 to 744 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	27 Total: 66
Schulze, 2001[36]	Compression: AWD used: Alginate + Film	22	45	Mean: 72.4 Range: 32 to 90	Mean: 45.6 months Range: 0.5 to 396 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	12 Total: 66
Schulze, 2001[36]	AWD used: Alginate + Swabs	37	32	Mean: 72.7 Range: 28 to 97	Mean: 35 months Range: 0.2 to 360 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	27 Total: 66

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Scurr JH, 1993[54]	AWD used: alginate foam	10	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 0
Scurr JH, 1993[54]	AWD used: transparent film alginate	10	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 0
Scurr JH, 1994[53]	Compression: graduated elastic compression stocking AWD used: alginate	20	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 0
Scurr JH, 1994[53]	Compression: graduated elastic compression stocking AWD used: hydrocolloid	20	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 0
Sigala, 2007[78]	surgery: SEPS	67	33	Mean: 62 Range: 39 to 78	Mean: 3.7 years Range: 0.9 to 7.5 years	smoking NR diabetes NR systemic disease NR	NR steroid NR Shaving	
Smith, 1992[50]	Compression: 2 layer compression linear, graduated (Tubigrip or Venosan 2002) AWD used: Betadine/Jelonet	62	gender NR	Mean: 72	Median: 3 months Range: 12 to months	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR Venosan stocking: 77%	14 Total: 60
Smith, 1992[50]	Compression: linear, graduated (Tubigrip or Venosan 2002) AWD used: Betadine/Jelonet	39	gender NR	Mean: 73	Median: 17 months Range: 68 to months	smoking NR Diabetes: 0% systemic disease NR	IMM NR steroid NR Venosan stocking: 69%	19 Total: 60
Smith, 1992[50]	Compression: linear, graduated (Tubigrip or Venosan 2002) AWD used: hydrocolloid Biofilm powder+Biofilm dressing	64	gender NR	Mean: 74	Median: 5 months Range: 20 to months	smoking NR Diabetes NR systemic disease NR	IMM NR steroid NR Venosan stocking: 70%	21 Total: 60

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Smith, 1992[50]	Compression: linear, graduated (Tubigrip or Venosan 2002) AWD used: hydrocolloid Biofilm powder+Biofilm dressing	35	gender NR	Mean: 76	Mean: months Median: 14 months Range: 56 to months	smoking NR Diabetes NR systemic disease NR	IMM NR steroid NR Venosan stocking: 63%	6 Total: 60
Sottiurai, 1991[67]	Compression: pump Unna boot elastic stocking or ace wrap surgery: vein stripping	33	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Sottiurai, 1991[67]	Compression: pump Unna boot elastic stocking or ace wrap surgery: vein stripping, valvuloplasty	21	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Sottiurai, 1991[67]	Compression: pump Unna boot elastic stocking or ace wrap surgery: vein stripping, transposition	14	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Sottiurai, 1991[67]	Compression: pump Unna boot elastic stocking or ace wrap surgery: vein stripping, transplantation	8	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR additional procedure NR	
Taradaj, 2011[75]	Compression: pressure of 25-32 mmHg at the ankle surgery: vein stripping, ligation	35	37	Mean: 61.43 Range: 43 to 80	Mean: 33.5 months Range: 6 to 180 months	23 diabetes NR systemic disease NR	NR steroid NR micronized flavonoid fraction	
Teepe, 1993[40]	Compression: short stretch AWD used: hydrocolloid	21	24	Mean: 69 Range: 39 to 85	Mean: 26 months Range: 3 to 360 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	4

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Teepe, 1993[40]	Compression: short stretch AWD used: cellular or ECM	22	27	Mean: 74 Range: 60 to 90	Range: 3 to 240 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	5
van Gent, 2006[65]	Compression: 2 layer compression	102	gender NR	Mean: 68	Median: 17 weeks Range: to weeks	smoking NR 17 systemic disease NR	NR steroid NR concomitant superficial vein surgery	
van Gent, 2006[65]	Compression: 2 layer compression surgery: SEPS	94	gender NR	Mean: 64	Median: 17 weeks Range: to weeks	smoking NR 7 systemic disease NR	NR steroid NR concomitant superficial vein surgery	
Vanscheidt, 2007[26]	Compression: short stretch AWD used: contact layer	109	41.3	Range: 33 to 88	Range: 3 to >12 months	Smoker 21.1% diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Vanscheidt, 2007[26]	Compression: short stretch AWD used: contact layer cellular or ECM	116	32.8	Range: 29 to 89	Range: 3 to >12 months	Smoker: 17.2% diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Vowden, 2006[30]	Compression: high-compression AWD used: amelogenin proteins (Xelmat)	62	32.3	Mean: 72 Median: 73.5 Range: 48 to 89	Mean: 32.4 months Median: 12 months Range: 6 to 360 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Vowden, 2006[30]	Compression: high-compression AWD used: alginate	61	36.1	Mean: 70.9 Median: 73 Range: 44 to 90	Mean: 41.9 months Median: 24 months Range: 6 to 360 months	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	
Vowden, 2007[25]	Compression: high	41	37	Mean: 72.7 Median: 75.5 Range: 33.5 to 93.4	Mean: 32.4 months Median: 24 months Range: 6 to 120 months	smoking NR Diabetes: 10% systemic disease NR	IMM NR Steroids NR additional procedure NR	15 Total: 24

Author, year	Intervention used	N enrolled	% Male	Age (years)	Ulcer duration	Smoking status Diabetes status Systemic disease status	Immunosuppressant use Corticosteroid use Additional procedures	Withdrawals
Vowden, 2007[25]	Compression: high AWD used: acellular or ECM	42	41	Mean: 68.5 Median: 71 Range: 25.6 to 91.2	Mean: 55.3 months Median: 30 months Range: 6 to 240 months	smoking NR Diabetes: 10% systemic disease NR	IMM NR Steroids NR additional procedure NR	9 Total: 24
Weiss RA, 1996[52]	Compression: Jobst UlcerCare stocking AWD used: foam slightly adhesive hydroactive foam dressing (Cutinova foam)	10	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 3
Weiss RA, 1996[52]	Compression: Jobst UlcerCare stocking AWD used: foam non-adhesive absorptive foam dressing (Allevyn)	8	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	IMM NR steroid NR additional procedure NR	Total: 3
Wolters, 1997[79]	Compression: unspec compression surgery: SEPS	74	42	Mean: 55.7 Range: 28 to 82	Mean: 8 months Range: 6 to 13 months	smoking NR 18 kidney insufficiency	NR steroid NR additional procedure NR	
Zamboni, 2003[61]	Compression: 20-30mmHg AWD used: foam	24	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure; Foam dressing and Zinc Oxide dressing & Antibiotics	0 Total: 0
Zamboni, 2003[61]	Compression: 20-30mmHg pressure surgery: vein stripping	21	gender NR	age NR	duration NR	smoking NR diabetes NR systemic disease NR	NR steroid NR Additional procedure; Foam dressing and Zinc Oxide dressing & Antibiotics	0 Total: 0

Abbreviations**:** absorp = absorption; AWD = advanced wound dressing; ECM = extracellular matrix; GSV = great saphenous vein; IMM = immunosuppressant; impreg = impregnated; mm Hg = millimeters of mercury; MTC= M. tenuiflora cortex; NR = not reported; RFA = radio frequency ablation; SEPS = subfascial endoscopic perforator surgery; SSV = short saphenous vein; unspec = unspecified

Table D-3a. Intervention characteristics of studies evaluating advanced wound dressings for the treatment of chronic venous ulcers

Author, year	Compression	Advanced wound dressing type	Duration of intervention
Arnold, 1994[39]	Unna boot gradient and zinc oxide paste	impreg gauze; paraffin in US, salin/betadine in UK	10 weeks
Arnold, 1994[39]	Unna boot gradient and zinc oxide paste	hydrocolloid	10 weeks
Backhouse, 1987[43]	multi layer	Hydrocolloid; Granuflex (occlusive hydrocolloid)	12 weeks
Backhouse, 1987[43]	multi layer	Non-adherence non-occlusive dressing	12 weeks
Beckert, 2006[31]	2 layer compression	Hydrogel; mildly antimicrobial shale oil	20 weeks
Beckert, 2006[31]	2 layer compression	hydrogel	20 weeks
Falanga V, 1999[51]	Unna boot		NR
Falanga V, 1999[51]	Unna boot	cellular or ECM	NR
Falanga, 1998[38]	Unna boot	cellular or ECM	NR
Falanga, 1998[38]	Unna boot		NR
Franks, 2007[28]	short stretch multi layer	foam	24 weeks
Franks, 2007[28]	short stretch multi layer	foam	24 weeks
Gatti, 2011[45]	Unna boot	Essential fatty acid	8 weeks
Gatti, 2011[45]	Unna boot	Essential fatty acid and fibrin sealant	8 weeks
Gethin, 2009[24]	multi layer	Manuka honey	4 weeks
Gethin, 2009[24]	multi layer	hydrogel	4 weeks
Gottrup, 2007[27]	unspec compression	Foam; Ibuprofen	42 days
Gottrup, 2007[27]	unspec compression	foam	42 days
Gottrup, 2008[23]	kept a constant circumference at the ankle	foam; contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S	weeks
Gottrup, 2008[23]	kept a constant circumference at the ankle	Foam; NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S)	weeks
Greguric, 1994[48]	2 layer compression	Hydrocolloid; Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam)	NR
Greguric, 1994[48]	2 layer compression	magnesium sulfate paste + vaseline + gauze	NR
Hansson, 1998[37]	short stretch	paraffin gauze	12 weeks
Hansson, 1998[37]	short stretch	Hydrocolloid; Duoderm	12 weeks
Hansson, 1998[37]	short stretch	antibacterial dressings; cadexomer iodine paste	12 weeks
Harding, 2005[33]	2 layer compression	Hydrocolloid; keratinocyte lysate	10 weeks
Harding, 2005[33]	2 layer compression	hydrocolloid	10 weeks
Harding, 2005[33]		cellular or ECM	10 weeks
Harding, 2011[20]	UK Class III compression system	specialty absorp; antibacterial dressings	4 weeks
Harding, 2011[20]	UK Class III compression system	antibacterial dressings impreg gauze	4 weeks
Holloway, 1989[42]	Toe-to-knee elastic compression bandage	Hydrocolloid; antibacterial dressings	
Holloway, 1989[42]	Toe-to-knee elastic compression bandage		
Krishnamoorthy, 2003[47]	multi layer; Profore	cellular or ECM; Dermagraft 4pc	12 weeks
Krishnamoorthy, 2003[47]	multi layer; Profore	Dermagraft 1pc	12 weeks

Author, year	Compression	Advanced wound dressing type	Duration of intervention
Krishnamoorthy, 2003[47]	multi layer; Profore	Dermagraft 12 pcs	12 weeks
Krishnamoorthy, 2003[47]	multi layer; Profore		
Kucharzewski, 2003[46]	unspec compression	(Bioprocess) Cellulose membrane	140 days
Kucharzewski, 2003[46]	Unna boot		140 days
Lammoglia-Ordiales, 2011[56]	2 layer compression	hydrogel	8 weeks
Lammoglia-Ordiales, 2011[56]	2 layer compression	MTC-2G	8 weeks
Limova, 2003[35]	2 layer compression	alginate	6 weeks
Limova, 2003[35]		alginate	6 weeks
Maggio, 2011[21]	multi layer	alginate	70 days
Maggio, 2011[21]	multi layer	Alginate; Vulnamin- glycine, leucine, proline, lysine, sodium hyaluronate	70 days
Michaels, 2009[22]	multi layer	antibacterial dressings	1 years
Michaels, 2009[22]	multi layer	seem to be matched various dressings	1 years
Michaels, 2009[22]	enzymatic debridement	hydrocolloid	
Moffatt, 1992[49]	4-layer	hydrocolloid ; Comfeel, Coloplast	12 weeks
Moffatt, 1992[49]	4-layer	Non-adherent	12 weeks
Mostow, 2005[32]	multi layer; Unspecified Compression+ Debridementement		12 weeks
Mostow, 2005[32]	multi layer	Composite; acellular or ECM	12 weeks
Nelson, 2007[29]	multi layer	Pentoxifylline, Knitted viscose	24 weeks
Nelson, 2007[29]	multi layer	hydrocolloid; Placebo	24 weeks
Nelson, 2007[29]	multi layer	Knitted viscose, Placebo	24 weeks
Nelson, 2007[29]	multi layer	Hydrocolloid; Pentoxifylline	24 weeks
Omar, 2004[34]	4-layer	cellular or ECM; Dermagraft	12 weeks
Omar, 2004[34]	4-layer		12 weeks
Ormiston MC, 1983[55]	unspec compression	Cadexomer iodine	24 weeks
Ormiston MC, 1983[55]	unspec compression	antibacterial dressings	24 weeks
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD)	Gentian violet and Polyfax	12 weeks
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD)	Cadexomer iodine	12 weeks
Pessenhofer, 1989[41]	Unna boot		NA
Pessenhofer, 1989[41]	Unna boot	foam	NA
Schulze, 2001[36]		Alginate + Film	4 weeks
Schulze, 2001[36]		Alginate + Swabs	
Schulze, 2001[36]		Specialty absorp	4 weeks
Scurr JH, 1993[54]	Compression stocking	alginate foam	6 weeks
Scurr JH, 1993[54]	Compression stocking	transparent film alginate	6 weeks
Scurr JH, 1994[53]	graduated elastic compression stocking	alginate	6 weeks
Scurr JH, 1994[53]	graduated elastic compression stocking	hydrocolloid	6 weeks
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002)	Hydrocolloid; Biofilm powder+Biofilm dressing	
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002)	Hydrocolloid; Biofilm powder+Biofilm dressing	

Author, year	Compression	Advanced wound dressing type	Duration of intervention
Smith, 1992[50]	2 layer compression; linear, graduated (Tubigrip or Venosan 2002)	Betadine/Jelonet	4 months
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002)	Betadine/Jelonet	4 months
Teepe, 1993[40]	short stretch	hydrocolloid	6 weeks
Teepe, 1993[40]	short stretch	cellular or ECM	6 weeks
Vanscheidt, 2007[26]	short stretch	contact layer	182 days
Vanscheidt, 2007[26]	short stretch	contact layer, cellular or ECM	182 days
Vowden, 2006[30]	high-compression	alginate	12 weeks
Vowden, 2006[30]	high-compression	amelogenin proteins (Xelmat)	12 weeks
Vowden, 2007[25]	high	acellular or ECM	12 weeks
Vowden, 2007[25]	high		12 weeks
Weiss RA, 1996[52]	Jobst UlcerCare stocking	Foam; non-adhesive absorptive foam dressing (Allevyn)	16 weeks
Weiss RA, 1996[52]	Jobst UlcerCare stocking	Foam; slightly adhesive hydroactive foam dressing (Cutinova foam)	16 weeks

Table D-3b. Intervention characteristics of studies evaluating antibiotics for the treatment chronic venous ulcers

Author, year	Compression	Antibiotics used	Duration of intervention
Alinovi, 1986[82]	Bandages; merbromin 2% solution to ulcer surface, thin layer of dipropionate 0.05% cream on whole leg except ulcer and 2cm perilesional, gauze impregnated with zinc oxide and ichthammol, stocking	NA	10 days
Alinovi, 1986[82]	Bandages; merbromin 2% solution to ulcer surface, thin layer of dipropionate 0.05% cream on whole leg except ulcer and 2cm perilesional, gauze impregnated with zinc oxide and ichthammol, stocking	systemic antibiotics, selected by sensitivity test	10 days
Huovinen, 1994[57]	encouraged to use Coprilan elastic bandage and local therapy (Varitube sock and 0.2 g zinc in 1g potrlatum-parrafin-based ointment)	Placebo (twice daily)	12 weeks
Huovinen, 1994[57]	encouraged to use Coprilan elastic bandage and local therapy (Varitube sock and 0.2 g zinc in 1g potrlatum-parrafin-based ointment)	Ciprofloxacin (750 mg twice daily) or tripethoprim (160 mg twice daily)	12 weeks

Table D-3c. Intervention characteristics of studies evaluating surgery for the treatment chronic venous ulcers

Author, year	Compression	Surgical intervention	Duration of intervention
Barwell, 2000[62]	4-layer	vein stripping; SEPS	NR
Barwell, 2000[62]	4-layer	refused surgery	NR
Barwell, 2004[60]	multi layer	NA	Until ulcer healing
Barwell, 2004[60]	multi layer	vein stripping	Until ulcer healing
Bello, 1999[71]	4-layer	other surgery	NA
Cambal, 2008[69]	multi layer	vein stripping	NR
Cambal, 2008[69]	multi layer	Sclerotherapy, Sigg's and Fegan's techniques	NR
Cambal, 2008[69]	multi layer	SEPS	NR
El-Hafez, 2004[68]	multi layer; hydrocolloid	ligation	NA
El-Hafez, 2004[68]	multi layer; hydrocolloid	vein stripping	NA
Galimberti, 1988[66]	2 layer; hydrocolloid	NA	NA
Galimberti, 1988[66]	2 layer; hydrocolloid	Sclerotherapy	NA
Gohel, 2007[59]	multi layer	NA	NR
Gohel, 2007[59]	multi layer	vein stripping	NR
Guest, 2003[64]	4-layer	NA	26 weeks
Guest, 2003[64]	4-layer	vein stripping; SEPS	NA
Harlander-Locke, 2011[74]	Multi-layer	RFA	NA
Labas, 2009[76]	Multi layer; elastic compression for 10 days postsurgery	valvuloplasty of the popliteal vein and reflux in GSV and SSV treated with compression sclerotherapy	NA
Lane, 2003[77]	Multi layer	angioplasty stenting	
Lawrence, 2011[14]	Multi layer	RFA	NR
Masuda, 1994[72]	Elastic stocking	vein stripping	NA
Nash, 1991[73]	30-40mmHg	vein stripping	NA
O'Hare, 2010[58]	Multi layer	sclerotherapy	NR
O'Hare, 2010[58]	Multi layer	NA	NR
Pang, 2010[70]	2 layer compression	sclerotherapy	1 weeks
Rojas, 2009[63]	Unna boot	NA	21 days average followup
Rojas, 2009[63]	Unna boot	Sclerotherapy; ultrasound guided	21 days average followup
Sigala, 2007[78]	23-32 mmHg, Class II compression	SEPS	NA
Sottiurai, 1991[67]	pump Unna boot elastic stocking or ace wrap	vein stripping	NA
Sottiurai, 1991[67]	pump Unna boot elastic stocking or ace wrap	vein stripping; valvuloplasty	NA
Sottiurai, 1991[67]	pump Unna boot elastic stocking or ace wrap	vein stripping; transplantation	NA
Sottiurai, 1991[67]	pump Unna boot elastic stocking or ace wrap	vein stripping; transposition	NA
Taradaj, 2011[75]	pressure of 25-32 mmHg at the ankle	vein stripping; ligation	7 weeks
van Gent, 2006[65]	2 layer compression	SEPS	Until ulcer healing
van Gent, 2006[65]	2 layer compression	NA	Until ulcer healing
Wolters, 1997[79]	unspec compression	SEPS	NA

Author, year	Compression	Surgical intervention	Duration of intervention
Zamboni, 2003[61]	20-30mmHg pressure	vein stripping	Until ulcer healing
Zamboni, 2003[61]	20-30mmHg	NA	Until ulcer healing

Abbreviations**:** absorp = absorption; ECM = extracellular matrix; impreg = impregnated; mg = milligrams; mm Hg = millimeters of mercury; MTC= M. tenuiflora cortex; NA = not applicable; NR = not reported; pc = piece; SEPS = subfascial endoscopic perforator surgery; STD = standard; UK = United Kingdom; unspec = unspecified; US = United States

Table D-4a. Reported outcomes of studies evaluating advanced wound dressings as treatment for chronic venous ulcers

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Arnold, 1994[39]	Unna boot gradient and zinc oxide paste; impreg gauze paraffin in US; salin/betadine in UK, 35	Unna boot gradient and zinc oxide paste; hydrocolloid, 35	prop ulcers healed ulcers (out of 90 total, 70 patients)	10 weeks	Events: 14 Denominator: total ulcers P: >0.05 ref: Grp2	Events: 11 Denominator: total ulcers
Arnold, 1994[39]	Unna boot gradient and zinc oxide paste; impreg gauze paraffin in US, salin/betadine in UK, 35	Unna boot gradient and zinc oxide paste; hydrocolloid, 35	time to complete closure (Mean time to healing in weeks)		Final Grp1 Mean(SE): 8.2(0.4) P: >0.05, ref Grp2	Final Grp2 Mean(SE): 7.09(0.2)
Arnold, 1994[39]	Unna boot gradient and zinc oxide paste; impreg gauze paraffin in US, salin/betadine in UK, 35	Unna boot gradient and zinc oxide paste; hydrocolloid, 35	wound healing rates no intermediate to complete(% area reduced)	10 weeks	% area reduced : 42	% area reduced: 71(71)
Backhouse, 1987[43]	multi layer; Non-adherence non-occlusive dressing, 28	multi layer; hydrocolloid Granuflex (occlusive hydrocolloid), 28	prop ulcers healed (healing at 6 wks); tracings	6 weeks	pts with event (%): 15(54)	pts with event (%): 15(54)
Backhouse, 1987[43]	multi layer; Non-adherence non-occlusive dressing, 28	multi layer; hydrocolloid Granuflex (occlusive hydrocolloid), 28	Infection (Not further specified)	12 weeks	pts with event (%): 3(11)	pts with event (%): 4(14)
Backhouse, 1987[43]	multi layer; Non-adherence non-occlusive dressing, 28	multi layer; hydrocolloid Granuflex (occlusive hydrocolloid), 28	prop ulcers healed (healed at 12 weeks; tracings	12 weeks	pts with event (%): 22(78) Final Grp1 Other PE	pts with event (%): 21(75) Final Grp2 Other PE
Beckert, 2006[31]	2 layer compression; hydrogel mildly antimicrobial shale oil, 62	2 layer compression; hydrogel, 57	prop ulcers healed (Number of ulcers healed)	20 weeks	Events: 33 Denominator: NA P: 0.177 ref: Grp2	Events: 21 Denominator: NA P: 0.177 ref: Grp1
Beckert, 2006[31]	2 layer compression; hydrogel mildy antimicrobial shale oil, 62	2 layer compression; hydrogel, 57	prop ulcers healed wound (ulcer size in cm^2)	20 weeks	Baseline Mean Grp1(SD): 15(15.9) Final Grp1 Mean(SD): 6.2(12.9) P: 0.0005; ref Grp2	Baseline Grp2(SD): 11.4(14.5) Final Grp2 Mean(SD): 10.8(15.7) P: 0.0005, ref Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Falanga V, 1999[51]	Unna boot; 72	Unna boot; cellular or ECM, 48	prop ulcers healed (wound closure)	24 weeks	pts with event (%): (19) Denominator: NA P: <0.005 ref: Grp2	pts with event (%): (47) Denominator: NA
Falanga V, 1999[51]	Unna boot; 54	Unna boot; cellular or ECM, 72	rate wound recurrence (photographs, wound tracings, clinical assessments and patient evaluations)	12 months	pts with event (%): 12 Denominator: people with healed wounds	pts with event (%): 13 Denominator: people with healed wounds
Falanga V, 1999[51]	Unna boot; 48	Unna boot; cellular or ECM, 74	time to complete closure (days) ; photographs, wound tracings, clinical assessments and patient evaluations	24 weeks	Final mean: not attained; P: 0.005 ref Grp2	RH: 1.66; P: <0.01; ref Grp1 Final mean: 181 days
Falanga, 1998[38]	Unna boot; 63	Unna boot; cellular or ECM, 92	rate wound recurrence (Not further specified)	12 months	10 / 63 (15.9) Denominator: NA	11 / 92 (12); *P* = 0.48 Denominator: NA
Falanga, 1998[38]	Unna boot; 129	Unna boot; cellular or ECM, 146	time to complete closure (Cox PH for chance for wound closure per unit time); planimetry	6 months	RH: P: <0.001, 95% CI: 1.275 to 1.855; Grp1-Grp2	RH: 1.54 P: <0.001, 95% CI: 1.275 to 1.855; Grp1-Grp2
Falanga, 1998[38]	Unna boot; 129	Unna boot; cellular or ECM, 146	Infection (Not further specified)	12 months	pts with event (%): 10(8) Denominator: NA	pts with event (%): 12(8) Denominator: NA
Falanga, 1998[38]	Unna boot; 129	Unna boot; cellular or ECM, 146	time to complete closure (days to "full epithelialization of the wound and no drainage from the site"); planimetry	6 months	Final Grp1 Median(range): 181(10 to232) P: 0.003, ref Grp2	Final Grp2 Median(range): 61(9 to 233)
Falanga, 1998[38]	Unna boot; 129	Unna boot; cellular or ECM, 146	prop ulcers healed (100% wound closure at 6 months) ; photographs and wound tracings	6 months	pts with event (%): 63(48.8) P: 0.02 ref: Grp2	pts with event (%): 92(63)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Falanga, 1998[38]	Unna boot; 129	Unna boot; cellular or ECM, 146	Mortality (Not further specified)	12 months	pts with event (%): 4(3)	pts with event (%): 5(3)
Franks, 2007[28]	short stretch multi layer; foam, 81	short stretch multi layer; foam, 75	prop ulcers healed (% Ulcer closure)	24 weeks	pts with event (%): 50(61.7) Denominator: 81 Persons P: NA Final Grp1 Hazard Ratio(95% CI): 1.48(0.87 to 2.54) P: 0.15, ref Grp2	pts with event (%): 50(66.7) Denominator: 81 Persons P: NA Final Grp2 Hazard Ratio(95% CI): 1.48(0.87 to 2.54) P: 0.15; ref Grp1
Gatti, 2011[45]	Unna boot; Essential fatty acid, 11	Unna boot; Essential fatty acid and fibrin sealant, 13	wound healing rates no intermediate to complete(evolved to good healing)	8 weeks	pts with event (%): 5(45) Denominator: NA	pts with event (%): 7(54) Denominator: NA
Gethin, 2009[24]	multi layer; hydrogel, 54	multi layer; Manuka honey, 54	wound healing rates (cm^2)		Baseline Mean Grp1(SD): 9.87(12.9) Final Grp1 Mean(SD; 95% CI): 8.24(12.11; 0.1 to 0.55) P: 0.16, ref Grp2	Baseline Grp2(SD): 10.52(12.3) Final Grp2 Mean(SD; 95% CI): 8.25(11.57)
Gottrup, 2008[23]	kept a constatnt circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 49	kept a constatnt circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 51	(Quality of life defined by 'sense of wellbeing' (% reporting being more content than usual'))		pts with event (%): 19(39) Events: 19	pts with event (%): 18(35) Events: 18
Gottrup, 2008[23]	kept a constatnt circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 60	kept a constatnt circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 62	prop ulcers healed (Not further specified)		Events: 10 Denominator: unclear if persons or ulcers	Events: 9 Denominator: unclear if persons or ulcers

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 60	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 62	wound healing rates no intermediate to complete (Reduction in wound area (cm^2))		Baseline Mean Grp1(SD): 7.3(5.7) Final Grp1 Mean(Not given): 3.8	Baseline Grp2(SD): 11(9.6) Final Grp2 Mean(Not given): 7.9
Gottrup, 2008[23]	kept a constatnt circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 49	kept a constatnt circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 51	General feeling / mood (% of patients reporting brighter or more cheerful than usual)		pts with event (%): 22(45) Events: 22	pts with event (%): 21(41) Events: 21
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 49	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 51	(Measures of well being here defined by reported improved pattern of sleep (percentage of group members reporting it))		pts with event (%): 26(53) Events: 26 Denominator: 47 Days	pts with event (%): 25(49) Events: 25 Denominator: 47 Days
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 46	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 47	(Dressing change-related pain intensity rating for days 45 & 47, entered in diary morning and evening during dressing changes, on a Validated on a 11 point Numeric Box Scale (NBS) with 0 = No pain and 11 = Worst imaginable scale.)		Mean diff from grp2: 0.7 Baseline Grp1: 0.3 Final Grp1 (Not given): 0.9	Mean diff from grp1: -0.7 Baseline Grp2: 2 Final Grp2: 2

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 62	kept a constatt circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 60	(Patients` wound pain rating at days 43-47, after switching treatment for the intervention group to comparator, entered in diary morning and evening during dressing changes, on a Validated 1-11 point Numeric Box Scale (NBS).)		Mean diff from grp2: 0.3 Mean difference: 0.3 P: not given Baseline Mean Grp1: 2.3 Final Grp1: 2.6	Mean diff from grp1: -0.3 Mean difference: 0 P: not given Baseline Grp2: 1.9 Final Grp2: 1.9
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 62	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 59	(Patient pain rating daily for first 5 days, entered in diary morning and evening during dressing changes, on a Validated on a 11 point Numeric Box Scale (NBS) with 0 = No pain and 11 = Worst imaginable scale.)		4.1 P: <0.003; Grp2-Grp1; confounders: Age, gender, size of ulcer, Measured wound pain intesnity increased with initial pain intensity Mean diff from grp2: 0.7 P: < 0.003; Grp2 Mean difference (Not given): 2.7 P: not given (vs. baseline) Baseline Mean Grp1: 6.8	4.6 P: <0.003; Grp2-Grp1; confounders: Age, gender, size of ulcer, Measured wound pain intesnity increased with initial pain intensity Mean diff from grp 1: -0.7 P: < 0.003; Grp2 Mean difference (Not given): 2(2) P: not given (vs. baseline) Baseline Mean Grp2: 6.6
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 62	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 59	(Proportion of patients experiencing pain relief on first evening of treatment)		pts with event (%): 46(74) Denominator: 1 Days P: < 0.05 ref: Grp2	pts with event (%): 34(58) Denominator: 1 Days P: < 0.05 ref: Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 60	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 62	Infection (Not further specified)		pts with event (%): 2(3)	pts with event (%): 3(5)
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 50	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 53	Quality of Life as defined by appetite (% reporting improvement - felt like eating more)		pts with event (%): 12(24) Events: 12	pts with event (%): 26(25) Events: 26
Gottrup, 2008[23]	kept a constant circumference at the ankle; foam NO ibuprofen (trade name: Biatain Non-adhesive, Coloplast A/S), 60	kept a constant circumference at the ankle; foam contained ibuprofen (112.5 mg released over 7 d in presence of exudate), trade name: Biatain-Ibu Non-Adhesive foam dressing, Coloplast A/S, 62	hypersensitivity contact derm sensitization (Not further specified)		pts with event (%): 4(7)	pts with event (%): 5(8)
Greguric, 1994[48]	2 layer compression; magnesium sulfate paste + vaseline + gauze, 55	2 layer compression; hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam), 55	wound healing rates no intermediate to complete (mm2/day by tracings)	NR	Final Grp1 Mean: 21	Final Grp2 Mean: 32 P: 0.0001
Greguric, 1994[48]	2 layer compression; magnesium sulfate paste + vaseline + gauze, 55	2 layer compression; hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam), 55	contact derm (Not further specified)	NR	Events: 0	Events: 1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Greguric, 1994[48]	2 layer compression; magnesium sulfate paste + vaseline + gauze, 55	2 layer compression; hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam), 55	Infection (Not further specified)	NR	Events: 0	Events: 1
Greguric, 1994[48]	2 layer compression; magnesium sulfate paste + vaseline + gauze, 55	2 layer compression; hydrocolloid Varihesive E (hydrocolloid in adhesive elastomeric polymer matrix with outer film coated w/ polyurethane foam), 55	prop ulcers healed (Proportion of ulcers epithelialized by number of dressing changes); physical exam (venous ulcer assessment)	NR	pts with event (%): 0(0)	pts with event (%): 3(5) P: NR ref: Grp1
Hansson, 1998[37]	short stretch; paraffin gauze, 49	short stretch; antibacterial dressings cadexomer iodine paste, 56	prop ulcers healed (mean ulcer area, cm^2)	12 weeks	Baseline Mean Grp1(SD): 7.1(7.1) Final Grp1 Mean(SD): 3.6(4.3)	Baseline Grp2(SD): 8.7(11.9) Final Grp2 Mean(SD): 3.7(4.3)
Hansson, 1998[37]	short stretch; hydrocolloid Duoderm, 48	short stretch; antibacterial dressings cadexomer iodine paste, 56	prop ulcers healed (mean ulcer area, cm^2)	12 weeks	Baseline Mean Grp1(SD): 10.7(20.6) Final Grp1 Mean(SD): 5.5(6.6)	Baseline Mean Grp2(SD): 8.7(11.9) Final Grp2 Mean(SD): 3.7(4.3)
Hansson, 1998[37]	short stretch; paraffin gauze, 49	short stretch; hydrocolloid Duoderm, 48	prop ulcers healed (mean ulcer area, cm^2)	12 weeks	Baseline Mean Grp1(SD): 7.1(7.1) Final Grp1 Mean(SD): 3.6(4.3)	Baseline Mean Grp2(SD): 10.7(20.6) Final Grp2 Mean(SD): 5.5(6.6)
Hansson, 1998[37]	short stretch; hydrocolloid Duoderm, 48	short stretch; antibacterial dressings cadexomer iodine paste, 56	Infection (Not further specified)	NR	pts with event (%): 5(10)	pts with event (%): 1(2)
Hansson, 1998[37]	short stretch; paraffin gauze, 49	short stretch; hydrocolloid Duoderm, 48	Infection (Not further specified)	NR	pts with event (%): 4(8)	pts with event (%): 5(10)
Hansson, 1998[37]	short stretch; hydrocolloid Duoderm, 14	short stretch; antibacterial dressings cadexomer iodine paste, 17	wound healing rates yes intermediate to complete (Ulcer area reduction % of baseline)	12 weeks	Mean (SD): 17.9(53.2)	Mean (SD): 66.1(66.1)
Hansson, 1998[37]	short stretch; paraffin gauze, 20	short stretch; antibacterial dressings cadexomer iodine paste, 17	wound healing rates yes intermediate to complete (Ulcer area reduction % of baseline)	12 weeks	Mean (SD): 50.9(53.2)	Mean (SD): 66.1(66.1)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Hansson, 1998[37]	short stretch; paraffin gauze, 20	short stretch; hydrocolloid Duoderm, 14	wound healing rates yes intermediate to complete(Ulcer area reduction % of baseline)	12 weeks	Mean (SD): 50.9(51.6)	Mean (SD): 17.9(17.9)
Hansson, 1998[37]	short stretch; paraffin gauze, 49	short stretch; antibacterial dressings cadexomer iodine paste, 56	Infection (Not further specified)	NR	pts with event (%): 4(8)	pts with event (%): 1(2)
Harding, 2005[33]	2 layer compression; hydrocolloid keratinocyte lysate, 45	2 layer compression; hydrocolloid, 53	time to complete closure (days)	14 weeks	Final Grp1 Mean(SE): 97.8(4.5) P: 0.366	Final Grp2 Mean(SE): 152.5(7.4) P: 0.366; ref Grp1
Harding, 2005[33]	2 layer compression; hydrocolloid, 53	cellular or ECM, 95	time to complete closure (days)	14 weeks	Final Grp1 Mean(SE): 152.5(7.4) P: 0.366; ref Grp1	Final Grp2 Mean(SE): 148.5(5.6) P: 0.366; ref Grp1
Harding, 2005[33]	2 layer compression; hydrocolloid keratinocyte lysate, 45	cellular or ECM, 95	time to complete closure (days)	14 weeks	Final Grp1 Mean(SE): 97.8(4.5) P: 0.366	Final Grp2 Mean(SE): 148.5(5.6) P: 0.366; ref Grp1
Harding, 2005[33]	2 layer compression; hydrocolloid keratinocyte lysate, 45	2 layer compression; hydrocolloid, 53	prop ulcers healed maceration (Number of ulcers healed)	14 weeks	Events: 13 Denominator: NA	Events: 13 Denominator: NA
Harding, 2005[33]	2 layer compression; hydrocolloid keratinocyte lysate, 45	cellular or ECM, 95	prop ulcers healed maceration (Number of ulcers healed)	14 weeks	Events: 13 Denominator: NA	Events: 36 Denominator: NA
Harding, 2005[33]	2 layer compression; hydrocolloid, 53	cellular or ECM, 95	prop ulcers healed maceration (Number of ulcers healed)	14 weeks	Events: 13 Denominator: NA	Events: 36 Denominator: NA
Harding, 2011[20]	UK Class III compression system; antibacterial dressings impreg gauze, 136	UK Class III compression system; specialty absorp antibacterial dressings, 145	wound healing rates no intermediate to complete (Not further specified)	8 weeks	Mean (SD): 0.14(0.43) P: 0.438 (vs. baseline)	Mean (SD): 0.17(0.17) P: 0.438 (vs. baseline)
Holloway, 1989[42]	Toe-to-knee elastic compression bandage	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings	quality wound bed (edema - mean rate of change); analog scale and photography	NR	Mean (SE): -1.4(0.2)	Mean (SE): -1.6(-1.6) P: 0.53 (vs. Grp1)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Holloway, 1989[42]	Toe-to-knee elastic compression bandage; 37	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings, 38	wound healing rates no intermediate to complete (cm^2/wk as function of baseline circumference) ; ulcer measured and traced	NR	mean healing (cm^2)/week as function of baseline circ (SE): 0.03(0.01) Baseline Median Grp1(Range): 9.75(3.0 to 37.0)	mean healing (cm^2/week) as function of baseline circ (SE): 0.04(0.04) P: 0.0720 (vs. Grp1) Baseline Grp2(Range): 10.7(0.6 to 136.0)
Holloway, 1989[42]	Toe-to-knee elastic compression bandage	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings	quality wound bed (exudate - mean rate of change) ; analog scale and color photograph	NR	Mean (SE): -2.51(0.3)	Mean (SE): -3.11(-3.11) P: 0.2 (vs. Grp1)
Holloway, 1989[42]	Toe-to-knee elastic compression bandage;	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings,	quality wound bed (granulation - mean rate of change) ; analog scale and color photograph		Mean (SE): 2.75(0.3)	Mean (SE): 3.43(3.43) P: 0.16 (vs. Grp1)
Holloway, 1989[42]	Toe-to-knee elastic compression bandage; 37	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings, 38	wound healing rates no intermediate to complete (cm^2 per week); ulcer measured and traced	NR	Mean (SE): 0.41(0.12) Baseline Median Grp1(range): 9.75(3.0 to 37.0)	Mean (SE): 0.95(0.95) P: 0.0025 (vs. Grp 1) Baseline Grp2(range): 10.7(0.6 to 136.0)
Holloway, 1989[42]	Toe-to-knee elastic compression bandage, 37	Toe-to-knee elastic compression bandage; hydrocolloid antibacterial dressings, 38	quality wound bed (pus and debris - mean rate of change); analog scale and color photograph	NR	Mean (SE): -2.43(0.3)	Mean (SE): -2.68(-2.68) P: 0.55 (vs. Grp1)
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 12 pcs, 13	Infection (Not further specified)	12 weeks	Events: 1	Events: 0
Krishnamoorthy, 2003[47]	multi layer Profore, 13	multi layer Profore; Dermagraft 1pc, 14	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 78.1 Baseline median area in cm^2 Grp1(range): 9.2(3.7 to 25.0)	% of reduction in wound area: 59.4(59.4) Baseline Grp2(range): 6.8(3.3 to 25.2)
Krishnamoorthy, 2003[47]	multi layer Profore, 13	multi layer Profore; Dermagraft 12 pcs, 13	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 78.1 Baseline median area in cm^2 Grp1(range): 9.2(3.7 to 25.0)	% of reduction in wound area: 81.4(81.4) Baseline median area in cm^2 Grp2(range): 8.6(3.2 to 22.1)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 1pc, 14	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 88.6 Baseline median area in cm^2 Grp1(range): 5.6(3.6 to 30.2)	% of reduction in wound area: 59.4(59.4) Baseline median area in cm^2 Grp2(range): 6.8(3.3 to 25.2)
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 12 pcs, 13	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 88.6 Baseline median area in cm^2 Grp1(range): 5.6(3.6 to 30.2)	% of reduction in wound area: 81.4(81.4) Baseline median area in cm^2 Grp2(range): 8.6(3.2 to 22.1)
Krishnamoorthy, 2003[47]	multi layer Profore; Dermagraft 1pc, 14	multi layer Profore; Dermagraft 12 pcs, 13	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 59.4 Baseline median area in cm^2 Grp1(range): 6.8(3.3 to 25.2)	% of reduction in wound area: 81.4(81.4) Baseline median area in cm^2 Grp2(range): 8.6(3.2 to 22.1)
Krishnamoorthy, 2003[47]	multi layer Profore; 13	multi layer Profore; Dermagraft 1pc, 14	infection(Not further specified)	12 weeks	Events: 0	Events: 0
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 1pc, 14	Infection (Not further specified)	12 weeks	Events: 1	Events: 0
Krishnamoorthy, 2003[47]	multi layer Profore; Dermagraft 1pc, 14	multi layer Profore; Dermagraft 12 pcs, 13	Infection (Not further specified)	12 weeks	Events: 0	Events: 0
Krishnamoorthy, 2003[47]	multi layer Profore; 13	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	wound healing rates no intermediate to complete (% reductions in ulcer area)	12 weeks	% of reduction in wound area: 78.1 Baseline median area in cm^2 Grp1(range): 9.2(3.7 to 25.0)	% of reduction in wound area: 88.6 Baseline Grp2(range): 5.6(3.6 to 30.2)
Krishnamoorthy, 2003[47]	multi layer Profore; 13	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	infection(Not further specified)	12 weeks	Events: 0	Events: 1
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 1pc, 14	prop ulcers healed(full epithelialization without drainage at two consecutive weekly visits) ; tracings	12 weeks	pts with event (%): 5(38) P: 0.38 ref: Grp1	pts with event (%): 1(14) P: 0.6 ref: Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 12 pcs, 13	prop ulcers healed (full epithelialization without drainage at two consecutive weekly visits) ; tracings	12 weeks	pts with event (%): 5(38) P: 0.38 ref: Grp1	pts with event (%): 5(38) P: 0.38 ref: Grp1
Krishnamoorthy, 2003[47]	multi layer Profore; 13	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	prop ulcers healed(full epithelialization without drainage at two consecutive weekly visits) ; tracings	12 weeks	pts with event (%): 2(15)	pts with event (%): 5(38) P: 0.38 ref: Grp1
Krishnamoorthy, 2003[47]	multi layer Profore; 13	multi layer Profore; Dermagraft 1pc, 14	prop ulcers healed(full epithelialization without drainage at two consecutive weekly visits) ; tracings	12 weeks	pts with event (%): 2(15)	pts with event (%): 1(14) P: 0.6 ref: Grp1
Krishnamoorthy, 2003[47]	multi layer Profore; Dermagraft 1pc, 14	multi layer Profore; Dermagraft 12 pcs, 13	Mortality (Not further specified)	12 weeks	pts with event (%): 0(0)	pts with event (%): 0(0)
Krishnamoorthy, 2003[47]	multi layer Profore; Dermagraft 1pc, 14	multi layer Profore; Dermagraft 12 pcs, 13	prop ulcers healed(full epithelialization without drainage at two consecutive weekly visits) ; tracings	12 weeks	pts with event (%): 1(14) P: 0.6 ref: Grp1	pts with event (%): 5(38) P: 0.38 ref: Grp1
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 12 pcs, 13	mortality(Not further specified)	12 weeks	pts with event (%): 0(0)	pts with event (%): 0(0)
Krishnamoorthy, 2003[47]	multi layer Profore; cellular or ECM Dermagraft 4pc, 13	multi layer Profore; Dermagraft 1pc, 14	Mortality (Not further specified)	12 weeks	pts with event (%): 0(0)	pts with event (%): 0(0)
Krishnamoorthy, 2003[47]	multi layer Profore; , 13	multi layer Profore; Dermagraft 1pc, 14	Mortality (Not further specified)	12 weeks	pts with event (%): 0(0)	pts with event (%): 0(0)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Kucharzewski, 2003[46]	Unna boot; 27	unspec compression; (Bioprocess) Cellulose membrane, 27	prop ulcers healed (Not further specified) ; homothetic congruent projections of the ulcers were plotted onto transparent foil after which planimetric measurements of the wounds were taken with the use of the digitizer	20 weeks	pts with event (%): 27(100) Denominator: NA	pts with event (%): 27(100) Denominator: NA
Kucharzewski, 2003[46]	Unna boot; 27	unspec compression; (Bioprocess) Cellulose membrane, 27	time to complete closure(weeks) ; homothetic congruent projections of the ulcers were plotted onto transparent foil after which planimetric measurements of the wounds were taken with the use of the digitizer	20 weeks	Final Grp1 time at complete closure in weeks: 20	Final Grp2 time at complete closure in weeks: 14
Lammoglia-Ordiales, 2011[56]	2 layer compression; hydrogel, 14	2 layer compression; MTC-2G, 18	wound healing rates no intermediate to complete(cm^2)		Mean: 5.85 95% CI: 3.58 to 8.12; P: 0.0001	Mean: 6.29; 95%CI: 3.28 to 9.29; P: 0.0001 (vs. baseline)
Lammoglia-Ordiales, 2011[56]	2 layer compression; hydrogel, 14	2 layer compression; MTC-2G, 18	wound healing rates no intermediate to complete(cm^2)		5.85 P: 0.815; Grp2	6.29 P: 0.815; Grp2
Lammoglia-Ordiales, 2011[56]	2 layer compression; hydrogel, 14	2 layer compression; MTC-2G, 18	prop ulcers healed(Number of ulcers healed)		Events: 3 Denominator: NA P: 0.334 ref: Grp2	Events: 4 Denominator: NA P: 0.334 ref: Grp1
Limova, 2003[35]	2 layer compression; alginate, 10	alginate, 9	prop ulcers healed (Number of ulcers healed)	6 weeks	Events: 0 Denominator: NA P: ref: Grp2	Events: 2 Denominator: NA P: ref: Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Limova, 2003[35]	2 layer compression; alginate, 10	alginate, 9	wound healing rates no intermediate to complete (Percentage wound size decrease)	6 weeks	Percentage wound size decrease : 33.7	Percentage wound size decrease : 29.6(29.6)
Maggio, 2011[21]	multi layer; alginate, 26	multi layer; alginate Vulnamin- glycine, leucine, proline, lysine, sodium hyaluronate, 26	prop ulcers healed (Number of patients with complete wound closure divided by number of patients in treatment arm) ; Digital camera measurement- Canon Digital Ixus 4000	70 days	pts with event (%): 7(27) Denominator: 26 Persons P: NR ref: Grp2	pts with event (%): 16(61) Denominator: 26 Persons P: NR ref: Grp1
Maggio, 2011[21]	multi layer; alginate, 2626	multi layer; alginate Vulnamin- glycine, leucine, proline, lysine, sodium hyaluronate, 2626	wound healing rates no intermediate to complete(cm^2)	70 days	Baseline Mean Grp1(SD): 15.14(4.7) Final Grp1 Mean(SD): 10.96(3.8) P: <0.05, ref Grp2	Baseline Grp2(SD): 13.95(4.5) Final Grp2 Mean(SD): 3.04(0.8) P: <0.05; ref Grp1
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	enzymatic debridement; hydrocolloid	time to complete closure (Secondary outcome measures time to healing)	12 months	67 95% CI: 54 to 80 P: 0.408; Grp2	P: 0.408; Grp2
Michaels, 2009[22]	multi layer; seem to be matched various dressings, 104	enzymatic debridement; hydrocolloid	rate wound recurrence (recurrence rates at 1 year)		pts with event (%): 13(14.44) Denominator: 90 Persons	pts with event (%): Denominator: 90 Persons
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	enzymatic debridement; hydrocolloid	rate wound recurrence(recurrence rates at 1 year)		pts with event (%): 11(11.58) Denominator: 95 Persons	pts with event (%): Denominator: 95 Persons

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	multi layer; seem to be matched various dressings, 104	rate wound recurrence (recurrence rates at 1 year)		pts with event (%): 11(11.58) Denominator: 95 Persons	pts with event (%): 13(14.44) Denominator: 95 Persons
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	multi layer; seem to be matched various dressings, 104	time to complete closure (Secondary outcome measures time to healing)	12 months	67 95% CI: 54 to 80 P: 0.408; Grp2	58 95% CI: 43 to 73 P: 0.408; Grp2
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	multi layer; seem to be matched various dressings, 104	prop ulcers healed (Secondary outcome measures were healing rates at 1 year)	12 months	pts with event (%): 95(96) Denominator: 99 Persons P: 0.94 ref: Grp2	pts with event (%): 90(96) Denominator: 99 Persons P: 0.94
Michaels, 2009[22]	multi layer; seem to be matched various dressings, 104	enzymatic debris; hydrocolloid, 104	time to complete closure (Secondary outcome measures time to healing)	12 months	58 95% CI: 43 to 73 P: 0.408; Grp2	95% CI: to P: 0.408; Grp2
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	multi layer; seem to be matched various dressings, 104	prop ulcers healed (The primary outcome measure for the study was the proportion of participants who had an ulcer that had healed completely at 12 weeks in the index leg.)	12 weeks	pts with event (%): 62(59.6) Denominator: 104 Persons P: 0.673 ref: Grp2	pts with event (%): 59(56.7) Denominator: 104 Persons P: 0.673
Michaels, 2009[22]	multi layer; antibacterial dressings, 104	multi layer; seem to be matched various dressings, 104	prop ulcers healed (Secondary outcome measures were healing rates at 6 months)	6 months	pts with event (%): 87(85.3) Denominator: 102 Persons P: 0.141 ref: Grp2	pts with event (%): 78(77.2) Denominator: 102 Persons P: 0.141
Moffatt, 1992[49]	4-layer; Non-adherent, 30	4-layer; hydrocolloid Comfeel, Coloplast, 30	time to complete closure(Not further specified); planimetry	12 weeks	RR: P: 0.077; 95% CI: 0.88 to 5.75; Grp1-Grp2	RR, 2.25 (95% CI, 0.88 to 5.75); *P* = 0.077

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Moffatt, 1992[49]	4-layer; Non-adherent, 30	4-layer; hydrocolloid Comfeel, Coloplast, 30	prop ulcers healed (Not further specified) ; planimetry	12 weeks	pts with event (%): 7(23) Denominator: NA	pts with event (%): 13(43) Denominator: NA
Mostow, 2005[32]	multi layer Unspecified Compression+ Debridement, 58	multi layer; composite acellular or ECM, 62	prop ulcers healed(Complete wound healing with full epithelization and absence of drainage at 12weeks)	12 weeks	pts with event (%): 20(34) Denominator: NA P: 0.0196 ref: Grp2	pts with event (%): 34(55) Denominator: NA P: 0.0196 ref: Grp1
Mostow, 2005[32]	multi layer Unspecified Compression+ Debridement, 58	multi layer; composite acellular or ECM, 62	Infection (Not further specified)	12 weeks	Events: 5 Denominator: NA P: 0.2611 ref: Grp2	Events: 1 Denominator: NA P: 0.2611 ref: Grp1
Nelson, 2007[29]	multi layer; Pentoxifylline, Knitted viscose, 25	multi layer; hydrocolloid Pentoxifylline, 32	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 20(80) Denominator: 25 Persons	pts with event (%): 21(66) Denominator: 25 Persons
Nelson, 2007[29]	multi layer; Knitted viscose, Placebo, 27	multi layer; hydrocolloid Placebo, 33	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 17(63) Denominator: 27 Persons	pts with event (%): 20(60) Denominator: 27 Persons
Nelson, 2007[29]	multi layer; hydrocolloid Pentoxifylline, 32	multi layer; hydrocolloid Placebo, 33	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 21(66) Denominator: 32 Persons	pts with event (%): 20(60) Denominator: 32 Persons
Nelson, 2007[29]	multi layer; hydrocolloid Pentoxifylline, 32	multi layer; Knitted viscose, Placebo, 27	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 21(66) Denominator: 32 Persons	pts with event (%): 17(63) Denominator: 32 Persons
Nelson, 2007[29]	multi layer; Pentoxifylline, Knitted viscose, 25	multi layer; Knitted viscose, Placebo, 27	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 20(80) Denominator: 25 Persons	pts with event (%): 17(63) Denominator: 25 Persons
Nelson, 2007[29]	multi layer; Pentoxifylline, Knitted viscose, 25	multi layer; hydrocolloid Placebo, 33	prop ulcers healed (Not further specified)	24 weeks	pts with event (%): 20(80) Denominator: 25 Persons	pts with event (%): 20(60) Denominator: 25 Persons

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Omar, 2004[34]	4-layer, 8	4-layer; cellular or ECM Dermagraft, 10	prop ulcers healed (number of patients healed) ; complete epithelialization without exudate/drainage; tracing/planimetry	12 weeks	pts with event (%): 1(12.5) P: 0.15 ref: Grp2	pts with event (%): 5(50)
Omar, 2004[34]	4-layer, 8	4-layer; cellular or ECM Dermagraft, 10	wound healing rates no intermediate to complete (cm^2/week)	12 weeks	Final Grp1 Mean(SD): 0.15(0.39) P: 0.001; ref Grp2	Final Grp2 Mean(SD): 0.82(0.33)
Omar, 2004[34]	4-layer; 1	4-layer; cellular or ECM Dermagraft, 5	wound healing rates yes intermediate to complete (m^2/week for healed ulcers)	12 weeks	Baseline Grp1: Final Grp1 Mean(SD): 0.92(NR)	Baseline Grp2: Final Grp2 Mean(SD): 1.01(0.27)
Omar, 2004[34]	4-layer; 8	4-layer; cellular or ECM Dermagraft, 10	wound healing rates no intermediate to complete(%)	12 weeks	Mean (SD): 16(22) Baseline mean area in cm^2 Grp1(SD): 12(7.6)	Mean (SD): 84(84) P: 0.002 (vs Grp1) Baseline Grp2(SD): 9.5(4.2)
Omar, 2004[34]	4-layer; 8	4-layer; cellular or ECM Dermagraft, 10	wound healing rates no intermediate to complete(linear rate of healing by Gilman equation in cm/wk)	12 weeks	Final Grp1 Mean(SD): 0.033(0.085)	Final Grp2 Mean(SD): 0.14(0.08) P: 0.006, ref Grp1
Ormiston MC, 1983[55]	unspec compression; Cadexomer iodine, 27	unspec compression; antibacterial dressings, 27	wound healing rates no intermediate to complete hypersensitivity contact derm sensitization skin irritation burn (Not further specified)	12 weeks	Mean : 85% P: <0.025 (vs. baseline)	Mean: 55%(55%) P: <0.025 (vs. baseline)
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD); Gentian violet and Polyfax, 30	crepe then cotton crepe compression bandage (STD; Cadexomer iodine,	prop ulcers healed (Number of ulcers healed/ number of people in arm) ; tracings	12 weeks	Events: 7	Events: 12 P: >0.05 ref: Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD); Gentian violet and Polyfax, 30	crepe then cotton crepe compression bandage (STD; Cadexomer iodine, 30	wound healing rates no intermediate to complete (cm^2/wk); tracings	12 weeks	Baseline mean (cm^2) Grp1(SD): 10.2(8.7) Final Grp1 Mean(SE): 0.46(0.1)	Baseline Grp2(SD): 12.1(13.9) Final Grp2 Mean(SE): 0.89(0.1) P: 0.0001, ref Grp1
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD); Gentian violet and Polyfax, 30	crepe then cotton crepe compression bandage (STD; Cadexomer iodine, 31	mortality(Not further specified)		pts with event (%): 0(0)	pts with event (%): 1(3)
Ormiston, 1985[44]	crepe then cotton crepe compression bandage (STD); Gentian violet and Polyfax, 30	crepe then cotton crepe compression bandage (STD; Cadexomer iodine, 30	quality wound bed (granulation as proportion of surface of ulcer on a linear scale (0-100) per week) ; subjective criterion'	12 weeks	Final Grp1 Mean(SE): 2.5(0.4)	Final Grp2 Mean(SE): 3.3(0.4) P: >0.05, ref Grp1
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete(average rate of change, diameter global (%/d))		Final Grp1 Mean(SD): (4.07) U-Test <5 %; ref Grp2	Final Grp2 Mean(SD): (2.4) U-Test <5 %; ref Grp1
Pessenhofer, 1989[41]	Unna boot , 17	Unna boot; foam, 24	wound healing rates no intermediate to complete (average rate of change, perimeter global (%/d))		Final Grp1 Mean(SD): (4.14) U-Test <5 %; ref Grp2	Final Grp2 Mean(SD): (2.42) U-Test <5 %; ref Grp1
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete (average rate of change, diameter differential (%/d))		Final Grp1 Mean(SD): (2.77) U-Test <5 %; ref Grp2	Final Grp2 Mean(SD): (2.15) U-Test <5 %; ref Grp1
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete(average rate of change, perimeter differentiell (%/d)		Final Grp1 Mean(SD): (2.97) U-Test <5 %; ref Grp2	Final Grp2 Mean(SD): (2.13) U-Test <5 %; ref Grp1

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete (average rate of change, area global (%/d)	2-281 days	Final Grp1 Mean(SD): (5.65)	Final Grp2 Mean(SD): (2.37)
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete(maximal diameter (mm)	2-281 days	Mean (SD): 28.60%(46.4) Baseline Mean Grp1(SD): 41(34.7) Final Grp1 Mean(SD): 28.60%(91.9) U-test <0.1%; ref Grp2	Mean (SD): -57.80% (-57.80%) Baseline Grp2(SD): 47.1(40.8) Final Grp2 Mean(SD): -57.80%(46.4) U-test <0.1%; ref Grp1
Pessenhofer, 1989[41]	Unna boot, 17	Unna boot; foam, 24	wound healing rates no intermediate to complete(area (mm2)	2-281 days	Mean (SD): 78.30%(47) Baseline Grp1(SD): 1170.2(2424.5) Final Grp1 Mean(SD): 78.3(215.8) U-test <0.1%; ref Grp2	Mean (SD): -65.60%(-65.60%) Baseline Mean Grp2(SD): 1078.3(1743.6) Final Grp2 Mean(SD): -65.60%(47) U-test <0.1%; ref Grp1
Pessenhofer, 1989[41]	Unna boot; 17	Unna boot; foam, 24	wound healing rates no intermediate to complete (perimeter (mm)	2-281 days	Mean (SD): 29.90%(46.6) Baseline Mean Grp1(SD): 121.5(103.9) Final Grp1 Mean(SD): 29.90%(107.1) U-test <0.1%; ref Grp2	Mean (SD): -57.10%(-57.10%) Baseline Grp2(SD): 130.8(106.2) Final Grp2 Mean(SD): -57.10%(46.6) U-test <0.1%; ref Grp1
Pessenhofer, 1989[41]	Unna boot; 17	Unna boot; foam, 24	wound healing rates no intermediate to complete(average rate of change, area differential (%/d)	2-281 days	Final Grp1 Mean(SD): (4.01) U-test<5 %; ref Grp2	Final Grp2 Mean(SD): (2.19) U-Test <5 %; ref Grp1
Schulze, 2001[36]	Alginate + Film, 22	Alginate + Swabs, 37	prop ulcers healed maceration (Not further specified)	4 weeks	pts with event (%): 3(14) Denominator: NA	pts with event (%): 1(3) Denominator: NA
Schulze, 2001[36]	Alginate + Film, 22	Alginate + Swabs, 37	wound healing rates no intermediate to complete (Area(cm^2))		Mean (SD): 0.05(0.45) Not statistically significant (not reported)	Mean (SD): 0(0) Not statistically significant (not reported)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Schulze, 2001[36]	Specialty absorp, 54	Alginate + Film, 22	wound healing rates no intermediate to complete (Area(cm^2))		Mean (SD): 0.17(0.29) Not statistically significant (not reported)	Mean (SD): 0.05(0.05) Not statistically significant (not reported)
Schulze, 2001[36]	Specialty absorp, 54	Alginate + Film, 22	prop ulcers healed maceration (Not further specified)	4 weeks	pts with event (%): 2(4) Denominator: NA	pts with event (%): (14)
Schulze, 2001[36]	Specialty absorp, 54	Alginate + Swabs, 37	wound healing rates no intermediate to complete (Area cm^2)		Mean (SD): 0.17(0.45) Not statistically significant (not reported)	Mean (SD): 0(0) Not statistically significant (not reported)
Schulze, 2001[36]	Specialty absorp, 54	Alginate + Swabs, 37	prop ulcers healed maceration (Not further specified)	4 weeks	pts with event (%): 2(4) Denominator: NA	pts with event (%): 1(3) Denominator: NA
Scurr JH, 1993[54]	Compression stocking and alginate foam, 10	Compression stocking and Transparent film alginate, 10	prop ulcers healed (Not further specified)	6 weeks	pts with event (%): 2(20) Denominator: 10 Persons	pts with event (%): 2(20) Denominator: 10 Persons
Scurr JH, 1994[53]	graduated elastic compression stocking; alginate, 20	graduated elastic compression stocking; hydrocolloid, 20	prop ulcers healed (size id ulcers healing rates)	6 weeks	pts with event (%): 6(30) Denominator: 20 Persons P: 0.14	pts with event (%): 2(10) Denominator: 20 Persons P: 0.14
Scurr JH, 1994[53]	graduated elastic compression stocking; alginate, 20	graduated elastic compression stocking; hydrocolloid, 20	prop ulcers healed wound healing rates no intermediate to complete (Not further specified)	6 weeks	Mean (SE): -80.2(14.5) Baseline Mean Grp1(SD): 2.28(1.49) Final Grp1 Mean(SE): 0.64(0.92) P: 0.086	Mean (SE): -90.7 Baseline Grp2(SD): 5.31(5.46) Final Grp2 Mean(SE): 0.34(0.42) P: 0.086
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 64	Mortality (people)	4 months	pts with event (%): 2(3) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	prop ulcers healed(healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 4(10) P: 0.02 ref: Grp4	pts with event (%): 12(34) P: 0.02 ref: Grp2

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	Mortality (people)	4 months	pts with event (%): 0(0) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 52	linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 24	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median(IQR): 0.062(0.039 to 0.086) P: 0.4; ref Grp3	Final Grp2 Median(IQR): 0.017(0.001 to 0.267) P: 0.09; ref Grp4
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 52	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 25	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median (IQR): 0.062(0.039 to 0.086) P: 0.4; ref Grp3	Final Grp2 Median (IQR): 0.184(0.115 to 0.338) P: 0.09, ref Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 24	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 50	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median(IQR): 0.017(0.001 to 0.267) P: 0.09; ref Grp4	Final Grp2 Median(IQR): 0.056(0.027 to 0.085) P: 0.4, ref Grp1
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 24	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 25	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median(IQR): 0.017(0.001 to 0.267) P: 0.09; Grp4	Final Grp2 Median(IQR): 0.184(0.115 to 0.338) P: 0.09; ref Grp2
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	Mortality	4 months	pts with event (%): 2(3) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	Mortality	4 months	pts with event (%): 2(3) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	Mortality	4 months	pts with event (%): 0(0) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 200)2; Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	Mortality	4 months	pts with event (%): 0(0) Denominator: Persons	pts with event (%): 0(0) Denominator: Persons
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	prop ulcers healed (healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 4(10) P: 0.02 ref: Grp4	pts with event (%): 38(59) P: 0.27 ref: Grp1
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	prop ulcers healed (healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 38(59) P: 0.27 ref: Grp1	pts with event (%): 12(34) P: 0.02 ref: Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 50	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 25	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median(IQR): 0.056(0.027 to 0.085) P: 0.4; ref Grp1	Final Grp2 Median(IQR): 0.184(0.115 to 0.338) P: 0.09; ref Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 64	linear, graduated (Tubigrip or Venosan 2002; hydrocolloid Biofilm powder+Biofilm dressing, 35	Infection (Not further specified)	4 months	pts with event (%): 0(0)	pts with event (%): 1(3)
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 52	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 50	wound healing rates no intermediate to complete (cm^2/day)	1 months	Final Grp1 Median(IQR): 0.062(0.039 to 0.086) P: 0.4; ref Grp3	Final Grp2 Median(IQR): 0.056(0.027 to 0.085) P: 0.4; ref Grp1
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	Infection (Not further specified)	4 months	pts with event (%): 1(2)	pts with event (%): 11(28) P: 0.0004 ref: Fisher's exact

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	Infection (Not further specified)	4 months	pts with event (%): 1(2)	pts with event (%): 0(0)
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	Infection (Not further specified)	4 months	pts with event (%): 1(2)	pts with event (%): 1(3)
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	prop ulcers healed (healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 43(69) Denominator: NA P: 0.27 ref: Grp3	pts with event (%): 12(34) Denominator: NA P: 0.02 ref: Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 35	Infection (Not further specified)	4 months	pts with event (%): 11(28) P: 0.0004 ref: Fisher's exact	pts with event (%): 1(3) P: ref: Fisher's exact
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, unclear	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, unclear	time to complete closure(HR for time to wound healing) ; tracings	4 months	RH: P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, unclear	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, unclear	time to complete closure(HR for time to wound healing) ; tracings	4 months	RH: P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, unclear	linear, graduated (Tubigrip or Venosan 2002) hydrocolloid Biofilm powder+Biofilm dressing, unclear	time to complete closure(HR for time to wound healing) ; tracings	4 months	P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, unclear	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, unclear	time to complete closure(HR for time to wound healing); tracings	4 months	RH: P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, unclear	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, unclear	time to complete closure(HR for time to wound healing) ; tracings	4 months	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement	RH: 1.16 P: 0.48; 95% CI: 0.77 to 1.77, Grp1 & Grp2; confounders: Age, duration of ulcer, size of ulcer, photoplethysmography deep vein involvement
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002; Betadine/Jelonet, 39	prop ulcers healed(healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 43(69) Denominator: NA P: 0.27 ref: Grp3	pts with event (%): 4(10) Denominator: NA P: 0.02 ref: Grp4
Smith, 1992[50]	2 layer compression linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 62	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	prop ulcers healed (healed in less than 4 months) ; tracings/planimetry	4 months	pts with event (%): 43(69) Denominator: NA P: 0.27 ref: Grp3	pts with event (%): 38(59) Denominator: NA P: 0.27 ref: Grp1
Smith, 1992[50]	linear, graduated (Tubigrip or Venosan 2002); Betadine/Jelonet, 39	linear, graduated (Tubigrip or Venosan 2002); hydrocolloid Biofilm powder+Biofilm dressing, 64	Infection (Not further specified)	4 months	pts with event (%): 11(28) P: 0.0004 ref: Fisher's exact	pts with event (%): 0(0)

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Teepe, 1993[40]	short stretch; hydrocolloid, 23	short stretch; cellular or ECM, 24	prop ulcers healed (number of ulcers healed)	6 weeks	3/23 (13)	3/24 (13)
Vanscheidt, 2007[26]	short stretch; contact layer, 109	short stretch; contact layer cellular or ECM, 116	time to complete closure(Days to complete healing of ulcer)	182 days	Final Grp1 Median (95% CI): >201(201 to Undefined) P: <0.0001; ref Grp2	Final Grp2 Median (95% CI): 176(114 to 184) P: <0.0001; ref Grp1
Vanscheidt, 2007[26]	short stretch; contact layer, 109	short stretch; contact layer cellular or ECM, 116	prop ulcers healed (% patients with complete healing of ulcers)	182 days	pts with event (%): 24(22.4) Denominator: 109 Persons P: 0.0106 ref: Grp2	pts with event (%): 44(38.3) Denominator: 109 Persons P: 0.0106 ref: Grp1
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 38	high-compression; alginate, 30	wound healing rates no intermediate to complete (Not further specified)	12 weeks	66.98	52.06(52.06)
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 10	high-compression; alginate, 8	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median : 25.5	Median : 7.9
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 16	high-compression; alginate, 16	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median: 61.6	Median: 10.9
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 33	high-compression; alginate, 28	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median: 25.0	Median: 7.9
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 27	high-compression; alginate, 34	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median: 29.3	Median: 10.88
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 58	high-compression; alginate, 59	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median : 33.8	Median : 25.6
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 21	high-compression; alginate, 13	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median : 61.2	Median : 13.37

Author, year	Compression; intervention, n Grp1	Compression; intervention, n Grp2	Outcome (definition)	Followup	Results, Grp1	Results, Grp2
Vowden, 2006[30]	high-compression; amelogenin proteins (Xelmat), 16	high-compression; alginate, 17	wound healing rates no intermediate to complete (Not further specified)	12 weeks	Median: 21.14	Median: 7.5(7.5)
Weiss RA, 1996[52]	Jobst UlcerCare stocking; foam slightly adhesive hydroactive foam dressing (Cutinova foam), 10	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 8	wound healing rates no intermediate to complete (Not further specified)	1 weeks	Mean: 46%	Mean: 40% (40%)
Weiss RA, 1996[52]	Jobst UlcerCare stocking; foam slightly adhesive hydroactive foam dressing (Cutinova foam), 10	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 8	wound healing rates no intermediate to complete (Not further specified)	2 weeks	12%	29%
Weiss RA, 1996[52]	Jobst UlcerCare stocking; foam slightly adhesive hydroactive foam dressing (Cutinova foam), 10	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 8	wound healing rates no intermediate to complete (Not further specified)	3 weeks	27%	13%
Weiss RA, 1996[52]	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 10	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 8	time to complete closure (Not further specified)	16 weeks	Mean: 5.6	Mean: 6.5
Weiss RA, 1996[52]	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 10	Jobst UlcerCare stocking; foam non-adhesive absorptive foam dressing (Allevyn), 8	prop ulcers healed (Not further specified)	16 weeks	pts with event (%): 8(80) Denominator: 10 Persons	pts with event (%): 4(50) Denominator: 8 Persons

Table D-4b. Outcomes reported for studies evaluating antibiotics for treatment of chronic venous ulcers

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
Alinovi, 1986[82]	Bandages, 26	Systemic antibiotics, 29	wound healing rates no intermediate to complete (initial-posttreatment/initial units of %)	20 days	Mean (SD): 57.2: (29.3) P: 0.56 (ref Grp2)	Mean (SD): 61.6: (25.8) P: 0.56 (ref Grp1)
Huovinen, 1994[57]	Placebo, 10	Trimethoprim/sulfamethoxazole, 9	wound healing rates no intermediate to complete (total cure rate, %)	16 weeks	% total cure: 30	% total cure: 33
Huovinen, 1994[57]	Placebo, 10	ciprofloxacin, 12	wound healing rates no intermediate to complete (total cure rate, %)	16 weeks	% total cure: 30	% total cure: 42
Huovinen, 1994[57]	Placebo, 10		wound healing rates no intermediate to complete (total cure rate, %)	16 weeks	% total cure: 30	
Huovinen, 1994[57]	Trimethoprim/ sulfamethoxazole, 9	ciprofloxacin, 12	wound healing rates no intermediate to complete (total cure rate, %)	16 weeks	% total cure: 33	% total cure: 42

Table D-4c. Outcomes reported for studies evaluating surgery as treatment of chronic venous ulcers (KQ3a)

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
Barwell, 2000[62]	Compression: refused surgery, 105	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 131	rate wound recurrence (epithelial breakdown in ipsilateral leg)	36 months	Total events recurrent ulcers (%): (26)	Total events recurrent ulcers (%): (24) P: 0.029 ref Grp1
Barwell, 2000[62]	Compression: refused surgery, 105	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 131	prop ulcers healed surg site infection (full ulcer re-epithelialization)	24 weeks	Total events (%): (74)	Total events (%): (72)
Barwell, 2004[60]	Compression: multi layer, 214	Superficial Vein Surgery-vein stripping; Compression: multi layer, 214	rate wound recurrence (epithelial breakdown anywhere between the knee and the malleoli of the study leg.)	14 months	Total events (%): 73 Denominator: 214 Persons RH: ref Final percentage: 28	Total events (%): 32 Denominator: 214 Persons RH: -2.76 Final percentage: 12 P: 0.737 (ref: Grp1)
Barwell, 2004[60]	Compression: multi layer, 185	Superficial Vein Surgery-vein stripping; Compression: multi layer, 156	prop ulcers healed wound healing rates no intermediate to complete surg site infection (complete epithelialization)	12 weeks	Total events (%): 141 Denominator: 185 Persons RH: ref Final percentage: 76	Total events (%): 128 Denominator: 156 Persons RH: 0.84; Final percentage: 82 P: <0.001 (ref: Grp1)
Galimberti, 1988[66]	Compression: 2 layer and hydrocolloid:	Sclerotherapy Compression: 2 layer and hydrocolloid	Wound healing	NA	pts with event (%): 72 (100) Time to healing: 23 weeks	pts with event (%): 46 (100) Time to healing: 20 weeks
Galimberti, 1988[66]	Compression: 2 layer and hydrocolloid:	Sclerotherapy Compression: 2 layer and hydrocolloid	Wound reccurence	NA	pts with event (%): 21/46 (29)	pts with event (%): 0 (0)
Gohel, 2007[59]	Compression: multi layer, 156	Superficial Vein Surgery-vein stripping; Compression: multi layer, 185	prop ulcers healed wound healing rates no intermediate to complete (complete re-epithelialization of the leg)	36 months	pts with event (%): 139 (89) Denominator: 3 Years Final percentage: 89	pts with event (%): 172 (93) Denominator: 3 Years Final percentage: 93

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
Gohel, 2007[59]	Compression: multi layer, 226	Superficial Vein Surgery-vein stripping; Compression: multi layer, 216	rate wound recurrence (any breakdown of epithelium between knee and malleoli after ulcer healing as ulcer recurrence.)	48 months	pts with event (%): 127 (56) Denominator: 4 Years RH: ref Final percentage: 31	pts with event (%): 67 (31) Denominator: 4 Years RH: 2.926 Final percentage: 56
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (Disease specific quality of life; CXVUQ)	6 months	Baseline Mean: 60.4 Final Mean: 45.5	Baseline Mean: 63 Final Mean: 41.1
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (mental health; SF-36)	6 months	Baseline Mean: 68.8 Final Mean: 73.1	Baseline Mean: 71.2 Final Mean: 72.3
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (role-emotional; SF-36)	6 months	Baseline Mean: 53.9 Final Mean: 62.2 P: significant' (ref: Grp2)	Baseline Mean: 55.8 Final Mean: 54.8 P: <0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (social functioning; SF-36)	6 months	Baseline Mean: 63.2 Final Mean: 63.7 P: <0.05 (ref: baseline)	Baseline Mean: 62.9 Final Mean: 62.1 P: >0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (Vitality; SF-36)	6 months	Baseline Mean: 57.5 Final Mean: 58.4 P: >0.05 (ref: baseline)	Baseline Mean: 59.9 Final Mean: 60.6 P: >0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (General health; SF-36)	6 months	Baseline Mean: 44.4 Final Mean: 45.9 P: <0.05 (ref: baseline)	Baseline Mean: 41.9 Final Mean: 54.8 P: >0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (bodily pain; SF-36)	6 months	Baseline Mean: 42.1 Final Mean: 54.1 P: >0.05 (ref: baseline)	Baseline Mean: 45.5 Final Mean: 46.6 P: >0.05 (ref: baseline)

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (role-Physical; SF-36)	6 months	Baseline Mean: 41 Final Mean: 48.8 P: >0.05 (ref: baseline)	Baseline Mean: 38.1 Final Mean: 46.1 P: <0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	functional status (Physical functioning; SF-36)	6 months	Baseline Mean: 36.7 Final : 37.5 P: >0.05 (ref: baseline)	Baseline Mean: 37.6 Final : 44.8 P: >0.05 (ref: Baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	time to complete closure wound healing rates no intermediate to complete (expressed in days for those whose ulcers did heal; acetate tracing used to identify date of healing)	26 weeks	Adjusted Hazard ratio: ref P: (ref) Final Median: 98 P: <0.05 (ref: baseline)	Adjusted Hazard ratio: 0.79 Final Median: 83 P: <0.05 (ref: baseline)
Guest, 2003[64]	Compression: 4-layer, 39	Superficial Vein Surgery-vein stripping Perforator-SEPS; Compression: 4-layer, 37	prop ulcers healed (percentage from time of randomization to six months post- randomization; acetate tracing used to identify date of healing)	26 weeks	Total events (%): 25 Denominator: 37 Persons Final : P: <0.05 (ref: baseline)	Total events (%): 25 Denominator: 37 Persons Final : P: <0.05 (ref: baseline)
O'Hare, 2010[58]	Compression: multi layer, 20	Perforator-sclerotherapy; Compression: multi layer, 13	prop ulcers healed wound healing rates no intermediate to complete (%)	24 weeks	pts with event (%): 17 (85) Denominator: Persons	pts with event (%): 12 (92) Denominator: Persons
Rojas, 2009[63]	Compression: Unna boot, 37	Perforator-sclerotherapy Other-ultrasound guided; Compression: Unna boot, 33	prop ulcers healed (healed)	NR	pts with event (%): 23 (62.1)	pts with event (%): 28 (84.9) Final : P: 0.029 (ref: Grp1)
Rojas, 2009[63]	Compression: Unna boot, 33	Perforator-sclerotherapy Other-ultrasound guided; Compression: Unna boot, 33	time to complete closure (weeks to healed)	NR	P: <0.001(ref Grp1-G2) Final Mean: 20	Final Mean: 8

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
van Gent, 2006[65]	Compression: 2 layer compression, 102	Perforator-SEPS; Compression: 2 layer compression, 94	mortality (Not further specified)	36 months	pts with event (%): 17 (17) Denominator: 102 limbs P: >0.05 (ref: baseline)	pts with event (%): 8 (9) Denominator: 94 limbs P: 0.41 (ref: Grp1)
van Gent, 2006[65]	Compression: 2 layer compression, 102	Perforator-SEPS; Compression: 2 layer compression, 94	prop ulcers healed (Not further specified)	36 months	pts with event (%): 74 (73) Denominator: 102 limbs	pts with event (%): 78 (83) Denominator: 94 limbs
van Gent, 2006[65]	Compression: 2 layer compression, 94	Perforator-SEPS; Compression: 2 layer compression, 94	time to complete closure (months)	NR	Final Median: 15	Final Median: 11
van Gent, 2006[65]	Compression: 2 layer compression, 102	Perforator-SEPS; Compression: 2 layer compression, 94	rate wound recurrence (Not further specified)	36 months	pts with event (%): 23 (23) Denominator: 102 limbs	pts with event (%): 21 (22) Denominator: 94 limbs
Zamboni, 2003[61]	Compression: 20-30mmHg, 24	Superficial Vein Surgery-vein stripping; Compression: 20-30mmHg pressure, 23	rate wound recurrence (Not further specified)	36 months	Total events (%): 9 (38) Denominator: 24 Persons: P: <0.001(ref Grp1-G2) Final percentage: 96	Total events (%): 2 (9) Denominator: 23 Persons: P: Grp1-G2(ref 000000000) Final percentage: 100 P: <0.001 (ref: Grp1)
Zamboni, 2003[61]	Compression: 20-30mmHg, 24	Superficial Vein Surgery-vein stripping; Compression: 20-30mmHg pressure, 23	time to complete closure wound healing rates no intermediate to complete (Not further specified)	36 months	Total events (%): (96) P: <0.001(ref Grp1-G2) Final Percentage: 96	Total events (%): (100) P: Grp1-G2(ref 010011100) Final Percentage: 100 P: 0.85 (ref: Grp1)

Table D-4d. Outcomes reported for studies evaluating surgery as treatment of chronic venous ulcers (KQ3b)

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results , Group1	Results, Group2
Bello, 1999[71]	Other-other surgery, 111	NA	time to complete closure (Ulcers were considered healed when full epithelialization had occurred; measured by computer- ized planimetry from tracings of the ulcer perimeter on transparent acetate sheets)	NA	Mean: 18 weeks (95% CI: 14 to 21)	NA
Bello, 1999[71]	Other-other surgery, 111	NA	prop ulcers healed (Ulcers were considered healed when epithelialization had occurred; measured by computer- ized planimetry from tracings of the ulcer perimeter on transparent acetate sheets)	18 months	Total events: 92	NA
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-SEPS; compression: multi layer, 56	prop ulcers healed (% patients with event)	NR	Total both groups: 95%	NA
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-SEPS; compression: multi layer, 56	time to complete closure (time to complete epithelialization in days)	NR	Final Mean (NS): 84 (8)	Final Mean (NS): 56 (6
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-sclerotherapy; compression: multi layer, 698	time to complete closure (time to complete epithelialization in days)	NR	Final Mean (NS): 84 (8)	Final Mean (NS): 39 (12)
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-SEPS; compression: multi layer, 56	rate wound recurrence (Not further specified)	NR	Pts with event (%): 12 (31)	Pts with event (%): 16 (29)
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-sclerotherapy; compression: multi layer, 698	rate wound recurrence (Not further specified)	NR	Pts with event (%): 12 (31)	Pts with event (%): 126 (18)
Cambal, 2008[69]	Superficial Vein Surgery-vein stripping; compression: multi layer, 39	Perforator-SEPS; compression: multi layer, 56	functional status (Inability to work in days)		Total time range : 56 to 84 days	
Cambal, 2008[69]	NA	Perforator-sclerotherapy; compression: multi layer, 698	functional status (Inability to work in days)	NR	NA	7 days
El-Hafez, 2004[68]	Superficial Vein Surgery-vein stripping; compression: multi layer, hydrocolloid, 10	Perforator-ligation; compression: multi layer, hydrocolloid, 26	prop ulcers healed (Not further specified)	12 months	Pts with event (%): 7 (70)	Pts with event (%): 22 (84.6)

El-Hafez, 2004[68]	Superficial Vein Surgery-vein stripping; compression: multi layer, hydrocolloid	Perforator-ligation; compression: multi layer, hydrocolloid	functional status (Initial walking disturbances)	12 months	Pts with event (%): 7 (70)	Pts with event (%): 5 (19.2)
Harlander-Locke, 2011[74]	Superficial Vein Surgery-RFA Perforator-RFA, 72	NA	mortality (Not further specified)	12 months	pts with events (%): 2 (3) Denominator: 72 Persons	NA
Harlander-Locke, 2011[74]	Superficial Vein Surgery-RFA Perforator-RFA, 110	NA	prop ulcers healed (Not further specified; Weekly photographs assessed by wound care software system)	6 months	Total events: 76 Denominator: 110 ulcers	NA
Harlander-Locke, 2011[74]	Superficial Vein Surgery-RFA Perforator-RFA, 60	NA	rate wound recurrence (Weekly photographs assessed by wound care software system)	12 months	pts with events (%): 4 (7) Total events: 6 Denominator: 60 Persons	NA
Harlander-Locke, 2011[74]	Superficial Vein Surgery-RFA Perforator-RFA,56	NA	time to complete closure (days)	NA	Mean Final (SD): 142 days (14)	NA
Harlander-Locke, 2011[74]	Superficial Vein Surgery-RFA Perforator-RFA, 110	NA	prop ulcers healed (Not further specified; Weekly photographs assessed by wound care software system)	12 months	pts with events (%): 60 (55) Total events: 84 Denominator: 110 ulcers	NA
Labas, 2009[76]	Other-valvuloplasty of the popliteal vein and reflux in GSV and SSV treated with compression sclerotherapy, 56	NA	time to complete closure (days)	NR	Median Final (SE): 39 days (12)	NA
Labas, 2009[76]	Other-valvuloplasty of the popliteal vein and reflux in GSV and SSV treated with compression sclerotherapy, 56	NA	rate wound recurrence (Not further specified)	60 months	pts with events (%): 10 (18) Denominator: 56 Persons	NA
Labas, 2009[76]	Other-valvuloplasty of the popliteal vein and reflux in GSV and SSV treated with compression sclerotherapy, 56	NA	prop ulcers healed (Not further specified)	NR	pts with events (%): 53 (95) Denominator: 56 Persons	NA
Lane, 2003[77]	Obstructive Reflux-angioplasty stenting, 42	NA	ulcers healed	86 months	Total events: 21	NA

Lane, 2003[77]	Obstructive Reflux-angioplasty stenting, 21	NA	wound healing rates yes intermediate to complete (Not further specified)	86 months	Baseline Mean (out of n= 52): 12.6 cm^2 Final Mean (out of n=21): 1.2 cm^2 P: <0.01 (ref baseline)	NA
Lawrence, 2011[14]	Perforator-RFA,	NA	time to complete closure (days)	NR	Final Mean: 138 days	NA
Lawrence, 2011[14]	Perforator-RFA,	NA	rate wound recurrence (Not further specified)	12.85 months	pts with events (%): (4) Denominator: healed ulcers, number not specified	NA
Lawrence, 2011[14]	Perforator-RFA,	NA	prop ulcers healed (Not further specified)	12.85 months	pts with events (%): (90)	NA
Masuda, 1994[72]	Superficial Vein Surgery-vein stripping, 51	NA	prop ulcers healed (Clinical class 0 or 1; SVS/ISCV)	120 months	pts with events (%): 31 (60)	NA
Nash, 1991[73]	Superficial Vein Surgery-vein stripping; compression: 30-40 mm Hg, 42	NR, 19	rate wound recurrence (Not further specified)	18 months	Total events: 1	Total events: 3
Pang, 2010[70]	Perforator-sclerotherapy, 82	NA	prop ulcers healed (complete re-epithelialisation of the leg for more than 2 weeks)		pts with events (%): 67 (82) Denominator: 82 Persons	NA
Pang, 2010[70]	Perforator-sclerotherapy, 82	NA	time to complete closure (median duration in months)	NA	Median (IQR): 1 month (1 to 2)	NA
Pang, 2010[70]	Perforator-sclerotherapy, 83	NA	mortality (Not further specified)	NA	pts with events (%): 7 (8) Denominator: 130 Persons	NA
Sigala, 2007[78]	Perforator-SEPS, 62	NA	prop ulcers healed (after 26 weeks (%))	26 weeks	pts with events (%): 32 (52)	NA
Sigala, 2007[78]	Perforator-SEPS, 62	NA	prop ulcers healed (after 1 a (%))	12 months	pts with events (%): 60 (97)	NA
Sigala, 2007[78]	Perforator-SEPS, 62	NA	prop ulcers healed (healing rate after 12 weeks (%))	12 weeks	pts with events (%): 18 (29)	NA

Sottiurai, 1991[67]	Superficial Vein Surgery-vein stripping; compression: pump Unna boot elastic stocking or ace wrap, 16	Superficial Vein Surgery-vein stripping Deep Vein Surgery-valvuloplasty; compression: pump Unna boot elastic stocking or ace wrap, 24	functional status (Improvement in venous function status; Kressman's technique)	NR	Total events: 9 Denominator: 16 persons	Total events: 22 Denominator: 24 persons P: <0.001 (ref Grp1)
Sottiurai, 1991[67]	Superficial Vein Surgery-vein stripping; compression: pump Unna boot elastic stocking or ace wrap, 33	Superficial Vein Surgery-vein stripping Deep Vein Surgery-valvuloplasty; compression: pump Unna boot elastic stocking or ace wrap, 46	rate wound recurrence (Not further specified)	NR	Total events: 19 Denominator: 33 persons	Total events: 9 Denominator: 49 persons P: <0.001 (ref Grp1)
Taradaj, 2011[75]	Superficial Vein Surgery-vein stripping Perforator-ligation	NA	rate wound recurrence (any breakdown of epithelium between the knee and malleoli after ulcer healing)	24 months	pts with events (%): (18.7)	NA
Taradaj, 2011[75]	Superficial Vein Surgery-vein stripping Perforator-ligation, 35	NA	prop ulcers healed (Complete re-epithelialization of the leg)	7 weeks	pts with events (%): 19 (53.1)	NA
Wolters, 1997[79]	Perforator-SEPS, 74	NA	prop ulcers healed (healing rate after 3 months(%); Reporting standards in venous disease; classification according to Rutherford and acoustic doppler sonography)	3 months	pts with events (%): 68 (92) Denominator: NA	NA
Wolters, 1997[79]	Perforator-SEPS, 74	NA	prop ulcers healed (healing rate after 12 months(%); Reporting standards in venous disease: classification according to Rutherford & acoustic doppler sonography)	12 months	pts with events (%): 57 (77) Denominator: NA	NA

Abbreviations: AWD = advanced wound dressings; CI = confidence interval; Grp1 = Group 1; Grp2 = Group 2; GSV = great saphenous vein; GSV = great saphenous vein; IQR = interquartile range; mm Hg = millimeters of mercury; NA = not applicable; NR = not reported; NS = not significant; P = P-value; prop = proportion; Pts = patients; RFA = radiofrequency ablation; RH = relative hazard; SD = standard deviation; SE = standard error; SEPS = subfascial endoscopic perforator surgery; SF – 36 = Short Form-36 Health Survey; SSV = short saphenous vein; surg = surgery; SVS/ISCV = Society for Vascular Surgery/International Society for Cardiovascular Surgery; unspec = unspecified

Table D-5a. Study quality evaluations for studies evaluating the treatment of chronic venous ulcers, reporting

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Alinovi, 1986[82]	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	1
Alinovi, 1986[82]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	2
Arnold, 1994[39]	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	1
Arnold, 1994[39]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	2
Backhouse, 1987[43]	No	No	Yes	No	No	No	Yes	No	No	No	1
Backhouse, 1987[43]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	2
Barwell, 2000[62]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Barwell, 2000[62]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	2
Barwell, 2004[60]		Yes		Yes	No	Yes	Yes	Yes	Yes	Yes	1
Barwell, 2004[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2
Beckert, 2006[31]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Beckert, 2006[31]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2
Bello, 1999[71]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	1
Bello, 1999[71]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	2
Cambal, 2008[69]	No	No	No	Yes	No	No	No	No	No	No	1
Cambal, 2008[69]	No	No	No	Yes	No	Yes	Yes		No	No	2
El-Hafez, 2004[68]	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	1

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
El-Hafez, 2004[68]	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	2
Falanga V, 1999[51]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	1
Falanga V, 1999[51]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	2
Falanga, 1998[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	1
Falanga, 1998[38]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	2
Franks, 2007[28]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Franks, 2007[28]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2
Galimberti, 1988[66]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	1
Galimberti, 1988[66]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	2
Gatti, 2011[45]	No	No	No	No	No	No	No	No	Yes	No	1
Gatti, 2011[45]	Yes	No	Yes	Yes	No	No	No	No	No	No	2
Gethin, 2009[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1
Gethin, 2009[24]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2
Gohel, 2007[59]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	1
Gohel, 2007[59]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	2
Gottrup, 2007[27]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Gottrup, 2007[27]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Gottrup, 2008[23]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	1
Gottrup, 2008[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	2
Greguric, 1994[48]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	1
Greguric, 1994[48]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	2
Guest, 2003[64]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Guest, 2003[64]	Yes		Yes	Yes	Yes	Yes	Yes	No	No	No	2
Hansson, 1998[37]	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	1
Hansson, 1998[37]	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes	2
Harding, 2005[33]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	1
Harding, 2005[33]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	2
Harding, 2011[20]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	1
Harding, 2011[20]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	2
Harlander-Locke, 2011[74]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	1
Harlander-Locke, 2011[74]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	2
Holloway, 1989[42]	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	1
Holloway, 1989[42]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	2
Huovinen, 1994[57]	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	1

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Huovinen, 1994[57]	Yes	Yes	No	Yes	No	No	No	No	Yes	No	2
Krishnamoorthy, 2003[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	1
Krishnamoorthy, 2003[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2
Kucharzewski, 2003[46]	Yes	No	Yes	Yes	No	No	No	No	Yes	No	1
Kucharzewski, 2003[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	2
Labas, 2009[76]	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	1
Labas, 2009[76]	Yes	Yes	Yes	Yes	No	Yes	No		No	No	2
Lammoglia-Ordiales, 2011[56]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	1
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	2
Lane, 2003[77]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	1
Lane, 2003[77]	Yes	Yes	Yes	Yes	No	Yes	No		No	Yes	2
Lawrence, 2011[14]	No	No	Yes	Yes	No	No	No	Yes	No	No	1
Lawrence, 2011[14]	Yes	Yes	No	Yes	No	No	Yes	No	No	No	2
Limova, 2003[35]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	1
Limova, 2003[35]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	2

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Maggio, 2011[21]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	1
Maggio, 2011[21]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	2
Masuda, 1994[72]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Masuda, 1994[72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	2
Michaels, 2009[22]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	1
Michaels, 2009[22]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	2
Moffatt, 1992[49]	Yes	No	No	Yes	No	No	Yes	No	No	Yes	1
Moffatt, 1992[49]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	2
Mostow, 2005[32]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes		1
Mostow, 2005[32]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2
Nash, 1991[73]	Yes	No	No	No	No	No	No	No	No	No	1
Nash, 1991[73]	Yes	No	No	No	No	No	No	No	No	No	2
Nelson, 2007[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1
Nelson, 2007[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2
O'Hare, 2010[58]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	1
O'Hare, 2010[58]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	2
Omar, 2004[34]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	1
Omar, 2004[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	2

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Ormiston MC, 1983[55]	Yes	No	Yes	Yes	No	No	No	Yes	No	No	1
Ormiston MC, 1983[55]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	2
Ormiston, 1985[44]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Ormiston, 1985[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	2
Pang, 2010[70]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	1
Pang, 2010[70]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	2
Pessenhofer, 1989[41]	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	1
Pessenhofer, 1989[41]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	2
Rojas, 2009[63]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	1
Rojas, 2009[63]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	2
Schulze, 2001[36]	No	Yes	No	Yes	No	No	Yes	Yes	No	No	1
Schulze, 2001[36]	No	No	No	No	No	No	Yes	Yes	Yes	No	2
Scurr JH, 1993[54]	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	1
Scurr JH, 1993[54]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	2
Scurr JH, 1994[53]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	1

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Scurr JH, 1994[53]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	2
Sigala, 2007[78]	No	Yes	Yes	Yes		Yes	No	Yes	No	No	1
Sigala, 2007[78]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	2
Smith, 1992[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	1
Smith, 1992[50]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	2
Sottiurai, 1991[67]	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	1
Sottiurai, 1991[67]	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	2
Taradaj, 2011[75]	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	1
Taradaj, 2011[75]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	2
Teepe, 1993[40]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Teepe, 1993[40]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	2
van Gent, 2006[65]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	1
van Gent, 2006[65]	Yes	Yes	Yes		Yes	Yes	Yes	No	Yes	Yes	2
Vanscheidt, 2007[26]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	1
Vanscheidt, 2007[26]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	2
Vowden, 2006[30]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	1

Author, year	Hypothesis objective clearly described	Main outcomes described	Subject characteristics described	Interventions of interest described	Principal confounders	Main findings	Random variability estimate	Adverse events consequence intervention	Loss to followup	Actual probability values	Reviewer
Vowden, 2006[30]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	2
Vowden, 2007[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Vowden, 2007[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	2
Weiss RA, 1996[52]	Yes	Yes	No	Yes	No	Yes	No	No		No	1
Weiss RA, 1996[52]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	2
Wolters, 1997[79]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	1
Wolters, 1997[79]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	2
Zamboni, 2003[61]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	1
Zamboni, 2003[61]	Yes	No	No	Yes	No	No	No	No	Yes	No	2

Table D-5b. Study quality evaluations for studies evaluating the treatment of chronic venous ulcers, external validity, power, and conflict of interest

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Alinovi, 1986[82]	Unable to determine	Unable to determine	Yes	No	No industry support	No loss to followup	1
Alinovi, 1986[82]	No	Unable to determine	Yes	No	No industry support	No loss to followup	2
Arnold, 1994[39]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	1
Arnold, 1994[39]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Backhouse, 1987[43]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	1
Backhouse, 1987[43]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	2
Barwell, 2000[62]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Barwell, 2000[62]	Yes	Unable to determine	Yes	No	Yes industry support	No loss to followup	2
Barwell, 2004[60]	Yes	Yes	Yes	No	Yes industry support	No loss to followup	1
Barwell, 2004[60]	Yes	Unable to determine	No	No	No industry support	No loss to followup	2
Beckert, 2006[31]	Yes	Yes	Unable to determine	Yes	No industry support	No loss to followup	1
Beckert, 2006[31]	Unable to determine	Unable to determine	Unable to determine	Yes	NR support	NR	2
Bello, 1999[71]	No	No	Unable to determine	Yes	No industry support	Yes loss to followup	1
Bello, 1999[71]	Unable to determine	Unable to determine	Yes	No	No industry support	Yes loss to followup	2
Cambal, 2008[69]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	1
Cambal, 2008[69]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	2
El-Hafez, 2004[68]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	1
El-Hafez, 2004[68]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	2
Falanga V, 1999[51]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Falanga V, 1999[51]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	2
Falanga, 1998[38]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	1
Falanga, 1998[38]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Franks, 2007[28]	Unable to determine	Unable to determine	Yes	Yes	Yes industry support	No loss to followup	1
Franks, 2007[28]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	2
Galimberti, 1988[66]	No	No	Unable to determine	No	No	No	1
Galimberti, 1988[66]	No	No	Unable to determine	No	No	No	2
Gatti, 2011[45]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	NR	1
Gatti, 2011[45]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	NR	2
Gethin, 2009[24]	Unable to determine	Unable to determine	Yes	Yes	NR support	No loss to followup	1
Gethin, 2009[24]	Unable to determine	Unable to determine	Yes	Yes	NR support	No loss to followup	2
Gohel, 2007[59]	Unable to determine	Unable to determine	Yes	No	No industry support	No loss to followup	1
Gohel, 2007[59]	Yes	Unable to determine	No	No	No industry support	No loss to followup	2
Gottrup, 2007[27]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Gottrup, 2007[27]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Gottrup, 2008[23]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	NR loss to followup	1
Gottrup, 2008[23]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	NR loss to followup	2
Greguric, 1994[48]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	1
Greguric, 1994[48]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	2
Guest, 2003[64]		Unable to determine	Unable to determine	No	No industry support	No loss to followup	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Guest, 2003[64]	Yes	No	Yes	No	No industry support	No loss to followup	2
Hansson, 1998[37]	Unable to determine	Unable to determine	Yes	No	Yes industry support	No loss to followup	1
Hansson, 1998[37]	Unable to determine		Yes	No	Yes industry support	No loss to followup	2
Harding, 2005[33]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	Yes loss to followup	1
Harding, 2005[33]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	Yes loss to followup	2
Harding, 2011[20]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Harding, 2011[20]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	2
Harlander-Locke, 2011[74]	Unable to determine	Unable to determine	Yes	No	No industry support	No loss to followup	1
Harlander-Locke, 2011[74]	Unable to determine	No	Yes	No	No industry support	No loss to followup	2
Holloway, 1989[42]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	1
Holloway, 1989[42]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Huovinen, 1994[57]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	1
Huovinen, 1994[57]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Krishnamoorthy, 2003[47]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Krishnamoorthy, 2003[47]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Kucharzewski, 2003[46]	Unable to determine	Unable to determine	Unable to determine	No	NR support	No loss to followup	1
Kucharzewski, 2003[46]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	2
Labas, 2009[76]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Labas, 2009[76]	No	No	Unable to determine		No industry support	No loss to followup	2
Lammoglia-Ordiales, 2011[56]	Yes	Unable to determine	Unable to determine	Yes	NR support	NR	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Yes	NR support	NR	2
Lane, 2003[77]	Unable to determine	Unable to determine	Yes	No	NR support	No loss to followup	1
Lane, 2003[77]	Unable to determine	Unable to determine	Unable to determine	No	NR support	No loss to followup	2
Lawrence, 2011[14]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Lawrence, 2011[14]		Unable to determine		No	No industry support	No loss to followup	2
Limova, 2003[35]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	1
Limova, 2003[35]	Yes	Yes	No	No	NR support	NR	2
Maggio, 2011[21]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	1
Maggio, 2011[21]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	NR	2
Masuda, 1994[72]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Masuda, 1994[72]	Unable to determine	Unable to determine	No	No	No industry support	No loss to followup	2
Michaels, 2009[22]	Yes	Yes	Yes	Yes	No industry support	No loss to followup	1
Michaels, 2009[22]	Unable to determine	Unable to determine	Unable to determine	Yes	No industry support	No loss to followup	2
Moffatt, 1992[49]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Moffatt, 1992[49]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	2
Mostow, 2005[32]	Unable to determine	No	Unable to determine	No	Yes industry support	Yes loss to followup	1
Mostow, 2005[32]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Yes loss to followup	2
Nash, 1991[73]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Nash, 1991[73]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	2
Nelson, 2007[29]	Yes	Yes	Unable to determine	Yes	NR support	NR	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Nelson, 2007[29]	Unable to determine	Unable to determine	Unable to determine	Yes	NR support	NR	2
O'Hare, 2010[58]	Yes	Unable to determine	Unable to determine	Yes	NR support	No loss to followup	1
O'Hare, 2010[58]	Yes	Unable to determine	Unable to determine	No	NR support	No loss to followup	2
Omar, 2004[34]	Unable to determine	Unable to determine	Unable to determine	No	NR support	No loss to followup	1
Omar, 2004[34]	Unable to determine	Unable to determine	Unable to determine	Yes	NR support	No loss to followup	2
Ormiston MC, 1983[55]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	1
Ormiston MC, 1983[55]	Unable to determine	Unable to determine	Unable to determine	No	NR support	NR	2
Ormiston, 1985[44]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Ormiston, 1985[44]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Pang, 2010[70]	Unable to determine	Unable to determine	Yes	No	NR support	No loss to followup	1
Pang, 2010[70]	Yes	No	Unable to determine	No	NR support	No loss to followup	2
Pessenhofer, 1989[41]	Yes	Unable to determine	Yes	No	NR support	No loss to followup	1
Pessenhofer, 1989[41]	No	No	No	No	NR support	No loss to followup	2
Rojas, 2009[63]	No	No	Yes	No	NR support	No loss to followup	1
Rojas, 2009[63]	Unable to determine	Unable to determine	Unable to determine	No	NR support	No loss to followup	2
Schulze, 2001[36]	Unable to determine	Unable to determine	Yes	No	Yes industry support	NR	1
Schulze, 2001[36]	Unable to determine	Unable to determine	Yes	No	Yes industry support	NR	2
Scurr JH, 1993[54]	Unable to determine	Unable to determine	Yes	No	Yes industry support	No loss to followup	1
Scurr JH, 1993[54]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Scurr JH, 1994[53]	Unable to determine	Unable to determine	Yes	No	Yes industry support	No loss to followup	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Scurr JH, 1994[53]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Sigala, 2007[78]	Unable to determine	Unable to determine	Yes	No	NR support	NR	1
Sigala, 2007[78]	Unable to determine	Yes	Yes	No	NR support	NR	2
Smith, 1992[50]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	1
Smith, 1992[50]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	No loss to followup	2
Sottiurai, 1991[67]	Unable to determine	Unable to determine		No	No industry support	Yes loss to followup	1
Sottiurai, 1991[67]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Yes loss to followup	2
Taradaj, 2011[75]	Yes	Unable to determine	Unable to determine	No	NR support	No loss to followup	1
Taradaj, 2011[75]	Yes	No	No	No	NR support	No loss to followup	2
Teepe, 1993[40]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Teepe, 1993[40]	Unable to determine	Unable to determine	Unable to determine	Yes	No industry support	No loss to followup	2
van Gent, 2006[65]	Unable to determine	Unable to determine	Unable to determine	Yes	No industry support	No loss to followup	1
van Gent, 2006[65]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	2
Vanscheidt, 2007[26]	Unable to determine	Unable to determine	Unable to determine	Yes	NR support	No loss to followup	1
Vanscheidt, 2007[26]	Unable to determine	Unable to determine	Unable to determine	Yes	NR support	No loss to followup	2
Vowden, 2006[30]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Vowden, 2006[30]	No	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	2
Vowden, 2007[25]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	1
Vowden, 2007[25]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes industry support	No loss to followup	2
Weiss RA, 1996[52]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Yes loss to followup	1

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation report	Support	More than 30% loss to followup	Reviewer
Weiss RA, 1996[52]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Yes loss to followup	2
Wolters, 1997[79]	Unable to determine	No	No	No	NR support	NR	1
Wolters, 1997[79]	Unable to determine	No	Yes	No	NR support	NR	2
Zamboni, 2003[61]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	No loss to followup	1
Zamboni, 2003[61]	No	Unable to determine	Unable to determine	Yes	No industry support	No loss to followup	2

Table D-5c. Study quality evaluations for studies evaluating the treatment of chronic venous ulcers, internal validity-bias

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Alinovi, 1986[82]	No	No	No	No	Yes	Yes	Unable to determine	1
Alinovi, 1986[82]	No	Unable to determine	No	No	Yes	No	Yes	2
Arnold, 1994[39]	No	Unable to determine	No	No	Unable to determine	Unable to determine	Yes	1
Arnold, 1994[39]	No	No	Unable to determine	No	Yes	Yes	Yes	2
Backhouse, 1987[43]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Backhouse, 1987[43]	No	No		Yes	Yes	Yes	Yes	2
Barwell, 2000[62]	No	No	Unable to determine	No	Yes	Yes	Unable to determine	1
Barwell, 2000[62]	No	No	Yes	Yes	Yes	No	Yes	2
Barwell, 2004[60]	No	No	No	No	Yes	Yes		1

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Barwell, 2004[60]	No	No	Yes	Yes	Yes	No	Yes	2
Beckert, 2006[31]	Yes	No	Yes	Yes	Yes	Yes	Yes	1
Beckert, 2006[31]	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes	2
Bello, 1999[71]	No	No	No	No	Yes	Yes	Yes	1
Bello, 1999[71]	No	No	Yes	Yes	Yes	Unable to determine	Yes	2
Cambal, 2008[69]	No	No	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	1
Cambal, 2008[69]	No	No	Unable to determine	No	Unable to determine	Yes	Yes	2
El-Hafez, 2004[68]	No	No	Unable to determine	No	Yes	Yes	Yes	1
El-Hafez, 2004[68]	No	Unable to determine	Yes	No	Yes	No	Unable to determine	2
Falanga V, 1999[51]	Unable to determine	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	1
Falanga V, 1999[51]	No	Unable to determine	No	No	Unable to determine	Unable to determine	Yes	2
Falanga, 1998[38]	Unable to determine	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	1
Falanga, 1998[38]	No	Unable to determine	Yes	No	Unable to determine	Yes	Yes	2
Franks, 2007[28]	No	No	Yes	Yes	Yes	Unable to determine	Yes	1
Franks, 2007[28]	Yes	No	Unable to determine	No	Yes	Unable to determine	Yes	2
Gatti, 2011[45]	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	1
Gatti, 2011[45]	No	No	Yes	Yes	No	Yes	No	2
Gethin, 2009[24]	No	No	Yes	Yes	Yes		Yes	1
Gethin, 2009[24]	No	No	Yes	Yes	Yes	No	Yes	2
Gohel, 2007[59]	No	No	Unable to determine	No	Yes	Yes	Yes	1

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Gohel, 2007[59]	No	No	No	Yes	Yes	No	Yes	2
Gottrup, 2007[27]	Yes	No	Unable to determine	No	Yes	Unable to determine	Yes	1
Gottrup, 2007[27]	Yes	No	Unable to determine	No	Yes	Unable to determine	Yes	2
Gottrup, 2008[23]	Yes	Yes	Yes	No	Yes	Yes	Yes	1
Gottrup, 2008[23]	Yes	Yes	Yes	No	Yes	Yes	Yes	2
Greguric, 1994[48]	No	Unable to determine	Yes	No	Unable to determine	Unable to determine	Unable to determine	1
Greguric, 1994[48]	Unable to determine	Unable to determine	Unable to determine	No	Yes	Yes	Yes	2
Guest, 2003[64]	Unable to determine		No	No	Yes	Yes	Yes	1
Guest, 2003[64]	No	No	Yes	Yes	Yes	Unable to determine	Yes	2
Hansson, 1998[37]	No	No	Yes	No	Yes	Yes	Yes	1
Hansson, 1998[37]	No	No	Yes	No	Unable to determine	Yes	Yes	2
Harding, 2005[33]	Unable to determine	Unable to determine	Yes	Yes	Yes	Yes	Yes	1
Harding, 2005[33]	No	No	Yes	Yes	Yes	Yes	Yes	2
Harding, 2011[20]	No	No	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Harding, 2011[20]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	2
Harlander-Locke, 2011[74]	No	No	Unable to determine	No	Yes	Yes	Yes	1
Harlander-Locke, 2011[74]	No	No	No	Yes	Yes	Unable to determine	Yes	2
Holloway, 1989[42]	Unable to determine	Unable to determine	No	No	No	Unable to determine	Yes	1
Holloway, 1989[42]	No	No	Yes	No	Yes	Yes	Yes	2

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Huovinen, 1994[57]	Yes	Yes	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	1
Huovinen, 1994[57]	Yes	Unable to determine	Yes	Yes	Unable to determine	Yes	Yes	2
Krishnamoorthy, 2003[47]	No	No	Unable to determine	Yes	Yes	Yes	Yes	1
Krishnamoorthy, 2003[47]	No	Yes	Yes	Yes	No	Yes	Yes	2
Kucharzewski, 2003[46]	No	Unable to determine	Yes	No	No	Unable to determine	No	1
Kucharzewski, 2003[46]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Yes	Yes	2
Labas, 2009[76]	No	No	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	1
Labas, 2009[76]	No	No	Unable to determine	No	Unable to determine		Unable to determine	2
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Unable to determine	Yes	Unable to determine	Yes	1
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Unable to determine	Yes	Unable to determine	Yes	2
Lane, 2003[77]	No	Unable to determine	Unable to determine	No	No	Unable to determine	No	1
Lane, 2003[77]	No	No	Unable to determine	No	Yes	Yes	Yes	2
Lawrence, 2011[14]	No	No	Unable to determine	No	Unable to determine	Unable to determine	Unable to determine	1
Lawrence, 2011[14]	No	No	Unable to determine	No	Yes	Yes	Yes	2
Limova, 2003[35]	No	No	No	Yes	Yes	Yes	Yes	1
Limova, 2003[35]	Unable to determine	No	No	Yes	Yes	Yes	Yes	2
Maggio, 2011[21]	No	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	1
Maggio, 2011[21]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	2

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Masuda, 1994[72]	No	No	No	No	Yes	Yes	Yes	1
Masuda, 1994[72]	No	No	Yes	Yes	Yes	Yes	Yes	2
Michaels, 2009[22]	Unable to determine	Unable to determine	No	Yes	Yes	Yes	Yes	1
Michaels, 2009[22]	Unable to determine	Unable to determine	Yes	Yes	Yes	Yes	Yes	2
Moffatt, 1992[49]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Yes	Yes	1
Moffatt, 1992[49]	No	Unable to determine	Yes	No	Unable to determine	Unable to determine	Yes	2
Mostow, 2005[32]	Yes	Yes	Unable to determine	Yes	Yes	Yes	Yes	1
Mostow, 2005[32]	No	Unable to determine	Unable to determine	Yes	Yes	Yes	Yes	2
Nash, 1991[73]	No	No	Yes	No	No	Unable to determine	Unable to determine	1
Nash, 1991[73]	Unable to determine	Unable to determine	Unable to determine	Unable to determine	No	Unable to determine	Unable to determine	2
Nelson, 2007[29]	No	No	Unable to determine	Yes	Unable to determine	Yes	Yes	1
Nelson, 2007[29]	No	No	Yes	Yes	Yes	Yes	Yes	2
O'Hare, 2010[58]	No	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	1
O'Hare, 2010[58]	No	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	2
Omar, 2004[34]	No	Yes	Yes	Yes	Yes	Yes	Yes	1
Omar, 2004[34]	Unable to determine	Yes	Unable to determine	No	Yes	Yes	Yes	2
Ormiston MC, 1983[55]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Ormiston MC, 1983[55]	No	No	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	2
Ormiston, 1985[44]	Unable to determine	Unable to determine	Unable to determine	No	Yes	Unable to determine	Yes	1
Ormiston, 1985[44]	No	No	No	No	Yes	Yes	Yes	2

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Pang, 2010[70]	No	No	No	No	Yes	Yes	Yes	1
Pang, 2010[70]	No	No	Yes	No	Yes	Unable to determine	Yes	2
Pessenhofer, 1989[41]	No	Unable to determine	Yes	No	Yes	Yes	Yes	1
Pessenhofer, 1989[41]	No	No	Yes	No	Yes	No	Yes	2
Rojas, 2009[63]	No	No	Unable to determine	No	Unable to determine	Unable to determine	Unable to determine	1
Rojas, 2009[63]	Unable to determine	Unable to determine	Unable to determine	No	Unable to determine	Unable to determine	Yes	2
Schulze, 2001[36]	Unable to determine	No	Yes	Yes	Yes	Unable to determine	Unable to determine	1
Schulze, 2001[36]	Unable to determine	No	Yes	Yes	Yes	No	No	2
Scurr JH, 1993[54]	No	No	Unable to determine	No	No	Yes	Yes	1
Scurr JH, 1993[54]	Unable to determine	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	2
Scurr JH, 1994[53]	Unable to determine	No	No	Unable to determine	Yes		Yes	1
Scurr JH, 1994[53]	Unable to determine	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	2
Sigala, 2007[78]	No	Unable to determine	Unable to determine	Unable to determine	Yes	Unable to determine	Yes	1
Sigala, 2007[78]	No	No	Yes	Unable to determine	Yes	Unable to determine	Yes	2
Smith, 1992[50]	Unable to determine	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Smith, 1992[50]	No	No	Yes	Yes	Yes	Yes	Yes	2
Sottiurai, 1991[67]	No	No	Unable to determine			Unable to determine	Yes	1
Sottiurai, 1991[67]	No	No	Yes	No	Unable to determine	Unable to determine	Yes	2
Taradaj, 2011[75]	No	No	No	No	Yes	Unable to determine	Unable to determine	1
Taradaj, 2011[75]	No	No	Unable to determine	No	Yes	Yes	Yes	2

Author, year	Attempt to blind	Blinding those measuring outcomes	Data dredging	Adjust for different followup length	Appropriate stats tests	Compliance reliable with interventions	Main outcome measures accurate	Reviewer
Teepe, 1993[40]	No	No	Unable to determine	Yes	Yes	Yes	Yes	1
Teepe, 1993[40]	No	No	Unable to determine	No	Unable to determine	Yes	Yes	2
van Gent, 2006[65]	No	Unable to determine	No	Yes	Yes	Unable to determine	Unable to determine	1
van Gent, 2006[65]	No		No	No			Yes	2
Vanscheidt , 2007[26]	No	No	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Vanscheidt , 2007[26]	No	No	Unable to determine	Yes	Yes	Unable to determine	Yes	2
Vowden, 2006[30]	Yes	Yes	Unable to determine	Unable to determine	Yes	Yes	Yes	1
Vowden, 2006[30]	Yes	Yes	Unable to determine	Yes	Yes	Unable to determine	Yes	2
Vowden, 2007[25]	No	No	Unable to determine	Unable to determine	Yes	Yes	Yes	1
Vowden, 2007[25]	No	No	Unable to determine	Unable to determine	Yes	Yes	Yes	2
Weiss RA, 1996[52]	No	No	Unable to determine	Yes	Unable to determine	Yes	Unable to determine	1
Weiss RA, 1996[52]	Unable to determine	Unable to determine	Unable to determine	No	No	Unable to determine	No	2
Wolters, 1997[79]	No	No	Yes	No	Yes	Yes	Yes	1
Wolters, 1997[79]	No	No	Yes	No	Yes	Yes	Yes	2
Zamboni, 2003[61]	No	No	Unable to determine	No	Yes	Yes	Yes	1
Zamboni, 2003[61]	No	No	Yes	Yes	Yes	Unable to determine	Unable to determine	2

Table D-5d. Study quality evaluations for studies evaluating the treatment of chronic venous ulcers, internal validity-confounding and selection bias

Author, year	Intervention groups from same population	Intervention groups recruited same time	Study subjects randomized	Assignment concealed until recruitment complete	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Reviewer
Alinovi, 1986[82]	Yes	Yes	Yes	Unable to determine	No	No	1
Alinovi, 1986[82]	Yes	Yes	Yes	Yes	Yes	Yes	2
Arnold, 1994[39]	Unable to determine	Unable to determine	Yes	Unable to determine	No	Yes	1
Arnold, 1994[39]	Yes	Yes	Yes	Unable to determine	Unable to determine	No	2
Backhouse, 1987[43]	Yes	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	1
Backhouse, 1987[43]	Yes	Yes	Yes	Unable to determine	Yes	Yes	2
Barwell, 2000[62]	Yes	Yes	No	No	No	Yes	1
Barwell, 2000[62]	Yes	Yes	No	No	Yes	Unable to determine	2
Barwell, 2004[60]	Yes	Yes		No	No	Yes	1
Barwell, 2004[60]	Yes	Yes	Yes	Yes	Yes	Yes	2
Beckert, 2006[31]	Yes	Yes	Yes	No	Yes	Yes	1
Beckert, 2006[31]	Yes	Yes	Yes	Unable to determine	Yes	Yes	2
Bello, 1999[71]	Unable to determine	Unable to determine	No	No	No	Yes	1
Bello, 1999[71]	No	Yes	No	No	Unable to determine	Yes	2
Cambal, 2008[69]	No	No	No	No	No	No	1
Cambal, 2008[69]	Unable to determine	Unable to determine	No	No	No	No	2
El-Hafez, 2004[68]	Yes	Yes	No	No	No	No	1
El-Hafez, 2004[68]	Yes	Yes	No	No	No	No	2
Falanga V, 1999[51]	Unable to determine	Unable to determine	No	Unable to determine	Unable to determine	No	1
Falanga V, 1999[51]	Yes	Unable to determine	Yes	Unable to determine	No	Unable to determine	2
Falanga, 1998[38]	Unable to determine	Unable to determine	Yes	Yes	No	No	1
Falanga, 1998[38]	Yes	Unable to determine	Yes	Yes	No	No	2
Franks, 2007[28]	Unable to determine	Unable to determine	Yes	Yes	Unable to determine	Yes	1
Franks, 2007[28]	Yes	Yes	Yes	Yes	Unable to determine	Yes	2
Galimberti, 1988[66]	Yes	Unable to determine	No	No	No	No	1
Galimberti, 1988[66]	Yes	Unable to determine	No	No	No	Yes	2

Author, year	Intervention groups from same population	Intervention groups recruited same time	Study subjects randomized	Assignment concealed until recruitment complete	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Reviewer
Gatti, 2011[45]	Unable to determine	Unable to determine	Unable to determine	No	No	Unable to determine	1
Gatti, 2011[45]	Unable to determine	Unable to determine	No	No	No	Unable to determine	2
Gethin, 2009[24]	Yes	Unable to determine	Yes	Yes	Yes	Yes	1
Gethin, 2009[24]	Yes	Yes	Yes	Yes	Unable to determine	Yes	2
Gohel, 2007[59]	Yes	Yes	Yes	No	No	No	1
Gohel, 2007[59]	Yes	Yes	Yes	No	Yes	Yes	2
Gottrup, 2007[27]	Yes	Yes	Yes	Yes		Unable to determine	1
Gottrup, 2007[27]	Yes	Yes	Yes	Yes	Unable to determine	Yes	2
Gottrup, 2008[23]	Unable to determine	Yes	Yes	Yes	Unable to determine	No	1
Gottrup, 2008[23]	Unable to determine	Yes	Yes	Unable to determine	No	No	2
Greguric, 1994[48]	Yes	Yes	Yes	No	Unable to determine	Unable to determine	1
Greguric, 1994[48]	Unable to determine	Yes	Yes	Unable to determine	No	Unable to determine	2
Guest, 2003[64]	Yes	Yes	Yes	No	No	Yes	1
Guest, 2003[64]	Yes	Yes	Yes	No	Yes	Unable to determine	2
Hansson, 1998[37]	Yes	Yes	Yes	No	No	Yes	1
Hansson, 1998[37]	Yes	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	2
Harding, 2005[33]	Yes	Unable to determine	Yes	Unable to determine	Yes	Yes	1
Harding, 2005[33]	Yes	Unable to determine	Yes	No	Yes	Yes	2
Harding, 2011[20]	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	1
Harding, 2011[20]	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	2
Harlander-Locke, 2011[74]	Yes	Yes	No	Unable to determine	No	Yes	1
Harlander-Locke, 2011[74]	Yes	Yes	No	No	No	No	2
Holloway, 1989[42]	Unable to determine	Unable to determine	Yes	Unable to determine	No	No	1
Holloway, 1989[42]	Yes	Yes	Yes	No	Unable to determine	No	2
Huovinen, 1994[57]	Yes	Yes	Yes	Yes		Unable to determine	1
Huovinen, 1994[57]	Yes	Yes	Yes	Yes	Unable to determine	Yes	2
Krishnamoorthy, 2003[47]	Unable to determine	Unable to determine	Yes	Yes	No	Yes	1

Author, year	Intervention groups from same population	Intervention groups recruited same time	Study subjects randomized	Assignment concealed until recruitment complete	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Reviewer
Krishnamoorthy, 2003[47]	Yes	Yes	Yes	No	Yes	Unable to determine	2
Kucharzewski, 2003[46]	Yes	Unable to determine	Yes	Unable to determine	No	Yes	1
Kucharzewski, 2003[46]	Unable to determine	Unable to determine	No	No	Unable to determine	Unable to determine	2
Labas, 2009[76]	Unable to determine	Unable to determine	No	No	Unable to determine	Unable to determine	1
Labas, 2009[76]	Unable to determine	Unable to determine		No	No	No	2
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Yes	No	Yes	1
Lammoglia-Ordiales, 2011[56]	Yes	Yes	Yes	Yes	No	Yes	2
Lane, 2003[77]	Yes	Yes	No	No	Unable to determine	Unable to determine	1
Lane, 2003[77]	Yes	No	No	No	No	No	2
Lawrence, 2011[14]	Yes	Yes	No	No	Unable to determine	Unable to determine	1
Lawrence, 2011[14]	Yes	Yes	No	No	No	No	2
Limova, 2003[35]	Unable to determine	Unable to determine	Yes	No	No	Yes	1
Limova, 2003[35]	Yes	Yes	Yes	No	No	Yes	2
Maggio, 2011[21]	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	1
Maggio, 2011[21]	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	2
Masuda, 1994[72]	Unable to determine	No	No	No	No	Yes	1
Masuda, 1994[72]	Yes	Yes	No	No	Yes	Yes	2
Michaels, 2009[22]	Yes	Yes	Yes	Unable to determine	Yes	Yes	1
Michaels, 2009[22]	Yes	Yes	Yes	Unable to determine	Yes	Yes	2
Moffatt, 1992[49]	Unable to determine	Unable to determine	Yes	Unable to determine	No	Yes	1
Moffatt, 1992[49]	Yes	Unable to determine	Yes	Unable to determine	No	Yes	2
Mostow, 2005[32]	Yes	Unable to determine	Yes	Yes	Yes	Yes	1
Mostow, 2005[32]	Yes	Unable to determine	Yes	Unable to determine	Yes	Yes	2
Nash, 1991[73]	No	Yes	Unable to determine	No	Unable to determine	Unable to determine	1
Nash, 1991[73]	Unable to determine	Unable to determine	No	No	No	No	2
Nelson, 2007[29]	Yes	Unable to determine	Yes	No	Yes	Yes	1
Nelson, 2007[29]	Unable to determine	Unable to determine	Yes	No	Yes	Yes	2

Author, year	Intervention groups from same population	Intervention groups recruited same time	Study subjects randomized	Assignment concealed until recruitment complete	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Reviewer
O'Hare, 2010[58]	Yes	Yes	Yes	Yes	No	Yes	1
O'Hare, 2010[58]	Yes	Yes	Yes	Yes	Unable to determine	Yes	2
Omar, 2004[34]	Yes	Yes	Yes	Yes	No	Yes	1
Omar, 2004[34]	Unable to determine	Unable to determine	Yes	Unable to determine	Yes	Yes	2
Ormiston MC, 1983[55]	Unable to determine	Unable to determine	Yes	Unable to determine	No	Unable to determine	1
Ormiston MC, 1983[55]	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	No	2
Ormiston, 1985[44]	Unable to determine	Unable to determine	Yes	Yes	No	Yes	1
Ormiston, 1985[44]	Yes	Yes	Yes	Yes	Yes	Yes	2
Pang, 2010[70]	Unable to determine	Unable to determine	No	No	No	No	1
Pang, 2010[70]	Unable to determine	Unable to determine	No	No	No	No	2
Pessenhofer, 1989[41]	Yes	Yes	Yes	No	Unable to determine	No	1
Pessenhofer, 1989[41]	Yes	Yes	Yes	Unable to determine	No	Yes	2
Rojas, 2009[63]	Yes	Yes	No	No	No	Yes	1
Rojas, 2009[63]	Yes	Yes	No	No	No	Unable to determine	2
Schulze, 2001[36]	Yes	Unable to determine	Yes	No	Yes	Yes	1
Schulze, 2001[36]	Yes	Unable to determine	Yes	No	Yes	Yes	2
Scurr JH, 1993[54]	Yes	Yes	Unable to determine	Unable to determine	Unable to determine	Unable to determine	1
Scurr JH, 1993[54]	Unable to determine	Unable to determine	Yes	Unable to determine	No	Yes	2
Scurr JH, 1994[53]	Unable to determine	Yes	Yes	No	Unable to determine	Yes	1
Scurr JH, 1994[53]	Yes	Unable to determine	Yes	Unable to determine	No	Yes	2
Sigala, 2007[78]	Unable to determine	Unable to determine	No	No	No	No	1
Sigala, 2007[78]	Unable to determine	Unable to determine	No	No	No	No	2
Smith, 1992[50]	Unable to determine	Unable to determine	Unable to determine	Unable to determine	No	Unable to determine	1
Smith, 1992[50]	Yes	Yes	Yes	No	No	Yes	2
Sottiurai, 1991[67]	Unable to determine		No	No		Unable to determine	1
Sottiurai, 1991[67]	Unable to determine	Yes	Unable to determine	No	Unable to determine	Unable to determine	2
Taradaj, 2011[75]	Yes	Unable to determine	No	No	No	No	1
Taradaj, 2011[75]	Yes	Unable to determine	Yes	Unable to determine	No	No	2
Teepe, 1993[40]	Yes	Yes	Yes	No	Yes	Yes	1

Author, year	Intervention groups from same population	Intervention groups recruited same time	Study subjects randomized	Assignment concealed until recruitment complete	Adequate adjustment for confounding in analyses	Losses to followup taken into account	Reviewer
Teepe, 1993[40]	Unable to determine	Yes	Yes	Unable to determine	Unable to determine	Yes	2
van Gent, 2006[65]	Yes	Yes	Yes	Yes	Yes	Yes	1
van Gent, 2006[65]	Yes	Yes	Yes	No	No	Yes	2
Vanscheidt, 2007[26]	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	Yes	1
Vanscheidt, 2007[26]	Unable to determine	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	2
Vowden, 2006[30]	Yes	Yes	Yes	Yes	Yes	Yes	1
Vowden, 2006[30]	No	Yes	Yes	Yes	Unable to determine	Unable to determine	2
Vowden, 2007[25]	Unable to determine	Unable to determine	Yes	No	Unable to determine	Yes	1
Vowden, 2007[25]	Unable to determine	Unable to determine	Yes	No	Unable to determine	Yes	2
Weiss RA, 1996[52]	Unable to determine	Unable to determine	Unable to determine	No	No	Yes	1
Weiss RA, 1996[52]	Unable to determine	Unable to determine	Unable to determine	Unable to determine	No	No	2
Wolters, 1997[79]	Unable to determine	Unable to determine	No	No	No	No	1
Wolters, 1997[79]	Unable to determine	Unable to determine	No	No	No	No	2
Zamboni, 2003[61]	Unable to determine	Unable to determine	Yes	No	No	No	1
Zamboni, 2003[61]	Unable to determine	Unable to determine	Yes	Unable to determine	No	Yes	2