Executive Summary – Jan. 27, 2014 (Update)

Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities

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Erratum: In the PDF of this report, Table A incorrectly lists “Cryopreserved human skin allograft (TheraSkin®)” as an acellular biological dressing. TheraSkin should be listed as a cellular biological dressing. It is correctly listed in the Tables section on this Web page.

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Background

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

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. Clinicians must consider other therapies for the large number of patients for whom compression therapy and debridement fail, but no consensus exists about which second-line treatments work best. These additional therapies commonly include wound dressings with active components (defined here as advanced wound dressings), local or systemic antimicrobials, and venous surgery.
Advanced Wound Dressings

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

Antibiotics

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

Surgical Interventions

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

Scope and Key Questions

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

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

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

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

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

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

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

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

![Analytic framework for the treatment of chronic venous leg ulcers](image)

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

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

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

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

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

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

The reviewers extracted information on general study characteristics (e.g., study design, study period, followup), study participants (e.g., age, sex, duration of ulcer, smoking status, diabetes status, other systemic diseases, concomitant use of immunosuppressives or steroids, other treatment), interventions (e.g., usual care/placebo, compression types [two–layer, short stretch, long stretch, multilayer, Unna boot], debridement types, advanced wound dressings, antimicrobials, surgical interventions, duration of treatment), comparisons, and outcome measures (e.g., definitions, results, measures of variability). We collected data on subgroups of interest (e.g., age, presence of comorbid conditions [diabetes, obesity], setting).

Quality Assessment
Two reviewers used the Downs and Black quality assessment tool to independently assess the quality of all
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). Our quality assessment tool included items on study reporting, internal validity, statistical power, and conflicts of interest.

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

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

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

Results

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

Figure B. Summary of literature search (number of articles)
Key Question 1. Benefits and Harms of Advanced Wound Dressings: Impact on Wound Healing, Pain, and Quality of Life

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

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

One RCT (N=120) compared a collagen dressing plus compression with compression alone in terms of the proportion of ulcers healed. After 12 weeks, a significantly higher proportion of ulcers were healed with the collagen dressing than with compression alone (SOE: Low). However, collagen dressings did not significantly affect
We were unable to draw a conclusion about the effectiveness of antimicrobial dressings compared with compression alone or with other antimicrobial dressings (SOE: Insufficient). Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with other types of dressings (SOE: Moderate). Three RCTs found significantly faster wound healing rates with antimicrobial dressings compared with other dressings.\(^\text{11, 24, 43}\) However, silver dressings did not improve wound healing as compared with nonsilver dressings. One RCT comparing silver dressings with nonsilver dressings did not show any improvement in terms of the wound healing rate.\(^7\)

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

Four studies (five publications) evaluated biological or cellular dressings.\(^\text{13, 21, 25, 34, 38}\) We graded the strength of the evidence separately for cryo–preserved human fibroblast derived dermal substitutes, allogenic bilayered human skin equivalents, and autologous keratinocytes in a fibrin sealant. Studies of a biodegradable mesh containing fibroblasts (Dermagraft\(^\text{®}\)) were limited in their sample size, limiting our ability to draw conclusions (SOE: Insufficient). One of the studies demonstrated a statistically significant improvement in ulcer healing as measured by total ulcer area, but another study with limited power showed no difference. One study, evaluating allogenic bilayered human skin equivalents, showed improvement in wound healing, especially in patients with ulcers lasting more than 1 month that had previously failed conservative treatment with ACE\(^\text{™}\) bandages and compression (SOE: Moderate). However, recurrence rates were not different between intervention and control groups. The fourth study reported a greater proportion of ulcers healed with the addition of autologous living keratinocytes than with compression alone (SOE: Low).

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

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

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

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

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

We did not find any studies addressing this KQ.

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

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

Surgical Procedures Targeting Superficial Vein Reflux

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

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. The surgical interventions in these studies included minimally invasive ligation of insufficient saphenous vein tributaries (conservative hemodynamic treatment of insufficiency of the venous system in an ambulatory setting [CHIVA]) (SOE: Low), subfascial endoscopic perforator surgery (SEPS) (SOE: High), and sclerotherapy (SOE: Insufficient). The study of CHIVA reported a faster time-to-healing with surgery than with compression alone (median of 31 vs. 63 days).

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

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

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. The other study found that SEPS did not perform better than compression alone when researchers measured quality of life with the Charing Cross Venous Ulcer Questionnaire.

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.

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

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

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

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

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

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

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

### Discussion

#### Key Findings and Strength of Evidence

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

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

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

**Key Question 1. Benefits and Harms of Advanced Wound Dressings**

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

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

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

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

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

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

We did not find any studies that addressed this question.

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

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

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

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

**Applicability**

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

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

**Key Question 1. Benefits and Harms of Advanced Wound Dressings**

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

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

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

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

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

**Limitations**

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

**Implications for Clinical Practice and Policy**

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

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

**Research Gaps**

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

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

**Need for Harmonization**

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

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

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

**Conclusions**

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

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

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

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

References


### Tables

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

<table>
<thead>
<tr>
<th>Functional Category</th>
<th>Classification</th>
<th>Characteristics</th>
<th>HCPS Classification</th>
</tr>
</thead>
</table>
| Dressings to enhance moisture retention | Hydrocolloids   | - Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet  
- Polymers form a gel on contact with wound exudate: allows for wound hydration and autolytic debridement | Hydrocolloid dressing, wound cover, sterile                                           |
| Transparent films                       | Hydrocolloids   | - Transparent sheets of polyurethane coated with an adhesive  
- Act as a “blister roof” to provide a moist wound-healing environment, promotes autolysis, and protects the wound and periwound tissues from external trauma | Transparent film, sterile                                                            |
| Exudate management                       | Alginates       | - Derived from seaweed and spun into a rope or sheet dressing  
- Fibrous and highly absorbent and can become gel-like when coming into contact with exudate to maintain a moist wound-healing environment | Alginates or other fiber gelling dressing, wound cover  
- Alginates or other fiber gelling dressing, wound filler                             |
| Foams                                   | Foams           | - Sterile, nonlinting, absorptive dressing made of open-cell, medical-grade expanded polymer  
- It is nonadherent                                                                  | Foam dressing, wound cover, sterile (with/without adhesive border)  
- Foam dressing,                                                                      |
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composites</td>
<td>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 semiahesive or nonadhesive property; and (4) adhesive border</td>
<td>Composite dressing, sterile with adhesive border</td>
</tr>
<tr>
<td>Special absorptive dressings</td>
<td>Unitized, multilayer dressings that provide either a semiadhesive quality or nonadhesive layer and highly absorptive layers of fibers such as absorbent cellulose, cotton, or rayon</td>
<td>Special absorptive dressing, wound cover, sterile with/without adhesive border</td>
</tr>
<tr>
<td>Wound bed protection</td>
<td>Contact layer Thin, nonadherent sheets placed directly on an open wound bed to protect the tissue from direct contact with other agents or dressings</td>
<td>Contact layer, sterile</td>
</tr>
<tr>
<td>Dressings to enhance hydration</td>
<td>Hydrogels ● A polymer gel composed mostly of water in a complex network of fibers ● Water is released to keep the wound moist ● Can be hydrophilic</td>
<td>Hydrogel dressing, wound cover, sterile with/without adhesive border ● Hydrogel dressing, wound filler</td>
</tr>
<tr>
<td>Collagen dressings</td>
<td>Sheets, wound filler gels or powder ● Freeze-dried bovine, porcine, or equine collagen ● Can contain cellulose or alginate for absorption ● Porcine small intestine submucosa extracellular matrix (Oasis®)</td>
<td>Collagen-based wound filler, dry form ● Collagen-based wound filler, gel/paste ● Collagen dressing, sterile, pad</td>
</tr>
<tr>
<td>Biological dressings</td>
<td>Acellular ● Extracellular matrixes that support new tissue growth ● Three-dimensional porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan (Integra™)</td>
<td>Skin substitute</td>
</tr>
<tr>
<td></td>
<td>Cellular ● Bioengineered, bilayered, living cell–based skin substitute (Apligraf®) ● Cryopreserved human skin</td>
<td>Skin substitute</td>
</tr>
</tbody>
</table>
Allograft (TheraSkin®)
- Cryopreserved human fibroblast-derived dermal substitute (Dermagraft®)

Antimicrobial effect
- See individual dressing characteristics
- Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, manuka honey, gentian violet, polyvinyl alcohol with methylene blue, cadexomer iodine, and chlorhexidine

HCPCS classifications as listed above

Gauzes
- Impregnated gauzes, made of woven and nonwoven fibers of cotton, polyester, or a combination in which substances have been added such as: iodinated agents, petrolatum, zinc compounds, crystalline sodium chloride, chlorhexidine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents
- Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad
- Gauze, impregnated, water or normal saline, sterile, pad
- Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad

Enhance further debridement
- Biologic enzymatic debriding agent (collagenase Santyl®)
- Derived from fermentation by Clostridium histolyticum
- Sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP and that is able to digest collagen in necrotic tissue

Table B. Antibiotic treatments for chronic venous ulcers

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
<th>Drug Names</th>
<th>Benefits</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antimicrobials (used primarily for Gram-positive activity)</td>
<td>Susceptible Staph (MSSA) and streptococci</td>
<td>cephalosporins (e.g., cephalaxin); amoxicillin/clavulanate; dicloxacillin</td>
<td>Inexpensive</td>
<td>Usually require multiple doses/day; major adverse events include rash,</td>
</tr>
<tr>
<td>MRSA</td>
<td>clindamycin</td>
<td>Also can treat anaerobes; allergy is rare; good bone and tissue penetration</td>
<td>Effective against only 50% of MRSA; requires multiple daily dosing; GI intolerance</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trimethoprim/sulfamethoxazole</td>
<td>Inexpensive; good bone and tissue penetration</td>
<td>Interacts with warfarin; not effective against streptococci; high rate of allergy for sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>Effective against enterococci and streptococci; high bioavailability</td>
<td>Multiple contraindications (e.g., patients taking an SSRI); expensive; high rate of symptomatic side effects; thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral drugs used for Gram-negative activity</th>
<th>Gram-negative organisms</th>
<th>quinolones (ciprofloxacin, levofloxacin, moxifloxacin)</th>
<th>Effective against most community acquired GNRs and <em>Pseudomonas</em>; rarely anaphylactoid reaction; can dose once daily; high bioavailability</th>
<th>GI intolerance; increased risk for <em>C. diff</em>; prolonged exposure can result in resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta lactams</td>
<td>(amoxicillin/clavulanate, cefixime, cefpodoxime)</td>
<td>Usually effective first round for community-acquired organisms</td>
<td>Requires multiple dosing</td>
</tr>
</tbody>
</table>

| Intravenous antibiotic regimens          | Gram-positive sensitive Staph (MSSA) | cefazolin, ampicillin/sulbactam | Requires multiple dosing; requires prolonged IV access (usually PICC line); requires weekly monitoring |
**Table C. Surgical treatments for chronic venous ulcers**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>ceftriaxone</td>
<td>Can be dosed once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires prolonged IV access (usually PICC line); requires weekly monitoring</td>
</tr>
<tr>
<td>Gram–positive organisms (MRSA)</td>
<td>vancomycin</td>
<td>Inexpensive; effective against MRSA; can be dosed post–dialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires weekly monitoring for drug toxicity; requires frequent adjustment of dosing</td>
</tr>
<tr>
<td></td>
<td>daptomycin</td>
<td>Used when intolerant to vancomycin; dosed once daily; can be dosed post–dialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive; toxicity is myositis; requires weekly CK monitoring</td>
</tr>
<tr>
<td>Gram–negative organisms (β–lactams)</td>
<td>ertapenem</td>
<td>Can be dosed once daily; broad spectrum for enteric gram–negative bacteria and anaerobes; requires minimal monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not effective for Pseudomonas or many MDR organisms</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>piperacillin/tazobactam, cefipime</td>
<td>Minimal toxicity profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires multiple daily doses</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>gentamicin, tobramycin, amikacin</td>
<td>Can be dosed once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major renal toxicity; requires close monitoring of dose, drug levels, renal function</td>
</tr>
</tbody>
</table>

*C. diff* = *Clostridium difficile*; CK = creatine kinase; GI = gastrointestinal; GNR = Gram–negative rods; IV = intravenous; MDR = multidrug resistant; MRSA = methicillin–resistant *Staphylococcus aureus*; MSSA = methicillin–sensitive *Staphylococcus aureus*; PICC = peripherally inserted central catheter; Staph = *Staphylococcus*; SSRI = selective serotonin reuptake inhibitor
<table>
<thead>
<tr>
<th>Venous System</th>
<th>Ligation</th>
<th>Stripping</th>
<th>Stab/micro phlebectomy</th>
<th>Ablation</th>
<th>Perforator venous system</th>
<th>Deep venous system</th>
<th>Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sapheno-femoral junction/high saphenous ligation involves the ligation and division of the great saphenous vein at the junction with femoral vein</td>
<td>Sapheno-femoral junction/high saphenous ligation involves the ligation and division of the great saphenous vein at the junction with femoral vein</td>
<td>Saphenous vein stripping involves the ligation and division of the sapheno-femoral junction at the point of union, followed by stripping a segment of the great saphenous vein to just below the knee using an invagination or inversion catheter</td>
<td>Thermal ablation involves the closing of the great or small saphenous veins using high temperature generated by laser light (endovenous laser treatment) or radiofrequency energy (radiofrequency ablation)</td>
<td>Perforator vein is directly ligated using ultrasound guidance</td>
<td>This involves bypassing the obstructive segment of deep vein using autogenous vein or polytetrafluoroethylene synthetic graft</td>
<td>Valve replacement (transposition or transplant) involves the replacement of the affected deep venous valve with an autogenous vein valve from the upper extremity</td>
</tr>
<tr>
<td></td>
<td>Sapheno-popliteal junction ligation involves the ligation and division of small saphenous vein at its junction with popliteal vein</td>
<td>Ligation and division of the small saphenous vein at its junction with the popliteal vein</td>
<td>Stab phlebectomy or micro phlebectomy of tributaries to great or lesser saphenous vein</td>
<td>Chemical ablation (sclerotherapy) involves injecting an irritant agent (such as sodium tetradecyl sulfate mixed with air or carbon dioxide) into the vein, which results in endothelial damage. Foam preparations increase the potency of sclerosing drug by increasing its surface area</td>
<td>Although rarely performed, this minimally invasive surgical procedure involves use of an endoscope through the unaffected area of skin and fascia. An elastic wrap is used to empty the leg veins of blood then a tourniquet is placed at the thigh. Clinicians insufflate the subfascial space with carbon dioxide. This creates a space for the endoscope to identify and ligate the Cockett’s perforating veins in the lower calf.</td>
<td>This involves balloon angioplasty with or without stenting of the stenotic area of the deep vein</td>
<td>Valve replacement involves repairing or reconstructing valves in the deep venous system of the lower limb</td>
</tr>
<tr>
<td></td>
<td>Ligation of tributaries</td>
<td></td>
<td></td>
<td>Thermal ablation of perforator veins (radiofrequency ablation)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table D. Summary of the comparative benefits of advanced wound dressings in terms of wound healing.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Strength of Evidence</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolloids vs. compression (3)</td>
<td>Low</td>
<td>Hydrocolloid dressings were not more effective than compression therapy alone in terms of the proportion of chronic venous ulcers healed. The results from the three studies addressing this comparison were imprecise and subject to some bias.</td>
</tr>
<tr>
<td>Hydrocolloids vs. other dressings (4)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Transparent films vs. compression (1)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Transparent films vs. other dressings (1)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Alginate dressings vs. compression (1)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Alginate dressings vs. alginate dressings (2)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Alginate dressings vs. other dressings (1)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Foam dressings vs. foam dressings (3)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Collagen dressings vs. compression (1)</td>
<td>Low</td>
<td>Collagen dressings healed a greater proportion of ulcers than compression alone.</td>
</tr>
<tr>
<td>Acellular human skin equivalent dressings vs. compression (3)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression (2)</td>
<td>Insufficient</td>
<td>We are unable to draw a conclusion.</td>
</tr>
<tr>
<td>Cellular human skin equivalents (allogenic bilayered cultured HSE) vs. compression (1)</td>
<td>Moderate</td>
<td>Studies of cellular human skin equivalent dressings in patients with chronic venous ulcers showed a higher proportion of ulcers healed and more rapid healing, especially those that had failed previous therapy and were present for over 1 year.</td>
</tr>
<tr>
<td>Cellular (autologous keratinocytes in a fibrin sealant) vs. compression (1)</td>
<td>Low</td>
<td>Autologous keratinocytes in fibrin sealant healed a greater proportion of ulcers and achieved a shorter median time to complete wound closure versus compression.</td>
</tr>
<tr>
<td>Cellular human skin equivalent dressings vs. other dressings (2)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Antimicrobial dressings vs. compression (2)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Antimicrobial dressings vs. antimicrobial dressings (2)</td>
<td>Insufficient</td>
<td>We were unable to draw a conclusion.</td>
</tr>
<tr>
<td>Antimicrobial containing dressings vs. other types of</td>
<td>Moderate</td>
<td>Some antimicrobial dressings improved wound area reduction by 20 percent or more as compared with</td>
</tr>
</tbody>
</table>
The strength of evidence for all comparisons not listed here were graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

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

---

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

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

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

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

PLSVS = perforator ligation and saphenous vein stripping

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

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