*Draft Comparative Effectiveness Review*

**Number XX**

# Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities

**Prepared for:**
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**Suggested Citation:**
XXX Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities. No. [#]. (Prepared by XXX Contract No. XXXX-XXX-XXXX-XXXXX-X.) Rockville, MD: Agency for Healthcare Research and Quality. [Month Year]. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

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

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# Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

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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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

# Acknowledgments
[Redacted]

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## 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 October 2011.

**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, post-surgical 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 66 studies. Most of the advanced wound dressings that regulate moisture, facilitate debridement, include antimicrobial activity, or incorporate putative wound healing accelerants was not statistically superior to adequate compression with simple dressings. However, the newer biological dressings containing living cells such as the cellular human skin equivalents facilitated the 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 wound-healing rates, quality of life measurements, and pain measures. We found insufficient evidence evaluating the benefits and harms of the routine use of antibiotics. Most venous surgery may not improve venous ulcer healing (low to moderate strength of evidence), although there was a trend towards greater durability of healing.

**Conclusions**: These findings do not mean that the interventions failed to have value. Rather, that the risk of bias and lack of adequate sample size prevented us from establishing statistically valid conclusions of therapeutic efficacy. 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 U.S. They affect between 500,000 and 2 million persons annually, and are responsible for over 50 percent of all lower extremity ulcers.[1] Venous leg ulcers are caused by elevated venous pressure, turbulent flow, and inadequate venous return which can be due to venous occlusion or venous reflux. 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, injecting drug users, phlebitis, and venous valvular dysfunction). The diagnosis of venous ulcers is made clinically on the basis of anatomic location, morphology, and characteristic skin changes. Clinical diagnosis is confirmed by functional assessment 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] Other therapies must be considered for the large number of patients for whom compression therapy and debridement fail, but no consensus exists about which second-line treatments work best. Widely used interventions 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, resulting in production of growth factors and cellular proliferation. Advanced wound dressings regulate moisture in the wound surface by moisture retention or exudate absorption, thereby protecting the wound base and peri-wound tissue. Some advanced wound dressings also include antiseptics, antimicrobials, cleansing agents, or autolytic debriding agents. These approaches are proposed to both improve healing and minimize patient discomfort before, during, and after dressing changes. Since dressings have been classified as devices and not drugs, the U.S. Food and Drug Administration (FDA) has not required that pre-marketing testing for safety and efficacy be as rigorous as it has been for approval of new drugs.

## Antibiotics

Antibiotic use is prevalent in the management of all types of skin ulcers. However, the indications for the use of systemic or topical antibiotics are not well defined for chronic venous leg ulcers. In clinical practice, empiric therapy or “culture-based treatment” is often used 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 is linked to 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. The minimally invasive endovenous approach has gained popularity and has been used routinely instead of vein stripping. However, each underlying vascular pathology has different surgical treatment options with no clear evidence about which is the safest and most effective in healing the ulcer. In addition, the indications for surgery have not been standardized.

## 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). These dressings are defined as those with either biological activity, debridement activity, antimicrobial activity, or enhanced absorptive/barrier properties. We also carefully analyzed the data on biological dressings, that are derived from human or animal skin and may contain living human or animal cells as a constituent.

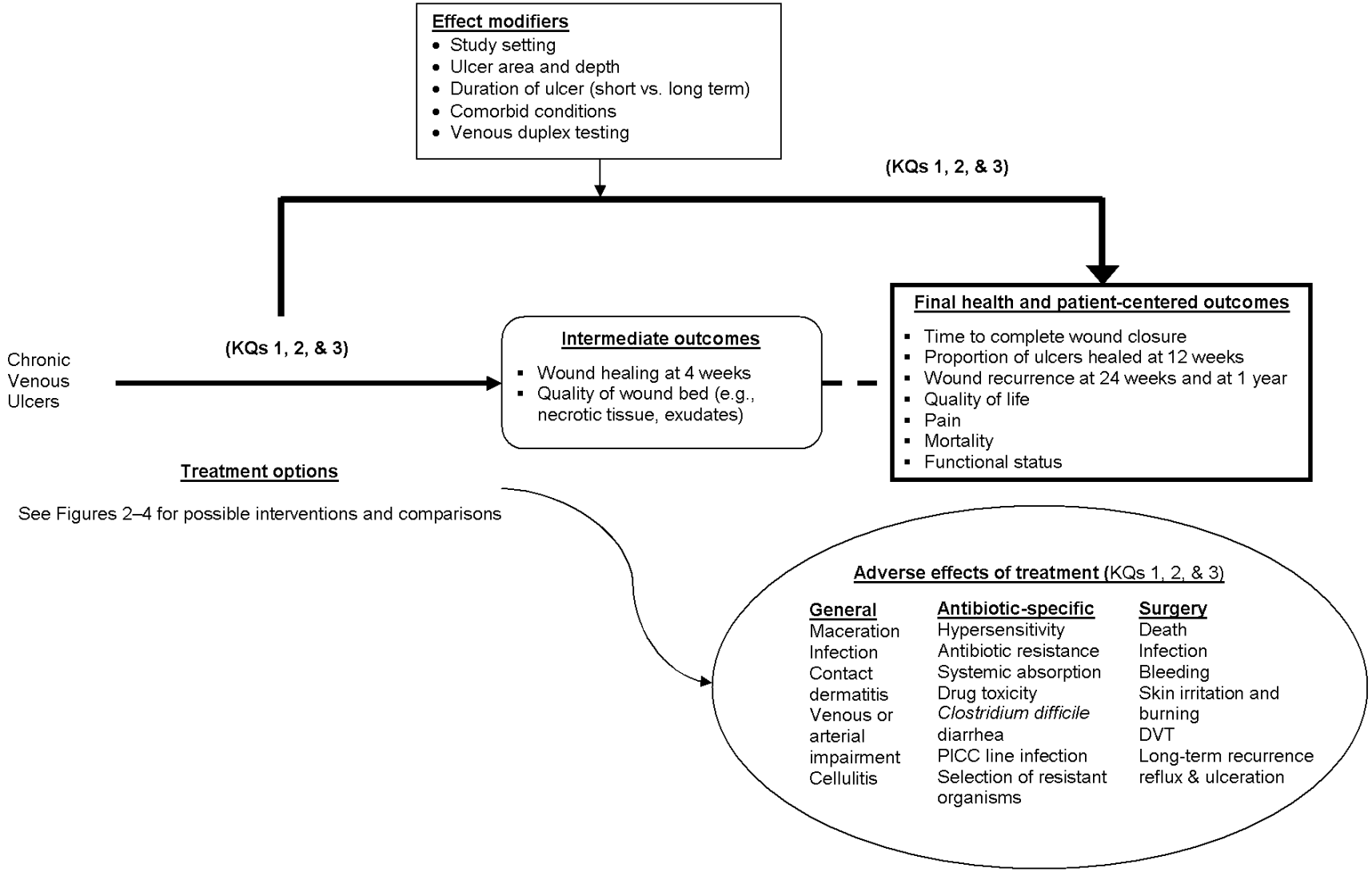
KQ 2a: For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

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**




Abbreviations: 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 KQ 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 20mm), so that the leg does not swell significantly during the day. For KQ2b, the comparator of interest was advanced wound dressings. For KQ3b, 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. Pain and quality of life outcome measures were included 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.

**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 increase moisture retention | Hydrocolloids | • Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet<br>• 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<br>• 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<br>• 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<br>• Alginate or other fiber gelling dressing, wound filler |
| | Foams | • Sterile, non-linting, absorptive dressing made of open cell, medical grade expanded polymer<br>• It is non-adherent | • Foam dressing, wound cover, sterile (with/without adhesive border)<br>• 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 non-adherent property; and 4) adhesive border | • Composite dressing, sterile with adhesive border |
| | Special absorptive dressings | • Unitized, multilayer dressings that provide either a semi-adherent quality or non-adherent 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, non-adherent 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<br>• Water is released to keep the wound moist<br>• Can be hydrophilic | • Hydrogel dressing, wound cover, sterile with/without adhesive border<br>• Hydrogel dressing, wound filler |
| Collagen dressings | Sheets, wound filler gels or powder | • Freeze-dried bovine, porcine, or equine collagen<br>• Can contain cellulose or alginate for absorption | • Collagen-based wound filler, dry form<br>• Collagen-based wound filler, gel/paste<br>• 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 |
|---|---|---|---|
| Human skin equivalents and extracellular matrixes | Acellular | • Extracellular matrixes that support new tissue growth<br>• Animal derived extracellular matrix (Oasis®)<br>• Cryopreserved human skin allograft (TheraSkin®)<br>• 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®)<br>• 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<br>• Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, muka honey, iodine, 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, chlorhexadine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents | • Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad<br>• Gauze, impregnated, water or normal saline, sterile, pad<br>• Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad |
| Enhance further debridement | Biologic enzymatic debriding agent (collagenase santyl) | • Derived from fermentation by *Clostridium histolyticum*<br>• 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: HCPS = Healthcare Common Procedure Coding System

**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 |

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 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 greater saphenous vein at the junction with femoral vein.<br>• Sapheno-popliteal junction ligation involves the ligation and division of small saphenous vein at its junction with popliteal vein. |
| | Stripping | • Saphenous vein stripping is performed by ligation and division of the sapheno-femoral junction, followed by stripping a segment of the greater saphenous vein to just below the knee using an invagination or inversion catheter. |
| | Ablation | • In thermal ablation, the greater or small saphenous veins are closed using high temperature generated by laser light (endovenous laser treatment [EVLT]) or radiofrequency energy (radiofrequency ablation [RFA]).<br>• Chemical ablation (sclerotherapy) is performed by 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 | Linton | • Linton procedure involves a long incision of the affected calf, exposing the superficial and perforator veins of the leg, which are then removed (superficial veins) or ligated (perforating/communicating veins). |
| | Ligation | • Perforator vein is directly ligated using ultrasound guidance. |
| | Subfascial endoscopic perforator surgery (SEPS) | • 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. The subfascial space is insufflated with carbon dioxide. This creates a space for the endoscope to identify and ligate the Cockett's perforating veins in the lower calf. |
| | Hach procedure | • This procedure involves paratibial fasciotomy and dissection of the posterior perforator veins. |
| Deep venous system | Obstructive | • Bypass of the obstructive segment of deep vein using autogenous vein or polytetrafluoroethylene synthetic graft.<br>• 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.<br>• Valvuloplasty involves repairing or reconstructing valves in the deep venous system of the lower limb. |

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

# 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. 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.

## Study Selection

Each title, abstract, and full article was evaluated by two independent reviewers. 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 compression therapy 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 (a) included at least 30 patients with chronic venous leg ulcers for at least 6 weeks; (b) described the sampling frame; (c) provided demographic and baseline characteristics for the patients with chronic venous ulcers; and (d) assessed ulcer healing rates. We decided to include noncomparative studies evaluating surgical interventions because we anticipated finding few, if any, comparative studies. There are an increasing number of vascular procedures being developed and diffusing into practice despite the lack of studies with comparison groups. Furthermore, it is unrealistic to expect that many studies with concurrent comparison groups will be conducted anytime soon because surgical practice evolves differently and does not have the same kinds of regulatory forces that motivate manufacturers of new drugs to perform trials. Although we had initially intended to use noncomparative studies to assess harms, we decided to include any data these studies provided on potential benefits because the overall volume of evidence on surgical outcomes was scant. By including only studies where adequate compression therapy had failed patients for at least 6 weeks, we felt that such 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, and 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 (including usual care/placebo, compression types [e.g., two-layer, short stretch, long stretch, multi-layer, or Unna boot], debridement types, advanced wound dressings, antimicrobials, surgical interventions, and duration of treatment), comparisons, and outcome measures (including definitions, results, and measures of variability). We collected data on subgroups of interest, including age, presence of comorbid conditions (e.g., diabetes, obesity), and setting.

## Quality Assessment

Two reviewers used the Downs and Black quality assessment tool to independently assess the quality of all included studies.[3] 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*).[4] 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 (age, duration of ulcer, comorbidity), interventions (treatment, co-interventions, 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 (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 were reported in the studies, but we did not conduct any additional sensitivity analyses.

## Strength of the Body of Evidence

We graded the strength of evidence 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*.[5] 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

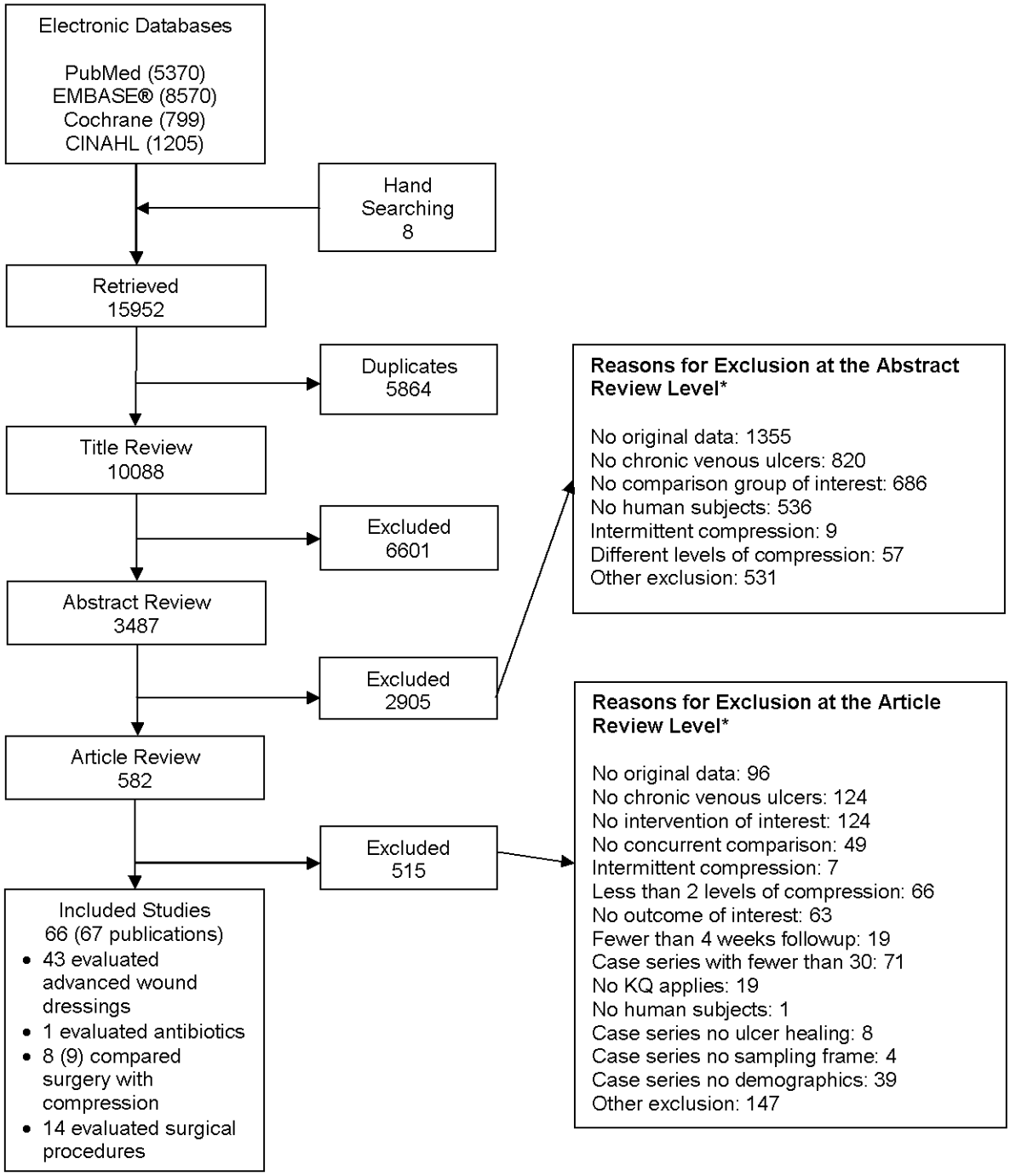
change the estimate); and 4) “insufficient” grade (evidence is unavailable or does not permit a conclusion).

# 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 66 studies (67 publications). We found 43 studies evaluating advanced wound dressings,[6-48] one study evaluating antibiotics,[49] eight studies (nine publications) comparing a surgical intervention with compression systems,[27, 50-57] three studies comparing at least two different surgical interventions,[58-60] and eleven evaluating a surgical intervention with no concurrent comparison group.[61-71]

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




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

## KQ 1: Benefits and Harms of Advanced Wound Dressings: Impact on Wound Healing, Pain, and Quality of Life

For KQ1, 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 (strength of evidence [SOE]: Low).[40] 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 to other dressings (SOE: Insufficient). A small study found improved rates in terms of area healed and overall healing rates compared to impregnated gauze.[28] Another trial found more rapid healing rates but no difference in ultimate full wound healing.[37] Two studies demonstrated no differences.[40, 44] One study compared alginate dressings compared with simple gauze under adequate compression, and found no difference in healing of the chronic venous leg ulcers (SOE: Insufficient).

In our evaluation of foam dressings that are often used to manage exudates, we found no studies that compared foam dressings with compression therapy. Three studies compared healing between different foam products. We are unable to draw conclusions because these studies 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 statistical difference.

For antimicrobial dressings, one crossover RCT (N = 75) study of cadexomer iodine showed significant improvement in healing at 12 weeks, but there was a high dropout rate (28 percent). Three studies were performed which evaluated acellular human skin equivalents.[18, 20, 34] 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 cellular human skin equivalent products, suggesting more rapid healing than with compression therapy alone (SOE: Moderate).[14, 22, 26, 36, 42] Studies of a biodegradable mesh containing fibroblasts (Dermagraft®) were limited in their sample size. 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 of autologous living keratinocyte showed improvement in wound healing, especially in patients with long-standing ulcers (over 1 year) that were treated with ACE™ bandages and compression. 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. 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 these outcomes were not evaluated in a consistent manner. When reported, mortality rates 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.

**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 healing chronic venous ulcers. The results from the three studies addressing this comparison were imprecise and subject to some bias. |
| Hydrocolloids vs. other dressings (4) | Insufficient | We are unable to draw a conclusion. |
| Transparent films vs. compression (1) | Insufficient | We are unable to draw a conclusion. |
| Transparent films vs. other dressings (1) | Insufficient | We are unable to draw a conclusion. |
| Alginate dressings vs. compression (1) | Insufficient | We are unable to draw a conclusion. |
| Alginate dressings vs. alginate dressings (2) | Insufficient | We are unable to draw a conclusion. |
| Alginate dressings vs. other dressings (1) | Insufficient | We are unable to draw a conclusion. |
| Foam dressings vs. foam dressings (3) | Insufficient | We are unable to draw a conclusion. |
| Collagen dressings vs. other types of dressings (1) | Low | One study reported a statistically faster wound healing rate with a collagen dressing compared with another type of dressing. The study did not report on the proportion of ulcers healed. |
| Acellular human skin equivalent dressings vs. compression (3) | Insufficient | We are unable to draw a conclusion. |
| Cellular human skin equivalents vs. compression (4) | Moderate | Studies of cellular human skin equivalent dressings in patients with chronic venous ulcers showed more rapid healing, especially those that had failed previous therapy and were present for over 1 year. |
| Cellular human skin equivalent dressings vs. other dressings (2) | Insufficient | We are unable to draw a conclusion. |
| Antimicrobial dressings vs. compression (2) | Insufficient | We are unable to draw a conclusion. |
| Antimicrobial dressings vs. antimicrobial dressings (2) | Insufficient | We are unable to draw a conclusion. |
| Antimicrobial containing dressings vs. other types of dressings (4) | Moderate | There was modest improvement with cadexomer iodine dressings in wound healing rates and wound area reduction as compared with non-antimicrobial dressings. Silver dressings did not significantly improve wound healing as compared to non-silver dressings. |

* 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.

# KQ 2a: Benefits and Harms of Systemic Antibiotics Compared With Compression Systems

For KQ2, only one randomized study evaluated the value of adding systemic antimicrobial use to compression therapy.[49] 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.

## KQ 2b: Benefits and Harms of Systemic Antibiotics Compared With Advanced Wound Dressings

We did not find any studies addressing this KQ.

## KQ 3a: Benefits and Harms of Surgical Interventions Compared With Compression

We identified eight unique studies meeting our inclusion criteria that compared a surgical intervention with two or more layers of compression.[27, 50-57] We did not identify any studies that compared the effectiveness of compression therapy alone with the effectiveness of deep vein surgery or radiofrequency ablation (RFA), endovenous laser therapy (EVLT), or vein stripping to treat superficial vein reflux.

### 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 undergo surgery during the RCT.[51] Ulcer recurrence rates at 3 years were significantly lower after surgery in these studies (31 percent versus 56 percent in the RCT, ($P < 0.01$) and 26 percent versus 44 percent in the cohort study ($P = 0.03$)).[51, 52, 54]

### 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.[27, 53, 56, 57] Surgical interventions in these studies were minimally invasive ligation of insufficient saphenous vein tributaries (Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting [CHIVA]) (SOE: Low);[53] open perforator ligation (Linton procedure) (SOE: Low);[27] subfascial endoscopic perforator surgery (SEPS) (SOE: High);[56, 57] and sclerotherapy (SOE: Insufficient).[50] The study of CHIVA did report a faster time to healing with surgery than with compression alone (median of 31 days versus 63 days).[53]

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 versus 9 percent; $P < 0.05$) in Zamboni, et al.[53] An RCT evaluating SEPS reported similar ulcer recurrence rates in the intervention and control arms.[57]

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 weeks versus 20 weeks).[55] The method of allocation was unclear in this study.[55]

### 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.[53] The other study found that SEPS did not perform better than compression alone when quality of life was measured with the Charing Cross Venous Ulcer Questionnaire.[56]

### 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.

## KQ 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[58-60] compared two surgical techniques.[58-60] We also included 11 studies that evaluated a surgical procedure without a concurrent comparison group.[61-71] Five of these were case series.[61, 65-67, 69] Five studies were cohorts,[62, 63, 68, 70, 71] and one had an unclear study design.[64] A variety of interventions were evaluated including venous valve surgery,[63, 64, 67] RFA,[65, 69] SEPS,[70, 71] saphenous vein stripping and/or ligation,[62, 66] sclerotherapy,[61] and angioplasty/stenting.[68] We did not find any studies evaluating surgical procedures for chronic venous leg ulcers associated with deep venous occlusion.

One non-randomized study of 46 patients compared perforator ligation plus saphenous vein stripping (PLSVS) versus PLSVS plus valvular surgery.[58] Wound healing rates were reported at 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 strength of evidence on this comparison was low 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 to vein stripping and found that the ligation group had a significantly higher healing rate (85 versus 70 percent; $P < 0.05$). This study had a high risk for bias with an imprecise effect estimate, and therefore, the strength of evidence was considered to be low.[59]

One non-randomized retrospective cohort study included subjects from a single author's clinical experience,[60] and evaluated four groups each of which received a different mix of surgical interventions. Sclerotherapy was found to result in more rapid wound healing. The study design was complex, but more important, the cases were derived 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 femoral and popliteal vein insufficiency was documented. In the group of patients with the shortest time to heal (up to 8 weeks), popliteal vein involvement was documented in 55 percent of patients. The group that required more than 12 weeks to heal had 94 percent popliteal vein involvement. The strength of evidence from this study was considered low because of the high risk of bias and the imprecise effect estimates.

From the 11 studies included in Part 2 of our review of KQ3b,[61-71] 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.

# Discussion

## Key Findings and Strength of Evidence

### KQ 1: Benefits and harms of advanced wound dressings

There were minimal data to suggest that hydrocolloid and foam provided advantages in healing rates and in ultimate wound healing (insufficient strength of evidence). There were many studies which had non-significant results. Dressings which contained cadexomer iodine provided advantage in improved healing, but there were no data to support the use of silver containing dressings (moderate strength of evidence).

For acellular skin equivalents, the there was insufficient strength of evidence to support the use of freeze dried intestinal pig mucosa. For cellular equivalents, benefit was limited to patients with long-standing ulcers, and there was no effect on post-treatment recurrence, indicating the importance of treating the underlying disease and the necessity of continuing post-treatment compression.

### KQ 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 how the benefits and harms of systemic antibiotics compared with compression.

### KQ 2b: Benefits and harms of systemic antibiotics compared with advanced wound dressings

We did not find any studies that addressed this question.

### KQ 3a: Benefits and harms of surgical interventions compared with compression

Among the few studies on this question, 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. For other surgical interventions used for chronic venous leg ulcers, the strength of evidence was low to high that healing may not be improved when compared with compression alone. We found insufficient evidence about the benefits and harms of sclerotherapy, vein stripping, radiofrequency ablation (RFA), or endovenous laser therapy (EVLT) for superficial vein reflux or surgery for deep vein disease in patients with chronic venous leg ulcers.

### KQ 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 with respect to the population screened or enrolled. 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 reported, the mean duration of chronic venous ulcers at baseline 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

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.

## 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 better studies are needed to demonstrate their clinical impact, or lack of efficacy.

These findings therefore have impact on policy, especially for agencies and payors that are interested in providing reimbursement and identifying critical research needs. Since the prevalence of chronic venous stasis disease is increasing,[72] and is expected to do so for the

foreseeable future, health care payors, regulatory agencies, and other policy makers should be interested in evidence that can provide better guidance on how to improve the outcomes of care for patients with chronic venous leg ulcers. We need high quality data to understand which therapeutic interventions have value to insure their reimbursement in an increasingly constrained health care environment and develop efficient algorithms to evaluate new therapies.

# Research Gaps

## Need for Harmonization

Our review demonstrated that studies of interventions for chronic venous leg ulcers are conducted by a variety of disciplines and in different practice and cultural settings, including nursing, dermatology, vascular surgery, and internal medicine as well as in different countries. This heterogeneity is associated with excessive variety in the methods that have been used in studies. To adequately address this problem, investigators in this field need to develop a consensus about a standard definition for the disease entity and establish better standards for how to define interventions, comparison groups, and outcome measures.

Consensus about how to harmonize studies in this area should be established among stakeholders from the academic and clinical communities, clinical researchers, government regulators, payors, and industry. The objective would be to develop clear and reproducible case definitions, and define appropriate clinical outcome measures, including intermediate outcomes, pain, and quality of life. The conference could also help to develop templates for study designs to demonstrate efficacy, which would include appropriate definition of outcomes. The Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds from the Center for Medical Technology Policy supports many of our conclusions, but it is not focused on chronic venous ulcers and does not cover surgical interventions.[73]

One of the major issues to be addressed is the limitation in study design — because of the nature of the interventions, and the difficulty in many cases of developing placebo or sham conditions, implementing traditional double blinded, or even single blinded randomized trials is 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 the three Key Questions to guide this review. We found the clinical evidence was marked by 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 cellular skin equivalents under very defined conditions. Evaluating systemic and local antimicrobial therapy was hampered by the general lack of data, and we found no evidence to support antimicrobial therapy for chronic venous leg ulcers in the absence of symptoms or signs of infection. 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 that have been used to manage this disease. However, more recent data suggest that surgical interventions may impact recurrence rates, and therefore there is a need to validate these findings.

We identified critical research needs largely focused on developing the needed evidence base to make therapy recommendations and to evaluate the efficacy and effectiveness of current and newly developed products and interventions. These include a standardized 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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# Introduction

## Background

Venous leg ulcers are extremely common in the U.S. and affect between 500,000 to 2 million people annually.[1] Venous leg ulcers constitute a majority of all ulcers seen in the U.S. 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, 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 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]

Venous leg ulcers are caused by 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), injecting drug users (skin poppers), phlebitis, and venous valvular dysfunction.

The diagnosis of venous ulcers is made clinically on the basis of anatomic location, morphology, and a series of characteristic skin changes. The diagnosis is confirmed by appropriate laboratory studies, which should include functional assessment of the venous system. The "gold standard" for diagnosing venous disease is venography, which is performed infrequently because of expense, morbidity, and the availability of noninvasive tests. Today, venous duplex ultrasound is the method used most often 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. Other therapies must be considered 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 healing of venous leg ulcers with different therapies, investigators may 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 (FDA) and the Centers for Medicare and Medicaid Services.[6, 7] More recently, a valuable set of surrogates for complete healing has been proposed. The most notable and best confirmed surrogate is the rate of wound healing over a 4-week period of time, as proposed by Margolis.[8] Healing can be quantified by tracing the wound margins and/or by using digital photography. Such healing parameters usually rely on epithelialization (area reduction). However, granulation (depth reduction) or vascularization may also be reported. Other outcomes of interest include quality of life, pain, and cost-effectiveness.

Below is an overview of the three major types of interventions that are used in the modern management of chronic venous leg ulcers.

## Advanced Wound Dressings

Over the past 20 years, much evidence has been generated to support the premise that a moist wound environment is essential for wound healing.[9, 10, 11] This has caused a proliferation of expensive new wound dressings (see Figure 2 and Table 1), leading to confusion as to appropriate use among wound care providers. Furthermore, since many wound dressings are classified as devices and not drugs, the FDA does not require rigorous clinical trial testing. This further compounds confusion among wound care providers.

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 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

Antibiotic use is prevalent in the management of skin ulcers. Although some clinical experts believe that antibiotics should only be used in patients that have symptoms or signs of an infected ulcer or adjacent cellulitis, many patients with chronic venous leg ulcers receive antibiotics even 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, the indications for the use of systemic or topical antibiotics are not well-defined. 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. Often, long term antibiotics are administered by peripherally inserted central catheters, which also may predispose to secondary infection complications.

## Surgical Interventions

Most patients with venous ulcers have significant reflux on duplex ultrasound. Reflux is defined 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 greater 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. Duplex ultrasound, which is now considered routine in most vascular laboratories, is needed to classify the underlying pathophysiology of a venous ulcer if surgery is being considered (see Figure 4). Invasive venography and ambulatory venous pressure are obtained 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.[12, 13] As shown in Figure 4 and Table 3, the surgical options depend

on the underlying type of reflux or obstruction. Yet, the indications for surgery have not been standardized, with no consensus about which 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,[14, 15] 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 are listed below. Tables 1-3 describe our classification schemes for the three major types of intervention: wound dressings, antibiotics, and vascular surgery.

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?

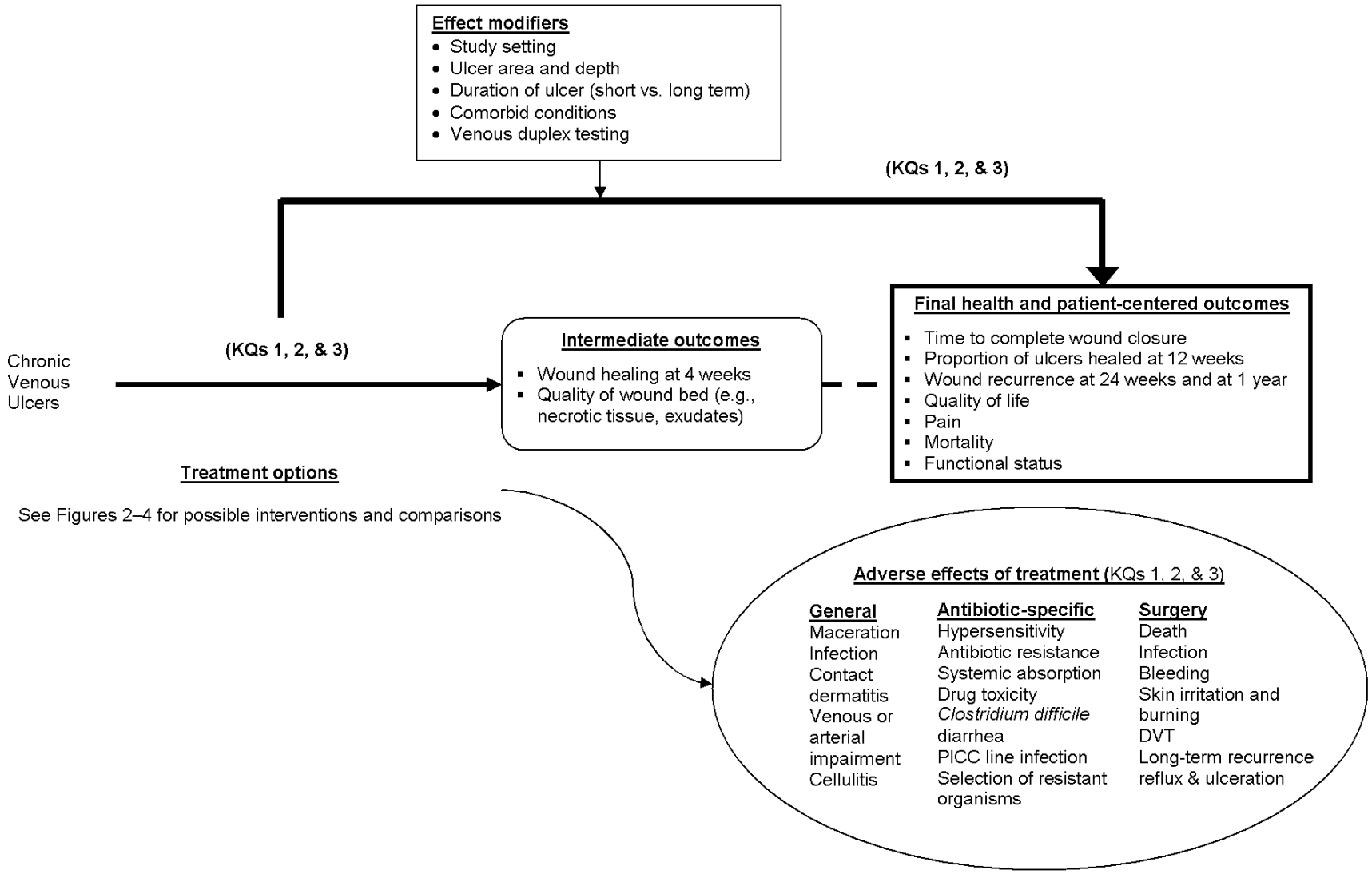
KQ 2a. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

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?

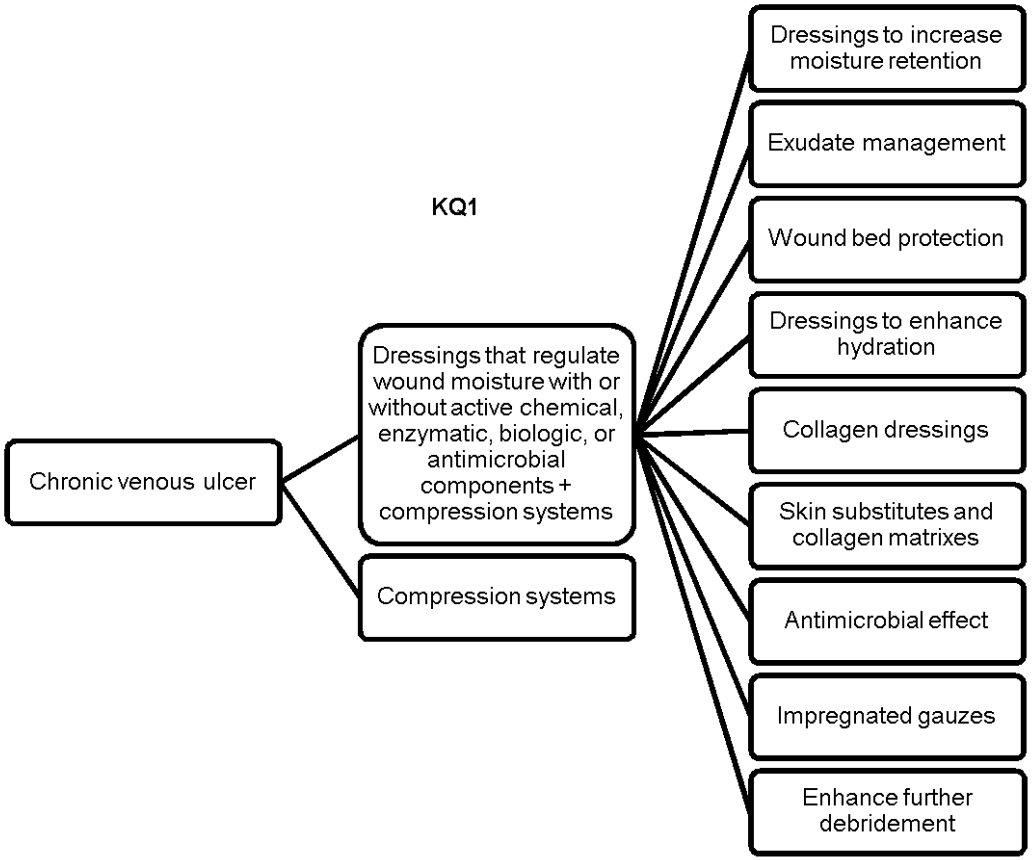
KQ 3b. For patients with chronic venous leg ulcers, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

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




Abbreviations: DVT = deep vein thrombosis; KQ = key question; PICC = peripherally inserted central catheter

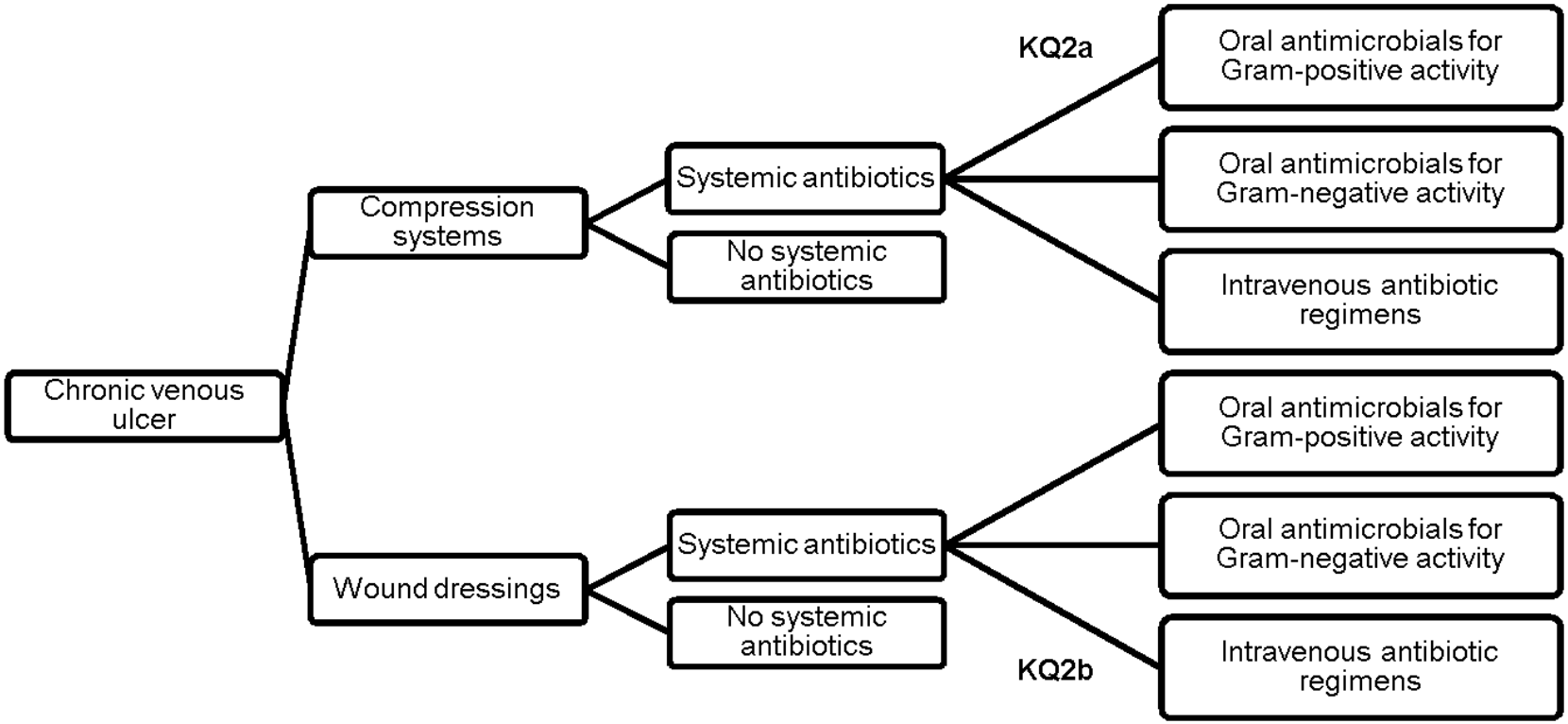
**Figure 2. Potential options for wound dressings with active chemical, enzymatic, or antimicrobial components for the treatment of chronic venous leg ulcers**




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 non-active 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**

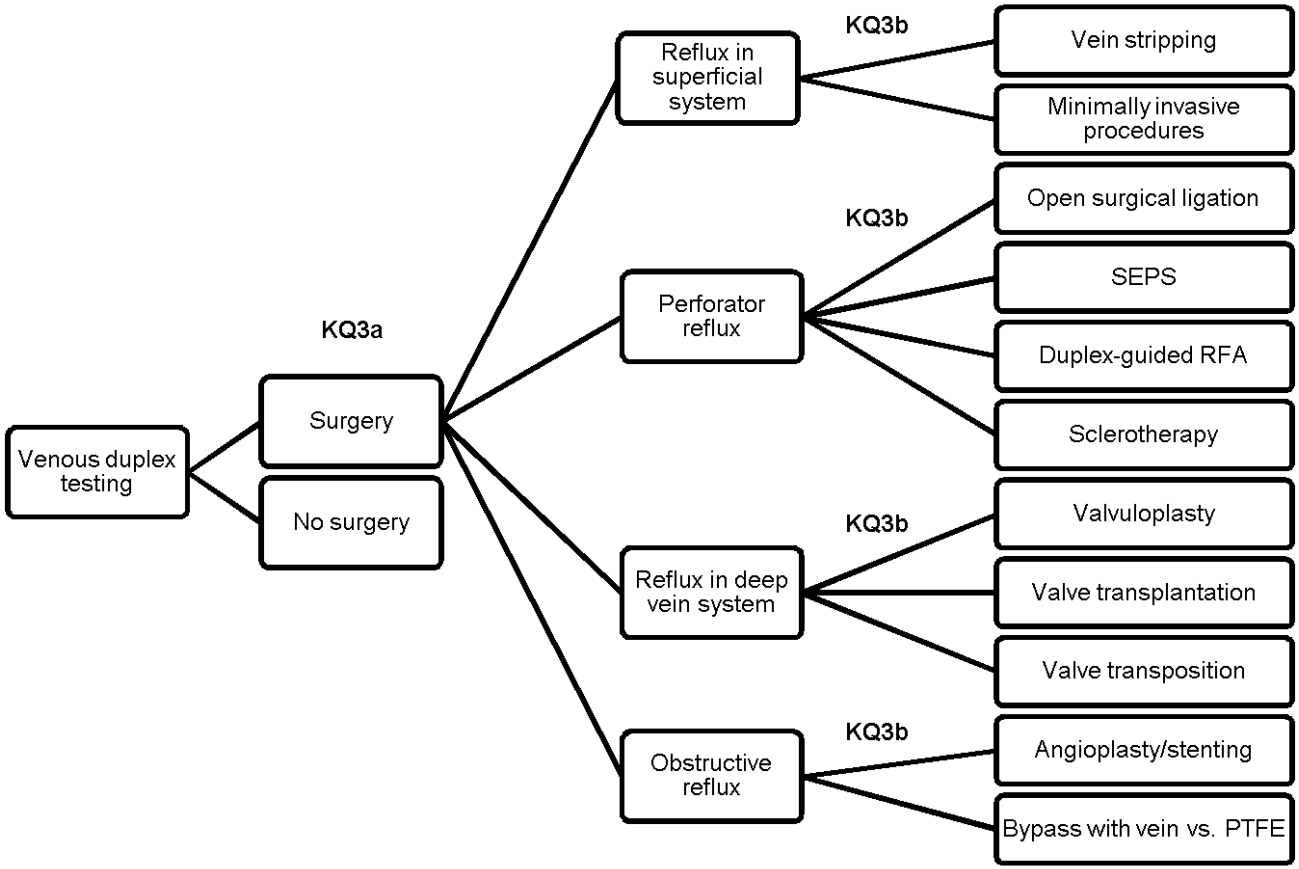



See Table 2 for a list of antibiotics.

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 non-active 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 increase moisture retention | Hydrocolloids | • Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet<br>• 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<br>• 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<br>• 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<br>• Alginate or other fiber gelling dressing, wound filler |
| | Foams | • Sterile, non-linting, absorptive dressing made of open cell, medical grade expanded polymer<br>• It is non-adherent | • Foam dressing, wound cover, sterile (with/without adhesive border)<br>• 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 non-adherent property; and 4) adhesive border | • Composite dressing, sterile with adhesive border |
| | Special absorptive dressings | • Unitized, multilayer dressings that provide either a semi-adherent quality or non-adherent 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, non-adherent 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<br>• Water is released to keep the wound moist<br>• Can be hydrophilic | • Hydrogel dressing, wound cover, sterile with/without adhesive border<br>• Hydrogel dressing, wound filler |
| Collagen dressings | Sheets, wound filler gels or powder | • Freeze-dried bovine, porcine, or equine collagen<br>• Can contain cellulose or alginate for absorption | • Collagen-based wound filler, dry form<br>• Collagen-based wound filler, gel/paste<br>• 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 |
|---|---|---|---|
| Human skin equivalents and extracellular matrixes | Acellular | • Extracellular matrixes that support new tissue growth<br>• Animal derived extracellular matrix (Oasis®)<br>• Cryopreserved human skin allograft (TheraSkin®)<br>• 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®)<br>• 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<br>• Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, muka honey, iodine, 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, chlorhexadine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents | • Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad<br>• Gauze, impregnated, water or normal saline, sterile, pad<br>• Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad |
| Enhance further debridement | Biologic enzymatic debriding agent (collagenase santyl) | • Derived from fermentation by *Clostridium histolyticum*<br>• 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

**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 greater saphenous vein at the junction with femoral vein.<br>• Sapheno-popliteal junction ligation involves the ligation and division of small saphenous vein at its junction with popliteal vein. |
| | Stripping | • Saphenous vein stripping is performed by ligation and division of the sapheno-femoral junction, followed by stripping a segment of the greater saphenous vein to just below the knee using an invagination or inversion catheter. |
| | Ablation | • In thermal ablation, the greater or small saphenous veins are closed using high temperature generated by laser light (endovenous laser treatment [EVLT]) or radiofrequency energy (radiofrequency ablation [RFA]).<br>• Chemical ablation (sclerotherapy) is performed by 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** | Linton | • Linton procedure involves a long incision of the affected calf, exposing the superficial and perforator veins of the leg, which are then removed (superficial veins) or ligated (perforating/communicating veins). |
| | Ligation | • Perforator vein is directly ligated using ultrasound guidance. |
| | Subfascial endoscopic perforator surgery (SEPS) | • 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. The subfascial space is insufflated with carbon dioxide. This creates a space for the endoscope to identify and ligate the Cockett's perforating veins in the lower calf. |
| | Hach procedure | • This procedure involves paratibial fasciotomy and dissection of the posterior perforator veins. |
| **Deep venous system** | Obstructive | • Bypass of the obstructive segment of deep vein using autogenous vein or polytetrafluoroethylene synthetic graft.<br>• 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.<br>• Valvuloplasty involves repairing or reconstructing valves in the deep venous system of the lower limb. |

Abbreviations: 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's (AHRQ) Web site. Our Evidence-based Practice Center (EPC) established a team and a work plan 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. We posted our draft Key Questions (KQs) on AHRQ'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 are 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 panel of technical experts to review a draft of the protocol for preparing this evidence report. The Technical Expert Panel included a variety of wound care experts, including dermatologists, vascular surgeons, nurses, and geriatricians. The Technical Expert Panel reviewed our protocol, and provided feedback on the proposed methods for addressing the KQs. With the feedback from the Technical Expert Panel and AHRQ representatives, we finalized the protocol and posted it on AHRQ'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 (CINAHL®) from January 1980 through October 2011. 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 (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.

## Study Selection

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

The abstract review phase was designed to identify studies reporting the effects of treatment options for chronic venous leg ulcers. Abstracts were reviewed independently by two investigators and were excluded 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). Differences between investigators regarding the inclusion or exclusion of abstracts were tracked and resolved through consensus adjudication.

Two independent investigators reviewed articles that were promoted on the basis of the abstract review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion were tracked and resolved through consensus adjudication.

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 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 (a) included at least 30 patients with chronic venous leg ulcers for at least 6 weeks; (b) described the sampling frame; (c) provided demographic and baseline characteristics for the patients with chronic venous ulcers; and (d) assessed ulcer healing rates. We decided to include noncomparative studies evaluating surgical interventions because we anticipated finding few, if any, comparative studies. There are an increasing number of vascular procedures being developed and diffusing into practice despite the lack of studies with comparison groups. Furthermore, it is unrealistic to expect that many studies with concurrent comparison groups will be conducted anytime soon because surgical practice evolves differently and does not have the same kinds of regulatory forces that motivate manufacturers of new drugs to perform trials. Although we had initially intended to use noncomparative studies to assess harms, we decided to include any data these studies provided on potential benefits because the overall volume of evidence on surgical outcomes was scant. By including only studies where adequate compression therapy had failed patients for at least 6 weeks, we felt that such 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.

**Table 4. Inclusion and exclusion criteria**

| | |
|---|---|
| **Population and condition of interest** | • All studies were confined to human subjects.<br>• We included studies of patients with chronic venous leg ulcers. We used the standard definition of a chronic venous ulcer:<br>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<br>• We included studies of patients with or without other comorbidity.<br>• 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.<br>• 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).<br>• 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.<br>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).<br>o We included systemic antibiotics that were used in the context of managing chronic wounds. The antimicrobials of interest included oral antimicrobials used primarily for Gram-positive activity, oral drugs used for Gram-negative activity, and intravenous antibiotic regimens (Table 2).<br>o We included surgical interventions, including interventions for superficial reflux, perforator reflux, and reflux in the deep venous system (Table 3).<br>o We excluded topical or hyperbaric oxygen because it is not FDA approved for venous ulcers. |
| **Comparisons of interest** | • We included studies that compared the interventions with conservative care or if possible with each other. Conservative care included:<br>o Debridement of necrotic tissue could be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement which lead to a clean wound base.<br>o Simple dressings containing non-active components such as moisturizers.<br>o At least moderate compression described either qualitatively or quantitatively (<20mm), so the leg does not swell significantly during the day.<br>• 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 (a) included at least 30 patients with chronic venous ulcers for at least 6 weeks; (b) described the sampling frame; (c) provided demographic and baseline characteristics for the patients with chronic venous ulcers; and (d) assessed ulcer healing rates.<br>• 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:<br>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)<br>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)<br>o Adverse events<br>– For topical antibiotics contained in dressings: hypersensitivity, contact dermatitis, sensitization, systemic absorption<br>– For systemic antibiotics: allergic and hypersensitivity reactions, drug toxicity, Clostridium difficile diarrhea, promotion of antibiotic resistance, selection of resistant organisms<br>– For intravenous antibiotics: peripherally inserted central catheter line and access infections<br>– For surgical interventions: surgical site infection, bleeding, skin irritation and burn, deep vein thrombosis, and long-term recurrent reflux and ulceration |
| **Type of study** | • We excluded articles with no original data (reviews, editorials, and commentaries).<br>• 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.<br>• We did not place any restrictions based on sample size for studies with a comparison group or language.<br>• 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.<br>• 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 were pilot tested. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Each article underwent double review by the study investigators for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. Reviewers were not masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

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 (including usual care/placebo such as compression types and debridement types, advanced wound dressings, antimicrobials used, and surgical interventions, the duration of use), comparisons (including type of compression used [e.g., two-layer, short stretch, long stretch, multi-layer, 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.

All information from the article review process was entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the individual completing the review. Reviewers entered comments into the system whenever applicable. The DistillerSR database was used 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.[16] 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*).[17] 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 probability 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, co-interventions, 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 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 were reported in the studies, but we did not 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. Any problems with a reviewer's data abstraction were discussed 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.[18] 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). 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%, 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.

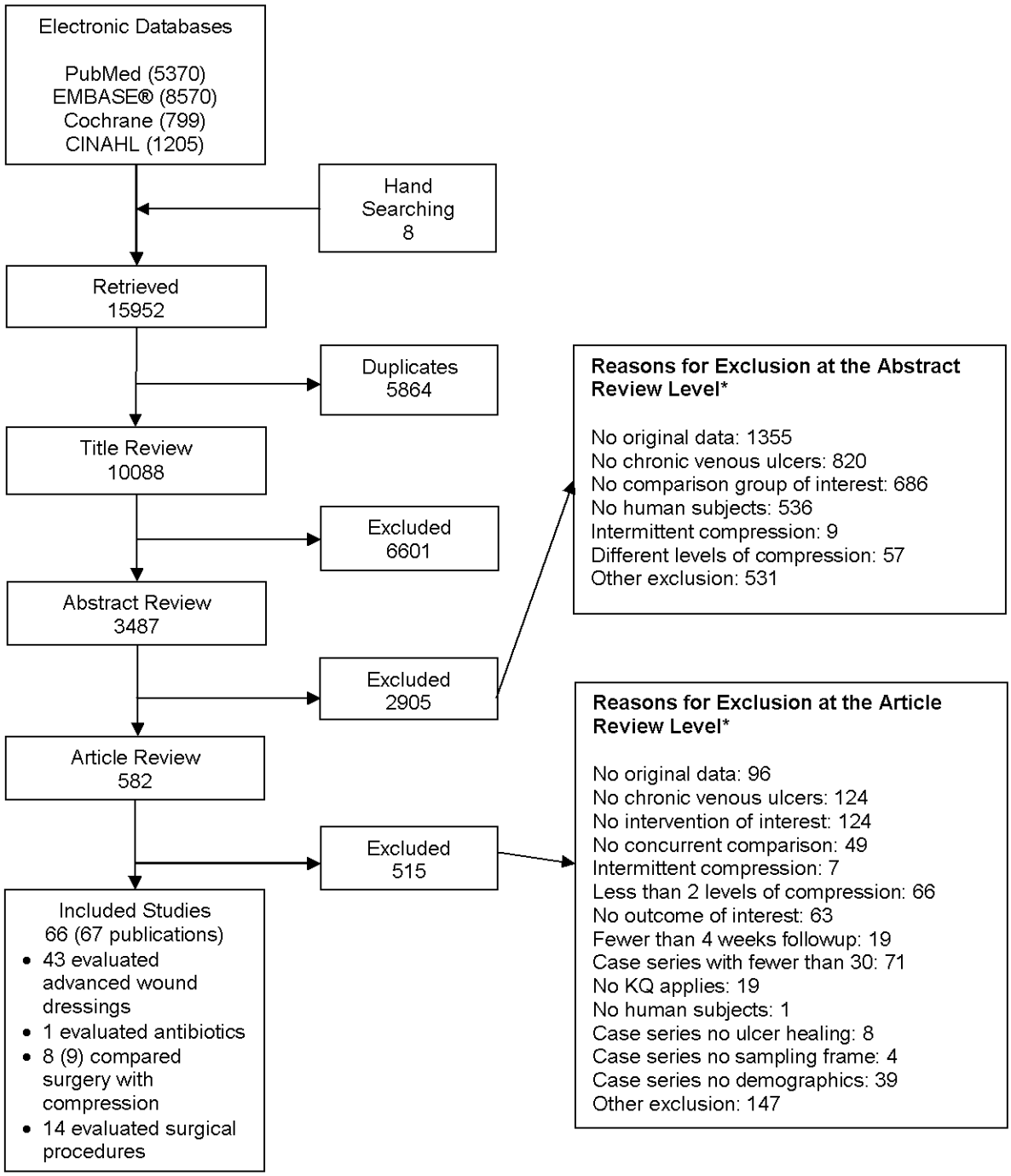
We classified the strength of evidence pertaining to the KQs into four basic grades: 1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating 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).

# 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 66 studies (67 publications). We found 43 studies evaluating advanced wound dressings,[19-61] one study evaluating antibiotics,[62] eight studies (nine publications) comparing a surgical intervention with compression systems,[40, 63-70] three studies comparing at least two different surgical interventions,[71-73] and eleven evaluating a surgical intervention with no concurrent comparison group.[13, 74-83]

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




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

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 studies that evaluated most advanced wound dressings (transparent films, alginate, acellular human skin equivalents, and antimicrobial dressings versus compression; hydrocolloid, transparent films, alginates, and cellular human skin equivalents versus 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 healing chronic venous ulcers. The results from the three studies addressing this comparison were imprecise and subject to some bias. (Low strength of evidence)
- One study reported a statistically faster wound healing rate with a collagen dressing compared with another type of dressing. The study did not report on the proportion of ulcers healed. (Low strength of evidence)
- Cellular human skin equivalent dressings provided as much as three times more rapid complete 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)
- Some antimicrobial dressings improved wound area reduction by twenty percent or more as compared with compression alone and other non-antimicrobial dressings. However, silver dressings did not improve wound healing as compared with non-silver 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 and quality of life 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, 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 infection rates.

# Study Design Characteristics

We included 43 studies for review (Appendix D, Tables 1 and 2).[19-61] These studies enrolled a total of 4107 patients with chronic venous ulcers (median, 79; range, 18 to 309). All, except two[21, 48] of the studies, were randomized controlled trials (RCTs). One was a non-randomized trial[48] and the other was a retrospective cohort study.[21] Three of the RCTs had a factorial design.[29, 30, 40] 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 were conducted in Europe.[20, 22-24, 29-31, 33-35, 37, 38, 40-42, 48-54, 57, 58] Six were conducted exclusively in the US,[21, 36, 39, 44, 55, 56] one was conducted in the US, Canada, and UK,[33] and one was conducted in the US and UK.[41] Five were conducted worldwide.[19, 25, 27, 28, 46] One study each was conducted in Canada and the UK,[49] Brazil,[47] and Mexico.[61]

Fifteen studies did not report the location from where the study patients were recruited.[19, 20, 26-28, 31, 35, 40, 41, 47, 55, 56, 58-60] Most of the other studies reported recruiting patients from some type of outpatient center: seven recruited from dermatology clinics,[22, 25, 33, 38, 42, 43, 54] 13 from wound centers,[21, 24, 25, 30, 32-34, 36, 37, 45, 52, 57, 61] and three from vascular clinics.[24, 33, 54] Four studies recruited patients from a hospital setting.[24, 29, 50, 54]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.[19-21, 23, 25, 27-29, 31, 33, 35-48, 50-52, 54-61] Among the studies that did report the number of patients screened, the percent enrolled ranged from 38 percent to 94 percent.[22, 24, 26, 30, 32, 34, 49, 53]

# Study Population Characteristics

The majority of studies 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. When weight was reported, patients tended to be overweight. Almost all study populations excluded patients with insulin dependent diabetes, but did include patients with elevated blood sugars. Uniformly, patients were evaluated for their arterial blood flow competence by obtaining ankle brachial indices; patients with ankle brachial index ratios of below 0.8 were excluded. Less than 50 percent of the studies included for final review of dressings had venous ultrasound studies or the equivalent. When reported, patients were most often found to have abnormal venous function usually of the reflux type.

All studies, to be eligible for inclusion in this report, used venous compression of at least two layers or, where measured, 20 mm Hg.

# Wound Healing, Including Time to Wound Healing, Wound Healing Rates, and Wound Recurrence

## Hydrocolloid Dressings

### Hydrocolloid Dressings Versus Compression Systems Alone

Three RCTs (total N = 361) compared hydrocolloid dressings with compressions systems alone (Appendix D, Table 4).[30, 45, 52] One trial was a factorial design that compared pentoxiphylline, knitted viscose, and hydrocolloid with single-layer and four-layer wraps.[30] The data 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 versus 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) healed in the knitted viscose group (hazard ratio for healing with hydrocolloid compared with knitted viscose of 1.1, 95 percent confidence interval [CI], 0.8 to 1.6).[30] The other two RCTs evaluated percent healing over time as well as percent ulcers healed.[45, 52] 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) ulcers healed completely in the compression group, but the difference was not statistically significant ($P > 0.05$).[52] 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 percent CI, 0.88 to 5.75).[52] 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.[45] Hydrocolloids healed 18.0 percent of the original ulcer size per week and compression dressings healed 20.5 percent of the original ulcer size per week.[45] After 12 weeks, 21 (75 percent) of the hydrocolloid group and 22 (78 percent) of the compression group healed completely ($P > 0.05$).[45]

### Hydrocolloid Dressings Versus Other Types of Dressings

Four RCTs (total N = 420) compared hydrocolloids with other types of dressings.[41, 50, 53, 57] 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 U.S. 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.[41] 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).[41] Complete healing occurred in 11 ulcers among 35 patients in the hydrocolloid group versus 14 ulcers among 35 patients in the impregnated gauze group ($P > 0.05$).[41] 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 versus 21 $mm^2$ per day for impregnated gauze ($P = 0.0001$).[50] Followup time was measured as number of dressing changes, one through 10 and not over time.[50] 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.[50] Another small trial did not find much of a difference in healing rates when comparing hydrocolloids with alginates over 6 weeks.[57] Two of 20 (10 percent) patients healed in the hydrocolloid group versus six of 20 (30 percent) patients healed in the alginate group.[57] Lastly, no clinically important difference in healing rates was found when hydrocolloids were compared with Betadine® and a contact layer over 4 months, taking into account the ulcer size at baseline (RR, 1.16, 95 percent CI, 0.8 to 1.8).[53] However, a clinically important and statistically significant difference was seen when the proportion of ulcers healed was evaluated among ulcers with an initial measurement of greater than 4 cm: 12 of 35 (34 percent) patients healed in the hydrocolloid group versus four of 39 (ten percent) patients healed in the Betadine® plus contact layer group ($P = 0.02$).[53]

## Transparent Film Dressings

### Transparent Film Dressings Versus Compression Systems Alone

Kucharzewski[48] compared adequate compression under an Unna boot with adequate compression over a cellulose film in carefully selected venous ulcers (see Table 5). 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. Data regarding healing rates in healed ulcers was not presented. Since the means of compression were quite different in the two treatment groups, and it would have been impossible to avoid bias since the modes of therapy were so different to the patients and observers.

**Table 5. Summary of the final outcomes among patients with chronic venous ulcers comparing transparent film dressings with compression systems alone**

| Author, year | Intervention | Compression used in both groups | Followup time | Ulcer healing, n / N (%) | Time to healing |
|---|---|---|---|---|---|
| Kucharzewski, 2003[48] | G1: Unna boot<br>G2: (Bioprocess) Cellulose membrane | Unspecified compression | 11 weeks | G1: 9 / 27 patients (33)<br>G2: 18 / 27 patients (67);<br>$P < 0.05$; RR, 0.5 (CI, 0.3 to 0.9)<br>RD, -33% (CI, -58% to -8%) | G1: Time at complete closure in weeks, 20<br>G2: Time at complete closure in weeks, 14 |

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

### Transparent Film Dressings Versus Other Types of Dressings

One small trial (N = 20) compared a transparent film with a foam as a secondary dressing over an alginate over 6 weeks.[58] No randomization was discussed in the report. The same investigator throughout the trial observed at the final evaluation that eighty 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 Compression Systems Alone

One study (N = 60) compared an alginate dressing with simple gauze dressing under adequate compression in uncomplicated patients with venous ulcers. They found no difference in total healing between patients using alginate dressings versus simple gauze under conditions of vigorous compression (40 mm) (Table 6).[59]

**Table 6. Summary of the final outcomes among patients with chronic venous ulcers comparing alginate dressings with compression systems alone**

| Author, year | Intervention | Compression used in both groups | Followup time | Ulcer healing, n / N (%) | Time to healing |
|---|---|---|---|---|---|
| Moffatt, 1992[59] | G1: Gauze - simple NA dressing (Johnson and Johnson)<br>G2: Alginate - Tegagel dressing | Multi-layer | 12 weeks | G1: 24 / 30 patients (80)<br>G2: 26 / 30 patients (87);<br>*P* > 0.05; RR, 0.9 (CI, 0.7 to 1.2)<br>RD, -7% (CI, -25% to 12%) | NR |

CI = 95 percent confidence interval; G = group; NA = nonadherent; NR = not reported; RD = risk difference; RR = relative risk

### Alginate Dressings Versus Other Alginate Dressings

Two RCTs compared different alginate dressings.[20, 36] 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.[36] This was not a statistically significant difference in healing rates ($P = 0.88$).[36] 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.[20] Ulcers treated with Vulnamin® had a mean decrease in area from 13.95 (SD, 4.5) $cm^2$ to 3.04 (SD, 0.8) $cm^2$.[20] This is significant when compared with the other alginate without glycine, leucine, proline, lysine, and sodium hyaluronate that had a mean reduction in ulcer area from 15.14 (SD, 4.7) $cm^2$ to 10.96 (SD, 3.8) $cm^2$ ($P < 0.05$).[20]

### 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.[37] However, part way through the trial, the investigators changed the transparent film to a cotton gauze swab believing that the transparent film over the alginate was causing maceration or erythema. Therefore, three treatment groups were evaluated: Hydropolymer, alginate plus transparent film, and alginate plus gauze swabs. 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 gauze swab respectively. The difference between groups was not statistically significant.[37] The proportion of ulcers healed did not differ between the groups.[37]

## 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 versus 17 percent in the foam dressing without ibuprofen, $P > 0.05$) (Table 3).[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 non-adhesive foam dressing, Allevyn™; however, no formal statistical comparisons between groups were shown.[56] Franks[29] noticed no difference in healing rates between two established foam products under appropriate aggressive compression (Table 7). This trial of 156 patients reported a 64 percent healing rate over 24 weeks.

**Table 7. Summary of the proportion of ulcers healed among patients with chronic venous ulcers comparing foam dressings with other foam dressings**

| Author, year | Intervention | Compression used in both groups | Followup time | Ulcer healing, n / N (%) | Time to healing |
|---|---|---|---|---|---|
| Franks, 2007[29] | G1: Foam (Allevyn™)<br>G2: Foam (Mepilex®) | Short stretch or multi-layer | 24 weeks | G1: 50 / 81 patients (62)<br>G2: 50 / 75 patients (67); $P > 0.05$<br>RR, 0.9 (0.7 to 1.2)<br>RD, -4% (-20% to 10%) | NR |
| Gottrup, 2008[23] | G1: Foam (Biatain® Non-adhesive, Coloplast A/S)<br>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)<br>G2: 9 / 62 patients (15); $P > 0.05$<br>RR, 1.15 (0.5 to 2.6)<br>RD, 2% (-10% to 15%) | NR |
| Weiss, 1996[56] | G1: Foam (Cutinova™ foam)<br>G2:Foam (Allevyn™) | Jobst® UlcerCare stocking | 16 weeks | G1: 8 / 10 patients (80)<br>G2: 4 / 8 patients (50); $P > 0.05$<br>RR, 1.6 (CI, 0.75 to 3.4)<br>RD, 30% (CI, -13% to 72%) | G1: Mean weeks, 5.6<br>G2: Mean weeks, 6.5 |

CI = 95 percent confidence interval; G = group; NR = not reported; RD = risk difference; RR = relative risk

## Collagen Dressings

### Collagen Dressings Versus Other Types of Dressings

One parallel group RCT (N = 117) compared Promogran®, a collagen matrix, with nano-oligosaccharide factor lipido-colloid matrix (NOSF matrix) to evaluate the effects on wound healing.[25] The mean wound healing rate of the NOSF matrix was significantly greater than in the Promogran® arm (-0.016; SD, 0.285 $cm^2$ per day versus +0.075; SD, 0.475 $cm^2$ per day, $P$ = 0.03). Lastly, 56 percent of the ulcers in the NOSF matrix group versus 35 percent of the ulcers

in the Promogran® group reached 40 percent wound area reduction, a clinically important and statistically significant difference ($P = 0.022$).[25]

## Acellular Human Skin Equivalent Dressings

### Acellular Human Skin Equivalent Dressings Versus Compression Systems Alone

Small intestinal freeze dried pig submucosa (OASIS Wound Matrix) has been carefully studied in the therapy of venous ulcers in a multicenter U.S. trial.[33] Fifty-five percent (34 out of 62 patients) of well-selected venous ulcer patients healed with application of small intestinal submucosa compared with 34 percent (20 out of 58 patients) of patients treated with standard compression therapy ($P = 0.02$).[33] Furthermore, after adjusting for baseline ulcer size, ulcers treated with the test intervention were three times more likely to heal than those treated with standard compression ($P = 0.01$). If an aggressive debridement was performed before beginning therapy, the odds ratio for healing rose to four. 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 that remained healed with standard therapy ($P > 0.05$).[33]

Preliminary results from a small trial of 24 non-randomized 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.[47] Patients in the fibrin sealant group had a higher percentage of deep wounds and cavities but five of the participants healed. However, no formal statistical comparisons were shown.[47] In a single-blinded RCT of 123 patients, no difference in healing rates was observed between Amelogenin protein 30 milligrams per milliliter solution (Xelma® extracellular matrix [ECM]) plus a soft silicone dressing versus control, seven percent polypropylene glycol alginate plus soft silicone dressing over 12 weeks.[31]

## Cellular Human Skin Equivalent Dressings

### Cellular Human Skin Equivalent Dressings Versus Compression Systems Alone and Versus Cellular Skin Replacements

Dermagraft® is a biodegradable mesh containing viable fibroblasts that produce growth factors. A carefully selected group of 53 patients with venous ulcers (average age over 70, more females than males, and no extraneous complications), were subjected to a 2-week run in period to eliminate patients who might heal on adequate compression alone.[49] They were randomized to groups of 13 who received: 12 weekly applications of Dermagraft®, four applications of the product over the 12 weeks, one application at the beginning of the trial, and a group that received no test material. Forty-seven patients completed the study and results were analyzed 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. No differences were seen in a statistical analysis of healing rates as measured by percent of ulcer resurfaced by epithelium at 12 weeks.

Another small prospective RCT pilot study of 18 patients compared healing rates of patients receiving human fibroblast derived dermal replacement, Dermagraft®, or compression alone over 12 weeks.[35] The treatment group (N = 10) received one piece of Dermagraft® on day zero 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 versus 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 versus 0.033 cm per week ($P = 0.006$).[35] The reduction in wound surface area was greater in the Dermagraft® group than in the compression alone group ($P = 0.02$).[35]

Another prospective, parallel group comparative trial (N = 293) compared allogeneic cultured human skin equivalent with compression alone over 6 months.[39] Both groups received adequate compression. Patients received no more than five applications of human skin equivalent, and no human skin equivalent was applied after week 3. Human skin equivalent was more effective than compression therapy in median time to complete wound closure (61 days versus 181 days; $P = 0.003$, log rank test) and median time to 75 percent wound closure (30 days versus 50 days, $P = 0.001$).[39] Human skin equivalent was more effective in healing than compression alone among large ulcers of over 1000 mm surface area ($P = 0.02$), deeper ulcers ($P = 0.003$), and ulcers older than 6 months ($P = 0.001$, log rank test). This was confirmed throughout the treatment period by 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 one year) over six 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 ($P < 0.005$).[55] 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).[55]

Addition of autologous living keratinocytes to non-healing venous ulcers is a novel therapeutic approach. Vanscheidt et al.[27] performed an open label RCT of 226 carefully selected patients.[27] 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.[27]

## 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.[34, 42] 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).[42] Also, in this trial, patients were treated for 6 weeks and any ulcer not healed at that time was crossed over to the alternate treatment.[42] 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.[34] These investigators noted that ulcers which were increasing in size when enrolled demonstrated a statistically improved healing rate with the epidermal lysate (30 percent versus 11 percent; $P =$

0.02) which was even more marked in smaller ulcers ($P = 0.008$). The study did not report data on recurrence.[34]

## Antimicrobial Dressings

### Antimicrobial Dressings Versus Compression Systems Alone

One cross-over RCT (N = 75) compared cadexomer iodine with saline wet to dry gauze dressings over 24 weeks.[44] Patients performed their own daily dressing cleaning and changes. Many patients withdrew or dropped out of the study (25 out of 75 patients) and only 54 out of 75 patients had data available for statistical analysis.[44] 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 were offered the opportunity to change to the alternate therapy.[44] 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. Formal statistical evaluation of this outcome was not reported.[44]

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 percent versus -19 percent; $P < 0.0001$).[32]

### Antimicrobial Dressings Versus Other Antimicrobial Dressings

One RCT (N = 281) compared Urgotul® Silver with Aquacel® Ag over 4 weeks.[19] One hundred forty-five patients were randomized to the Aquacel® Ag group followed by Aquacel® for another 4 weeks. One hundred thirty-six patients were randomized 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. No significant difference in healing rates between groups was found.[19]

A randomized optional cross-over trial compared cadexomer iodine with gentian violet and Polyfax ointment (standard treatment) over 24 weeks among 61 outpatients.[46] 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 ($P < 0.001$).[46]

### 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 non-antimicrobial dressing (including knitted viscose, foams, contact layers, and low adherent tulle).[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 non-silver dressings was clinician-guided based on wound characteristics. The overall median time to healing was 67 (95 percent CI, 54 to 80) days for the antimicrobial dressings and 58 (95 percent 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 with a 34 percent reduction in median wound size versus 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.[61] 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 percent CI, 3.28 to 9.29 $cm^2$, $P = 0.0001$) and 5.85 $cm^2$ (95 percent CI, 3.58 to 8.12 $cm^2$, $P = 0.0001$), respectively. However, no significant difference was found between the groups.[61]

Lastly, one RCT (N = 153) compared cadexomer iodine with hydrocolloid and paraffin gauze over a duration of 12 weeks.[38] 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 were excluded 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 to be significant. The mean ulcer area reduction per week was significantly greater in the cadexomer iodine group compared with the paraffin gauze group ($P = 0.04$).[38]

## 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

Overall, we found moderate strength of evidence that collagen dressings and cellular human skin equivalents have a small effect on wound healing when compared with compression systems alone (Table 8). We also found moderate strength of evidence that antimicrobial 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.

**Table 8. 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 Strength of evidence* |
|---|---|---|---|---|---|---|
| | | 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. compression | 1 (60) | 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. other dressings | 1 (117) | Medium | NA | Indirect | Precise | Small effect Low SOE |
| Acellular HSE vs. compression | 3 (267) | High | Unknown - heterogeneity in interventions | Direct | Imprecise | Unclear effect Insufficient SOE |
| Cellular HSE vs. compression | 4 (590) | Medium | Consistent | Direct | Precise | Small effect Moderate 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.

## Mortality

We included eleven studies that reported on mortality.[19, 22, 27, 29, 33, 34, 39, 46, 49, 52, 53] In most of these studies, deaths were rare, occurring in less than 5 percent of patients, and did not differ between intervention groups (Table 9).

**Table 9. Summary of the mortality rates among patients with chronic venous ulcers comparing advanced wound dressings with compression systems alone or other advanced wound dressings**

| Author, year | Intervention, group 1 | Intervention, group 2 | Compression used in both groups | Followup time | Mortality group 1, n / N (%) | Mortality group 2, n / N (%) |
|---|---|---|---|---|---|---|
| Smith, 1992[53] Among those with initial ulcer size of 2-4 cm | Betadine/Jelonet | Hydrocolloid Biofilm powder+Biofilm dressing | Linear, graduated (Tubigrip or Venosan 2002) | 4 months | 2 / 62 (3) | 0 / 64 (0) |
| Smith, 1992[53] Among those with initial ulcer size of >4 cm | Betadine/Jelonet | Hydrocolloid Biofilm powder+Biofilm dressing | Linear, graduated (Tubigrip or Venosan 2002) | 4 months | 0 / 39 (0) | 0 / 35 (0) |
| Moffatt, 1992[52] | Non-adherent | Hydrocolloid | 4-layer | 12 weeks | NR* / 30 | NR* / 30 |
| Franks, 2007[29] | Foam (Allevyn) | Foam (Mepilex) | Short stretch or multi-layer | 24 weeks | 1 / 81 (1) | 0 / 75 (0) |
| Mostow, 2005[33] | None | Composite | Multi-layer Debridement | 12 weeks | 1[†] / 15 (7) | 0 / 8 (0) |
| Falanga, 1998[39] | None | Cellular human skin equivalent | Unna boot | 12 months | 4 / 129 (3) | 5 / 146 (3) |
| Krishnamoorthy, 2003[49] | None | Cellular human skin equivalent - Dermagraft 12 pc | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 0 / 13 (0) |
| Krishnamoorthy, 2003[49] | None | Cellular human skin equivalent - Dermagraft 4pc | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 0 / 13 (0) |
| Krishnamoorthy, 2003[49] | None | Cellular human skin equivalent - Dermagraft 1pc | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 0 / 14 (0) |
| Vanscheidt, 2007[27] | Contact layer | Contact layer + Cellular human skin equivalent | Short stretch | 182 days | 1 / 109 (1) | 1 / 116 (1) |
| Ormiston, 1985[46] | Gentian violet and Polyfax | Cadexomer iodine | Crepe then cotton crepe compression bandage | 12 weeks | 0 / 30 (0) | 1 / 31 (3) |
| Harding, 2011[19] | Urgotul Silver for 4 weeks then Urgotul for 4 weeks | Aquacel Silver for 4 weeks then Aquacel for 4 weeks | UK Class III compression | 8 weeks | 2 / 136 (1) | 0 / 145 (0) |
| Michaels, 2009[22] | Antibacterial dressings (silver) | Hydrocolloid | Multi layer | 12 months | 4 / 106 (4) | 4 / 107 (4) |
| Harding, 2005[34] | Hydrocolloid keratinocyte lysate | Hydrocolloid | 2 layer compression | 14 weeks | 0 / 53 (0) | 0 / 45 (0) |
| Harding, 2005[34] | Hydrocolloid keratinocyte lysate | Cellular human skin equivalent | 2 layer compression | 14 weeks | 0 / 53 (0) | 1 / 95 (1) |
| Harding, 2005[34] | Hydrocolloid | Cellular human skin equivalent | 2 layer compression | 14 weeks | 0 / 45 (0) | 1 / 95 (1) |

cm = centimeters; NR = not reported; pc = pieces

* Two patients died during the 12-week study period, but the authors did not report in which treatment arm the deaths occurred.

[†] Death was due to cardiovascular disease.

## Quality of Life

In this report, we classified quality of life (QOL) measures as either general health-related QOL (non-specific 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, 41, 50] Table 10 categorizes these QOL assessment tools into general health-related QOL and ulcer-specific QOL.

**Table 10. 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 11).[41, 50] 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.[41] This study did not find a statistically significant difference in QOL between the two intervention arms.[41] 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).[50] This study found that hydrocolloid dressings were favored over conventional dressings for ulcer-specific QOL measures related to discomfort and convenience during dressing change.[50]

**Table 11. 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[41] | 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[50] | 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 12).[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 12. 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 2 study groups had no statistically significant differences in 4 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 non-antibacterial control dressings on general and ulcer-specific QOL in adults with venous leg ulcers (Table 13).[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 non-antibacterial 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 13. 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. non-silver dressing (106) | 213 patients (mean age 69 years for silver, 72 years for non-silver) with venous leg ulcers | After 12 months of followup, mean difference between silver (0.7526) and non-silver groups (0.6752) was -0.0774 ($P$ > 0.05) | Neither |
| SF-6D* | Michaels, 2009[22] | Silver (107) vs. non-silver dressing (106) | 213 patients (mean age 69 years for silver, 72 years for non-silver) with venous leg ulcers | After 12 months of followup, mean difference between silver (0.7092) and non-silver (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 quality of life.

# Pain

## Hydrocolloid Dressings

### Hydrocolloid Dressings Versus Other Types of Dressings

One trial compared hydrocolloids with Betadine® and a contact layer to evaluate ulcer pain (moderate to severe) and dressing comfort (very to fairly comfortable) for the first month of treatment.[53] The hydrocolloid group experienced less pain than the Betadine® and contact layer group among small and large ulcers ($P$ = 0.02). Ulcer size had an effect with more pain experienced among those 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).[53]

Another trial comparing hydrocolloid with impregnated gauze with magnesium sulfate and Vaseline® found that patients had no discomfort at dressing change number five 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).[50]

Another trial compared hydrocolloid with impregnated gauze containing paraffin or Betadine®. Patients rated their pain on a scale of zero (minimal pain) to 10 (maximal pain).[41] Patients in the hydrocolloid group reported less pain at follow-up 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 ($P = 0.3$).[41]

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.[57] Wounds treated with the alginate dressing were less painful at week zero ($P = 0.0004$) than those treated with the hydrocolloid and remained that way at week six ($P = 0.03$).[57]

## Transparent Film Dressings

### Transparent Film Dressings Versus Other Types of Dressings

In the trial comparing an alginate plus transparent film with an alginate plus foam, pain was evaluated on a one to four scale: 1 = painless, 2 = slightly painful, 3 = sufficiently painful to require analgesia, 4 = painful enough to interfere with lifestyle and not relieved with high levels of analgesia.[58] 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.[58]

## 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 one to five (1 = very good to 5 = very poor).[36] Patients in the Sorbsan alginate group experienced much more comfort during dressing wear ($P = 0.0005$) and dressing removal ($P = 0.003$).[36]

## 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 swab, the investigators asked the patients to rate comfort on a scale of one to five (1 = poor comfort and 5 = good comfort).[37] The hydropolymer dressings were rated higher in comfort by patients (mean comfort score, 4.27) than the alginate plus transparent film (mean comfort score, 3.37) or the alginate plus gauze swab (mean comfort score, 3.74; $P < 0.02$).[37]

## Acellular Human Skin Equivalent Dressings

### Acellular Human Skin Equivalent Dressings Versus Compression Systems Alone

Pain was evaluated on a scale of zero to 10 in a trial comparing Amelogenin protein 30 milligrams per milliliter solution (Xelma® ECM) plus a soft silicone dressing with a control dressing of seven percent propylene glycol alginate.[31] The mean baseline pain score for the treatment group was four compared with three for the control. Both groups had a pain score of one on the final visit. No statistical between group comparisons were shown.

## Antimicrobial Dressings

### Antimicrobial Dressings Versus Compression Systems Alone

In a trial comparing cadexomer iodine to saline wet to dry dressings, pain was reported but a specific scale was not reported making it difficult to interpret the findings.[44] However, the investigators reported that there was no statistically significant difference in pain between the two groups.[44] In another trial that compared pale sulfonated shale oil ten percent plus Jelonet to vehicle plus Jelonet, pain was reported on a visual analog scale of zero (no pain) to ten (maximal pain).[32] The investigators reported no significant difference in pain between groups.[32]

### Antimicrobial Dressings Versus Other Antimicrobial Dressings

A randomized optional cross-over 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 zero to 100.[46] The change in pain per week was compared and found not to be statistically significant.[46]

### Antimicrobial Dressings Versus Other Types of Dressings

In a trial comparing cadexomer iodine to a hydrocolloid dressing and a paraffin gauze dressing, the percentage of wounds with pain was reported at different time points in the trial.[38] 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 intensity of the pain was not reported nor was a statistical comparison made between groups.[38]

## Other Types of Advanced Wound Dressings

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

# Condition of the Wound Bed

## Transparent Film Dressings

### Transparent Film Dressings Versus Other Types of Dressings

In a trial comparing a transparent film with a foam as a secondary dressing over an alginate, wound appearance was evaluated on a scale of one to four (one = healed, two = clean and epithelializing, three = clean and sloughy or mildly sloughy, and four = infected, very sloughy and odorous).[57] 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. No statistical comparisons were made between groups.[57]

## Alginate Dressings

### Alginate Dressings Versus Other Alginate Dressings

In a trial comparing the alginate dressings, Sorbsan® and Tegagen™ HG, wound bed condition was evaluated for amount of exudate, purulent or serosanguinous exudate, necrotic

tissue, foul odor, and the need for debridement over 6 weeks.[36] 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. This was considered 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 ($P = 0.18$).[36]

## Specialty Absorptive Dressings

### Specialty Absorptive Dressings Versus Other Types of Dressings

The wound bed was evaluated for odor during 4 weeks in a trial comparing a hydropolymer dressing with an alginate plus transparent film and an alginate plus gauze swab on moderately to heavily exuding wounds.[37] The investigators used a scale of one to five to evaluate odor (1 = poor odor control and 5 = good odor control). Investigator evaluation of the wound bed showed a significantly better control of odor with the hydropolymer dressing (mean odor score, 4.24) than in the in the alginate plus transparent film group (mean odor score, 2.95; $P < 0.001$). The alginate plus gauze swab received the same mean odor score as the hydropolymer dressing. The patient evaluation of wound odor revealed that the hydropolymer dressing (mean odor score 4.45) was significantly better at controlling odor than alginate plus transparent film (mean odor score, 3.05) and the alginate plus gauze swab (mean odor score, 3.96; $P = 0.001$).[37]

## Acellular Human Skin Equivalent Dressings

### Acellular Human Skin Equivalent Dressings Versus Compression Systems Alone

In an RCT comparing amelogenin protein 30 milligrams per milliliter solution (Xelma® ECM) plus a soft silicone dressing with a control dressing of seven percent propylene glycol alginate, the wound bed was analyzed for percent of viable tissue and amount of exudate expressed over time.[31] These data were extrapolated from figures within the published study using the software DigitizeIt 1.5 (ShareIt Inc., Koln, Germany). However, no statistical comparisons were made of the within and between group differences. The percent viable tissue in wound bed of amelogenin at baseline was 52 percent 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 percent versus 92 percent for the comparison group. Zero percent of the wounds in the amelogenin and comparison groups were ranked 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.[31]

## Cellular Human Skin Equivalent Dressings

### Cellular Human Skin Equivalent Dressings Versus Compression Systems Alone

The histology of the wound bed was evaluated in a trial comparing Dermagraft® 12 pieces over 12 weeks, versus four pieces over 12 weeks, versus one piece over 12 weeks.[49] 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 week 6 correlated with an increased percentage of healing at weeks 6 and 12 as well as with the number of patients healed.

In another trial comparing the cellular human skin equivalent, Dermagraft®, with compression over 12 weeks, wound beds were histologically evaluated by biopsy at the beginning of treatment and at week 6 (if the ulcer was not healed).[35] 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 ($P = 0.55$).[35]

## Antimicrobial Dressings

### Antimicrobial Dressings Versus Compression Systems Alone

In a trial comparing cadexomer iodine with wet to dry saline gauze under compression over 24 weeks, no significant difference was found when wound beds were evaluated for granulation tissue ($P = 0.16$), exudate ($P = 0.96$), and pus/debris ($P = 0.55$).[44] Likewise, in a trial comparing pale sulfonated shale oil 10 percent plus Jelonet™ to vehicle plus Jelonet™ over 20 weeks, no significant difference was found between groups when evaluating wound beds for fibrinous discharge and necrotic tissue.[32]

### Antimicrobial Dressings Versus Other Types of Dressings

One trial compared cadexomer iodine versus hydrocolloid versus paraffin gauze over 12 weeks.[38] 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 ($P < 0.05$).[38]

In another trial that enrolled 32 patients, hydrogel was compared with hydrogel plus *M. tenuiflora* extract (MTC-2G), a substance with alleged antiseptic properties.[61] No significant difference was found in the clinical condition of the wound beds after 8 weeks when evaluated for percentage of granulation tissue, fibrin, maceration, wound exudates, and necrosis. However, the presence of epithelial islands was greater in the MTC-2G group (58 percent) than in the hydrogel only group (39 percent; $P = 0.02$). Biopsies were taken 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, only 21 patients were biopsied as it was deemed unethical to obtain biopsies from patients with healed wounds or wounds that decreased to less than five millimeters. No difference was seen 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 ($P = 0.05$).[61] 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 cross-over 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.[46] No significant differences were found between the treatment groups.[46]

### Other Types of Advanced Wound Dressings

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

## 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 Versus Compression Systems Alone

Four RCTs (463 participants analyzed at 3 to 4 months of follow up) compared a hydrocolloid dressing with a standard dressing in terms of the effects on wound infection rates.[38, 45, 50, 53] Infection rates were similar across arms for all studies[45, 50, 53] with the exception of the subgroup of participants with baseline ulcer size greater than 4 cm in Smith, 1992 et al.[53] 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; $P = 0.004$).[53] Infection rates were similar in the participants with a baseline ulcer size of 2 to 4 cm regardless of study arm.[53] Two studies did not provide definitions of infection,[38, 45] and the two others used different definitions ("acute infection[53]" and "erysipelas[50]") (Tables 14 and 15).

**Table 14. 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[45] | Non-adherent, non-occlusive dressing | Hydrocolloid - Granuflex (occlusive hydrocolloid) | Multi-layer | 12 weeks | 3 / 28 (11) | 4 / 28 (14) |
| Greguric, 1994[50] | 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[53]<br><br>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[53]<br><br>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 [38] | Jelonet paraffin gauze | Hydrocolloid Duoderm E | Comprilan short-stretch | 12 weeks | 4 / 49 (8) | 5 / 48 (10) |

cm = centimeters; NR = not reported

**Table 15. 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[33] | Not further specified |
| Hansson, 1998[38] | Not further specified |
| Falanga, 1998[39] | Not further specified |
| Backhouse, 1987[45] | Not further specified |
| Krishnamoorthy, 2003[49] | Characterized as: local wound infection, cellulitis, or osteomyelitis |
| Greguric, 1994[50] | Erysipelas cruis |
| Smith, 1992[53] | Acute infection |
| Lazareth, 2008[54] | Not further specified |

## Hydrocolloid Dressings Versus Other Hydrocolloid Dressings

A single RCT conducted in France compared the effect of a hydrocolloid dressing and impregnated gauze without silver sulfate with that of a hydrocolloid dressing and impregnated gauze with silver sulfate in 102 participants with chronic venous ulcers.[54] Wound infection rates were low and similar in both arms at 4 weeks. Infection occurred in one of 48 analyzed

participants in the study arm without silver sulfate (2 percent) and in no participants in the arm with silver sulfate (0 percent).[54] The study did not provide a definition of infection.[54] Notably, the drop-out rate was higher in the study arm not using silver sulfate (16 out of 50; 32 percent) compared with that in the arm using silver sulfate (four out of 52; 8 percent).[54] This appeared to be driven by aggravation of the ulcer or other adverse event in the control arm (not using silver sulfate).[54]

## Foam Dressings

### Foam Dressings Versus Other Foam Dressings

In a single, multi-center 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 this was not explicitly stated.[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 were withdrawn from the study because of adverse events or protocol violations) from the foam plus ibuprofen arm.[23] Infection was defined by the presence of several typical signs (Table 16).

**Table 16. 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 follow up time but unclear.

## Acellular Human Skin Equivalent Dressings

### Acellular Human Skin Equivalent Dressings Versus Compression Systems Alone

A single, multi-center RCT of 120 participants compared an extracellular matrix dressing with multi-layer compression and reported five wound infections in the control arm and one in the active intervention arm at 12 weeks ($P$=0.10).[33] The study did not provide a definition of infection (Table 17).

**Table 17. 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[33] | None | Composite acellular or extracellular matrix | Multi-layer Debridement | 12 weeks | 5 events / 58 patients | 1 event / 62 patients; *P* = 0.10 |

# Cellular Human Skin Equivalent Dressings

## Cellular Human Skin Equivalent Dressings Versus Compression Systems Alone

Two RCTs (N = 328) compared a cellular human skin equivalent with compression alone.[39, 49] Wound infection rates were similar across cellular human skin equivalent and compression arms (Table 18).[39, 49] Infection rates were very low in a study lasting 12 weeks with only a single infection occurring in one study arm[49] and occurred in 8 percent of participants in the RCT lasting 12 months.[39] In this larger study of longer duration, drop-out rates were substantial but similar across study arms (26 percent and 20 percent in the compression and intervention arms, respectively).[39] One study included local wound infection, cellulitis, or osteomyelitis in its definition of infection[49] while the other did not specify a definition.[39]

**Table 18. 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[49] | None | Cellular human skin equivalent Dermagraft 12 pcs | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 0 / 13 (0) |
| Krishnamoorthy, 2003[49] | None | Cellular human skin equivalent Dermagraft 4 pcs | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 1 / 13 (8) |
| Krishnamoorthy, 2003[49] | None | Cellular human skin equivalent Dermagraft 1 pc | Multi-layer Profore | 12 weeks | 0 / 13 (0) | 0 / 14 (0) |
| Falanga, 1998[39] | None | Cellular human skin equivalent | Unna boot | 12 months | 10 / 129 (8) | 12 / 146 (8) |

# Antimicrobial Dressings

## Antimicrobial Dressings Versus Compression Systems Alone

A single, multi-center 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.[33] Participants in a third arm received a hydrocolloid dressing with five of 48 participants (10 percent) developing an infection (Table 19).[38] The study did not provide a definition of infection (Table 15).

**Table 19. 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 [38] | 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 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 2-layer compression (Table 20).[50] 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).[50] The number of dressing changes required for complete wound healing dictated the maximum followup time with a maximum of 10 dressing changes allowed.[50] Dressing changes were anticipated to occur every 5 days in the intervention arm and nearly daily in the control arm.[50] The authors did not report followup time explicitly.[50] On average, participants had chronic venous ulcers for five years at baseline.[50]

**Table 20. 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[50] | 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 follow up 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, multi-center 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 21).[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 patients were likely followed for 42 days although this was not explicitly stated.[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 were withdrawn from the study because of adverse events or protocol violations) from the foam plus ibuprofen arm.[23]

**Table 21. 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 follow up 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 the dressings of interest 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 non-healing lower extremity ulcers in the setting of chronic venous stasis disease, we found only one randomized study that addressed KQ2.[62] This small study evaluated systemic oral antimicrobials, was conducted in Finland, and was published 18 years ago. The Finnish study[62] 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.

## Strength of Evidence

The study that addressed KQ2 had a high risk of bias. It evaluated a small number of subjects in a referral center. The most important bias was ascertainment bias. This study evaluated the microbiology of ulcers using methods that are now known to be inaccurate (swab culture). Furthermore, the sensitivity of culture technique was likely lower, as anaerobes were infrequently reported. Consistency cannot be determined 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 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. (Moderate strength of evidence)
- Adding minimally invasive surgical hemodynamic correction of reflux to compression therapy may increase the ulcer-healing rate. (Low strength of evidence)
- The Linton procedure with or without ulcer debridement and skin grafting may not add any benefit for venous ulcer healing when compared with compression therapy alone. (Low strength of evidence)
- Subfascial endoscopic perforator surgery (SEPS) with superficial vein surgery does not improve the rate of healing of chronic venous leg ulcers in comparison with compression alone. (High strength of evidence)
- Sclerotherapy may improve the healing of chronic venous leg ulcers 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 8 studies (9 publications) (Appendix D, Table 1).[63-70] Two publications[64, 65] reported on the same trial (Effect of Surgery and Compression on Healing and Recurrence [ESCHAR]). Barwell et al.[65] reported the short-term results and Gohel et al.[64] reported the long-term results.

These studies enrolled a total of 1043 (range, 40 to 500) patients with chronic venous leg ulcers between 1995 and 2008. The average number of patients screened was 596 patients, and the average number of patients enrolled was 151 patients. The enrollment rate was 13 to 93 percent, with an average of 33 percent. Six of the eight studies were RCTs,[63-67, 69, 70] one was a cohort study,[67] and one a non-randomized trial.[68] The studies had 1 to 5 years of reported followup.

Four of the studies were done in the United Kingdom,[63-65, 67, 69] one in Italy,[66] one in the Netherlands,[70] one in Denmark,[67] and one in Mexico.[68] The clinic setting also varied — two studies recruited from specialist nurse-led venous ulcer clinics,[63-65] one recruited from 12 centers across the Netherlands,[70] one from an out-patient community base clinic,[67] and four studies did not describe the source of the study population.[66-69]

All of these studies had at least one surgical arm: superficial vein surgery,[64-67] open perforator ligation,[67] SEPS,[69, 70] and sclerotherapy (Appendix D, Table 2).[63, 68] All of the patients treated surgically had multilayer compression therapy. The comparison groups in these studies

received compression therapy alone. In one study,[67] the comparison group also received a hydrocolloid dressing.

## Study Population Characteristics

Age was reported in seven of the eight studies with a median of 69 years (Appendix D, Table 3). When gender was reported,[64, 65, 67-70] the most patients were female. The studies varied in how diabetes was factored into the study design. Diabetes was an exclusion criterion in three studies.[66, 67, 69] One study[63] excluded only patients with poorly-controlled diabetes. The other three studies[64, 65, 67, 70] included patients with diabetes which was more prevalent in the compression group. One study[68] did not report diabetes status of the subjects.

All patients had vascular evaluation with venous duplex ultrasound studies and were evaluated for arterial insufficiency by measuring the ankle brachial index. Patients with arterial insufficiency, defined by an ankle brachial index less than 0.8, were excluded from enrollment, but two studies used an ankle brachial index less than 0.85,[64, 65, 67] and another used an ankle brachial index less than 0.9[66] as a cut-off for exclusion. Smoking status was not reported in any of the 8 studies. Most of the publications did not describe the presence of other systemic diseases;[63, 64, 66-70] only two publications reported on the prevalence of rheumatoid arthritis.[65, 67]

## Wound Healing

### Superficial Vein Surgery Versus Compression

One RCT[64, 65] and one prospective cohort study[67] compared superficial vein surgery with compression alone, and reported on wound healing (Table 22 and Appendix D, Table 4). These two studies were too different to be combined in a meta-analysis.

Gohel et al.[64] reported the short-term results, and Barwell et al.[65] 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: 242 patients were included in the surgical intervention group and 258 patients were included in the compression only group. The study was limited by contamination of the defined groups – after randomization, three patients in the comparison group requested surgery, and 47 patients in the surgical group refused surgery. The analysis was performed 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 were excluded from the study 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 was conducted in an outpatient clinic setting in England.[67] Over a 4-year period (1995 to 1999), 669 patients (766 legs) with chronic venous leg ulcers were evaluated. All patients underwent measurement of the ankle brachial index, and 120

legs had an ankle brachial index less than 0.85 and were excluded. 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 only those patients were offered 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 surgical procedure was performed on the long saphenous vein in 97 legs (74 percent), 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 SEPS was not performed 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, $P = 0.67$). A limitation of the statistical analysis was that each leg was treated 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 22. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing superficial vein surgery with compression alone**

| Author, year<br><br>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<br>Risk difference |
|---|---|---|---|---|---|---|---|
| Gohel, 2007[64]<br><br>RCT | Compression alone | Superficial vein surgery plus compression | Multi-layer | 48 months | 165 / 185 patients (89%) | 145 / 156 patients (93%); *P* = 0.73 | RR, 0.96 (CI, 0.90 to 1.02)<br>RD, -4% (CI, -10 to 2%) |
| Barwell, 2003[65]<br><br>RCT | Compression alone | Superficial vein surgery plus compression | Multi-layer | 12 weeks | 141 / 185 patients (76%) | 128 / 156 patients (82%); *P* = 0.85 | RR, 0.93 (CI, 0.83 to 1.04)<br>RD, -6% (CI, -14% to 3%) |
| Barwell, 2000[67]<br>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 percent confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

## Minimally Invasive Ligation of Insufficient Saphenous Vein Tributaries (CHIVA) Versus Compression Alone

Zamboni et al.[66] compared compression alone with minimally invasive surgical hemodynamic correction of reflux (Conservative Hemodynamic treatment of Insufficiency of the Venous system in an Ambulatory setting [CHIVA] procedure) in addition to compression (Table 23). This was a randomized non-blinded 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 non-ambulatory, or had diabetes mellitus, a history of deep vein thrombosis, congenital angiodysplasia, or ankle brachial index less than 0.9. All patients underwent venous duplex ultrasound and were excluded if deep venous obstruction was identified. The median ulcer size was similar in both groups: 11 $cm^2$ (range, 3 to 12 $cm^2$) in the compression group versus 10 $cm^2$ (range, 2.6 to 11.8 $cm^2$) in the surgical group. Patients with ulcers less than 2 or greater than 12 $cm^2$ were excluded from the study. 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 ($P < 0.02$).

**Table 23. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing CHIVA with compression therapy alone**

| Author, year<br><br>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[66]<br><br>RCT | Compression + foam dressing | CHIVA | 20-30 mmHg elastic stocking | 36 months | 23 / 24 patients (96%) | 23 / 23 patients (100%); *P* < 0.02 | RR, 0.96 (0.88 to 1.04)<br>RD, -4% (-12% to 4%) |

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

## Open Perforator Ligation (Linton Procedure) Versus Compression

One factorial RCT was conducted in Denmark with a 1-year followup (Table 24).[67] This study randomized 47 patients into one of three groups: open surgical ligation of incompetent perforator veins using the Linton procedure (group A), Linton procedure plus ulcer excision followed by skin grafting (group B), or compression alone (group C). All patients were treated with compression bandages (Wero Medium) and patients in groups A and C were treated, in addition, with hydrocolloid wound dressings. The groups had no statistically significant differences in their baseline characteristics. Wound healing rates were similar in all three groups, reported at 40 percent for group A (Linton procedure), 40 percent for group B (Linton plus ulcer excision and grafting), and 42 percent for the control group ($P > 0.05$). The median time to wound healing was 3 months for group A (range, 1 to 12 months), 5.5 months for group B (range, 1.2 to 12 months), and 5 months for group C (range, 3 to 12 months).

**Table 24. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing Linton perforator ligation versus Linton plus wound debridement and skin grafting versus a hydrocolloid dressing plus compression**

| Author, year<br><br>Study design | Group 1 | Group 2 | Group 3 | Compression used | Followup time | Ulcer healing in group 1, n / N (%) | Ulcer healing in group 2, n / N (%) | Ulcer healing in group 3, n / N (%) |
|---|---|---|---|---|---|---|---|---|
| Warburg, 1994[67]<br><br>RCT | Open perforator ligation with Linton procedure plus hydrocolloid dressing | Open perforator ligation with Linton procedure plus ulcer excision and skin grafting | Hydrocolloid dressing | Elastic bandage | 1 year | 6 / 15 patients (40) | 5 / 13 patients (40) | 5 / 12 patients (42) |

RCT = randomized controlled trial

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

Two studies included patients undergoing SEPS (Table 25).[69, 70] Both studies were prospective RCTs.[69, 70] 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,[69] and the other used two layers of compression.[70] One study[69] reported results per patient while the other[70] reported results per limb.

One RCT screened 121 patients with chronic venous leg ulcers.[69] 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 4-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 surgical procedure was tailored 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.[70] 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 2-layer compression, and 103 ulcers to 2-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). Four patients were lost 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 25. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing SEPS with compression systems alone.**

| Author, year<br><br>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[69]<br><br>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)<br>RD, -3% (CI, -25% to 18%) |
| Van Gent, 2006[70]<br><br>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 percent 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 Versus Compression

Two studies compared sclerotherapy with compression in patients with chronic venous leg ulcers (Table 26).[63, 68] These two studies were too different to be combined in a meta-analysis.

One was a prospective RCT conducted in a nurse-led clinic.[63] 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. Of the patients evaluated, 40 patients were randomized. Twenty-two patients were in the 4-layer compression group, and 18 patients were in the 4-layer compression in addition to foam sclerotherapy group. Four patients withdrew and two patients in the sclerotherapy group were found not to meet inclusion criteria after randomization. One unrelated death occurred in the compression group (the cause of death was not reported). 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 other study compared sclerotherapy of saphenous and perforator veins with compression alone.[68] Patients underwent ankle brachial index measurement and venous ultrasound. Patients with an ankle brachial index less than 0.8 were excluded. 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 the patients were allocated to the treatment groups or whether it was randomized. At 21 weeks of followup, the ulcer healing rate was 62 percent in the compression group and 85 percent in the sclerotherapy group ($P = 0.06$).

**Table 26. Summary of the proportion of ulcers healed among patients with chronic venous leg ulcers comparing sclerotherapy with compression systems alone**

| Author, year<br><br>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[63]<br><br>RCT | Compression | Sclerotherapy - saphenous vein | Multi-layer | 24 weeks | 17 / 20 (85%) | 12 / 13 (92%); *P* = 0.72 | RR, 0.92 (CI, 0.72 to 1.17)<br>RD, -7% (CI, -29% to 14%) |
| Rojas, 2009[68]<br><br>Unclear | Compression | Sclerotherapy - saphenous vein + perforator | Multi-layer + 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)<br>RD, -23% (CI, -43% to -3%) |

CI = confidence interval; mmHg = millimeters of mercury; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

### Other Surgical Interventions 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 (CHIVA) 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.[66]

### Open Perforator Ligation (Linton Procedure) Versus Compression

In addition to reporting on ulcer healing rates as indicated above, Warburg[67] et al. reported no statistically significant difference in time to healing between open surgical ligation of incompetent perforator veins using the Linton procedure (group A), Linton procedure plus ulcer excision followed by skin grafting (group B), or compression alone (group C). The median time to wound healing was 3 months for group A (range, 1 to 12 months), 5.5 months for group B (range, 1.2 to 12 months), and 5 months for group C (range, 3 to 12 months).

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

In addition to reporting on ulcer healing rates as indicated above, Guest et al.[69] reported no statistically significant difference between the time to ulcer 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 percent CI, 0.45 to 1.39).

In addition to reporting on ulcer healing rates as indicated above, van Gent et al.[70] 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 Versus Compression

In addition to reporting on ulcer healing rates as indicated above, Rojas et al.[68] reported a median of 8 weeks to complete wound healing in the surgical group compared with 20 weeks among patients in the control group.

### Other Surgical Interventions Versus Compression

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

# Ulcer Recurrence

## Superficial Vein Surgery Versus Compression

The ESCHAR study mentioned above also evaluated ulcer recurrence in short-term[64] and long-term followup (Table 27).[65] 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 percent versus 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.[67] 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 percent versus 28 percent, and 20 percent versus 30 percent, respectively).

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

**Table 27. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing superficial vein surgery with compression treatment alone**

| Author, year<br><br>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[64]<br><br>RCT | 48 months | 165 / 185 patients (89%) | 145 / 156 patients (93%);<br>$P = 0.74$ | 56% | 31%; $P < 0.01$ |
| Barwell, 2004[65]<br><br>RCT | 12 weeks | 141 / 185 patients (76%) | 128 / 156 patients (82%);<br>$P = 0.85$ | 28% | 12%; $P = 0.85$ |
| Barwell, 2000[67]<br><br>RCT | 36 months | 74% of limbs | 72% of limbs;<br>$P = 0.67$ | 44% | 26%; $P = 0.03$ |

RCT = randomized controlled trial

## Minimally Invasive Ligation of Insufficient Saphenous Vein Tributaries (CHIVA) Versus Compression Alone

As reported above, one RCT[66] compared compression alone with minimally invasive surgical hemodynamic correction of reflux (CHIVA) in addition to compression (Table 28). 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 28. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing vein CHIVA with compression systems alone**

| Author, year<br><br>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[66]<br><br>RCT | 36 months | 23 / 24 patients (96%) | 23 / 23 patients (100%);<br>$P < 0.02$ | 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 Versus Compression

In the previously mentioned trial comparing SEPS with compression, the main study outcome was ulcer-free time during followup (Table 29).[70] 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 29, the recurrence rate was similar in both groups. However, patients with first-time ulcers had a lower recurrence rate than recurrent ulcers (13 percent versus 29 percent; $P = 0.01$) regardless of the treatment group.

**Table 29. Summary of ulcer recurrence rates among patients with chronic venous leg ulcers comparing SEPS with compression systems alone**

| Author, year<br><br>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[70]<br><br>RCT | 36 months | 25 / 39 patients (64%) | 25 / 37 patients (68%);<br>$P = 0.75$ | 22% | 23%; $P > 0.05$ |

RCT = randomized controlled trial

## Sclerotherapy Versus Compression

Neither of the studies that evaluated this comparison reported on ulcer recurrence rates.

## 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

Health-related quality of life was reported in only two studies.[66, 69] Zambani et al.[66] evaluated general health-related quality of life 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.[69] 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. These results need to be considered in the context of the non-blinded design, small sample size and other bias issues that we previously mentioned.

## Mortality

None of the eight studies on KQ3a 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 30).

**Table 30. 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[64] RCT | Compression alone | Superficial vein surgery plus compression | Multi-layer | 3 years | 49 / 258 (19) | 39 / 242 (16); *P* = 0.25 |
| Barwell, 2003[65] RCT | Compression alone | Superficial vein surgery plus compression | Multi-layer | 12 months | 26 / 258 (10) | 19 / 242 (8) |
| Barwell, 2000[67] Prospective cohort | Compression alone | Superficial vein surgery plus compression | 4-layer | 24 weeks | 0* | 0* |
| Guest, 2003[69] RCT | Compression alone | SEPS + compression | 4-layer | 26 weeks | 0 / 39 (0) | 0 / 37 (0) |
| van Gent, 2006[70] RCT | Compression alone | SEPS + compression | 2-layer | 36 months | 8 / 102 legs† | 17 / 94 legs† |
| O'Hare, 2010[63] RCT | Compression | Sclerotherapy - saphenous vein | Multi-layer | 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 number of patients randomized to each treatment group was not reported.

† 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.

## Adverse Events

Adverse events were reported at a very low incidence rate, and 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). Six of the eight studies were randomized,[63-67, 69, 70] but only one had adequate allocation concealment.[63] None of the studies were blinded. Generally, the intervention groups were recruited from the same population and time, and had adequate reporting of 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 31). The data is supported by 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 increases the ulcer-healing rate. The data is supported by one RCT with a small number of patients. Although this study had a low risk of bias, no other RCT has been performed to confirm the findings. The use of multiple interventions in the patients evaluated may also bias the results.

The strength of evidence is low to moderate that the Linton procedure with or without ulcer debridement and skin grafting does not provide much improvement in venous ulcer healing when compared with compression therapy. This is based on one RCT with a limited number of patients in each group. The risk of bias was medium because the authors did not specify the method of randomization. Consistency is unknown as only one trial addressed this comparison. The evidence otherwise is direct and precise.

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[69, 70] with low risk of bias. The evidence is consistent between the two studies and is direct and precise.

The strength of evidence is low that sclerotherapy is beneficial when added to compression therapy in healing chronic venous ulcers. This is based primarily on one RCT[63] that failed to enroll enough patients to detect a statistically significant difference between the two groups. Power calculation called for 170 patients, but only 40 patients were randomized. 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.

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 31. 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**

| Comparison | 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 | 1 RCT (500); 1 cohort (669) | Medium | Consistent | Direct | Precise | Small effect Moderate SOE |
| CHIVA vs. compression alone | 1 RCT (47) | Low | NA | Direct | Imprecise | Small effect Low SOE |
| Ligation vs. compression alone | 1 RCT (47) | Medium | NA | Direct | Imprecise | Small effect Low SOE |
| SEPS vs. compression alone | 2 RCTs (146) | Low | Consistent | Direct | Precise | Small effect High SOE |
| Sclerotherapy vs. compression alone | 1 RCT (40) 1 cohort (70) | High | Inconsistent | Direct | Imprecise | Unclear effect Insufficient SOE |
| RFA vs. compression alone | 0 | NA | NA | NA | NA | Unclear effect Insufficient SOE |
| EVLT vs. compression alone | 0 | NA | NA | NA | NA | Unclear effect Insufficient SOE |
| Surgical techniques to treat deep vein reflux vs. compression alone | 0 | NA | NA | NA | NA | Unclear effect Insufficient SOE |
| Surgical techniques to treat deep vein obstruction vs. compression alone | 0 | NA | NA | NA | NA | 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

* 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 Key Question 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. For a few comparisons, we found low strength of evidence about the comparative effectiveness of different surgical procedures, but none of the studies provided precise estimates. We graded the evidence as insufficient or low 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).[71-73] Two studies were cohort studies.[72, 73] The first[72] was conducted 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[73] was conducted 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 with an anti-reflux valvular procedure on the deep veins among 793 patients. The last study[71] was conducted in the U.S., 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.[13, 74-83]

Five of these studies were case series.[13, 74, 78-80] Five were cohort studies,[75, 76, 81-83] and one had an unclear study design.[77]

Three of these studies were conducted in the U.S.,[13, 76, 78] two were conducted in the United Kingdom,[74, 75] two were conducted in Germany,[82, 83] two in Australia,[77, 81] one in Poland,[79] and one in the Slovak Republic.[80] The years of enrollment ranged from 1968 to 2010. The length of

followup ranged from 1 year 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),[76, 77, 80] two evaluated RFA,[13, 78] two evaluated SEPS,[82, 83] two studies[75, 79] evaluated saphenous vein stripping and/or ligation, one study evaluated sclerotherapy,[74] and one evaluated angioplasty/stenting.[81]

## Study Population Characteristics

None of the three studies with a comparison group[71-73] reported baseline and demographic characteristics by study group (Appendix D, Table 3). The mean age of the patients among the two studies that reported age was 42 years[72] and 59 years.[73] Seventy-eight percent of the participants were women. Two studies[72, 73] 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[13, 75, 78-83] 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.[13, 74, 75, 78-83]

The average duration of the ulcer at baseline was reported in all 11 studies. Three studies[74, 75, 80] reported a median duration of 5 to 8 months (range, 3 to 1680 months), while eight studies[13, 76-79, 81-83] reported a mean duration of 8 to 100 months (range, 2 to 432 months). One study[77] 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.[79] In three studies, the percent of patients with diabetes ranged from 18 to 21 percent.[13, 78, 83] In one study, two percent of the patients were taking immunosuppressives. None of the studies reported on the use of corticosteroids.[13]

## 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 non-randomized 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.[71] Wound healing rates were reported 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 time to complete wound healing was not reported. Patients were followed 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.[72] 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; $P < 0.05$).

### Classical Linton and Stripping Versus Limited Linton and Stripping Versus Sclerotherapy Versus Valvular Surgery

We included one non-randomized retrospective cohort study in which subjects were enrolled from a single author's clinical experience (Table 32).[73] The study evaluated four groups. Group I was treated with a classical Linton procedure, vein stripping, and varicose vein extirpation. Group II was treated with Linton SPS (small incision using a hook instrument), stripping, and varicose vein extirpation. Group III was treated with compression sclerotherapy (Sigg's and Fegan's techniques). Group IV was treated with an anti-reflux operation on the deep venous system including valvuloplasty and valve interposition. Group III with sclerotherapy had the shortest time to healing with 95 percent of venous ulcers healed. The time to heal was significantly longer when femoral and popliteal vein insufficiency was documented. In the group of patients with the shortest time to heal (up to 8 weeks), popliteal vein involvement was documented in 55 percent of patients. However, the group that required more than 12 weeks to heal had 94 percent popliteal vein involvement.

**Table 32. 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 |
|---|---|---|---|---|---|
| I – Linton procedure, vein stripping, varicose vein extirpation | 39 | 21 | 84±8 | 31% | NS |
| II – Linton SPS, stripping, and varicose vein extirpation | 57 | 13 | 56±6 | 29% | |
| III – Compression sclerotherapy | 698 | 0 | 39±12 | 18% | |
| IV – Anti-reflux operation on deep venous system | 32 | 7 | 12-120 | Not reported | |

LOS = hospital length of stay; NS = not significant

## Mortality

Mortality rates were not reported in any of the above three trials included under this section.

## 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 33).[72]

**Table 33. 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 |

### Classical Linton and Stripping Versus Limited Linton and Stripping Versus Sclerotherapy Versus Valvular Surgery

One cohort study reported a statistically significant reduction in complication rates (not further specified) among patients who received compression sclerotherapy compared with those who received the Linton procedure (Table 34).[73]

**Table 34. Summary of the complication rate in patients with chronic venous leg ulcers treated with the Linton procedure and vein stripping, a limited Linton procedure and vein stripping, sclerotherapy, or valvular surgery reported in one cohort study**

| Group | Number of patients | Complication rate | P-value |
|---|---|---|---|
| I – Linton procedure, vein stripping, varicose vein extirpation | 39 | 29% | 0.05 |
| II – Linton SPS, stripping, and varicose vein extirpation | 57 | 24% | |
| III – Compression sclerotherapy | 698 | 7% | |
| IV – Anti-reflux operation on deep venous system | 32 | 6% | |

### Quality of Life and Pain

Quality of life outcomes and pain measures were not reported in any of the studies we reviewed.

### 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.[13, 74-83]

### 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.[76] 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 were treated with perforator ligation and/or saphenous vein stripping/ligation before, during, or after the primary procedure. 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 percent versus 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.[77] The surgical procedures performed were related to their 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).[80] 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 complete 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.[78] One hundred forty consecutive endovenous ablation procedures were performed (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 four patients were lost 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 one year.

Lawrence el al. evaluated patients who had chronic venous leg ulcers for longer than 3 months despite compression treatment.[13] All patients underwent venous duplex ultrasound to assess incompetence of superficial, perforating, and deep veins. Perforator vein ablation was performed on patients with demonstrated perforator incompetence (greater than 3 mm). All of these patients either had functional saphenous veins or had their saphenous vein already ablated. 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, 1.5 incompetent perforator veins were ablated for ulcer healing.

### Subcutaneous Paratibial Fasciotomy and SEPS

Sigala et al. described a single center experience with paratibial fasciotomy and dissection of the posterior perforator veins (Hach procedure) for the treatment of patients with chronic venous leg ulcers.[82] 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. Vacuum-assisted therapy was used in 28 ulcers for a median time of 8 days. Autologous skin grafting was performed 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.[83]

## 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.[74] Eighty three of the patients had active ulcers. Patients were followed 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.

### Superficial Vein Surgery

Bello et al. was a prospective study that aimed to determine the ability of superficial venous surgery to heal venous leg ulcers.[75] Patients with isolated superficial venous incompetence were offered saphenofemoral and/or saphenopopliteal surgery. None of the patients underwent perforator surgery or skin grafting. Postoperative compression hosiery or bandaging was not used. The investigators performed superficial venous surgery on 122 legs with normal deep veins. Cumulative healing rates at 6, 12, and 18 months were 57 percent, 74 percent, and 82 percent. 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. These groups were then randomly assigned 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 Key Questions, 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 of ulcer recurrence rates in other groups, 25.9 to 37.5 percent).

### 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.[81] 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 implanted was associated with an increased number of ulcers healing.

### Mortality, Quality of Life, Functional Status

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 randomized, and only three had a comparison group.[71-73] Among the three studies with a comparison group, it was often difficult to determine the comparability of the different intervention groups because baseline and demographic characteristics were often not reported separately by group. Adjusting for confounding was not described. One study recruited patients from different time periods.[73] 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-randomized studies, often from a single institution. The studies had populations that were diverse and incompletely described. Surgical interventions in some of the studies were patient-specific, which minimized generalizability. None of these studies included a non-surgical 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. For a few comparisons, we found low strength of evidence about the comparative effectiveness of different surgical procedures, but none of these provided precise estimates (see Table 35).

**Table 35. 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 | Low |
| Isolated sapheno-femoral junction ligation vs. vein stripping | 1 (36) | High | NA | Direct | Imprecise | Low |
| Classical Linton and stripping versus limited Linton and stripping versus sclerotherapy versus valvular surgery | 1 (826) | High | NA | Direct | Imprecise | Low |
| Valvuloplasty, valve transposition, valve transplantation | 3 (195) | High | Consistent | Indirect | Imprecise | Insufficient |
| RFA | 2 (unable to determine) | High | Consistent | Indirect | Imprecise | Insufficient |
| Subcutaneous paratibial fasciotomy and SEPS | 2 (136) | High | Consistent | Indirect | Imprecise | Insufficient |
| Sclerotherapy | 1 (82) | High | NA | Indirect | Imprecise | Insufficient |
| Superficial vein surgery | 2 (153) | High | Unable to determine | Indirect | Imprecise | Insufficient |
| External valvular stenting | 1 (41) | High | NA | Indirect | Imprecise | Insufficient |

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

### KQ 1: Benefits and harms of advanced wound dressings

There were minimal data to suggest that hydrocolloid and foam provided advantages in healing rates and in ultimate wound healing. There were many studies which had negative results. Dressings which contained cadexomer iodine provided advantage in improved healing, but there were no data to support the use of silver containing dressings. The strength of the evidence for these recommendations is low.

For acellular skin equivalents, the there was low strength of evidence to support the use of freeze dried intestinal pig mucosa. For cellular equivalents, benefit was limited to patients with long-standing ulcers, and there was no effect on post-treatment recurrence, indicating the importance of treating the underlying disease and the necessity of continuing post-treatment compression.

### KQ 2a: Benefits and harms of systemic antibiotics compared with compression systems

We did not find any studies that addressed this question.

### KQ 2b: Benefits and harms of systemic antibiotics compared with advanced wound dressings

We found only one study that addressed this question, and it provided insufficient evidence to determine how the benefits and harms of systemic antibiotics compared with advanced wound dressings.

### KQ 3a: Benefits and harms of surgical interventions compared with compression

Among the few studies on this question, we found low strength of evidence that minimally invasive surgical hemodynamic correction of reflux or sclerotherapy may increase the rate of healing of chronic venous leg ulcers compared with compression therapy alone. For other surgical interventions used for chronic venous leg ulcers, the strength of evidence was low or moderate that healing may not be improved when compared with compression alone. We found insufficient evidence about the benefits and harms of vein stripping, radiofrequency ablation (RFA), or endovenous laser therapy (EVLT) for superficial vein reflux or surgery for deep vein disease in patients with chronic venous leg ulcers.

### KQ 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 with respect to the population screened or enrolled. 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 reported, the mean duration of chronic venous ulcers at baseline 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. 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.

### 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.

## 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 better studies are needed to demonstrate their clinical impact, or lack of efficacy.

These findings therefore have impact on policy, especially for agencies and payors that are interested in providing reimbursement and identifying critical research needs. Since the prevalence of chronic venous stasis disease is increasing,[84] and is expected to do so for the foreseeable future, health care payors, regulatory agencies, and other policy makers should be interested in evidence that can provide better guidance on how to improve the outcomes of care for patients with chronic venous leg ulcers. We need high quality data to understand which therapeutic interventions have value to insure their reimbursement in an increasingly constrained health care environment and develop efficient algorithms to evaluate new therapies.

# Research Gaps

## Need for Harmonization

Our review demonstrated that studies of interventions for chronic venous leg ulcers are conducted by a variety of disciplines and in different practice and cultural settings, including nursing, dermatology, vascular surgery, and internal medicine as well as in different countries. This heterogeneity is associated with excessive variety in the methods that have been used in studies. To adequately address this problem, investigators in this field need to develop a consensus about a standard definition for the disease entity and establish better standards for how to define interventions, comparison groups, and outcome measures.

Consensus about how to harmonize studies in this area should be established among stakeholders from the academic and clinical communities, clinical researchers, government regulators, payors, and industry. The objective would be to develop clear and reproducible case definitions, and define appropriate clinical outcome measures, including intermediate outcomes, pain, and quality of life. The conference could also help to develop templates for study designs to demonstrate efficacy, which would include appropriate definition of outcomes. The Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds from the Center for Medical Technology Policy supports many of our conclusions, but it is not focused on chronic venous ulcers and does not cover surgical interventions.[6]

One of the major issues to be addressed is the limitation in study design — because of the nature of the interventions, and the difficulty in many cases of developing placebo or sham conditions, implementing traditional double blinded, or even single blinded randomized trials is 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 the three Key Questions to guide this review. We found the clinical evidence was marked by 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 cellular skin equivalents under very defined conditions. Evaluating systemic and local antimicrobial therapy was hampered by the general lack of data, and we found no evidence to support antimicrobial therapy for chronic venous leg ulcers in the absence of symptoms or signs of infection. 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 that have been used to manage this disease. However, more recent data suggest that surgical interventions may impact recurrence rates, and therefore there is a need to validate these findings.

We identified critical research needs largely focused on developing the needed evidence base to make therapy recommendations and to evaluate the efficacy and effectiveness of current and newly developed products and interventions. These include a standardized 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
FDA = U.S. Food and Drug Administration
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
U.S. = United States