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Review

Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds

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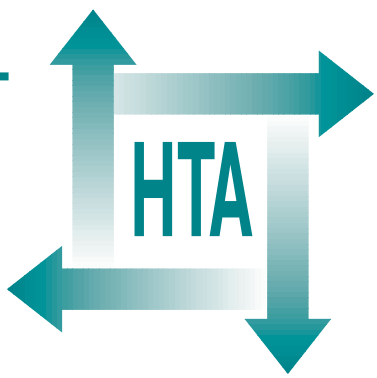
Health Technology Assessment
NHS R&D HTA Programme



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Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 93/29/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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Contents

List of abbreviations

ABPI	ankle brachial pressure index*
b-FGF	basic fibroblast growth factor
C	comparator*
CI	confidence interval
CRD	Centre for Reviews and Dissemination
df	degree of freedom
DMSO	dimethyl sulfoxide
ES	effect size
I	intervention*
ITT	intention-to-treat
M/F	male/female*
OR	odds ratio
PMN	polymorphonuclear
RCT	randomised controlled trial
r-PDGH-BB	recombinant platelet-derived growth factor
SD	standard deviation
SEM	standard error of the mean

* Used only in tables and figures

Executive summary

Background

Wound dressings are designed to keep the wound clean and free from contamination and also to promote wound healing, particularly in chronic wounds where there may be significant tissue loss.

Objectives

This review evaluates the evidence for effectiveness and cost-effectiveness of dressings and topical preparations in pressure sores, leg ulcers and surgical wounds healing by secondary intention.

Methods

Nineteen electronic databases, including MEDLINE, EMBASE, CINAHL and the Cochrane Wounds Group's specialised trials register and wound care journals were searched until October 1997. Organisations, manufacturers, researchers and healthcare professionals concerned with wound care were contacted for additional trials. The reference sections of obtained studies were also searched for further trials.

Inclusion criteria

Randomised controlled trials (RCTs), published or unpublished, which assessed the effectiveness of a dressing or topical agent in the treatment of pressure sores, leg ulcers, sinuses and surgical wounds healing by secondary intention were included in the review. Where a particular dressing was not evaluated by an RCT, prospective controlled trials were included. Studies were only included if they reported either the proportion of wounds healed within a time period or the percentage or absolute change in wound area.

Data extraction and synthesis

Trial data were extracted by one researcher and checked by a second. The results from each study were calculated as odds ratios and/or effect sizes and where appropriate, similar studies have been pooled in a meta-analysis.

Results

Surgical wounds healing by secondary intention

Only five studies met the inclusion criteria. All the studies were of poor quality and had small sample size. One study found a statistical benefit for wet-to-dry dressings compared with topical applications of aloe vera. However, neither of these products is commonly used in the UK.

Pressure sores

Twenty-eight trials evaluated 31 comparisons of treatments for the healing of pressure sores. The majority of trials were of poor quality. A single report suggested that the topical application of insulin was of significant benefit for wound healing when compared with standard nursing care. A meta-analysis of five reports comparing a hydrocolloid dressing with a traditional treatment suggested that treatment with the hydrocolloid resulted in a statistically significant improvement in the rate of pressure sore healing.

Leg ulcers

Sixty studies were included that had evaluated dressings or topical agents in arterial and venous ulcers. Both mononuclear cultured cells in culture medium and topical ketanserin significantly increased healing rates compared with a control preparation in one trial of arterial leg ulcers. Collagen sponges appeared to be effective in two trials of leg ulcers but there were insufficient data to determine the significance of these results.

Nine trials compared hydrocolloids with traditional dressings for venous ulcers but meta-analysis demonstrated no significant difference in the proportion of ulcers healed over the trial period. Two trials compared semi-permeable films with traditional dressings; one found a larger reduction in wound area under the film dressing but the other found no significant difference in healing rates. Two trials compared foam dressings and traditional or control therapies; one favoured the foam dressing but the other found no difference between treatments. Woven zinc oxide paste bandage was more effective

than either an alginate dressing or a zinc oxide-impregnated stockinette in one trial.

In two trials comparing different hydrocolloids, no significant difference in healing rates was found. Comparisons of hydrocolloids with foam dressings found no difference in effectiveness.

In trials of topical agents, allopurinol and dimethyl sulfoxide improved healing in one trial compared with inert powder. Of two trials comparing hyaluronic acid with control, one found a difference in daily healing rate and the other found no difference in proportion of ulcers healed over the trial period.

Four trials compared biological dressings with traditional therapies. None found statistically significant differences in results.

Two trials compared dressings with topical preparations. There was no difference in the proportion of ulcers healed between patients treated with cryopreserved cultured allografts or a hydrocolloid, though the former-treated ulcers had a higher rate of epithelialisation. A collagen dressing was more effective than treatment with daily antiseptic.

A comparison of buffered acidifying ointment and ointment reported there was no difference in the proportion of ulcers healed, but there was a higher rate of epithelialisation with the buffered ointment group. In another, trial there were higher healing rates when two amino acid solutions were compared with two groups treated in saline soaks.

Publication bias

A funnel plot of all trials showed no evidence of publication bias. However, publication bias was indicated in a comparison of traditional and hydrocolloid dressings.

Cost-effectiveness analysis

Nine trials provided data on costs of dressing materials and nursing visits. Six evaluated cost-effectiveness in pressure sore treatments and three papers reported cost-effectiveness data in leg ulcer trials.

Conclusions

Implication for practice

There is little evidence to indicate which dressings or topical agents are the most effective in the treatment of chronic wounds. However, there is evidence that hydrocolloid dressings are better than wet-to-dry dressings for the treatment of pressure sores. In the treatment of venous ulcers, low adherent dressings are as effective as hydrocolloid dressings beneath compression bandaging.

Recommendations for research

Research methodology could be significantly improved and commissioning groups may wish to consider the following aspects for future research.

- The number of patients in a trial should be based on an *a priori* sample size calculation.
- A truly objective outcome measure should be used or wound healing should be expressed as both percentage and absolute change in area.
- For each patient a single reference wound should be selected.
- Experimental groups should be comparable at baseline.
- Head-to-head comparisons of contemporary dressings are required and should use agents that are recommended for wounds of a similar nature.
- A complete and thorough description of concurrent treatments, including secondary dressings, should be given in trial reports.
- Assessment of outcomes should ideally be blind to treatment, or completely objective.
- Survival rate analysis should be adopted for all studies that assess wound healing.
- Studies to determine the biological mechanisms involved in wound healing are needed.
- Future trials should include cost-effectiveness and quality of life assessments, as well as objective measures of dressing performance.
- Economic evaluations should be incorporated within trials that are sufficiently large to detect appropriate economic and clinical outcomes.
- To prevent publication bias and ensure the inclusion of unpublished trials in systematic reviews, those involved in primary research should make their data available to those undertaking systematic reviews.

Chapter 1

Introduction

This review is the second in a series of systematic reviews of wound care management. The research was commissioned by the NHS R&D Health Technology Assessment (HTA) Programme under the project number 93/29/01. To expediate dissemination, some reports will be published as separate HTA monographs. The complete series will include the following topics.

- *The debridement of chronic wounds (*Health Technol Assess *1999;***3***(17 Pt 1)).*
- *Dressings and topical agents used in the healing of chronic wounds (*Health Technol Assess *1999;* ***3****(17 Pt 2)).*
- *Pressure relief (in preparation).*
- *Compression for venous leg ulcers (in preparation).*
- *Diabetic foot ulcers (in preparation).*
- *Antimicrobial agents (in preparation).*
- *Physical therapies (in preparation).*

The Editors

The earliest documentation concerning wound management is found in the Papyrus Ebers, which dates from around BC 1500. This document indicates that crude treatments based on oiled frog skins, honey, lint and animal grease were commonly used by the Egyptians as wound coverings. An early Hindu document, the Susrutu Sanhita reported skin grafts being used as early as BC 700.[1] Jeter and Tintle[2] report that spiders webs, new-born puppies boiled in oil of white lilies, and red-hot pokers to cauterise wounds have been used at various times throughout history. George[3] states that the Sumerians were the first to fashion occlusive dressings, which are capable of maintaining a moist environment, using clay.

In the 19th century, Pasteur advocated that wounds should be covered and kept dry because he believed this would keep them 'germ' free. The dressings developed at this time, made from cloth, cotton and gauze, have dominated wound management in recent history and in some countries they continue to be the main products used.[3]

The first manufactured dressings were probably Gamgee wadding and tulle gras. Gamgee[4] discovered that degreased cotton wrapped in bleached lint would absorb fluids, and he introduced his first dressing in the 19th century. During the 1914–18 war, Lumiere in France developed a cotton gauze that was impregnated with paraffin to prevent the dressing sticking to the wound. Wound management technology did not progress significantly beyond these early developments until the 1960s, when comparisons were made of wound healing in dry and moist environments.[5,6] Although initial attempts were made to only alter the moisture at the surface of a wound, researchers are now investigating the whole wound healing process in order to establish what factors impede wound healing and what characteristics of the environment could be manipulated to accelerate healing. A description of the process of wound healing will provide the rationale for the majority of the wound products evaluated within this review.

The physiology of wound healing

When the skin is wounded, a complex series of cellular and chemical events are initiated which act on the damaged tissues – blood vessels, dermis, and epidermis.

Wounds that result in limited tissue loss, such as surgical wounds, have a tendency to heal rapidly on the surface as opposing edges of the wound are in close proximity for cellular and structural repair. The wound is healed in about a week, but will continue to mature for a year or more. During this time the structural architecture of the wound changes, the scar usually flattens, and the skin regains most of its pre-wound tensile strength.

In wounds where significant tissue loss occurs the damaged edges are usually unsuitable for primary closure. In this case, the tissue defect must be made up before the wound can heal. To facilitate healing, dressings are applied to try to protect the wound from contamination and keep the wound surface moist to maintain the integrity of the cells present in the defect. In a dry wound environment, dividing cells at the wound edges are unable to migrate into those areas occupied by dry scab material.

Where healing is protracted as a result of significant tissue loss (e.g. as in deep pressure

sores) or due to underlying pathology (e.g. venous leg ulcers) chronic wounds occur. Although not initially chronic in nature, both surgical wounds and pilonidal sinuses can develop into chronic wounds if they fail to heal by primary intention. Chronic wounds are those most commonly seen by health professionals and estimates suggest that the cost of treating leg ulcers alone in the UK is more than £300 million per annum.[7]

The wound healing process

The biological mechanism associated with wound healing is complex and still not well understood. Although there is much to learn about the detail of the processes involved, some of the general concepts of healing are understood.

Chronic open wounds, such as leg ulcers and pressure sores, heal by secondary intention or granulation, rather than primary intention (the means by which a surgical incision heals). Platelet aggregation during haemostasis liberates a number of soluble mediators, including platelet-derived growth factor, which initiate the healing process. Haemostasis is followed by an early inflammatory phase that is characterised by vasodilatation, increased capillary permeability, complement activation and polymorphonuclear (PMN) and macrophage migration into the wound.[8]

PMNs predominate during the first days of post-wound occurrence, with the macrophage becoming the predominant inflammatory cell within 3 days. Macrophages are large, mobile and actively phagocytic, engulfing bacteria and devitalised tissue and acting effectively as the body's own debridement system. Additionally, macrophages are considered to play a key role in regulating subsequent events in the healing process. This is achieved by secretion of a number of factors that regulate their own and other cell functions. These factors are responsible for the chemotactic attraction of more macrophages and the migration and induction of proliferation by fibroblasts and endothelial cells. The increasing number of fibroblasts and endothelial cells forming granulation tissue around the fifth day post-injury heralds the 'proliferative phase'.[9]

Fibroblasts are the 'factory cells' of the wound healing module. They are rich in mitochondria, endoplasmic reticulum, and Golgi apparatus essential for protein synthesis. Fibroblasts synthesise collagen and ground substance (proteoglycans and fibronectin), which support new cells, and the fragile capillary buds, which appear around this time (angiogenesis). The endothelial buds become canalised, and are thus able to increase the vascularity and hence oxygen tension of the new tissue, so responding to the large metabolic demand of tissue repair. Epithelialisation requires the migration of epithelial cells across the granulation tissue, to close the epidermal defect.

Collagen synthesis continues for many months after wound closure, but also undergoes continual lysis, so a delicate balance exists between the two processes. This final remodelling phase, accompanied by increasing tensile strength of the wound, and a decreasing cellularity, may continue for up to a year.

Little research has been carried out to investigate the differences between acute and chronic wounds, though this comparison is now becoming the focus of recent work. Most studies of the wound healing process have been undertaken on acute wounds, usually in experimental animals. How closely the healing of a chronic wound follows the healing pattern of an acute wound is not clear. The question of what makes a chronic wound 'chronic' has yet to be answered.[10]

The healing process is considered to be regulated by cytokines and growth factors, and recent studies have demonstrated that the cytokine environment in a healing chronic wound is different from that in a non-healing wound.[11] However, the precise nature of the defect(s) leading to non-healing remain to be defined.

Moisture and wound healing

In 1962, Winter[5] published his seminal text on the effect of occlusion on wound healing. Winter made experimental wounds in Large-White pigs, and covered half with occlusive film and left the other half exposed to the air. The occluded, and hence moist wounds, had an epithelialisation rate twice that of those left to form a scab.

Experimental, acute wounds in humans and animals appear to heal more rapidly in a moist environment. The relevance of this to chronic, pathological wounds is unclear.

The role of oxygen in wound healing

Oxygen is essential for cell metabolism, and demand is increased by synthetic processes such as those occurring during wound healing. Shortly

after injury, the oxygen tension in a wound falls, so that by day 3, the pO_2 in the dead space of a wound is below 10 mmHg.[12] This fall in oxygen tension is accompanied by an increase in the concentration of carbon dioxide, and a fall in pH. A low pO_2 provides optimal conditions for fibroblast regeneration, possibly stimulating the process and increasing the rate of advance of granulation tissue.[13] The concept that hypoxia stimulates healing was further supported by Knighton and co-workers[14] who demonstrated a positive relationship between a steep oxygen gradient between capillaries and hypoxic tissue, and angiogenesis.

pH and wound healing

Few studies have examined the effect of pH on wound healing. In 1973, Leveen[15] demonstrated that the acidification of wound surfaces increased healing. Varghese and co-workers[16] found wound fluid to be more acidic under a Granuflex® dressing (ConvaTec Ltd) than under an Opsite® dressing (Smith & Nephew Healthcare Ltd), the more acidic pH being compatible with *in vitro* antibacterial activity. However, there are no high-quality randomised controlled trials (RCTs) examining the effects of wound pH on ulcer healing.

Micro-organisms and ulcer healing

The effect of micro-organisms on ulcer healing remains an area of intense debate. That chronic wounds are usually colonised by bacteria is accepted, and an important distinction should be made between colonisation and infection. Infection is characterised by the stigmata of pain, inflammation, purulent exudate and heat, and by the more objective measures of a PMN response and tissue concentrations of organisms in excess of 10^5/g.[17]

The effect of occlusive dressings on infection rates is controversial. A review of the impact of antiseptics and antibiotics is currently in preparation.

Chronic wounds

Wounds come in a variety of shapes and sizes and may be classified in terms of aetiology, duration, and degree or depth of tissue loss. Wounds with little tissue loss include surgical incisions, minor abrasions, scalds and minor bites. Those with significant tissue loss include leg ulcers, pressure sores, and fistulae (all chronic) and severe lacerations, gunshot wounds, burns and stab wounds (acute wounds).

George[3] estimates that the worldwide prevalence of wounds is:

- surgical: 40–50 million
- leg ulcers: 8–10 million
- pressure sores: 7–8 million
- burns: 7–10 million.

In the UK it has been estimated that 0.15–0.18% of the adult population has an open leg ulcer at any one time.[18] This would mean that about 60,000 people in the UK are currently being treated for a leg ulcer. The prevalence of pressure sores may vary widely according to setting and whether grade 1 sores, where the tissue is damaged but the skin remains unbroken, are counted. Barbenel and co-workres[19] found a mean pressure sore prevalence of 8.8% in patients cared for in hospitals and the community. More recently, a study by O'Dea,[20] found the prevalence in hospitalised patients (excluding obstetric and psychiatric patients) to be 18.6%, including grade 1 sores, and 10.1% excluding them. In high-risk groups, such as elderly patients with fractured neck or femur, 66% of hospitalised patients will develop a pressure sore.[21] The importance of preventing and treating pressure sores has recently been acknowledged in Government policy.[22]

Management of the wound patient

The chronic, non-healing, wounds discussed within this review frequently occur through a combination of precipitating (often extrinsic) and perpetuating (often intrinsic) factors. Pressure sores may be precipitated by the patient having been seated for a number of hours but this is unlikely if the patient is conscious, able to shift position and in good health. The more likely reason for pressure sore occurrence is through a combination of localised, sustained, high tissue pressure with other factors, such as severe concurrent illness. Treatment, therefore, generally focuses on the local 'symptom' of poor tissue perfusion (the wound) and also the contributory factors of interface pressure and poor health.

This review will only consider the contribution of dressings and local applications used for wound healing. Other interventions commonly used in the treatment of pressure and leg ulcers, where

healing rates are low if the underlying pathology is not addressed, have been reviewed previously.[23,24] It is strongly recommended that decisions on treatment choice should be made in light of all the available information.

Local wound management

Traditional wound dressings are regarded as **passive** devices that protect the wound from further injury, while wound healing takes place naturally beneath. Examples of traditional dressings are gauze, gauze soaked in saline, knitted viscose dressings, and tulle dressings all of which are considered in this review. Winter,[5] however, introduced the concept of interactive dressings, which can alter the local wound environment. These **interactive** dressings have a range of properties and are currently the subject of intense research.

The vast majority of these 'modern' dressings are described as occlusive or semi-occlusive. They prevent or reduce the rate of moisture vapour transmission from the wound surface. Completely occlusive dressings (e.g. polythene bags) produce a very moist wound environment and lead to maceration of the surrounding skin. Semi-occlusive dressings have a range of moisture vapour transmission rates, which permit a lower volume of moisture to pass to the surface than is produced by the wound. The result is an accumulation of water vapour at the surface which helps to maintain a moist wound environment.

Interactive dressings may also insulate the wound surface from excessive heat loss, which is thought to inhibit fibroblast activity. The interactive dressings that are considered in this review include alginates, collagen, films, foams, hyaluronic acid products, hydrocolloids and hydrogels.

Despite treatment with passive and interactive dressings, which provide optimal conditions for healing, many wounds still persist. In a more aggressive approach **active** dressings have been developed, which have various properties that are believed to have a direct role in changing the chemical and cellular make-up of the wound. Examples of active dressings include skin grafts, growth factors and cellular suspensions.

A number of characteristics of the 'ideal dressing' have been described by pharmacists and many manufacturers refer to these characteristics when marketing their products. These are out-lined in *Box 1*. However, as this is an ideal list, none of the dressings in current use fulfil all of the criteria.

BOX 1 The functions of an "ideal" dressing[25]

- Allow excess exudate to be removed from the wound surface
- Provide a moist micro-environment
- Be sterile/contaminant free
- Do not shed dressing material in the wound
- Reduce wound pain
- Easy to remove and apply
- Do not cause allergic reactions
- Act as a semi-permeable membrane
- Cause no trauma when removed
- Be impermeable to micro-organisms
- Provide thermal insulation

To bring order to the vast range of products available to a practitioner, the British National Formulary[26] has developed a classification system based on a products' properties and mode of action.

- **Wound dressing pads** This group of traditional dressings include knitted viscose dressings and gauze dressings. They are usually in the form of woven cotton pads that are applied directly to the wound surface. Some have a perforated film layer to reduce adherence to the wound surface (e.g. Tricotex®, Smith & Nephew Healthcare Ltd).

- **Tulle gras dressings** Made from cotton or cotton and viscose woven fabric, which has been impregnated with white soft paraffin. The dressing is used as a primary wound contact layer and the paraffin is present to reduce the adherence of the product to the surface of a granulating wound. Antimicrobial substances may also be included (e.g. povidone iodine or chlorhexidine) (e.g. Paratulle®, Seton Scholl Healthcare Ltd).

- **Semi-permeable film dressings** This is a transparent film dressing. A thin layer of acrylic adhesive keeps it adherent to the skin but not the wound surface. These dressings are semi-permeable and allow some gaseous exchange but they are impervious to bacteria[27] (e.g. Tegaderm®, 3M Ltd).

- **Hydrocolloid dressings** These occlusive dressings contain a hydrocolloid matrix (e.g. gelatin, pectin and carboxymethylcellulose) with elastomeric and adhesive substances attached to a polymer base.[27] On contact with wound exudate the hydrocolloid matrix

absorbs water, swells and liquefies to form a moist gel (e.g. Granuflex).

- **Hydrogels** These consist of a starch polymer, such as polyethylene oxide or carboxymethylcellulose polymer and up to 80% water. They have the ability to absorb wound exudate or rehydrate a wound depending on whether the wound is exuding heavily or dry and necrotic (e.g. Intrasite®, Smith & Nephew Healthcare Ltd). These dressings have been evaluated in a systematic review of debriding agents.[28]

- **Alginate dressings** These are made from seaweed, prepared as a salt of alginic acid. When in contact with serum, wound exudate or solutions containing sodium ions, the insoluble calcium alginate is partially converted to the soluble sodium salt, and a hydrophilic gel is produced[27] (e.g. Kaltostat®, ConvaTec Ltd).

- **Bead dressings** These consist of sterile, dextranomer beads, 0.1–0.3 mm in diameter. When introduced into an exuding wound, the beads will absorb up to four times their weight of exudate. Bacteria and cellular debris present in the wound are taken up by capillary action and become trapped in the spaces between the beads. When the dressing is changed, this debris is washed away. They require a secondary dressing to maintain their position in the wound (e.g. Debrisan®, Pharmacia & Upjohn). These dressings have been evaluated in a systematic review of debriding agents.[28]

- **Foam dressings** These consist of either a hydrophobic, polyurethane foam sheet or a liquid that expands to fill the wound cavity. They absorb liquid by capillary action (e.g. Lyofoam®, Seton Scholl Healthcare Ltd).

Topical preparations

Topical preparations covered in the present review include growth factors, oxygen free radical scavengers, zinc oxide paste, tripeptide copper complex, and silver sulphadiazine cream. Topical antiseptics and antibiotics are not covered here but are currently under review.

Several of these preparations are applied to the wound to compensate for a deficiency in a particular element considered necessary for wound healing. An example of such a topical agent is zinc oxide; zinc deficiency has been associated with poor wound healing. Other preparations are thought to modify the wound environment by removing harmful bacteria (e.g. silver sulphadiazine).

The use of oxygen free radicals is thought to mediate tissue destruction following prolonged venous hypertension caused by venous insufficiency. Coleridge-Smith and co-workers[29] proposed that venous hypertension reduces flow in the capillaries to such a level that the white cells are effectively trapped, which causes the release of toxic oxygen metabolites and proteolytic enzymes. DL-cysteine, DL-methionine-methyl sulphonium chloride, allopurinol and dimethyl sulfoxide (DMSO) all bind the oxygen free radicals and so are intended to protect the ulcer from further damage.

Iloprost has also been applied topically because of its action on the micro-vasculature. It reduces platelet aggregation and has profibrinolytic effects that may facilitate the removal of fibrin cuffs around capillaries in the skin of patients with venous insufficiency. In patients with peripheral arterial disease it is used systemically, but in this review it has only been evaluated as a topical preparation.

Sucralfate is applied topically because of its ability to bind to, and protect, angiogenic growth factors, such as basic fibroblast growth factor to increase its angiogenic activity in the wound.

Chapter 2
Methods

A systematic review of primary research was undertaken using the NHS Centre for Reviews and Dissemination (CRD) structured guidelines.[30]

Literature search

Nineteen electronic research databases were searched using a sensitive search strategy designed in collaboration with an information specialist (appendix 1). The electronic search was supplemented by a handsearch of five specialist wound care journals, 12 conference proceedings, and a search of systematic reviews held on the NHS CRD Database of Abstracts of Reviews of Effectiveness (DARE). The bibliographies of all retrieved and relevant publications were searched for further studies. Companies with an interest in wound care products were approached for unreported trials. An advisory panel of experts in wound management, established to comment on the review as it progressed, were also asked to identify any additional trials (appendix 2). Relevant economic evaluations were identified by adding economic-related search terms to those used in the search for clinical trials. Authors of trials published after 1985 were contacted and asked to provide details of any associated economic evaluations.

Study selection and data extraction

Retrieved studies were assessed for relevance by a single reviewer and decisions on final inclusion checked by a second reviewer; disagreements were resolved by discussion with a third reviewer. Trials, irrespective of date, language and publication status, were included if they were human-based RCTs that evaluated the efficacy of a dressing or topical agent in relation to wound healing and had an outcome measure that was considered an objective measure of healing. Where study details were lacking, the authors were invited to provide further information. Retrieved trials that did not meet the inclusion criteria are recorded in appendix 3.

Data from included trials were extracted by a single reviewer into data extraction tables and then checked independently by a second reviewer.

Assessing the presence of publication bias

When trials evaluating an intervention are grouped and reviewed there is a potential for misleading interpretations and inappropriate treatment choices if all the available information is not represented. A systematic review attempts to reduce the influence of this bias by undertaking an extensive search for all published trials, but it is inevitable that information not readily available in the public domain may be overlooked. Studies with negative results frequently remain unpublished, and therefore there is a potential for over-reporting of positive results in review articles. The results of a systematic review can therefore be susceptible to publication bias. It is desirable then for systematic reviews to demonstrate that where a difference is indicated between two treatments it is not as a result of publication bias.

The presence of publication bias can be demonstrated by a funnel plot where the estimate of the trial effect is plotted against the sample size. This is a visual tool that relies on the relationship between sample size and precision of the treatment effect. Small studies show a wide variation in the reported treatment effect and so scatter widely at the bottom of the plot, larger studies show less variation and so tend to aggregate together towards the top of the plot. When publication bias is absent the visual effect is that of an inverted symmetrical funnel, while in the presence of bias the plot is frequently skewed and asymmetrical.[31]

Although a funnel plot is a useful indication of publication bias, it remains a relatively insensitive technique relying on visual assessment. Its validity is dependent on there being a sufficient number of studies from which to assess the spread of data. In this review only comparisons between traditional and modern dressings provided sufficient numbers of trials to allow the construction of a funnel plot. In addition the large number of trials that compared a hydrocolloid dressing with a traditional treatment allowed a separate funnel plot to be constructed.

Assessment of outcome measures

A single standard outcome measure for wound healing does not exist. Both objective and subjective measures are widely used by researchers, but little effort has been made to determine the validity of many of these measurements.

Comfort, ease of application, ease of removal, exudate, handling and cosmesis are frequently used measures of dressing performance, but they are not validated outcomes on which to base decisions of effectiveness. In this review the most commonly validated outcome measures encountered were based on wound healing. The unambiguity of complete healing and its importance to clinicians and patients alike (because of its potential impact on quality of life and burden of care), make it the preferred outcome measure with which to compare studies of clinical effectiveness.

In accordance with the peer-reviewed protocol, subjective outcome measures such as visual assessments of oedema, erythema, granulation and pus and debris were not included unless the authors assessed their validity. We were unable to find any study that validated the subjective outcome measures reported.

Objective measures of healing are usually based on wound area. Planimetry, often aided by computer analysis, is the most frequently used method of calculating wound area, though other methods, such as the measurement of wound diameter or weight of a tracing drawn around the area of the wound, are also used.

Measurements of wound volume are infrequently reported in the literature; these methods are often cumbersome and their accuracy has not been proven.[32] Computerised image analysis may in the future, as the equipment becomes more affordable and portable, prove to be a useful technique for the assessment of wound volume.

Even though objective measures reduce or eliminate subjective biases and reduce random measurement errors, they have certain inherent biases if the patients being compared have wounds with different baseline size.

A change in wound area is often expressed as the percentage change, which unlike the absolute change in area, takes into account the initial size of the wound. For two wounds healing at the same linear rate (as measured by diameter reduction) percentage area calculations will show a larger change for a small wound than for a big wound. The converse is true when the absolute change in area is measured, as for any unit reduction in wound radius, a bigger area reduction will occur for a large wound. This has important consequences for the validity of trial results where there is poor comparability in initial wound size at baseline between the treatment groups. This is illustrated in *Table 1*.

In large trials, randomised allocation should ensure that the mean wound size and variance in each group is similar. In a small trial random allocation is unlikely to result in an even distribution of wound sizes. This problem will persist in small trials, even when the average wound size appears to be comparable between groups, because the distribution of wound sizes about the mean is likely to differ. This is illustrated in *Table 2*.

In a trial where there is poor comparability between groups for wound size at baseline, and

TABLE 1 *Percentage and absolute measures of wound healing can give different results for relative effectiveness*

	Group A	Group B
Baseline mean area (cm^2)	50	60
Follow-up mean area (cm^2)	35	43
Mean of % reduction in area	30	28
Mean absolute reduction in area (cm^2)	15	17
Using % change, wounds in group A appear to have healed more rapidly than those in group B. The converse is true when the outcome is expressed as absolute change in wound area		

TABLE 2 *Groups with similar means may have different distributions*

	Group C	Group D
Wound size at baseline (cm^2)	10, 10, 30, 30	4, 4, 4, 70
Mean area (cm^2)	20	20.5
Standard deviation (SD)	11.5	33
Groups C and D have approximately the same mean area. If both groups of wounds heal at the same rate (the treatments are equally effective) it could be expected that the three small wounds in group D will heal before those in group C. Therefore measuring outcome based on the number of wounds healed within a certain time period will be biased. Similarly, the percentage change in area will appear greater in group D, while the absolute change in area will appear greater in group C		

the outcome is based on the change in area, the result can only be considered valid if it is obtained either against the anticipated direction of the bias for wound size, or where percentage area change and absolute area change are in the same direction. If baseline data are not given then it is not possible to determine the direction of bias and the validity of the result cannot be determined.

Despite the potential for objective outcomes to be biased by differences in wound size at baseline, they remain the most reliable assessment of wound healing as, unlike subjective measures, they reduce the biases of the assessor which cannot be estimated.

Valid and reliable condition-specific outcome measures for patients with chronic wounds are lacking. Such measures would encapsulate those aspects of quality of life on which wounds most impact, from a patients perspective; they would be sensitive to meaningful changes in quality of life generated by a change in the wound, including post-healing of the wound. We have only identified one such measure, the Hyland Leg Ulcer Specific Quality of Life Measure.[33] However this tool ceases to be applicable when a wound has healed, thus making it impossible to determine changes in leg-ulcer-related quality of life with ulcer healing.

Chapter 3
Results

Presentation of results

The plots used in this systematic review combine the results of individual RCTs. Outcomes can either be dichotomous or continuous. Dichotomous outcomes (e.g. healing or recurrence) are usually compared statistically by odds ratios (ORs) or risk ratios. Continuous outcomes (e.g. rate of healing) are measured on a continuous scale. Continuous outcomes are compared statistically by mean differences.

Forest plots

The results of both the ORs and mean differences in healing rates are presented in forest plots to allow a quick comparison to be made with the results from other studies. Guidance on how to interpret these figures can be found in appendix 4. Summary tables of all the studies included in the review are presented in appendices 5–10.

Quality assessment of studies

Trials that evaluated surgical wounds healing by secondary intention and pressure sores are considered together for the purpose of quality assessment, as they are small in number and suffer from similar methodological flaws.

Thirty-five studies were identified for inclusion: 29 reports, describing 28 trials, were evaluations of pressure sores, while an further six examined surgical wounds healing by secondary intention.

The majority of trials had methodological weaknesses (appendix 5, *Tables 4* and *5*). Fewer than 6% of studies reported an *a priori* estimate of the number of participants required to have sufficient power to detect a clinical effect as statistically significant, the median number of wounds recruited to a trial was 50 (range, 14–168). Blinding of investigators at outcome assessment was reported in fewer than 18% of trials. One or more patient characteristics were recorded by treatment group in 80% of studies, but wound size at baseline was reported in only 60%. Withdrawals occurred in most trials and were recorded by group and cause in 88% of trials where it was appropriate, but only 13% analysed the results on an intention-to-treat (ITT) basis. Seventy-six per cent of trials described inclusion criteria, but information that indicated whether participants had been truly randomised to alternative treatments was given in only 20%.

Treatments for surgical wounds healing by secondary intention

Three trials compared a dressing with a recognised traditional treatment, one trial compared different dressings and one trial compared a topical agent with standard care.

Dressing versus traditional treatment

Three trials compared a silicone foam cavity dressing with a traditional gauze dressing.[34–36] In each case the gauze had been impregnated with a different cleansing agent and therefore pooling the results was inappropriate (*Figure 1*; appendix 6, *Table 7*). There was no statistically significant effect in favour of either treatment for an outcome measure of time to complete healing.

Dressing versus dressing

Comparisons between dressings for the treatment of surgical wounds healing by secondary intention are rare; only a single study met the inclusion criteria. In this study[37] a silicone foam cavity dressing was compared with a polyurethane foam dressing (*Figure 2*; appendix 6, *Table 8*). No statistically significant difference was found between the treatments.

Topical agents versus traditional treatment

In a comparison between topical application of the plant extract aloe vera and standard wet-to-dry dressings (popular in the USA), the latter treatment appeared to be more or equally effective depending on the nature of the surgical wound under evaluation[38] (*Figure 1*; appendix 6, *Table 9*). Wet-to-dry dressings significantly reduced the healing time for vertical incisions, but there was no statistical difference between the treatments for transverse incisions. When all wounds where included in the analysis the overall estimate was significantly in favour of wet-to-dry dressings.

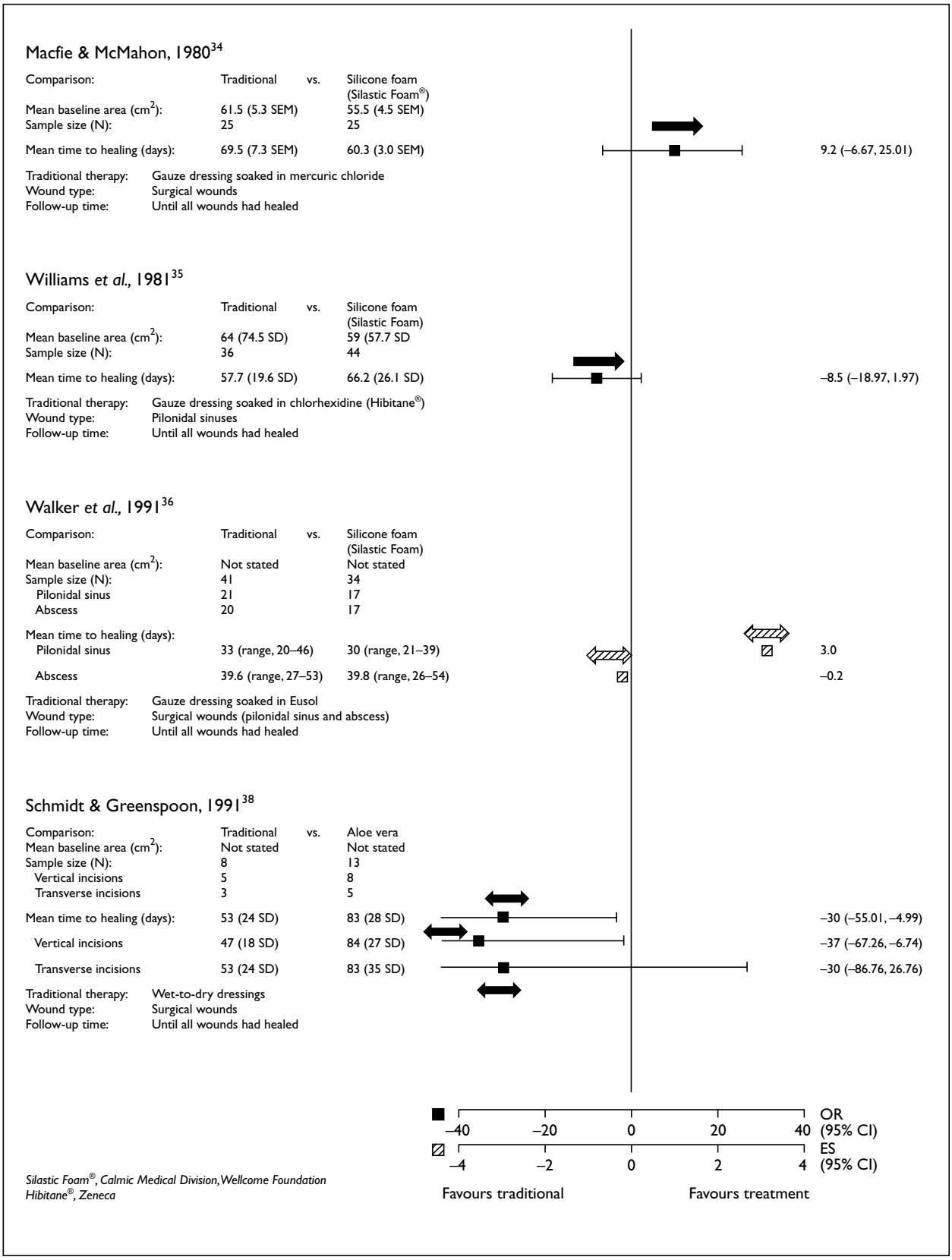

FIGURE 1 Dressings and topical agents compared with traditional treatments for healing surgical wounds. Study results are presented as OR and/or effect size (ES) enclosed by their 95% CI. A single arrow by a trial indicates that the results were biased by poor comparability between groups for wound size at baseline; the direction of the arrow suggests which intervention was favoured by the bias. Convergent arrows suggest that the groups were reasonably comparable for wound size, while divergent arrows indicate that the bias could not be determined from the data presented

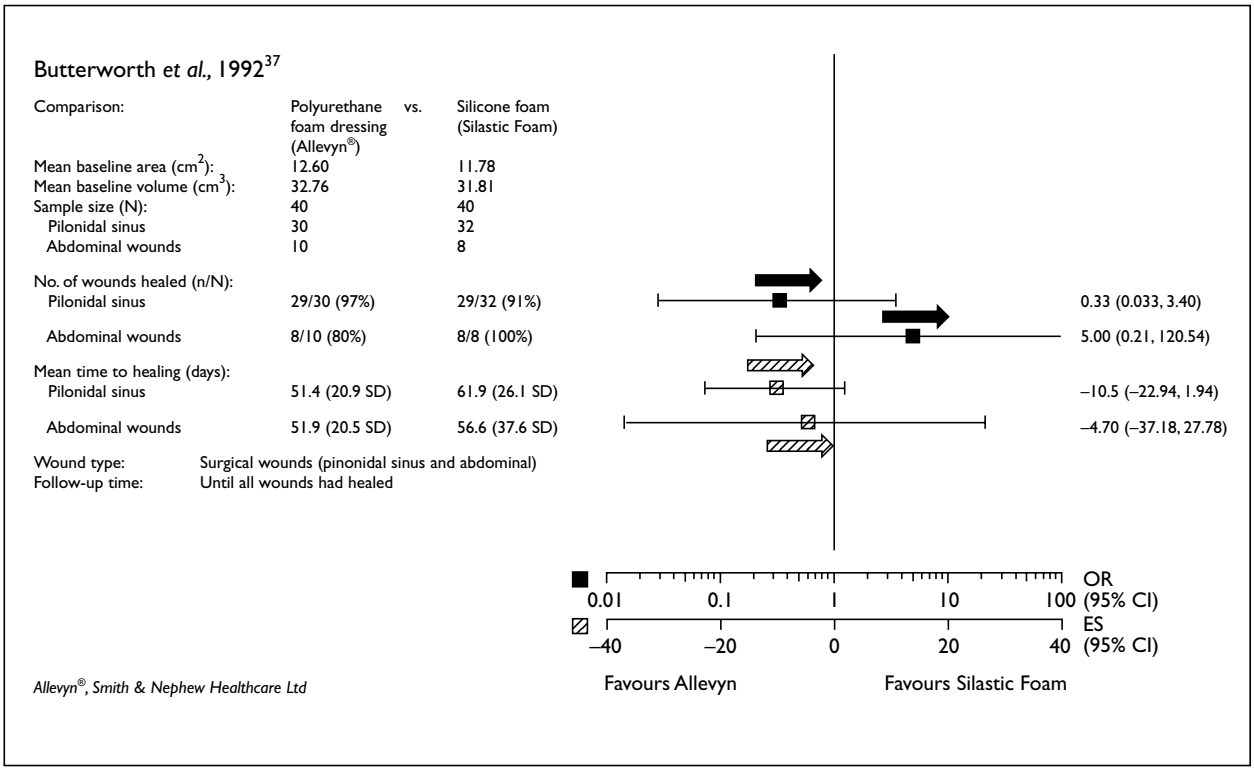

FIGURE 2 *Various dressings for healing pilonidal sinuses*

Treatments for pressure sores

A single trial compared a topical agent with no direct treatment, six studies compared a topical agent with a placebo, three studies directly compared different topical agents and five trials compared a topical agent with a dressing. In addition nine studies (11 reports) that compared a dressing with a traditional treatment were included, and a further seven trials were head-to-head comparisons between dressings.

Topical agents versus no treatment

The incremental benefit of topical insulin in addition to routine supportive nursing care was assessed in a single trial[39] (appendix 7, *Table 10*). The routine care given to patients included: position changes, increased fluid intake, a high protein diet and local massage. The statistical analysis presented indicates that the addition of insulin resulted in a significant improvement in both the healing rate and the number of days that treatment was required. However, this trial was small and the primary data were not presented.

Topical agents versus placebo

Six studies compared a topical agent with a placebo: one assessed an active cream, only referred to as F14001[40] (formulation not stated but contains a barley plant extract), another assessed ketanserin[41] (*Figure 3*; appendix 7, *Table 11*), and four evaluated biologically active agents, which with the exception of one trial,[42] were growth factors[43–45] (*Figure 4*; appendix 7, *Table 11*).

A statistically significant improvement in outcome was observed only when active cream F14001 was compared with placebo; the active cream showed a significantly faster healing rate than placebo.[40] The other studies were too small to detect a statistically significant difference.

Topical agent versus topical agent

All three trials included in this category compared biologically active topical agents; two were comparisons of growth factors given at different concentrations,[43,45] while the third compared different doses of the cytokine interleukin 1-beta[42] (*Figure 5*; appendix 7, *Table 11*).

Recombinant platelet-derived growth factor (r-PDGF-BB) given at 100 µg/ml resulted in a statistically significant reduction in wound volume when compared with a concentration of 10 µg/ml, but not when compared with 1 µg/ml.[45] There was no statistically significant difference between treatment with concentrations of 10 µg/ml and 1 µg/ml.[46] These inconsistent results may be due to random variation reflecting the small sample size, which never exceeded

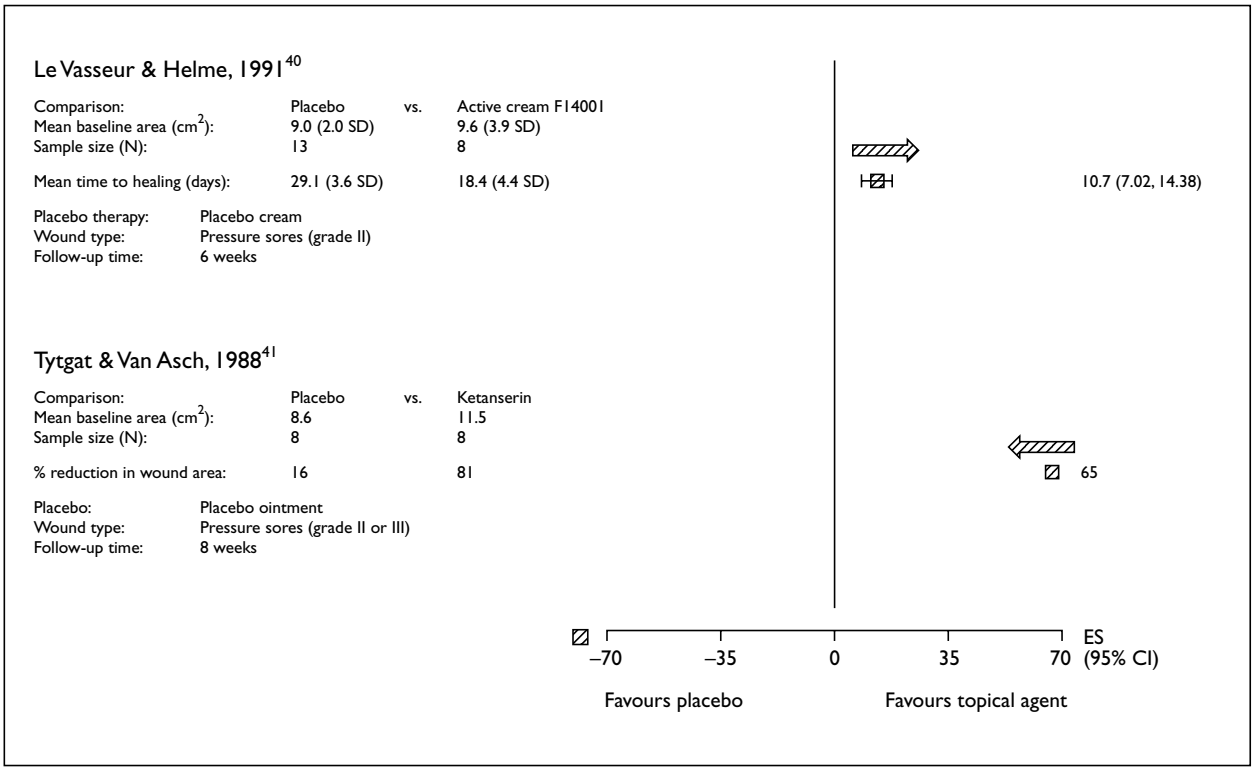

FIGURE 3 *Topical agents compared with placebo formulations for healing pressure sores*

more than five patients in each arm. A further trial found no statistically significant difference between concentrations of 300 μg/ml and 100 μg/ml of the same growth factor.[43]

No statistically significant difference in healing rate was found between comparisons of interleukin 1-beta given at different concentrations.[42]

Topical agents versus dressings

Five trials that met the inclusion criteria compared a topical agent with a dressing.[46–50] Three trials compared a hydrocolloid with a hydrogel[46–48] (*Figure 6*; appendix 7, *Table 12*), and two studies compared polysaccharide beads with either a calcium alginate dressing[49] or a collagen sponge dressing[50] (*Figure 7*; appendix 7, *Table 12*).

One hydrogel resulted in more pressure sores being completely healed when compared with a hydrocolloid dressing.[47] However, a smaller, more recent trial, which compared a hydrogel with a modified version of the previous hydrocolloid, found no statistically significant difference in healing rate between the two groups.[48] A further comparison of a hydrogel with the same modified hydrocolloid, reported insufficient data to estimate 95% confidence intervals (CIs) and statistical analysis was therefore not possible.[46] As these trials either provided insufficient data or used different outcome measures (i.e. proportion healed and healing rate), it was not possible to pool them.

In both comparisons between a polysaccharide dressing and an alternative dressing, the ORs indicated a benefit for the alternative treatment. However, this only reached statistical significance in the comparison with calcium alginate dressings.[49]

Dressings versus traditional treatment

Five trials (six reports) meeting the inclusion criteria compared a hydrocolloid with a traditional treatment (*Figure 8*; appendix 7, *Table 13*). In four of the trials (five reports), the traditional treatment comprised saline soaked gauze,[51–55] while in the fifth, wet-to-dry dressings and Dakin's solution were employed.[56]

Three of the trials found that treatment with the hydrocolloid dressing resulted in a statistically significant increase in the number of wounds healed,[51,54,56] while two found no statistically significant difference between treatments.[52,53,55] Pooling the five trials ($\chi^2 = 5.76$, df = 4) indicated that the hydrocolloid dressings increased the odds of healing by three-fold (OR, 2.57; 95% CI, 1.58–4.18).

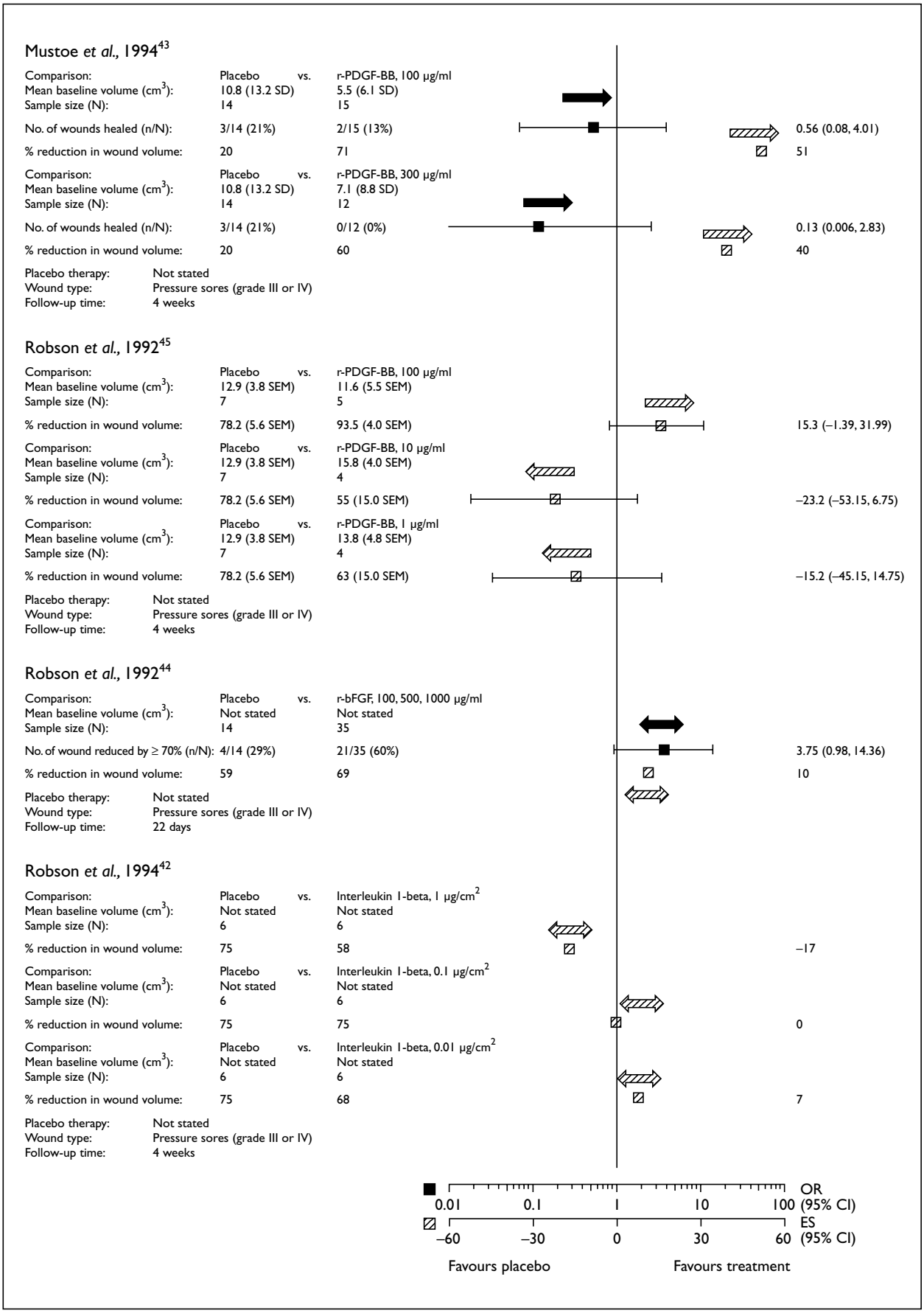

FIGURE 4 *Biologically active dressings compared with placebo formulations for the healing of pressure sores*

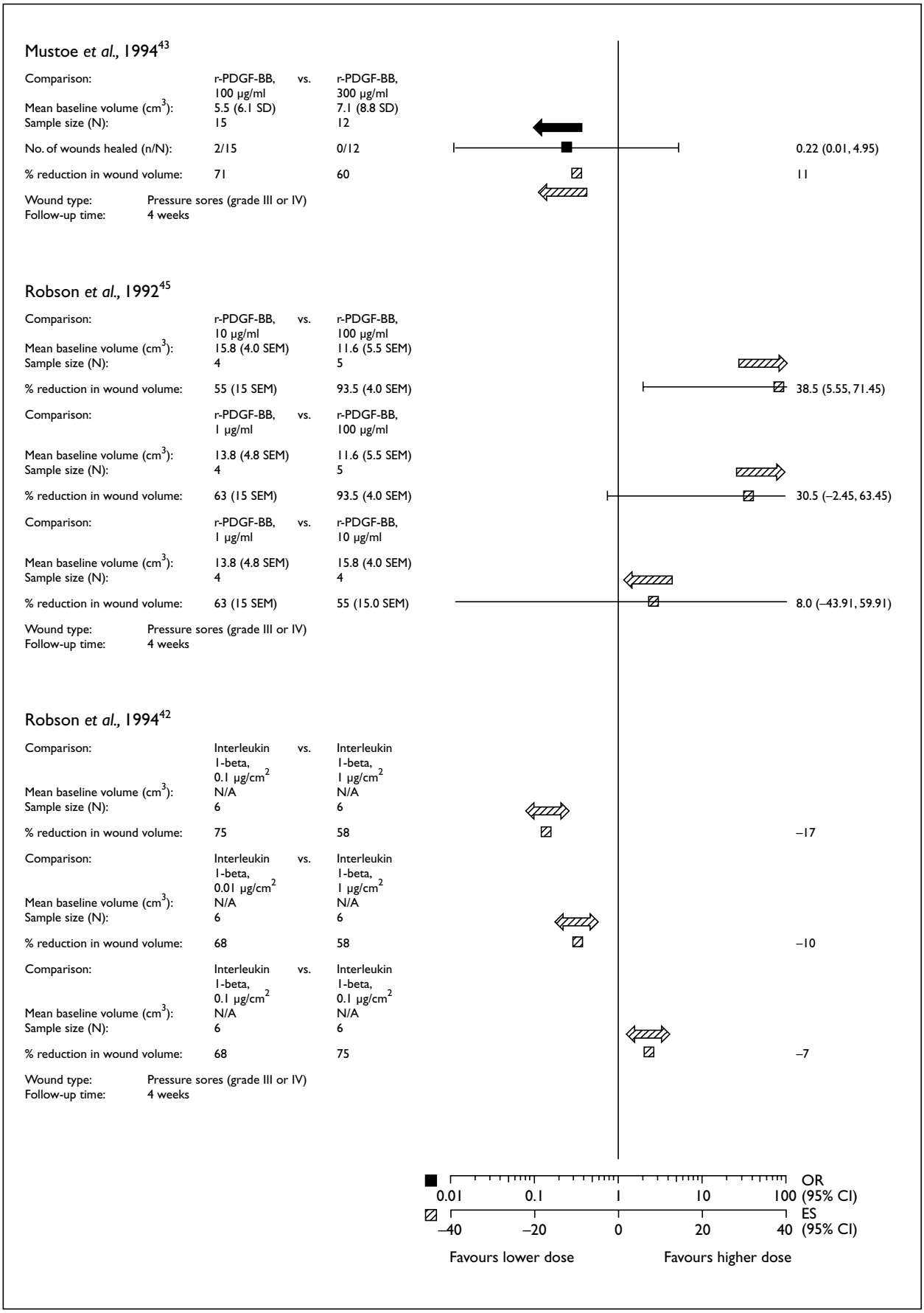

FIGURE 5 *Comparisons of biologically active agents for healing pressure sores*

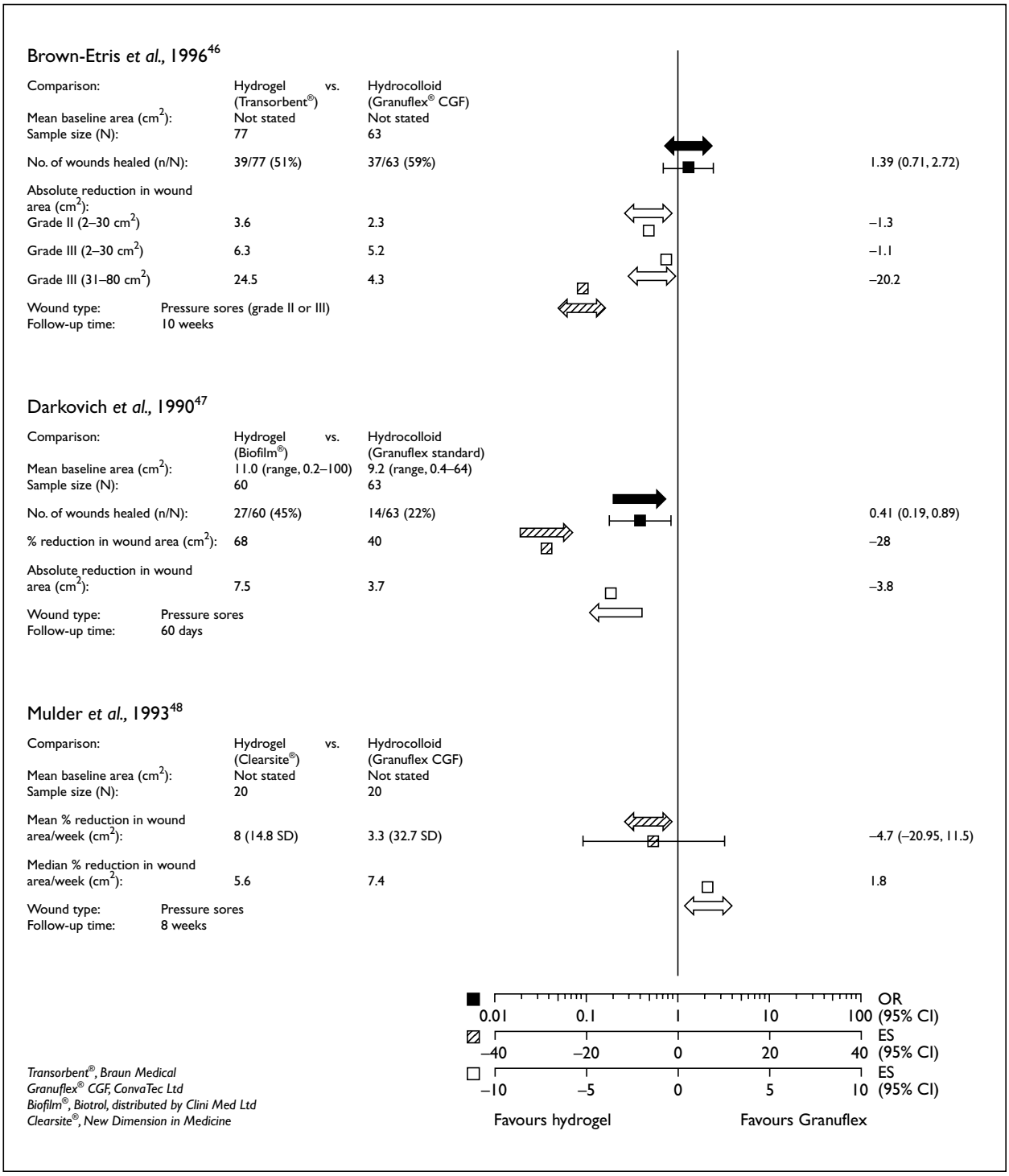

FIGURE 6 *Granuflex dressings compared with hydrogels for healing pressure sores*

A further four trials (five reports) were included that compared a dressing with a traditional form of treatment.[57–61] Only one of the trials found a statistically significant difference between treatments (*Figure 9*; appendix 7, *Table 13*). This trial showed that absorption dressings resulted in a quicker reduction in wound depth, but not in wound length when compared with treatment with povidone iodine.[60]

Dressings versus dressings

Four trials compared the same hydrocolloid with a polyurethane dressing.[62–65] No statistically significant difference was found between these treatments either when considered individually or pooled (*Figure 10*; appendix 7, *Table 14*).

In addition, no statistically significant difference was observed between hydrocolloid dressings

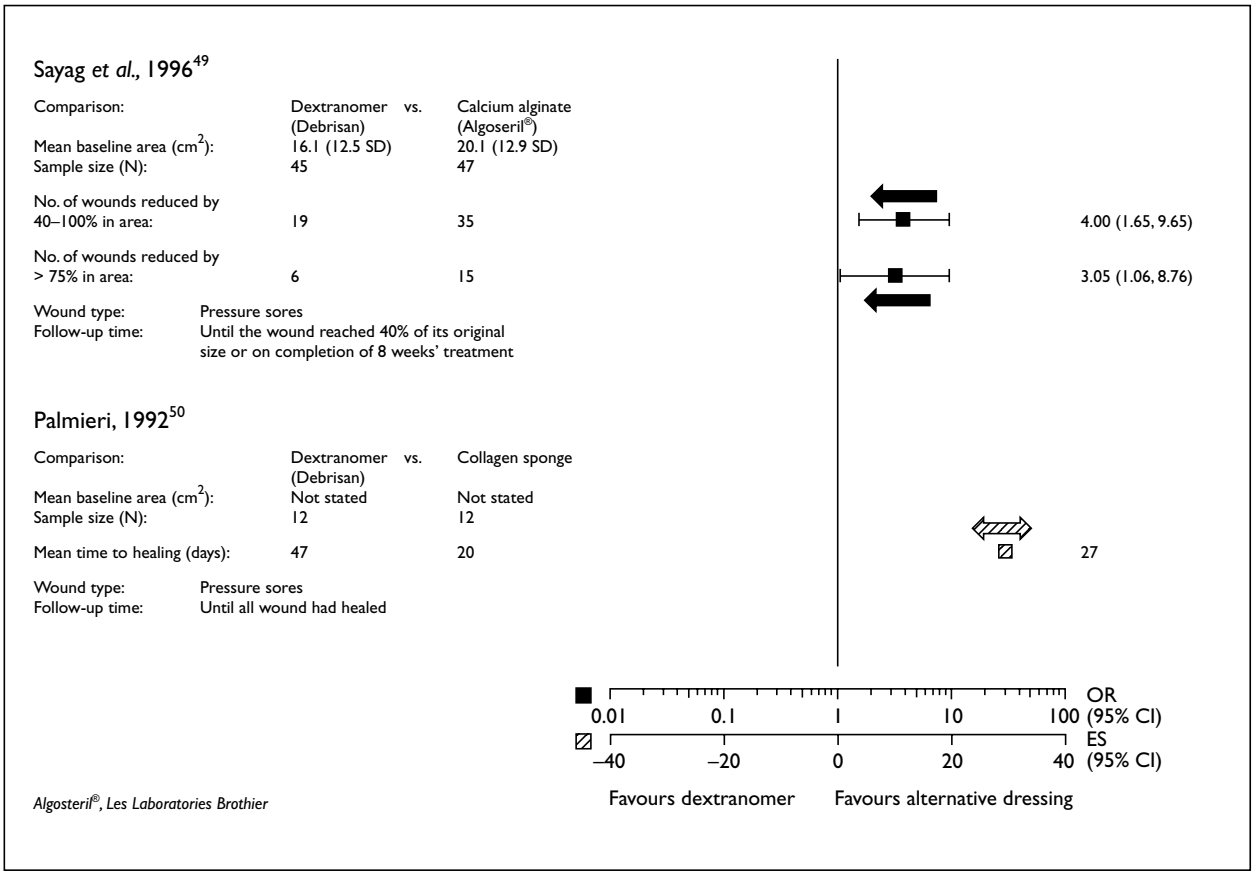

FIGURE 7 *Calcium alginate and collagen sponge dressings compared with topical dextranomer for the healing of pressure sores*

(Granuflex and Comfeel) and either a polyhydroxyethyl methacrylate,[66] or an amino acid copolymer membrane,[67] (*Figure 11*; appendix 7, *Table 14*). Similarly there was no statistical difference between a semipermeable adhesive dressing and a polyurethane foam dressing[68] (*Figure 10*; appendix 7, *Table 14*).

Treatments for leg ulcers

Three trials evaluated primary dressings or topical agents in the treatment of arterial leg ulcers: hydrocolloid dressing versus a low adherent dressing,[69] mononuclear cultured cells versus placebo,[70] and ketanserin versus vehicle alone.[71]

Twelve trials studied patients with ulcers of diverse aetiologies without presenting the results according to the leg ulcer aetiology. Three trials (seven reports) compared a 'modern' dressing with a traditional dressing, five trials (six reports) compared topical agents with a placebo or traditional treatments, three trials were head-to-head comparisons of dressings, and one trial compared a topical agent with a dressing.

Fifty-one trials of dressings and topical agents for venous leg ulcers were identified. Eighteen trials compared dressings with traditional treatments (normally gauze-type dressings). Ten trials compared two or more dressings, and seventeen compared a topical preparation with a control. Three trials compared dressings with topical preparations and three reported head-to-head comparisons of topical agents.

The majority of trials had methodological weaknesses (appendix 5, *Table 6*). Fewer than 9% of studies reported an *a priori* estimate of the number of participants required for the trial to have sufficient power to detect a clinical difference as statistically significant. The median number of wounds recruited to a trial was 48.5 (range, 9–233). Blinding of investigators at outcome assessment was reported in fewer than 7% of trials. One or more patient characteristics were recorded by treatment group in 36 out of 48 (75%) studies, but wound size at baseline (by group) was reported in only 30 of the 48 (62%) studies. Withdrawals occurred in most trials and the number and cause were recorded by group in 46% of trials where it was appropriate, but only 18% performed an ITT analysis. Sixty-two per cent described relevant inclusion criteria, but

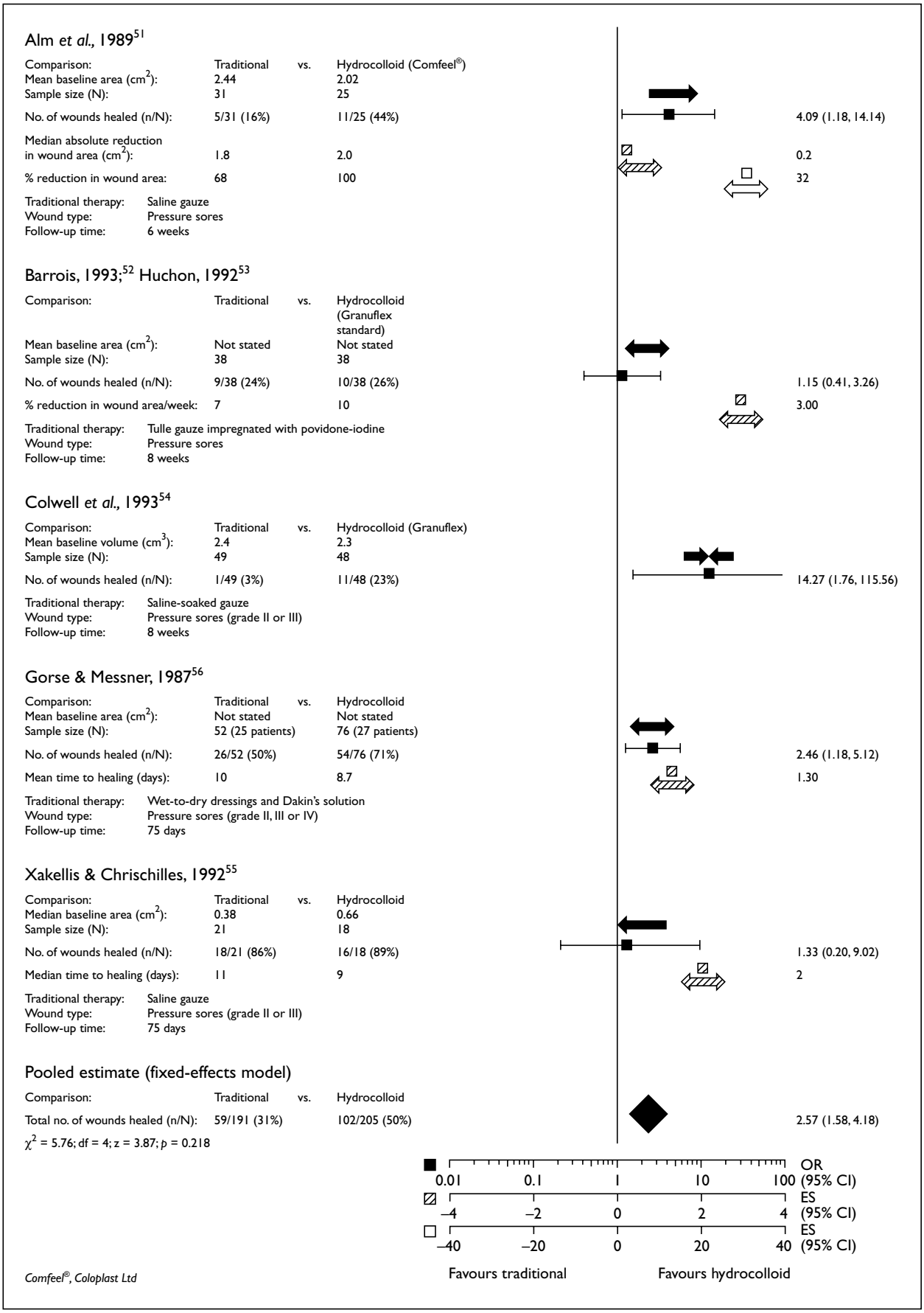

FIGURE 8 *Hydrocolloid dressings compared with traditional treatments for the healing of pressure sores*

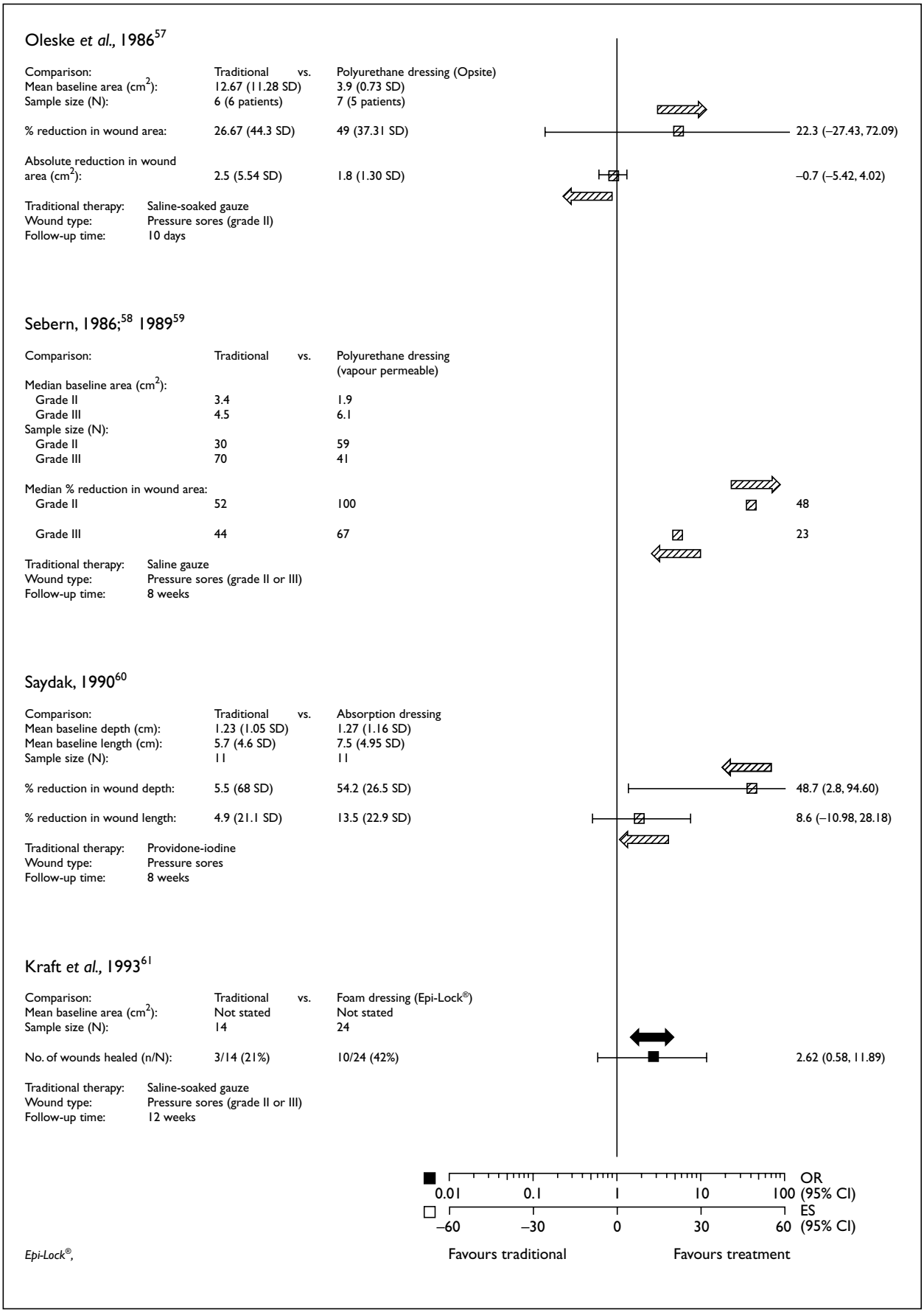

FIGURE 9 *Dressings compared with traditional treatments for healing pressure sores*

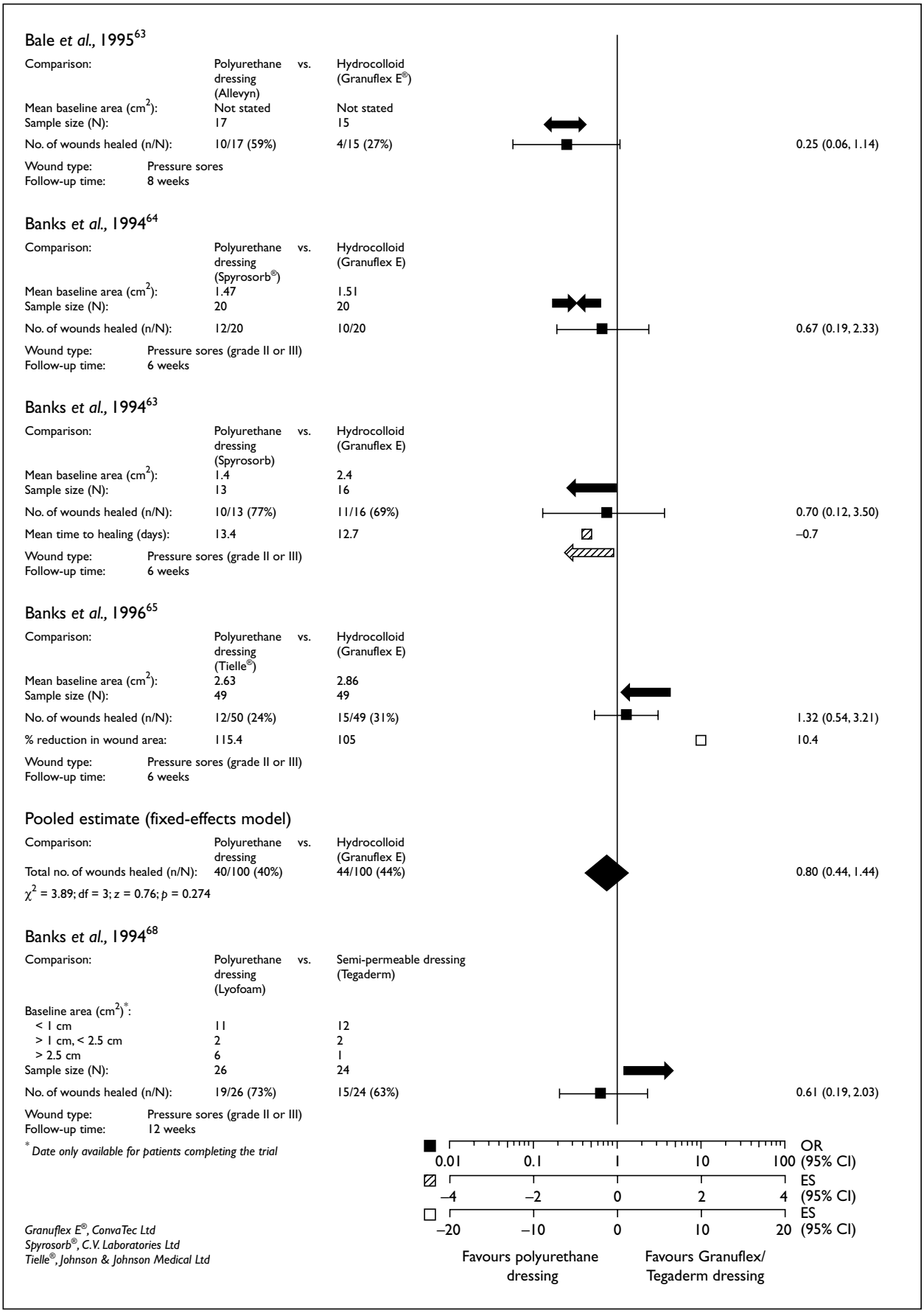

FIGURE 10 *Dressings compared with polyurethane dressings for healing pressure sores*

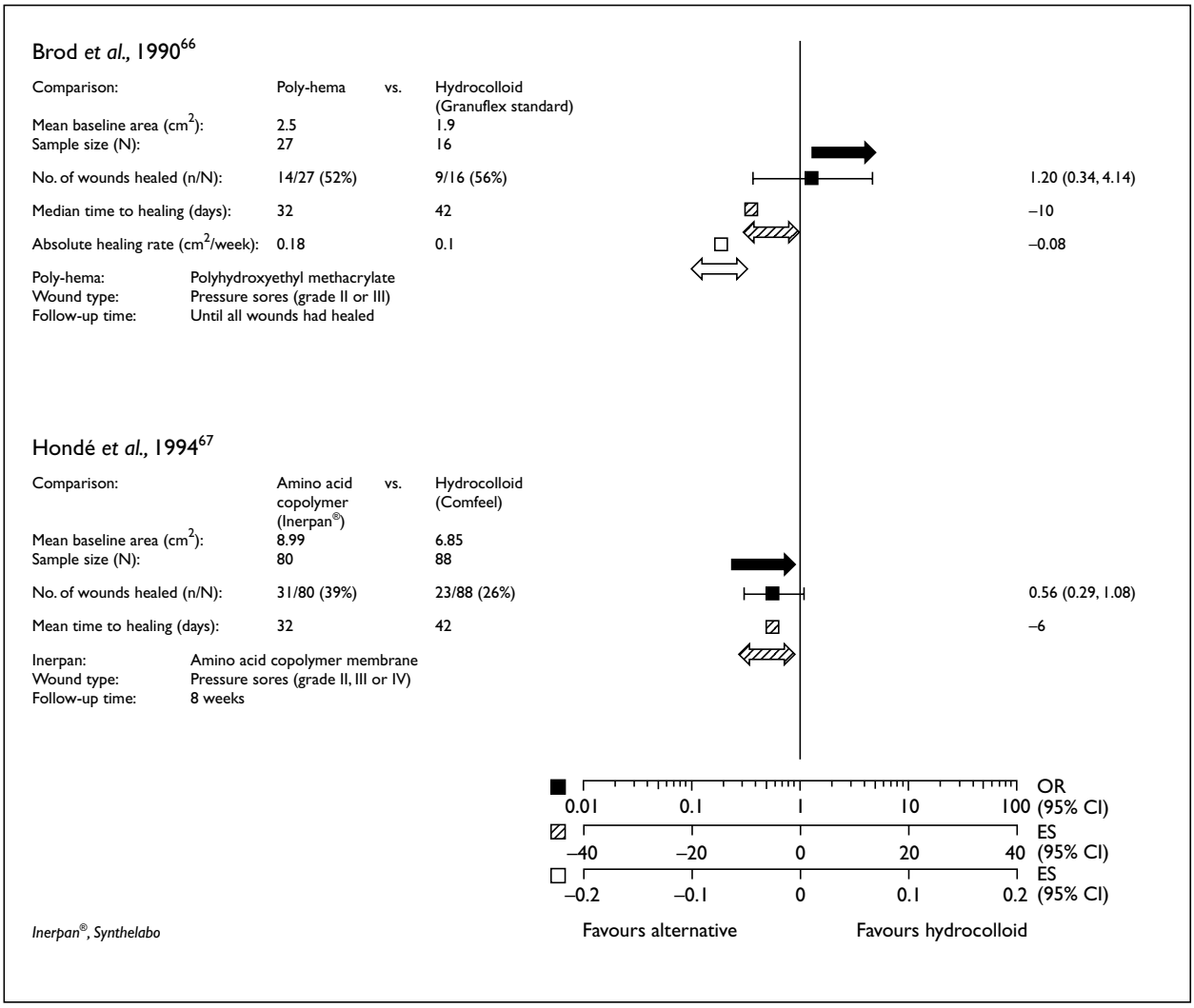

FIGURE 11 *Hydrocolloid dressings compared with alternative treatments for healing pressure sores*

information which indicated that participants had been randomised with allocation concealment was given in only 10% of trials.

Arterial leg ulcers

Dressing versus traditional or control

Gibson and co-workers[69] compared a hydrocolloid dressing with a knitted viscose dressing. There was no difference in healing rates but patients withdrew earlier from the knitted viscose dressing group than the hydrocolloid group due to pain (9/9 patients withdrew in a mean of 19 days in the knitted viscose group compared with 4/5 withdrawals due to pain and maceration in the hydrocolloid group (mean time to withdrawal, 104 days) (appendix 8, *Table 15*).

Topical agents versus placebo

Holzinger and co-workers[70] compared mononuclear cultured cells in a culture medium with the culture medium alone. There was a statistically significant improvement in the proportion of arterial ulcers healing during the trial period in the group treated with the cultured monocytes (appendix 8, *Table 16*).

Janssen[71] compared topical ketanserin with a placebo. There was a significantly higher rate of epithelialisation in the ketanserin group, but insufficient data on baseline size were given to allow any bias to be assessed. There were no data on the number of ulcers completely healed in the trial period (appendix 8, *Table 16*).

Undifferentiated leg ulcers

Thirteen trials studied patients with ulcers of diverse aetiologies without presenting the results according to the leg ulcer aetiology.

Dressing versus control

Three trials (seven reports) compared an interactive dressing with a traditional dressing.[72–78] In the one trial[72–75] comparing a hydrocolloid with saline gauze, a higher proportion of ulcers healed beneath the hydrocolloid (47% versus 13%), but this was not statistically significant (OR for healing, 5.7; 95% CI, 0.94–34.4). Mian and co-workers[76,77] reported a larger reduction in the wound area under collagen sponges but there were insufficient data to determine the significance of this result. Another comparison between a film and a saline gauze dressing found no significant effect of dressings on healing[78] (appendix 9, *Table 17*).

Dressing versus dressing

Four trials were head-to-head comparisons between dressings. Brandrup and co-workers[79] reported a larger percentage reduction in wound area under adhesive zinc oxide tape in a comparison with hydrocolloid dressings, but there were insufficient data to determine the significance of this result. A comparison between alginate and hydrocolloid fibrous dressings found no difference.[80] Palmieri[50] compared a collagen sponge dressing with dextranomer and found no difference in healing rates. There was no difference in healing rates between a hydrocellular foam and a hydrocolloid[62] (appendix 9, *Table 18*).

Topical agents versus control/ traditional treatments

Four trials compared topical agents with a placebo, or traditional treatment. Platelet-derived wound healing factor,[81,82] zinc oxide paste[83] and hyaluronic acid[84] were all found to heal a significantly greater proportion of ulcers over the trial period, but in each case the wound size bias at baseline favoured the experimental treatment group. No differences were detected in healing rates in a comparison between various treatments (including low adherent dressings and hydrocolloids) and fibrin glue[85] (appendix 9, *Table 19*).

Topical agents versus dressings

A single comparison of a growth hormone and a hydrocolloid dressing versus a hydrocolloid dressing alone found no difference in healing rates[86] (appendix 9, *Table 20*).

Venous leg ulcers

Forty-eight trials were identified: 21 trials reported 32 unique comparisons and 25 trials reported replicated comparisons.

Modern dressing versus traditional treatment

Eighteen trials compared dressings with traditional treatments (usually gauze-type dressings). Three trials reported the results of five 'unique' comparisons:

- activated charcoal and silver versus gauze[87]
- alginate dressing versus knitted viscose dressing[88]
- alginate versus zinc oxide stockinette[89]
- alginate versus zinc oxide cotton gauze bandage[89]
- zinc oxide stockinette versus zinc oxide cotton gauze bandage.[89]

The comparisons between alginate versus knitted viscose dressing,[88] activated charcoal and silver dressing,[87] and alginate against stockinette impregnated with zinc oxide paste[89] found no difference in proportion of ulcers healed over the trial period. However, Stacey and co-workers[89] did report that a cotton bandage impregnated with zinc oxide paste healed a higher proportion of ulcers over the trial period than either an alginate dressing or a zinc oxide-impregnated stockinette (*Figure 12*; appendix 10, *Table 21*).

Two trials compared foam dressings with traditional or control therapies.[90–92] One trial[91,92] found a reduction in wound area with a polyurethane foam dressing, which contrasted with a net increase in mean wound size under a sterile gauze compress. In the other trial[90] there was no significant difference in the proportion of ulcers healed using a hydrocellular foam compared with a knitted viscose dressing during the trial period (*Figure 13*; appendix 10, *Table 21*).

Two papers report comparisons between semipermeable film dressings and traditional or control therapies.[93,94] One trial[93] found a significantly greater reduction in wound area under a film dressing compared with treatment with an Unna's Boot (zinc oxide, calamine and gelatin paste) bandage. The other trial[94] found no significant difference in the proportion of ulcers healed either with a film dressing or paraffin-impregnated tulle (*Figure 13*; appendix 10, *Table 21*).

Nine trials compared hydrocolloid dressings with traditional or control dressings.[95–104] Of these nine trials, only one found a statistically significant increase in the proportion of ulcers healed over the trial period; this was for a comparison between a hydrocolloid dressing and paraffin-impregnated tulle. The groups in this trial, however, were not comparable at baseline, with larger ulcers being

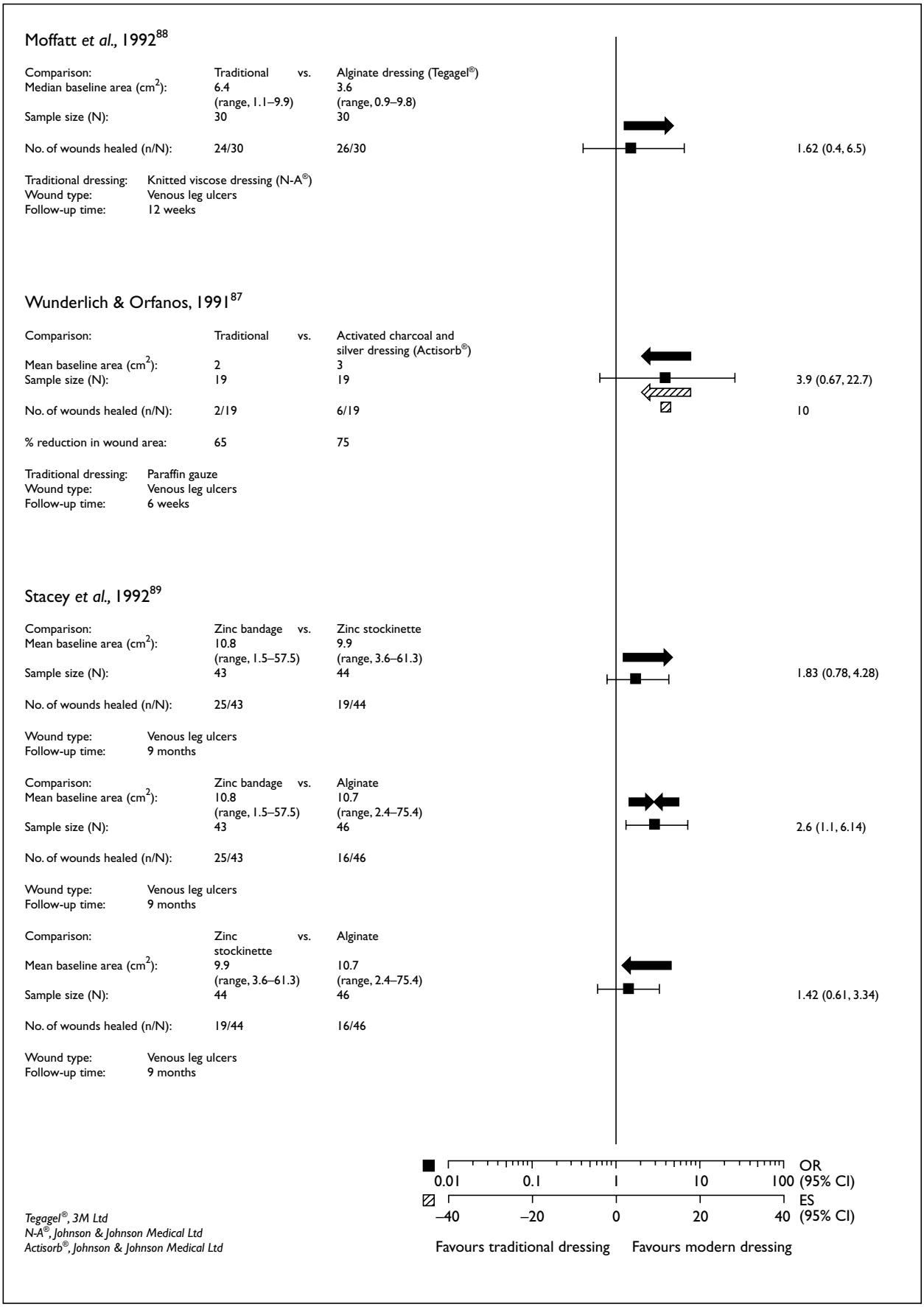

FIGURE 12 *Modern compared with traditional dressings for venous leg ulcers*

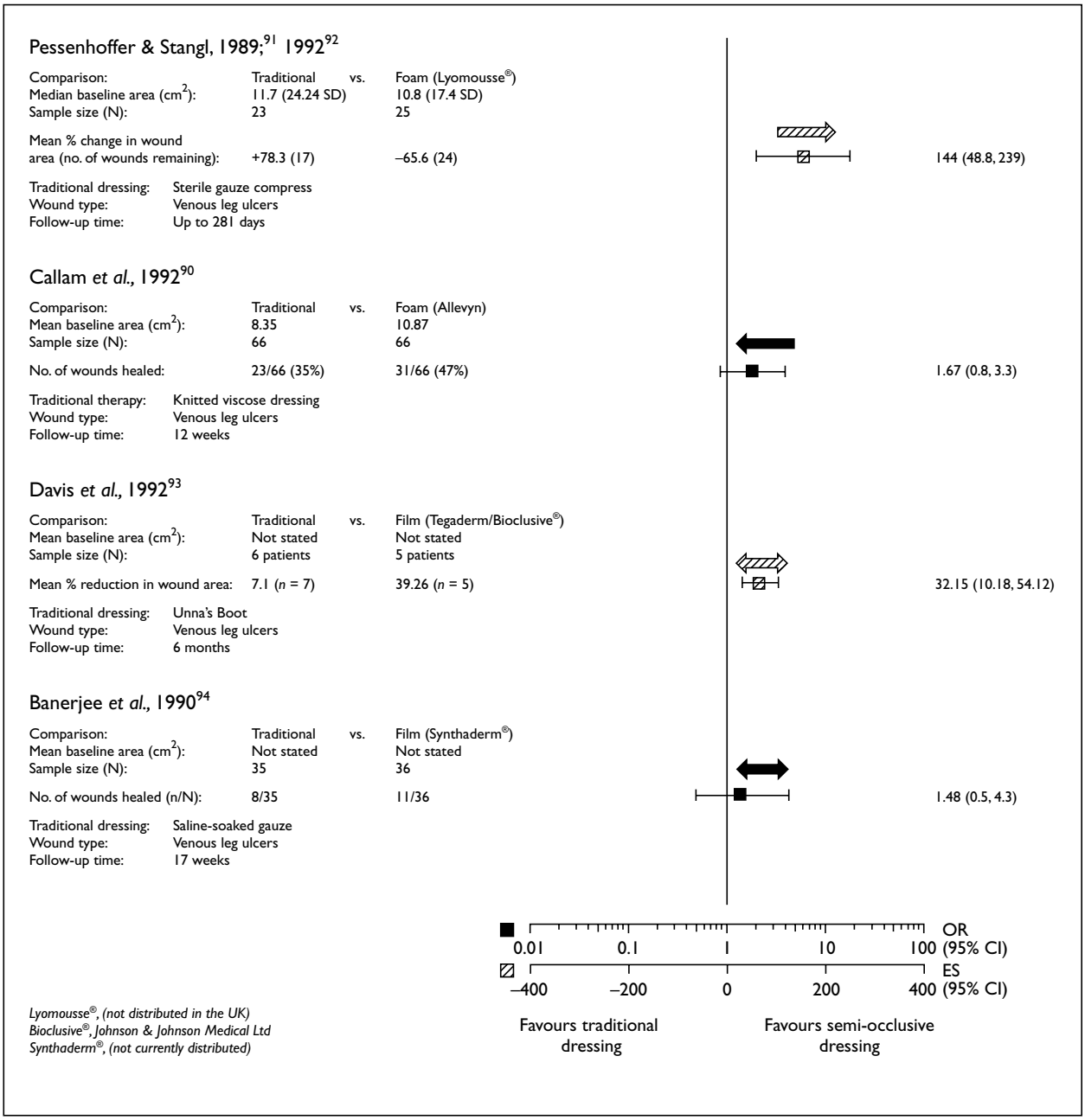

FIGURE 13 *Foam or film compared with control for venous leg ulcers*

allocated to the control group. The eight studies that provided data on the proportion of ulcers completely healed during the trial period were pooled using a random effects model. There was no significant difference in the proportion of ulcers healed at follow-up (pooled OR, 1.4; 95% CI, 0.83–2.34) (*Figure 14*; appendix 10, *Table 21*). A random effects model was used to estimate the overall ES, as it assumes that variation in the meta-analysis is a combination of random error within studies and variation between studies. Random effects models are more conservative than fixed effects models, giving estimates with wider CIs. As there was significant statistical heterogeneity in this meta-analysis (χ^2 for heterogeneity, 16.72; df = 7; $p = 0.019$), a random effects model is appropriate.

Sensitivity analysis was undertaken by further meta-analyses to explore what influence certain studies had on the overall analysis. Excluding the trial by Moffatt and co-workers,[97] in which the ulcers were more chronic (inclusion criteria included failure to heal with a four-layer regimen after 24 weeks, or failure to reduce ulcer size by a minimum of 20% in 12 weeks), yielded an OR

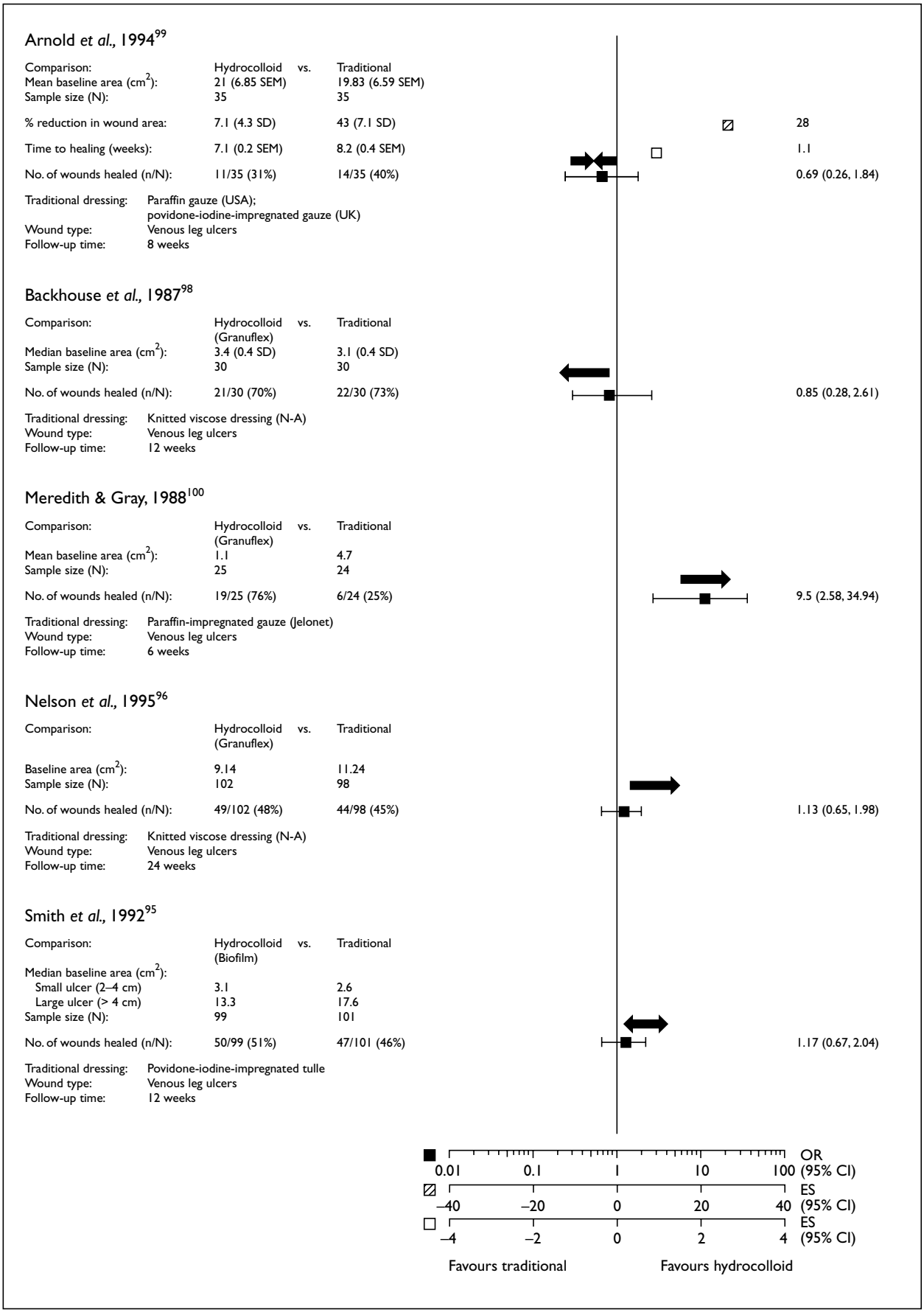

FIGURE 14 *Hydrocolloid compared with traditional dressing for venous leg ulcers*

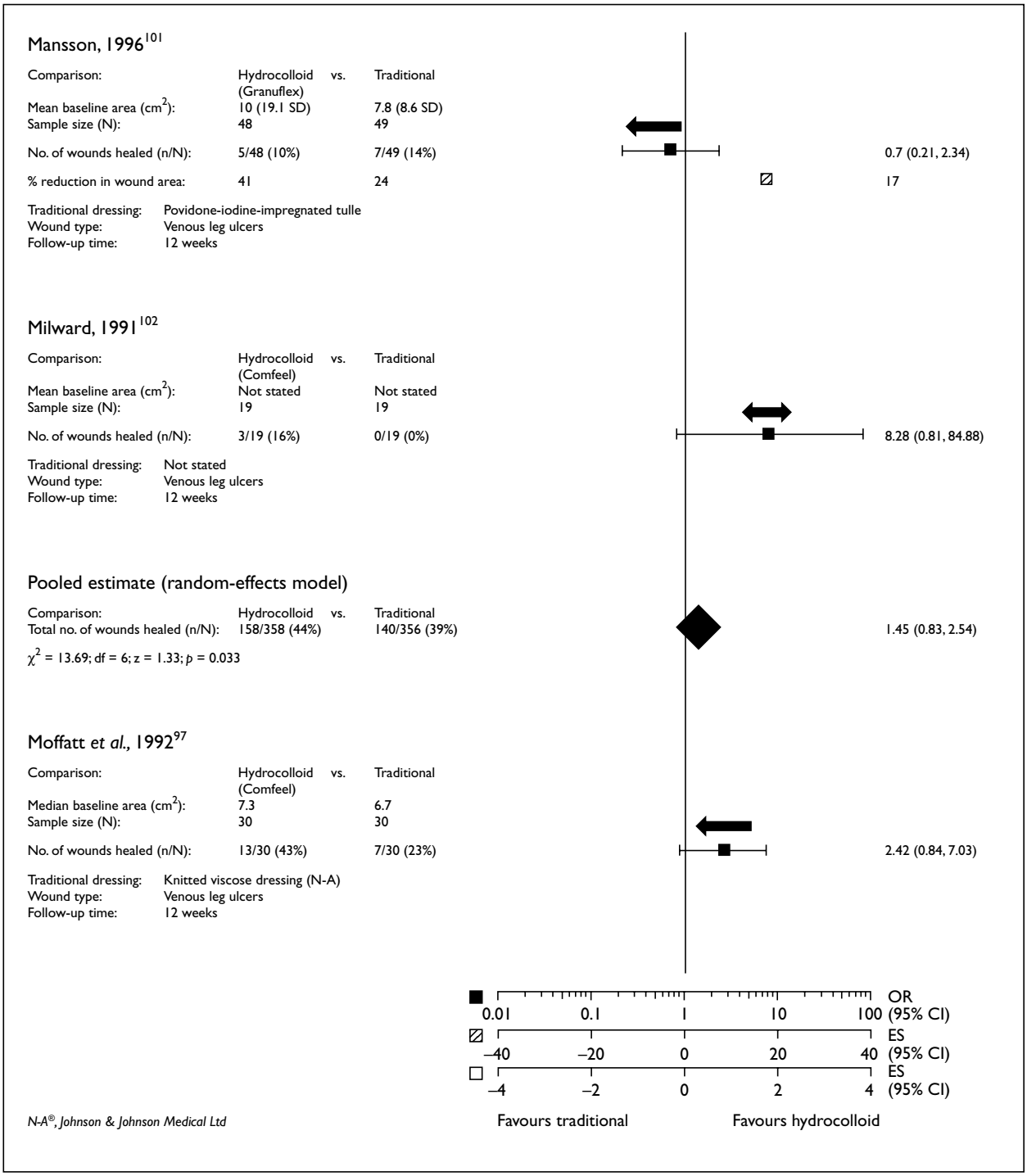

FIGURE 14 contd *Hydrocolloid compared with traditional dressing for venous leg ulcers*

for healing of 1.45 (95% CI, 0.83–2.54). Including the trial by Lindholm and co-workers,[72–75] in which both venous and mixed arterio/venous ulcers were assessed, produced an overall OR of 1.53 (95% CI, 0.91–2.57). Thus, the result of no significant difference is robust to the inclusion/exclusion of certain studies and we can reliably conclude that there is no evidence for a difference in venous ulcer healing beneath hydrocolloid dressings compared with traditional (tulle, knitted viscose or gauze-type) dressings.

Dressing versus dressing

Eleven trials were head-to-head comparisons of dressings. A significantly shorter healing time was reported with a collagen sponge dressing when compared with dextranomer beads.[50] There was no significant difference in the number of ulcers

healed under a lyophilised collagen dressing compared with a hydrocolloid dressing.[105] There was a larger reduction in wound area with the hydrocolloid, but insufficient data were given to allow this to be tested for statistical significance, and baseline ulcer size was not given (*Figure 15*; appendix 10, *Table 22*).

In a trial between a hydropolymer dressing and hydrocolloid dressing, similar numbers of leg ulcers were healed in both treatment groups.[65] The wounds in the hydropolymer dressing group had a greater reduction in actual wound area, but this was potentially confounded by the larger ulcer area at baseline in this group (the outcome as reported by the authors in terms of percentage reduction in wound area favoured the hydrocolloid). Similarly, Smith[106] found no difference in either the proportion of ulcers healing or change in ulcer size in a comparison of an unnamed alginate and a hydrocolloid dressing (*Figure 15*; appendix 10, *Table 22*).

A further six trials (eight reports) were identified which had head-to-head comparisons of dressings for venous leg ulcers.[107–114] Four trials compared hydrocolloid dressings. One trial found no significant difference in the proportion of ulcers healed in a comparison between a newer formulation hydrocolloid and a hydrocolloid incorporating calcium.[107] In a comparison between three hydrocolloid dressings (an original formulation, Granuflex; a newer formulation, Granuflex E; and a third hydrocolloid, Comfeel) sufficient data were not available to test the statistical significance of the reported results that indicated a greater reduction in wound area occurred with the improved hydrocolloid.[108–110] The mean reduction in ulcer area per day was highest with the Granuflex E dressing and lowest with the Comfeel dressing. However, data were not provided on baseline ulcer size, suggesting that confounding of the results by poor comparability of the groups for wound size at baseline cannot be ruled out (appendix 10, *Table 22*). A further two trials compared a hydrocolloid dressing (DuoDerm CGF®, ConvaTec Ltd, equivalent to Granuflex E) with alternative hydrocolloid dressings (Tegasorb®, 3M Ltd and Comfeel Plus®, Coloplast Ltd).[111,112] They found no significant difference in healing rates between the different products.

Two trials compared the same hydrocolloid dressing with foam dressings[113,114] and neither found a statistically significant difference in proportion of ulcers healed over the trial period. Pooling the data from the two trials again showed no difference in healing rates with either product (OR for healing, 1.0; 95% CI, 0.48–2.07) (*Figure 16*; appendix 10, *Table 22*).

Topical agents versus traditional/ control dressings

Two trials reported comparisons between hyaluronic acid and control dressings.[115,116] One reported a significant difference in the daily healing rate, which favoured the hyaluronic acid,[115] and the other found no significant difference between the two treatments in proportion of ulcers healed[116] (*Figure 17*; appendix 10, *Table 23*).

Five papers reported comparisons between biological dressings (cellular suspensions, porcine dermis or amnion) and traditional therapies.[70,117–119] Of these, two reported shorter median healing times with the biological dressing (porcine dermis and a tissue engineered product made from human skin) when compared with a paste bandage or a non-adherent dressing,[117,118] but there were insufficient data to calculate the statistical significance of these results. The other three trials found no difference in the proportion of ulcers healed in a comparison between autologous activated mononuclear cells and tissue culture medium,[70] keratinocyte allografts with paraffin gauze soaked in culture medium,[119] or amnion applied beneath saline gauze[70,119] (*Figure 18*; appendix 10, *Table 23*).

Six trials compared topical preparations with controls. The comparisons were:

- iloprost versus control[120,121]
- sucralfate versus control[122]
- allopurinol versus control[123]
- DMSO versus control[123]
- DL-cysteine versus control[124]
- DL-methionine-methyl sulphonium chloride[124]
- copper ointment versus silver versus cream[125] (*Figure 19*; appendix 10, *Table 23*).

Salim[124] compared DL-cysteine powder, DL-methionine-methyl sulphonium chloride and a placebo (inert powder). There was no significant difference in the proportion of ulcers healed with either treatment over the trial period. In a similar study Salim[123] reported a higher proportion of ulcers that healed with allopurinol (inert powder) and with DMSO powder compared with placebo. In both of these studies the healing rates were higher than those reported in any of the other trials (58–85% healed in 12 weeks when analysed on an ITT basis), and the patients were younger (mean age, 56–59 years). This may have consequences

Caprio *et al.*, 1995[105]

Comparison:	Hydrocolloid	vs.	Collagen
Mean baseline area (cm^2):	Not stated		Not stated
Sample size (N)*:	Not stated		Not stated
Absolute reduction in wound area (cm^2):	12.22		8.29
No. of wounds healed (n/N):	25		20

Wound type: Venous leg ulcers
Follow-up time: 8 weeks

93 patients with 98 ulcers

Banks *et al.*, 1996[65]

Comparison:	Hydrocolloid (Comfeel)	vs.	Hydropolymer (Tielle)
Median baseline area (cm^2):	3.35		4.31
Sample size (N):	50		50
No. of wounds healed (n/N):	19/50		18/50
Mean absolute reduction in woundarea (cm^2):	17.7		19.3
% reduction in wound area:	53		45

Wound type: Venous leg ulcers
Follow-up time: 13 weeks

Smith, 1994[106]

Comparison:	Hydrocolloid	vs.	Alginate
Mean baseline area (cm^2):	12.74		22.17
Sample size (N):	22		18
No. of wounds healed (n/N):	4/22		2/18
% reduction in wound area:	57.1		34.9

Wound type: Venous leg ulcers
Follow-up time: 6 weeks

Palmieri, 1992[50]

Comparison:	Dextranomer	vs.	Collagen sponge
Baseline area (cm^2):	Not stated		Not stated
Sample size (N):	24		24
Mean time to healing (days):	60		36

Wound type: Venous leg ulcers
Follow-up time: Unclear

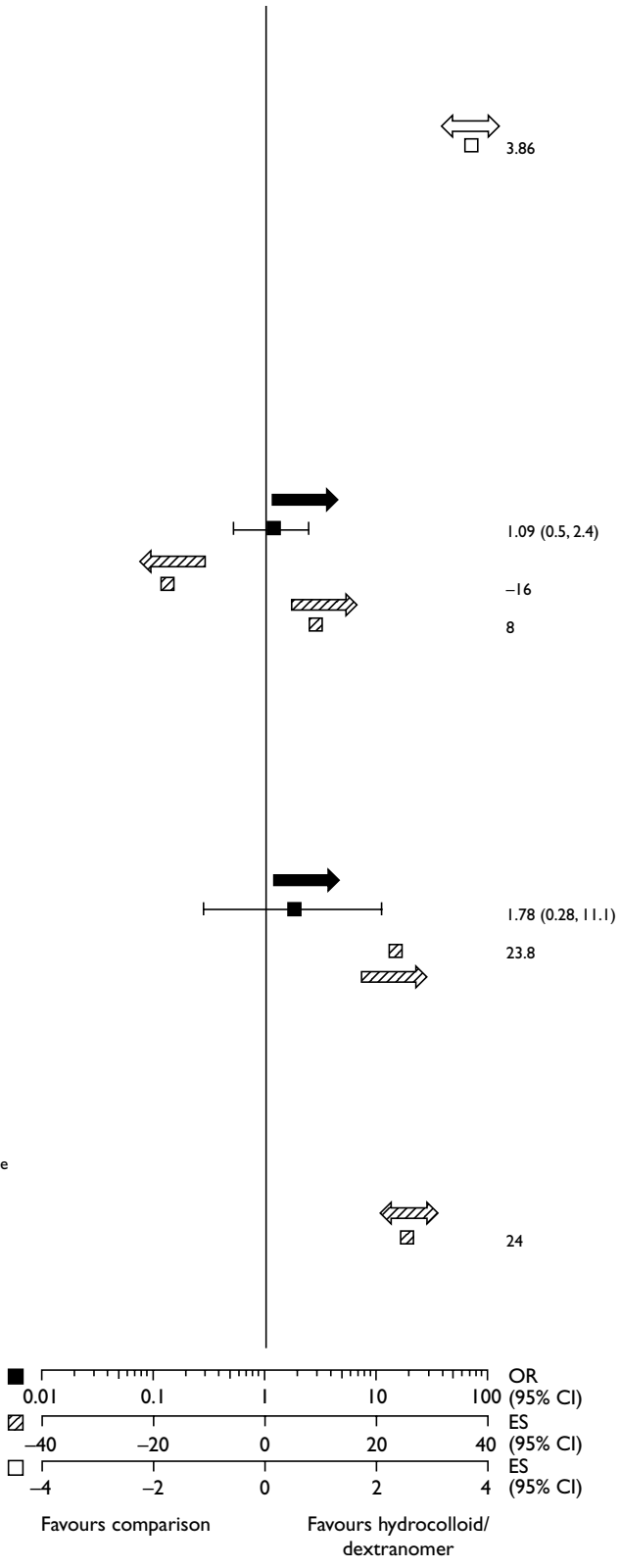

FIGURE 15 *Comparison of modern dressings for venous leg ulcer*

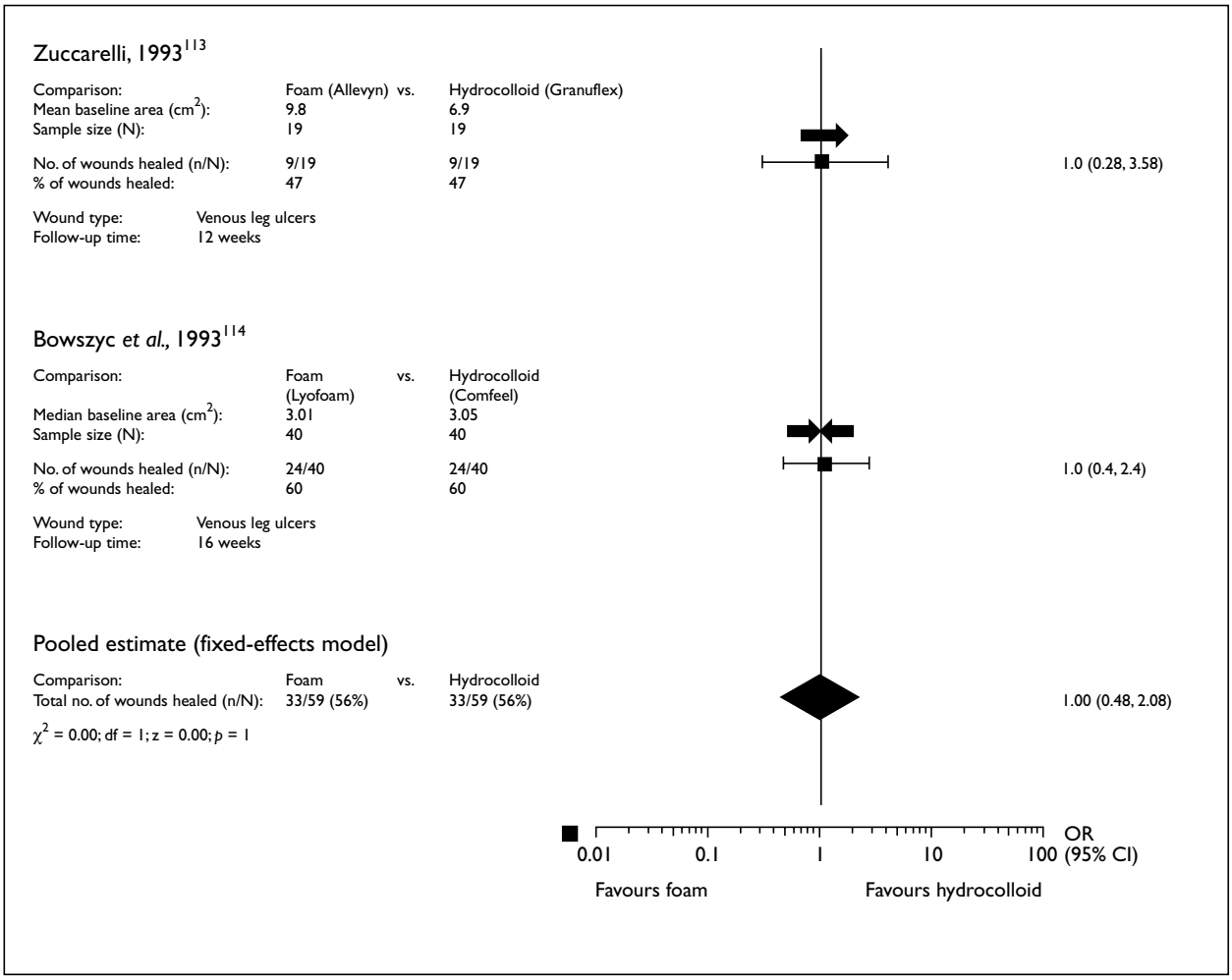

FIGURE 16 *Hydrocolloid compared with foam dressing for venous leg ulcer*

for the generalisability of the results to all leg ulcer patients treated in the UK.

Tsakayannis and co-workers[122] compared sucralfate ointment (a substance capable of binding basic fibroblast growth factor, and hence preventing its breakdown), with the cream vehicle alone and found no difference in the proportion of ulcers healed.

Werner-Schlenka and co-workers[120,121] reported two trials that evaluated topical iloprost. One trial[121] compared two solutions of iloprost (0.0005% and 0.002%), and in the other[120] patients received either 10 µg/ml (0.001%) for the first 3 days, increasing to 40 µg/ml (0.004%) for the rest of the study period, or placebo. There was no significant difference in either the proportion of ulcers healed or the reduction in ulcer area over the trial period (*Figure 20*; appendix 10, *Table 23*).

Bishop and co-workers[125] compared a tripeptide copper complex cream with silver sulphadiazine and a control of vehicle cream alone. He found no difference in the reduction in wound area with the copper cream but there was a reduction in wound area with the silver sulphadiazine compared with both the control and the copper complex (appendix 10, *Table 23*).

Topical agents versus placebo

Three trials (five reports) reported comparisons between growth factors and a placebo.[126–130] None found a significant difference for either the reduction in ulcer area or proportion of ulcers healed during the trial period. The trials by Freak and co-workers[127,128] and Rasmussen and co-workers[126,129] were similar in that they both compared three dose regimens of biosynthetic human growth hormone and placebo. Pooling the results from these two trials (using a fixed effect model) for the concentrations used (0.17 IU/ml versus placebo, 1.0 IU/ml versus placebo, and 11.2 IU/ml versus placebo) found no significant benefit for using the growth hormone at any concentration. The study by Falanga and co-workers[130]

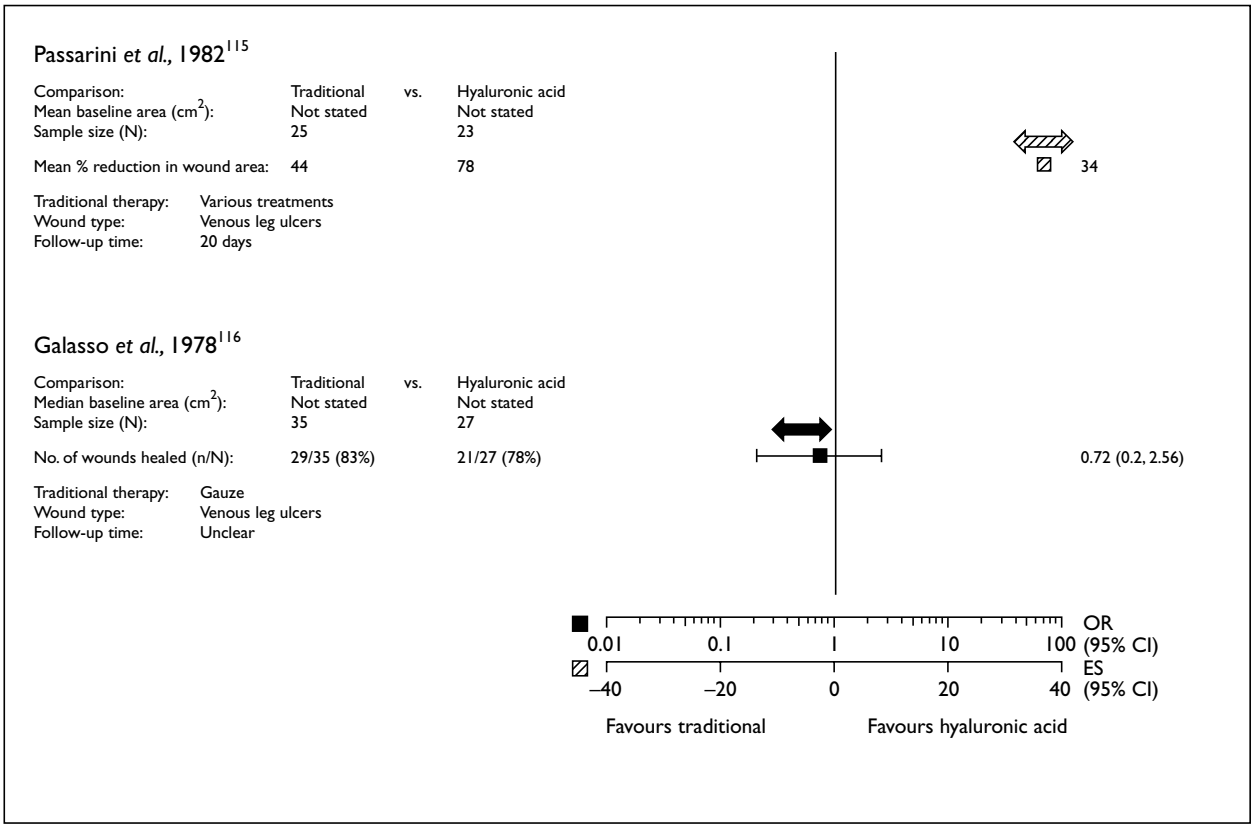

FIGURE 17 *Hyaluronic acid compared with traditional dressings for venous leg ulcers*

compared one dose of human recombinant epidermal growth factor with placebo (*Figure 21*; appendix 10, *Table 24*).

Topical agents versus dressings

Three trials compared dressings with topical preparations for venous ulcers. The comparisons were:

- cryopreserved cultured allografts versus hydrocolloid dressing[131]
- daily antiseptic versus collagen[132]
- magnesium sulphate paste versus hydrocolloid.[133]

Teepe and co-workers[131] compared a hydrocolloid dressing with cryopreserved cultured allografts. There was no difference in the proportion of ulcers healed, but cryopreserved cultured allografts were associated with a greater reduction in the percentage area of wound healed (*Figure 22*; appendix 10, *Table 25*).

A collagen dressing healed a higher proportion of ulcers than treatment with a daily application of antiseptic.[132] There was no significant difference in the proportion of ulcers healed in a comparison between magnesium sulphate paste and a hydrocolloid.[133] The rate of ulcer healing expressed as area epithelialised per day was reported as significantly higher with the hydrocolloid dressing, but baseline comparability for ulcer size at randomisation could not be estimated and the presence of underlying bias cannot therefore be excluded (*Figure 22*; appendix 10, *Table 25*).

Topical agent versus topical agent

Only three trials reported head-to-head comparisons of topical agents. The comparisons were:

- buffered acidifying ointment versus ointment[134]
- amino acid solution (two concentrations) versus saline (two concentrations)[135,136]
- copper versus silver.[125]

Wilson and co-workers[134] compared a buffered acidifying ointment with emulsifying ointment and found no difference in the numbers of ulcers healed. There was a higher healing rate (expressed as percentage area healed per day) in the buffered ointment group, but this was confounded by the inequalities in baseline ulcer area, which was biased towards the buffered ointment (appendix 10, *Table 26*).

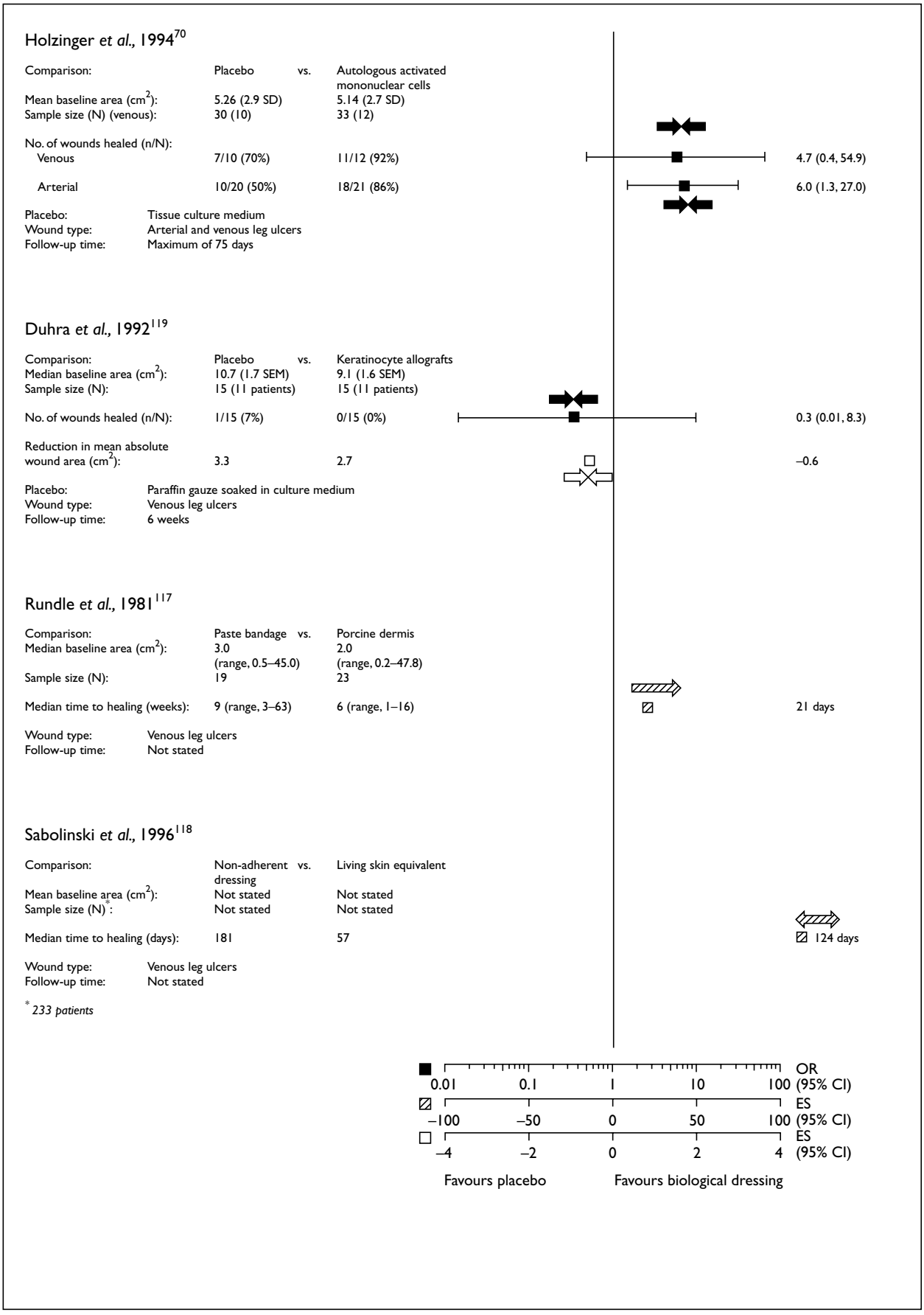

FIGURE 18 *Biologically active agents compared with placebo or traditional dressings for venous and arterial leg ulcers*

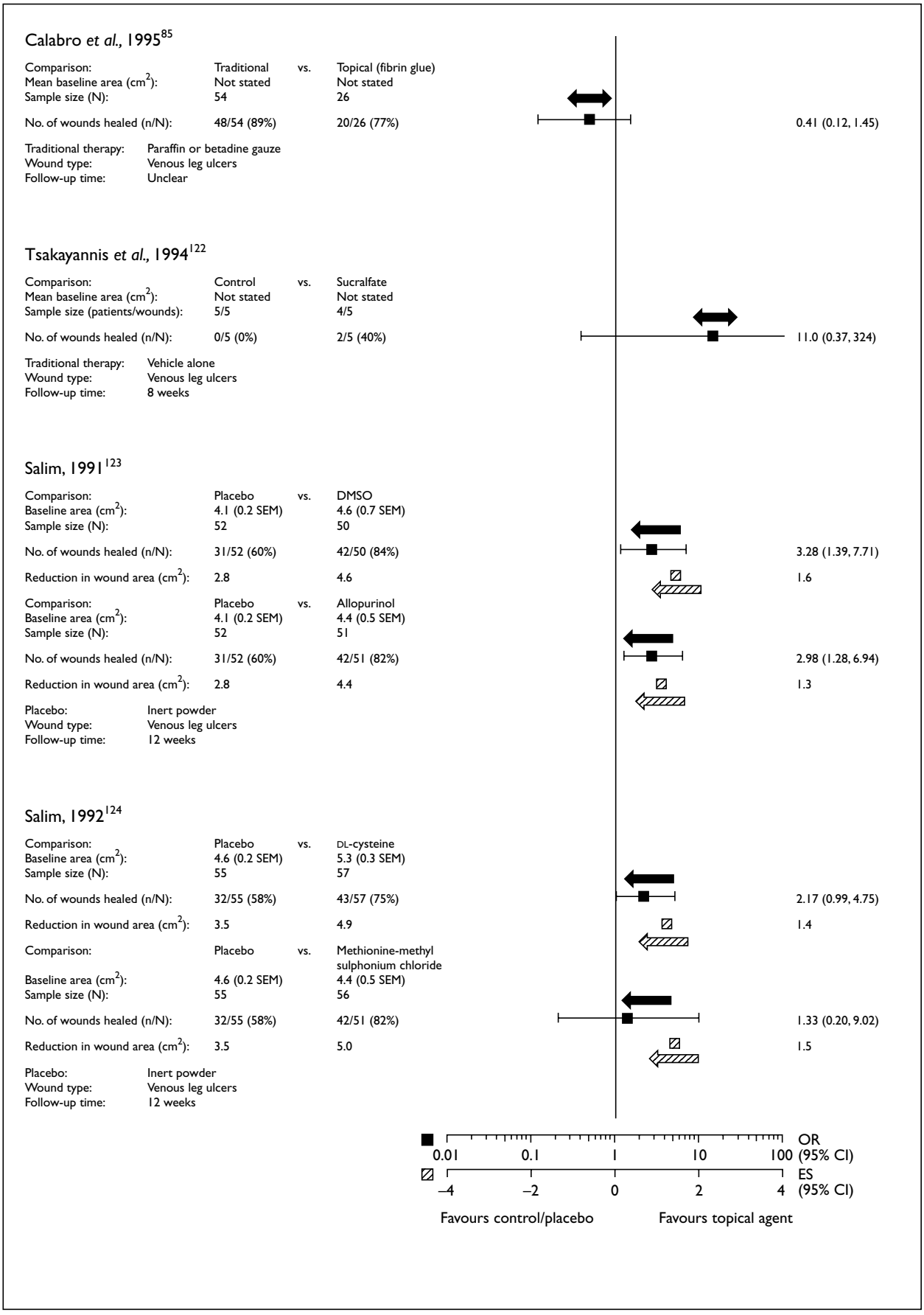

FIGURE 19 *Topical dressings compared with placebo/traditional dressings for venous leg ulcers*

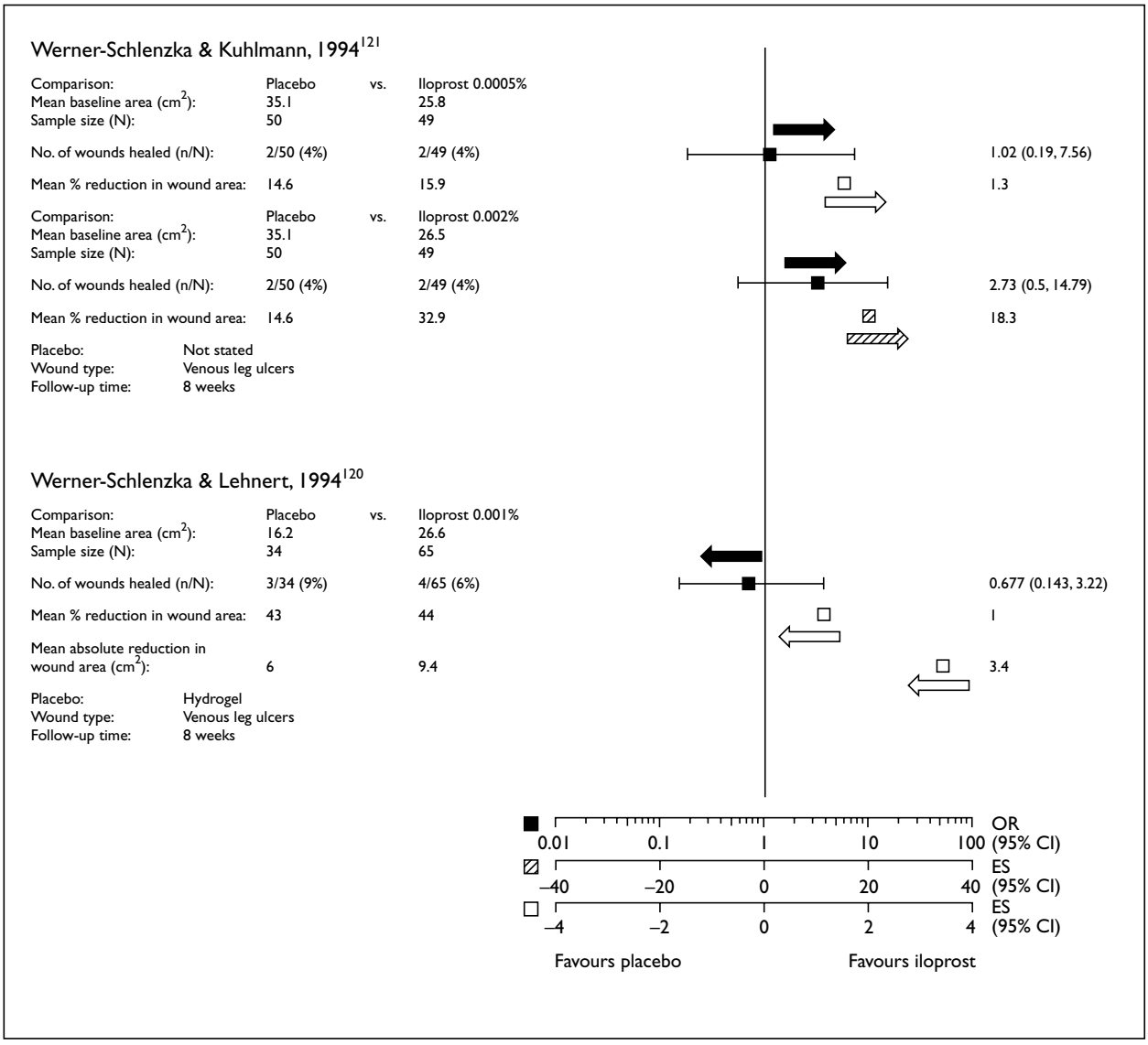

FIGURE 20 *Iloprost compared with placebo for venous leg ulcers*

Bulstrode and co-workers[135,136] compared two saline soaks (0.9% saline (150 mosmol/l), 5% saline (850 mosmol/l)) with two amino-acid soaks (150 mosmol/l and 850 mosmol/l) in hospitalised patients. Treatment with the amino acid soaks resulted in a significantly higher healing rate than with saline soaks, but the smaller mean ulcer size in the amino acid group may have introduced bias favouring the amino acid group (appendix 10, *Table 26*). There was no difference in the numbers of ulcers healing between the amino acid group or the saline-treated group.

Publication bias

Studies with 'positive' findings (i.e. those which show that a new treatment is more effective than a traditional treatment), may be more likely to get published than studies that have 'negative' results (i.e. traditional treatment is better) or 'null' results (i.e. no difference between new and traditional treatment). The published results, therefore, may not accurately reflect the results of all the trials that have been undertaken, and this potentially introduces bias into a summary of results. Publication bias is more likely to occur for small, single-centre trials, than large multicentre trials.

The presence of publication bias can be assessed by using a funnel plot, which graphically summarises the ORs and sample sizes of trials. Publication bias is thought unlikely when the ORs of small trials are equally distributed about the ORs of large trials. Asymmetry, however, indicates that there may be some trials missing from the set of

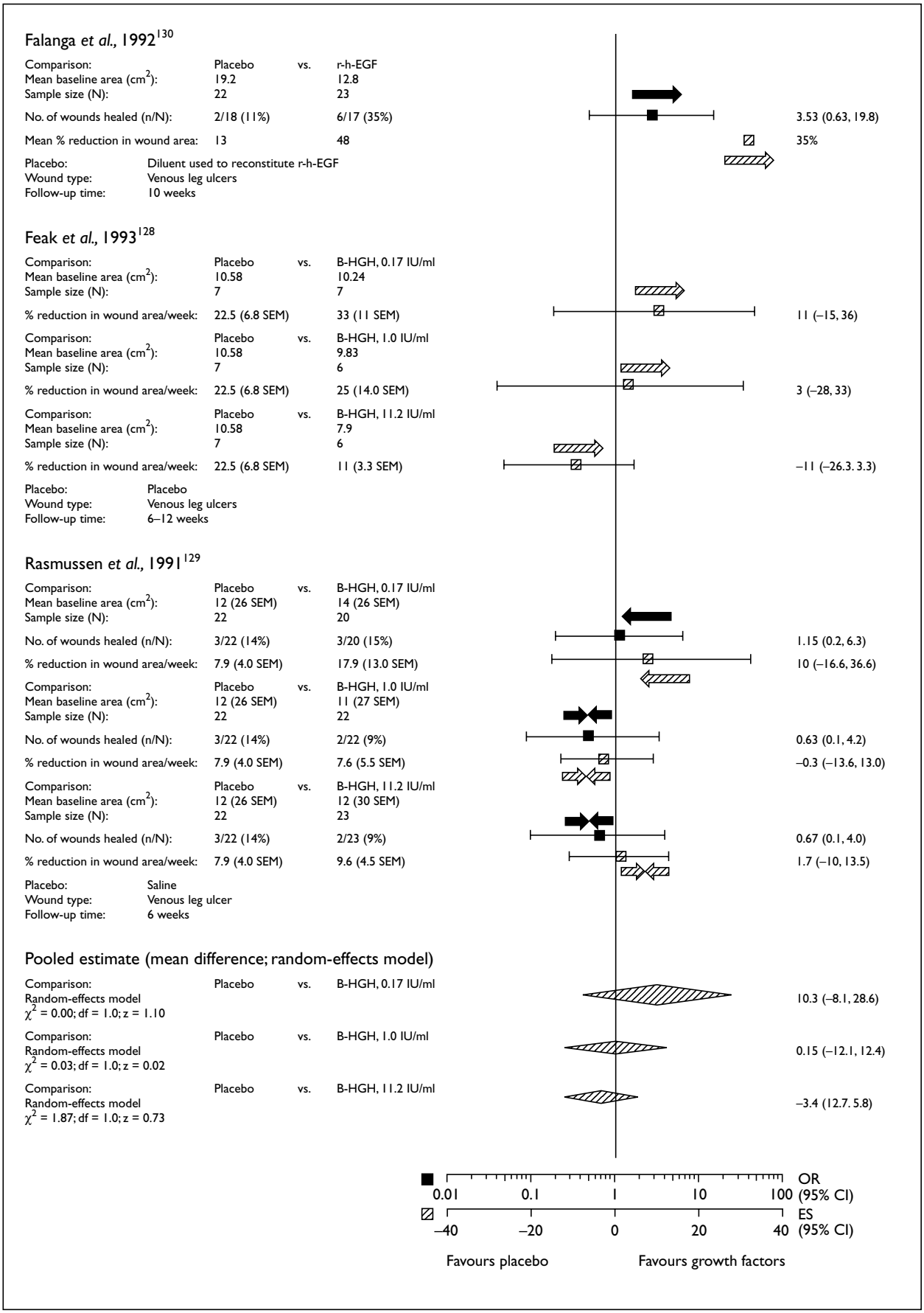

FIGURE 21 *Growth factors compared with placebo for venous leg ulcer*

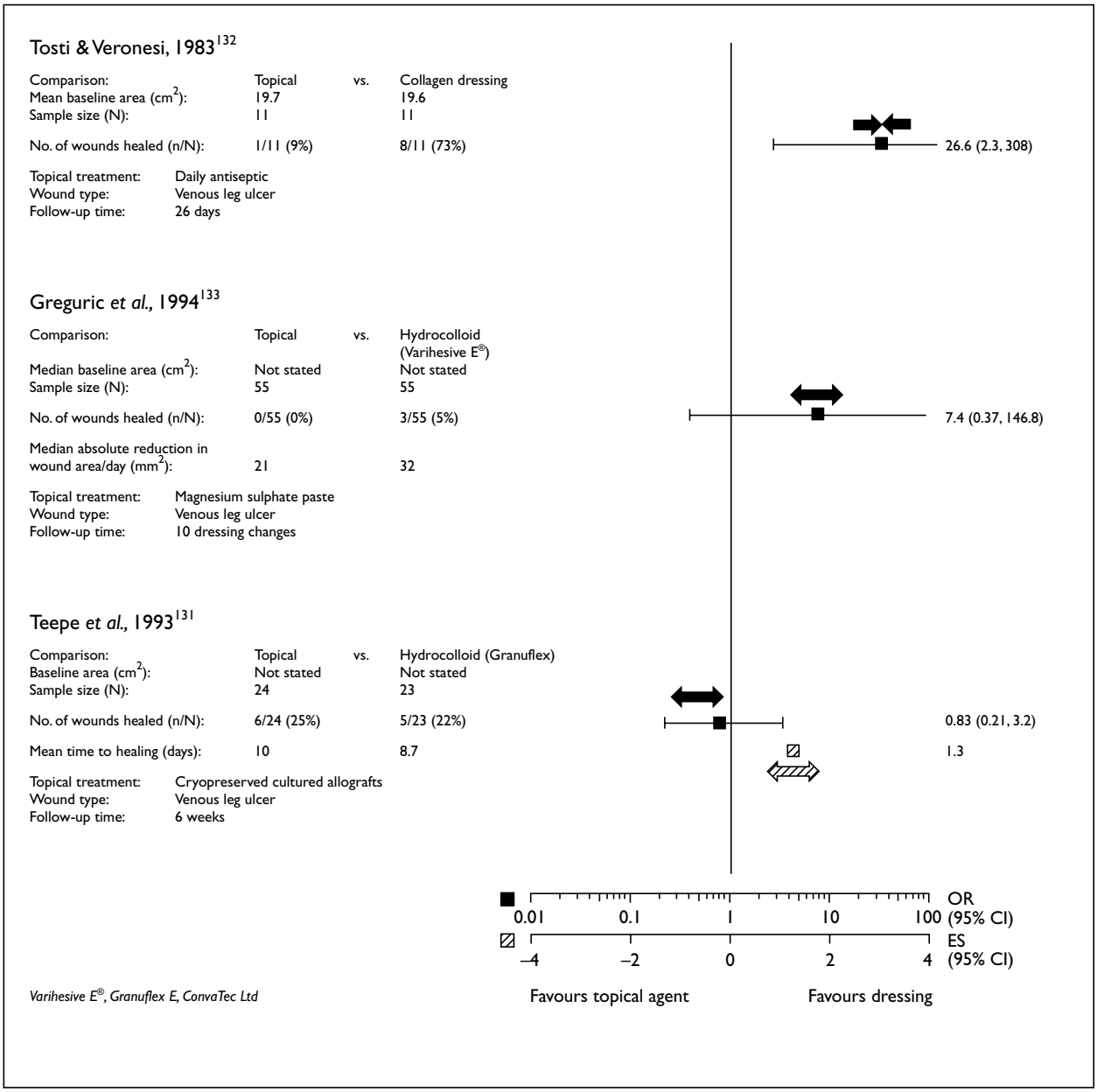

FIGURE 22 *Topical agents compared with dressings for venous leg ulcer*

published trials. The overall funnel plot of all studies that compared a traditional treatment with a modern therapy showed little evidence of asymmetry (*Figure 23*). However, for the subgroup of trials that compared a hydrocolloid dressing with a traditional treatment asymmetry was clearly evident (*Figures 23* and *24*). Publication bias for studies favouring hydrocolloid treatment may be responsible for this result.

Cost-effectiveness

The unit cost of dressings and topical agents are many times the cost of the traditional comparators such as gauze. The newer agents, however, require less-frequent dressing changes, for example every few days instead of twice daily, and hence require less nursing time. In addition, the cost of treating a wound for a long period with an inexpensive dressing may exceed that of treating the same wounds with a dressing that has a higher unit cost, but which is only required for a short period as a result of its effectiveness. These arguments have led to speculation that 'modern' dressings may be more cost-effective than gauze-type comparators.

Nine trials provided sufficient data on costs of treatment to allow cost-effectiveness analysis (appendix 11).

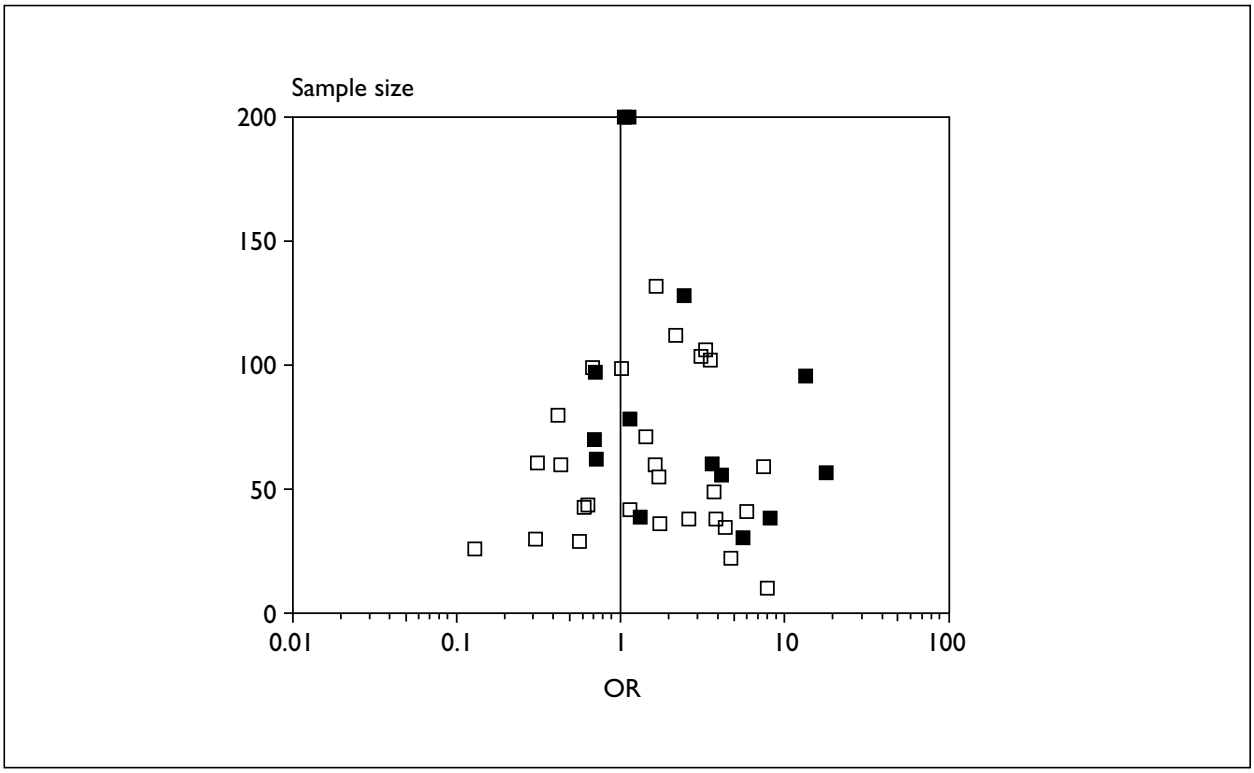

FIGURE 23 *A funnel plot for traditional treatments compared with modern dressings or topical agents for the treatment of leg ulcers and pressure sores. The plotted points indicate the ORs for wound healing for each trial included in the review. In the absence of publication bias the points should take the form of an upturned funnel; in the presence of publication bias, the points will be skewed in the direction of the bias (□, Traditional vs. dressing/topical agent other than hydrocolloid; ■, traditional vs. hydrocolloid dressing only)*

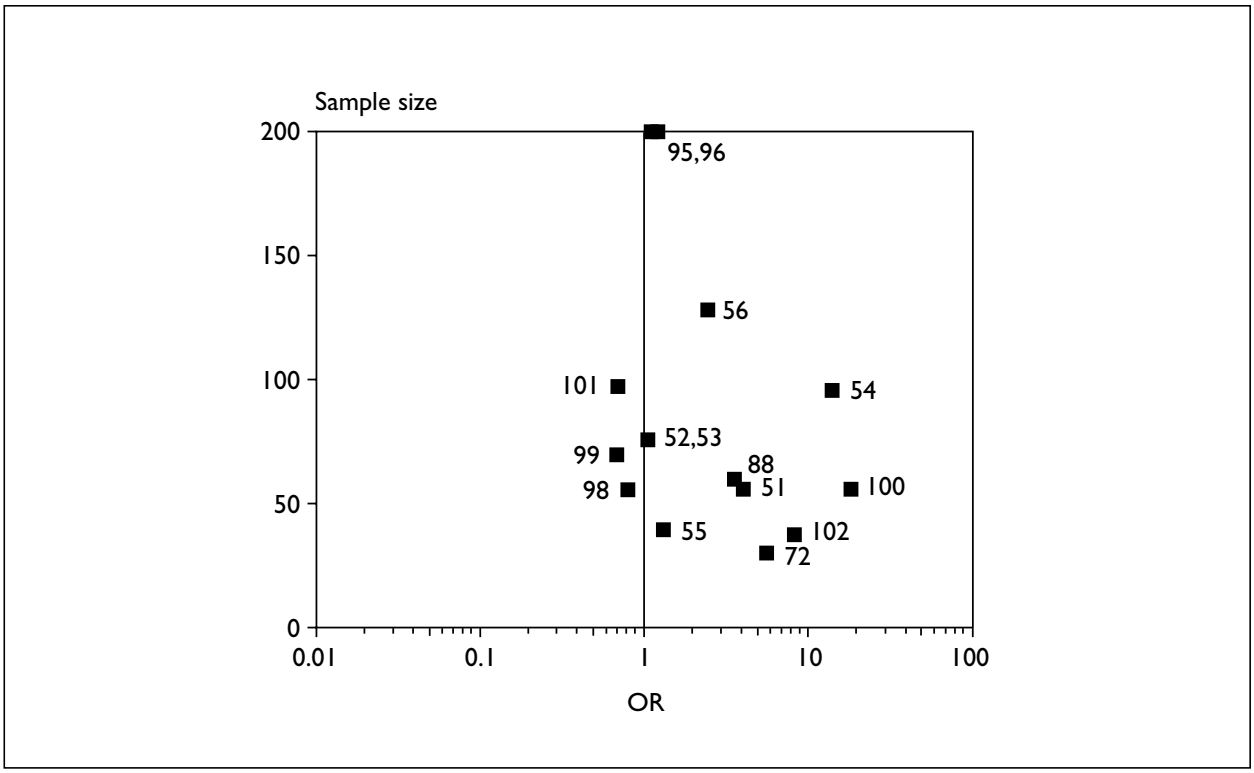

FIGURE 24 *A funnel plot for traditional treatments compared with hydrocolloid dressings for the treatment of leg ulcers and pressure sores*

Six trials evaluated cost-effectiveness in pressure sore treatments. These were saline gauze versus hydrocolloid (two comparisons), vapour-permeable dressing versus gauze, and foam dressing versus saline gauze.[54,55,58,59,61,62,72] One trial reported that the hydrocolloid was significantly cheaper than gauze.[72] Analysis of median costs in one study[55] demonstrated that hydrocolloids were cheaper, but that this was dependent upon price assumptions of nurse time. Another trial found that the moisture vapour-permeable dressing was more cost-effective than gauze for grade II pressure sores, but that there was no difference in outcome for grade III sores and in these patients gauze was more cost-effective, though due to the small sample size there is a possibility of a type 2 error (i.e. concluding that no difference in effectiveness exists when there is one).[58,59] In the third comparison the foam dressing was more effective but the cost-effectiveness was not tested for statistical significance even though the data were stochastic and therefore evaluable.[61]

Bale and co-workers[62] compared a hydrocolloid with a hydrocellular foam in 100 patients with pressure sores, leg ulcers or other chronic wounds. There was no evidence that the costs were different between the two groups. CIs on cost data overlapped, thus the incremental cost difference was not statistically significant.

Colwell and co-workers[54] compared a hydrocolloid with a moist gauze dressing. Costs of the dressing materials were higher in the hydrocolloid group, but fewer dressing changes were required. It would have been appropriate to statistically analyse the cost-effectiveness but this was not done.

Three papers reported cost-effectiveness data in leg ulcer trials. These were comparisons of:

- gauze versus hydrocolloid[102]
- paraffin-impregnated tulle versus hydrocolloid[100]
- alginate versus hydrocolloid.[106]

In the first two comparisons, the material costs were higher for patients treated with the traditional dressing. This may be due to the increased frequency of dressing changes in this group (five per week compared with two per week in Milward's[102] study). Given the current emphasis on applying compression bandages that are capable of remaining in place for up to 7 days it is unclear whether these results are relevant to current practice.

The comparison between a hydrocolloid dressing and foam dressing did not include any significance testing.

Overall a comparison between cost-effectiveness of hydrocolloid and gauze for venous leg ulcers and pressure sores was made using five trials.[54,55,72,100,102] The number of dressing changes required was lower for the hydrocolloid group than the gauze group. Estimates of incremental variable costs per patient of hydrocolloid versus gauze ranged from £14–19 cheaper than hydrocolloid dressing (in venous leg ulcers) to US$0.65–12 (£0.14–7.50) more expensive for pressure sores.

Chapter 4
Discussion

Quality of the studies

Quality assessment suggests that methodological flaws are an issue affecting the validity of most studies in chronic wound care. In general, the studies were too small to ensure that wounds of different sizes (and other prognostic variables) were evenly distributed across trial arms, resulting in a bias at baseline in most trials. The majority of studies also had a short follow-up and did not analyse the data by survival analysis, which would account for both whether and when a wound healed and which would be a more efficient method for estimating the rate of healing.

If future trials perpetuate many of the methodological flaws highlighted in this review, they are unlikely to provide the necessary evidence to determine an effective wound management strategy. The variability between wounds at baseline for prognostic variables including size, indicates that recruitment numbers need to be large and that trials should probably be multicentred. If small single-centred trials are to be continued they could be improved by the use of matched or stratified randomisation to ensure a similar distribution of wound sizes between treatment groups at baseline, and the data should be analysed by matched pairs analysis where appropriate. However, even with this improved design a trial still needs to be large enough to ensure comparability for both unknown and known confounding factors.

Pressure sores and surgical wounds healing by secondary intention

Overall, the number of studies meeting the inclusion criteria is surprisingly small considering the relatively open inclusion criteria. To have applied more rigorous criteria that addressed specific methodological issues would have reduced this small number even further, reflecting again the poor methodology in many of the trials. The small number of eligible trials, the lack of replication of comparisons, and the high variability in quality has prevented a detailed evaluation of many products in this review.

The focus for the majority of trials were pressure sores, while a smaller number assessed surgical wounds healing by secondary intention. Results from this latter group of studies were generally inconclusive and of poor quality suggesting that to date this type of wound has been poorly studied and that more research is required before decisions on effective treatments can be made. At present the only study to find a significant benefit for an intervention in the treatment of granulating surgical wounds suggests that wet-to-dry dressings, which are not commonly used in the UK, are more effective for healing than the topical application of aloe vera.[38] This trial is however, of little relevance in the UK where neither treatment is commonly used.

Studies that compare treatment with no treatment are very rare in the wound care literature because of concern over ethical issues associated with withholding treatment from a patient. In this review a single trial was included that assessed the incremental benefit of topical insulin when given in addition to routine supportive care (not including direct management of the wound) for the treatment of pressure sores.[39] This trial suggested that application of topical insulin did have a statistically significant benefit on wound healing. However, the results were of borderline statistical significance ($p = 0.05$) and this effect requires further exploration and replication.

The alternative to withholding treatment from a patient is to employ a placebo. In wound care trials such placebo treatments are unlikely to be inert as the application of the placebo or vehicle is likely to change the local environment of the wound, thereby modifying the biological processes associated with healing. A placebo is therefore not a substitute for withholding treatment in studies to determine the rationale for active treatment. The possible interaction between the vehicle and the healing process together with small sample size, may provide some explanation for why so few of the trials showed a statistically significant difference between an active treatment and a placebo. Another explanation for the lack of benefit with topical agents is that, provided the wound environment is conducive to healing, little can be gained from topical applications.

Several trials evaluated a hydrocolloid dressing with a traditional form of care for the treatment of pressure sores.[51–56] The combined OR showed that there was a statistically significant increase in the number of wounds healed when treated with the hydrocolloid dressing. However, the traditional treatments were poor comparators and are unlikely to be used with any frequency within the UK, thus the relevance for modern practice is unclear. The finding does however support current nursing practice, which has eschewed gauze-based dressings for the management of pressure sores.

Studies directly comparing topical agents for the treatment of pressure sores focused primarily on biologically active agents. Most of these trials were too small to provide conclusive results and their heterogeneity prevented pooling. At present the results are highly inconsistent both within and between trials, and further, better-designed studies with larger numbers are required.

Trials comparing hydrocolloids with hydrogels, which also absorb exudate and maintain a moist wound surface, are equivocal.[46,47]

Although several trials have compared alternative dressings with one another, none has shown a statistically significant difference between treatments.

Leg ulcers

There were insufficient trials evaluating arterial leg ulcers to recommend any particular dressing for general use. It is interesting to note that the trial by Gibson and co-workers[69] was abandoned due to rapid withdrawal from the trial in patients allocated to a knitted viscose dressing, though there was no difference in the proportion of ulcers healed.[69]

Both mononuclear cultured cells[70] and ketanserin[71] appeared to increase healing and these topical agents may be worthy of further study.

Only two trials in which the outcome was not reported by ulcer aetiology demonstrated a difference in healing rates. These trials suggested that treatment with a growth factor,[81,82] or hyaluronic acid[84] were beneficial treatments, but further evaluations of these preparations in venous ulcers alone showed no difference in healing rates.

Several trials evaluated a hydrocolloid dressing with a traditional dressing, usually paraffin-impregnated or knitted viscose gauze, in venous leg ulcers. Combining these studies in a meta-analysis using a random effects model showed that there was no difference between the treatments for the proportion of ulcers healed. The two largest trials in this analysis had ORs of 0.92 and 0.88 (odds of healing in the control). The smaller trials were, in general, more favourable for the hydrocolloid, suggesting that publication bias may be present.

These results conflict with the evidence for pressure sore treatment where the trials suggested that hydrocolloid dressings are more effective than traditional treatments. This apparent disparity between wound types may be related to method of application used for the traditional treatment. A dry dressing, such as a knitted viscose dressing, will produce a moist wound environment when used under a compression bandage, but may not when used over a pressure sore, depending on the secondary dressings used. Wu and co-workers[137] evaluated the moisture loss through compression bandage(s) and dressings. They found that a dry dressing covered with a multi-layer bandage still had a vastly reduced water vapour transmission rate compared with the ulcer surface or the dressing alone. Hence the sum total of materials applied over a wound may influence the conditions for healing at the wound surface. Many of the trials do not indicate whether secondary dressings were used, and as secondary dressings influence the interface conditions (e.g. temperature and moisture), then they may well influence healing rates.

There is currently insufficient evidence for either foam or film dressings having a beneficial effect on leg ulcer healing.

The one trial of a traditional zinc paste bandage with a modern (alginate) dressing found the zinc paste to be more effective. However, this may have been confounded by the greater magnitude of compression beneath the paste (effectively a multi-layer bandage system).[138]

Comparisons between modern dressings (hydrocolloid dressing, lyophilised collagen, collagen sponge, dextranomer, hydropolymer dressing, alginate dressing, hydrocellular foam, or polyurethane foam) did not indicate that any of the modern products was more effective than another.

Comparisons between topical agents and control treatments revealed only two preparations that produced a statistically significant difference in healing rates. These were DMSO and allopurinol,

both of which are oxygen free radical scavengers and were evaluated in the same trial. This trial needs to be replicated as the possibility that the comparator (an inert powder) may have had a detrimental effect on healing cannot be ruled out. DMSO has also been found to be effective in the treatment of diabetic foot ulcers and is worthy of further investigation.[139]

Biologically active topical agents, cells or membranes, were not found to be more effective than control dressings, such as paraffin gauze or culture medium. Similarly, growth factors were not demonstrated to be more effective than the tissue culture medium alone. This is in contrast with evaluations in the treatment of diabetic foot ulcers where they have been shown to be effective.[139] There may be two explanations for this.

- There may be differences in microcirculatory pathology between diabetic and venous ulcers; the former being amenable to treatment by growth factor.
- Growth factors are effective in the treatment of venous leg ulcers but the method of application and/or the power of the studies has resulted in a type 2 error. One striking difference in the application of growth factors to the two different wound types is the amount of debridement performed. During the treatment of diabetic foot ulcers, the skin and wound are frequently debrided to remove dead tissue.[139] A bleeding wound bed may be prepared prior to the application of the growth factors. Sharp debridement is rarely performed on venous leg ulcers and there was no pretreatment debridement in the trials reported here.[127–130]

Comparisons between dressings and topical agents indicated that a collagen dressing was preferable to the daily application of an antiseptic, while a hydrocolloid dressing healed more ulcers than magnesium paste. However, neither magnesium paste nor topical antiseptic are widely used today in the UK suggesting that the generalisability of these results is limited.

Publication bias

Funnel plots indicated that publication bias may be present for trials that compared hydrocolloids with traditional treatments. Asymmetry of the funnel plot can result from:[140]

- publication bias
- language bias
- multiple publication bias
- poor methodological design amongst smaller studies
- true heterogeneity (i.e. ES differs according to study size due to intensity of intervention)
- chance.

It is inevitable that despite searching for unpublished studies this review relies heavily on published trials. There is at present no standardised method to ensure a comprehensive search for unpublished data. Careful screening of all included studies was undertaken to reduce the potential for multiple studies and the search strategy was designed to improve sensitivity for non-English publications. True heterogeneity is unlikely to have influenced publication bias as the largest studies did not employ interventions that differed from the smaller ones. The almost uniform direction of the bias suggests that it was not purely a chance result. Poor methodological design of the smaller studies could be responsible for skewing the funnel plot; the smaller effect size demonstrated in the larger, more rigorous studies may indicate this. However, publication bias remains the most likely cause of asymmetry.[140] This type of bias may result from restrictive practices that prevent all the evaluative research entering the public domain. There are several reasons why publication bias could skew the data, two of the most common causes are:

- pharmaceutical companies are unlikely to favour the publication of sponsored trials where a result favoured the standard, generic alternative. Such suppression of publication is more likely for small, under-powered studies than for large, multicentre trials
- journal editors or researchers may not favour publication of small studies with 'null' (i.e. non-significant) results, particularly if they have been preceded by larger studies that indicated a positive benefit for an intervention. This does not appear to be the case here as the majority of trials were non-significant.

Analysis of the funnel plot by date of publication suggests there is little evidence that the year of publication was related to the outcome reported. In other words, commercial considerations may be the causative factor of asymmetry (*Figure 24*). Hydrocolloid dressings were amongst the first modern dressings to be intensively marketed and companies would be unlikely to publish research with negative results. A similar publication bias

may also exist for other commercially important dressings or topical agents other than hydrocolloid dressings, but the absence of multiple trials prevents an assessment by funnel plot.

Prospective registration of trials would help prevent this kind of publication bias and ensure the inclusion of unpublished trials in systematic reviews should become mandatory. Furthermore, those involved in primary research should make their data available to those undertaking systematic reviews.

Cost-effectiveness analysis

In appendix 11, *Table 27*, the results of studies that undertook a contemporaneous economic evaluation are summarised. Costs were considered in two ways. First, the variable cost of treatment was estimated. The variable cost is essentially the cost of the dressings used. Second, the differences in semi-fixed cost, in this instance nurse time, were estimated for each type of dressing. The rationale for considering these two costs separately is that changing to a dressing type that has a higher or lower purchase cost has immediate effects on the healthcare budget. In contrast, changing to a form of dressing that decreases or increases nurse time may not lead to budgetary changes, at least not in the short term. Thus, it is not always clear that the saving of a few minutes per patient, allows either budgetary saving or the nursing time to be re-allocated. Similarly, increases in dressing time of a similar magnitude may not lead to increases in healthcare budgets.

The economic studies identified in the review tended to be of poor quality.

- The studies were all small, which did not allow modest differences in costs to be identified.
- Statistical testing was not always carried out when it should have been.
- When statistical testing was undertaken, inappropriate tests were used.
- Average cost-effectiveness ratios were reported rather than incremental cost-effectiveness ratios.

The results of studies in both leg ulcers and pressure sores indicate that hydrocolloid dressings lead to fewer dressing changes compared with dry gauze. The differences in daily dressing changes between gauze and hydrocolloid are summarised in appendix 11, *Table 28*. On average the studies using hydrocolloids changed the dressing once every 2 days, while dry gauze was changed at least twice a day. In addition, the two UK trials in venous ulcers, in contrast to the non-UK study (appendix 11, *Table 29*), both indicated that hydrocolloid dressings were less expensive in dressing costs than the alternatives (i.e. dry gauze and paraffin gauze). Given that for pressure sores the least-expensive dressings (hydrocolloid) also appeared to be more effective, this is the most cost-effective treatment. For venous leg ulcers hydrocolloid dressings appeared more cost-effective as fewer dressing changes occurred in the studies (five compared with two). However, this may not reflect current UK practice, where dressing frequency is in part determined by the need to renew compression bandages. These are usually changed once or twice weekly.

Chapter 5
Conclusions

There is insufficient evidence of effectiveness of any particular dressing or topical agent for surgical wounds healing by secondary intention; the few studies there are, are small and of poor quality.

There is good evidence to suggest that hydrocolloid dressings are preferential to traditional therapies (i.e. saline gauze and antiseptics) for the treatment of pressure sores, but there may be publication bias, which has resulted from more trials with positive results being published than those with more negative results. Where topical agents have been compared with a placebo for the treatment of pressure sores there is no evidence to suggest that the active treatment has a pronounced effect on healing. Comparisons between topical agents and dressings for the treatment of pressure sores suggest that the application of a topical hydrogel promotes the healing above that experienced with an early hydrocolloid dressing but not for comparisons with the improved formulation of the dressing. Conversely topical polysaccharide beads were less effective than calcium alginate dressings. Comparisons between dressings were unable to show any statistically significant difference in healing rates.

Evidence for the effectiveness of dressings or topical agents in the healing of venous and arterial leg ulcers is also lacking. Meta-analysis of the studies comparing hydrocolloid and traditional dressings found no difference. In addition, other comparisons of modern products and traditional dressings found no significant differences.

Topical agents were, on the whole, not found to expedite the healing of venous leg ulcers. Only two preparations showed any evidence of effectiveness and may be worthy of further study, allopurinol and DMSO.

Of the two trials of the treatment of arterial leg ulcers, only the study evaluating a biological dressing was demonstrated to have an influence on healing. This single study needs replicating.

Poor methodological quality may not be the only reason the included studies failed to generate conclusive evidence for effectiveness. Another explanation is that given that certain environmental requirements are met (e.g. moisture and oxygen), further topical application makes little difference. Furthermore, significant local and patient factors that influence wound healing are not well understood and this lack of understanding may results in the wrong hypotheses/interventions being tested.

Implication for practice

There is little evidence to indicate which dressings or topical agents are the most effective in the treatment of chronic wounds. However, there is evidence to suggest that wet-to-dry dressings and saline soaks are not suitable for the treatment of pressure sores, and that hydrocolloids are more effective for this indication.

Recommendations for research

This review has highlighted several ways in which research methodology could be improved and has identified specific areas which commissioning groups may wish to consider prioritising for future research.

Improving study methodology

Much of the research concerning wound dressings and topical agents is of poor quality. In those trials reviewed, sample sizes were rarely sufficient to detect clinically important effects, and poor baseline comparability of the groups introduced bias. Several important messages can be identified for future studies.

- Recruitment numbers should be based on an *a priori* sample size calculation. In most trials the sample size is too small to find a statistically significant difference between treatment groups. Multicentre trials should be considered in order to recruit sufficient patient numbers. These large trials have been undertaken in other areas of health care, and although the field of wound care presents its own difficulties, there is no reason why such trials should not be successful. If these trials are to be commissioned they will require a strong infrastructure to provide

support, promote collaboration and establish a common knowledge base.

- A truly objective outcome measure should be used, for example time to complete healing of the wound, or wound healing should be expressed as both percentage and absolute change in area.

- For each patient a single reference wound should be selected. Multiple wounds on a patient should not be included in the analysis as they are not independent unless specialised statistical analysis is performed to separate out the effects of the intervention, (i.e. matched-pairs analysis).

- Experimental groups should be comparable at baseline. In small RCTs, randomisation alone will not achieve comparability; in such situations patients should be paired by prognostically important baseline characteristics and then the individuals of each pair randomised to treatment. Such randomisation is particularly important if ulcers of different aetiologies are to be assessed in the same trial.

- Head-to-head comparisons of modern wound dressings are required and should use agents that are recommended for wounds of a similar nature.

- A complete and thorough description of concurrent treatments including secondary dressings should be given in trial reports.

- Assessment of outcomes should be blind to treatment.

- Survival rate analysis should be adopted for all studies that assess wound healing.

- Studies to determine the biological mechanisms involved in wound healing are needed. A better understanding of the healing process may lead to the development of validated outcome measures.

- All trials should be published where possible. Those involved in primary research should make their data available to those undertaking systematic reviews.

- Future trials should include cost-effectiveness and quality of life assessments, as well as objective measures of dressing performance. These measures would encapsulate those aspects of patient quality of life on which wounds most impact and would be sensitive to meaningful changes in quality of life generated by a change in the wound, including post-healing of the wound.

- Economic evaluations should be incorporated within trials that are sufficiently large to detect appropriate economic and clinical outcomes.

- Economic evaluations should be planned carefully to include appropriate outcome measures (e.g. incremental cost-effectiveness ratio). Consultation with health economists would be advantageous.

Prioritising future research

The following questions have not been addressed by the trials conducted to date and are worth considering when prioritising primary research in the future.

- The development of valid and reliable condition-specific outcome measures for patients with chronic wounds, which would encapsulate those aspects of quality of life on which wounds most impact.

- Trials of hydrocolloid dressings versus contemporary comparators (rather than saline gauze) for the treatment of pressure sores.

- Trials evaluating the cost-effectiveness of hydrocolloid dressings versus traditional dressings in the treatment of recalcitrant, large or painful venous leg ulcers.

- Trials comparing modern with traditional dressings in the treatment of surgical wounds healing by secondary intention (including pilonidal sinuses).

- Trials of growth factors in the treatment of pressure sores and leg ulcers in which there is sharp debridement prior to treatment (as this therapy has shown some benefit in the treatment of diabetic ulcers).

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Appendix 1

Search strategies

MEDLINE search strategy

MEDLINE was searched for RCTs from 1966 to October 1997 using a mixture of free text terms and the following subject headings:

Wound infection
Pilonidal cyst
Wounds and injuries
Wound healing
Leg ulcer
Varicose ulcer
Skin ulcer
Decubitus

The MEDLINE search strategy used was as follows:

1. decubitus ulcer/ or foot ulcer/
2. leg ulcer/ or varicose ulcer/
3. pilonidal cyst/
4. skin ulcer/
5. diabetic foot/
6. ((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer$).tw.
7. ((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer$).tw.
8. ((pressure or bed) adj sore$).tw.
9. ((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore$).tw.
10. ((diabetic adj foot) or (cavity adj wound)).tw.
11. ((varicose or leg or skin) adj ulcer$).tw.
12. (decubitus or (chronic adj wound$)).tw.
13. ((sinus adj wound$) or (cavity adj wound$)).tw.
14. or/1–13
15. debridement/ or biological dressings/ or bandages/
16. occlusive dressings/ or clothing/ or wound healing/
17. antibiotics/ or growth substances/ or platelet-derived growth factor/
18. fibroblast growth factor/ or electrical stimulation therapy.ti,ab,sh.
19. lasers/ or nutrition/ or surgery/ or surgery, plastic/
20. surgical flaps/ or skin transplantations/ or homeopathy/ or homeopathic/
21. acupuncture therapy/ or acupuncture/ or alternative medicine/
22. alternative medicine/ or massage/ or iloprost/ or alginates/
23. zinc/ or zinc oxide/ or ointments/ or anti-infective agents/
24. dermatologic agents/ or colloids/ or cushions/ or wheelchairs/
25. beds/ or wound dressings/
26. (debridement or dressing$ or compress$ or cream$ or (growth adj factor$)).tw.
27. (pressure-relie$ or (recombinant adj protein$) or bandag$ or stocking$).tw.
28. (antibiotic$ or (electric adj therapy) or laser$ or nutrition$ or surg$).tw.
29. (homeopath$ or acupunture or massage or reflexology or ultrasound).tw.
30. (iloprost or alginate$ or zinc or paste$ or ointment$ or hydrocolloid$).tw.
31. ((compression adj therapy) or (compression adj bandag$) or wrap$).tw.
32. (bed$ or mattress$ or wheelchair$ or (wheel adj chair) or cushion$).tw.
33. ((wound adj dressing$) or vitamin$ or bind$ or gauze$ or heals or healing).tw.
34. (diet or lotion$ or infect$ or reduc$ or (wound adj healing)).tw.
35. (treat$ or prevent$ or epidemiol$ or aetiol$ or etiol$ or therap$ or prevalence or incidence).tw.
36. or/15–35
37. 14 and 36
38. random allocation/ or randomized controlled trials/
39. controlled clinical trials/ or clinical trials phase I/ or clinical trials phase II/
40. clinical trials phase III/ or clinical trials phase IV/ or clinical trials overviews/
41. single-blind method/ or double-blind method/
42. publication bias/ or review/ or review, academic/
43. review tutorial/ or meta-analysis/ or systematic review/
44. ((random$ adj controlled adj trial$) or (prospective adj random$)).tw.
45. ((random adj allocation) or random$ or (clinical adj trial$) or control$).tw.
46. ((standard adj treatment) or compar$ or single-blind$ or double-blind$).tw.
47. (blind$ or placebo$ or systematic$ or (systematic adj review)).tw.
48. (randomized controlled trial or clinical trial).pt. or comparative study.sh.
49. or/38–48

50. 37 and 49
51. limit 50 to human
52. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
53. peptic ulcer/ or duodenal ulcer/ or stomach ulcer/
54. ((peptic adj ulcer) or (duodenal adj ulcer) or traum$).tw.
55. ((aortocaval adj fistula) or (arteriovenous adj fistula)).tw.
56. (bite adj wound$).tw.
57. or/52-56
58. 51 not 57

CINAHL search strategy

The Cumulative Index of Nursing and Allied Health Literature (CINAHL) search strategy was as follows:

1. pressure ulcer/ or foot ulcer/ or leg ulcer/ or skin ulcer/
2. diabetic foot/ or diabetic neuropathies/
3. diabetic angiopathies/ or diabetes mellitus/co
4. pilonidal cyst/ or surgical wound infection/
5. ((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer$).tw.
6. ((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer$).tw.
7. ((pressure or bed) adj sore$).tw.
8. ((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore).tw.
9. ((diabetic adj foot) or (cavity adj wound)).tw.
10. ((varicose or leg or skin) adj ulcer$).tw.
11. (decubitus or (chronic adj wound$)).tw.
12. ((sinus adj wound$) or (cavity adj wound$)).tw.
13. or/1–12
14. debridement/ or biological dressings/ or occlusive dressings/
15. (bandages.ti,sh,ab,it. and "Bandages and Dressings"/) or
16. compression garments/ or antibiotics/
17. electric stimulation/ or Laser Surgery/ or lasers/th lasers/ or Nutrition Care (Saba HHCC)/ or diet therapy/ or Nutrition Therapy (Iowa NIC)/
18. surgery, reconstructive/ or surgery, plastic/ or surgical flaps/
19. surgical stapling/ or skin transplantation/ or alternative therapies/
20. acupuncture/ or massage/ or zinc/ or ointments/
21. antiinfective agents, local/ or antibiotics/ or dermatologic agents/
22. dermatology nursing/ or colloids/ or beds and mattresses/
23. flotation beds/ or wheelchairs/ or positioning:wheelchair/ or positioning:therapy/
24. patient positioning/ or positioning/ or wound care/ or wound healing/
25. (debridement or dressing$ or compress$ or cream$).tw.
26. ((growth adj factor$) or pressure relie$ or (recombinant adj protein$) or bandag$).tw.
27. (stocking$ or antibiotic$ or (electric adj therapy) or laser$ or nutrition$ or surg$).tw.
28. (iloprost or alginate$ or zinc or paste$ or ointment$ or hydrocolloid$).tw.
29. ((compression adj therapy) or (compression adj bandag$) or wrap$).tw.
30. (bed$ or mattress$ or wheelchair$ or (wheel adj chair) or cushion$).tw.
31. ((wound adj dressing$) or vitamin$ or bind$ or gauze$ or heals or healing).tw.
32. (diet or lotion$ or infect$ or reduc$ or etiol$ or (wound adj healing)).tw.
33. (treat$ or prevent$ or epidemiol$ or aetiol$ or therap$ or prevalence or incidence).tw.
34. "Bandages and Dressings"/ or skin transplantation/ or homeopathy/ or ointments/ or "beds and mattresses"/
35. or/14–34
36. 13 and 35
37. clinical trials/ or single-blind studies/ or double-blind studies/
38. control group/ or placebos/ or meta analysis/
39. ((random$ adj clinical adj trial$) or (prospective adj random$)).tw.
40. ((random adj allocation) or random$ or controlled clinical trial$ or control).tw.
41. (comparison group$ or (standard adj treatment) or compar$).tw.
42. (single-blind$ or (single adj blind) or double-blind or (double adj blind)).tw.
43. (blind$ or placebo$ or systematic or (systematic adj review)).tw.
44. (meta analysis or meta-analysis).tw. or (trials or trial or prospective).tw.
45. (clinical trials).sh. or (comparative studies).sh.
46. or/37–45
47. 36 and 46
48. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
49. peptic ulcer/ or duodenal ulcer/
50. ((peptic adj ulcer) or (duodenal adj ulcer) or trauma).tw.
51. (burn$ or (gunshot adj wound$) or (corneal adj ulcer) or dentist$ or (bite adj wound)).tw.
52. or/48-51
53. 47 not 52

Additional databases searched

ISI Science Citation Index (on BIDS)

BIOSIS (on Silver Platter)

British Diabetic Association Database

CISCOM, the database of the Research Council for Complementary Medicine

Cochrane Database of Systematic Reviews (CDSR)

Cochrane Wounds Group register of trials

Current Research in Britain (CRIB)

Database of Abstract of Reviews of Effectiveness (DARE)

Dissertation Abstracts

DHData (on Datastar, The Dialog Corporation)

EconLit

EMBASE (on Datastar, The Dialog Corporation)

Index to Scientific and Technical Proceedings (searched on BIDS)

National Research Register (to locate ongoing research in NHS)

NHS Economic Evaluation Database (NHS CRD)

Royal College of Nursing Database (CD-ROM)

System for Information on Grey Literature in Europe (SIGLE, on Blaise Line)

Appendix 2

Expert advisory panel

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*Also commented on a draft of this review and provided helpful comments.

In addition, Dr Keith Moore, Wound Healing Research Unit, University of Wales College of Medicine, University Department of Surgery, Cardiff, commented on parts of this review.

Appendix 3

Excluded studies

TABLE 3 *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Anzai T, Shiratori A, Ohtomo E, Honda S, Yamamoto T, Nishikawa T, *et al.* Evaluation of clinical utility of N1-009 on various cutaneous ulcers. Comparative study with base. 1989:133–4.	N1-009 vs. base	For consideration in review of antimicrobials
Atri SC, Misra J, Bisht D, Misra K. Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. *Surgery* 1989;**108**(3):508–12.	Homologous platelet factors HPDWHF silver sulfadiazine dressing	Non-comparative trial
Attwood AI. Calcium alginate dressing accelerates split skin graft donor site healing. *Br J Plast Surg* 1989;**42**(4):373–9.	Calcium alginate dressing	Not an RCT. Donor sites not considered
Barnes J, Burns K. Management of pressure sores: a comparison of Granuflex hydrocolloid dressing and Granuflex E hydrocolloid dressing. Going into the '90's: The Pharmacist and Wound Care. Eurosciences Communication, 1992:19–21.	Hydrocolloid	Not possible to determine the number of ulcers improved or healed
Barnett AH, Odugbesan O. Seaweed-based dressings in the management of leg ulcers and other wounds. *Intensive Ther Clin Monit* 1988;**9**:70–6.	Alginate fibre	Review paper
Beaconsfield T, Genbacev O, Taylor RS. The treatment of long-standing venous ulcers with an extract of early placenta – pilot study. *Phlebology* 1991;**6**:153–8.	Placental cream	No data on proportion healed in control group
Berry DP, Bale S, Harding KG. Dressings for treating cavity wounds. *J Wound Care* 1996;**5**(1):10–13.	Polyurethane foam vs. alginate	Subjective outcome measure
Blair SD, Wright DD, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. *BMJ* 1988;**297**(6657):1159–61.	Four-layer bandage	Considered for bandage review
Brady SM. Management of pressure sores with occlusive dressings in a select population. *Nurs Manag* 1987;**18**:47–50.	Duoderm or Opsite vs. traditional dressing	Did not measure healing rate
Bucknall T. Experimental and clinical studies on abdominal wound infection [unpulished PhD thesis]. London, UK: London University; 1981:196–252.	Monofilament nylon sutures vs. polyglycolic acid sutures	Evaluates sutures rather than wound or topical application dressing
Butler CM, Topp SM, Coleridge-Smith PD. A comparative randomized study on the performance of Comfeel Plus ulcer dressing and Granuflex in the healing of leg ulcers. In: Cherry GW, Gottrup F, Lawrence JC, Moffatt CJ, Turner TD, editors. Proceedings of the 5th European Conference on Advances in Wound Management; 1995 Nov 21–24; Harrogate, UK. London: Macmillan Magazines, 1996:274–5.	Comfeel Plus vs. Granuflex	No data provided on healing rates
Callaghan DP. Assessment of the effectiveness of Debrisan in healing ulceration on pressure areas of diabetic patients' feet. In: Harding KG, Cherry G, Dealey C, Turner TD, editors. Proceedings of the 2nd European Conference on Advances in Wound Management; 1992, Oct 20–23; Harrogate, UK. London: Macmillan Magazines, 1993:**82**.	Debrisan vs. disdaine dressings	No data on healing in one group
Chaloner DM, Milward PA, Skitt PJ. A community-based clinical trial of three dressings in the treatment of leg ulceration. Proceedings of the 1st European Conference on Advances in Wound Management; 1991 Sep 4–6; Cardiff, UK. London: Macmillan Magazines, 1992:148–9.	Activated charcoal and silver dressing vs. paraffin gauze	Outcome not healing

continued

TABLE 3 contd *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Cheneworth CC, Hagglund KH, Valmassoi B, Brannon C. Portrait of practice: healing heel ulcers. *Adv Wound Care* 1994;**7**(2):44–8.	Foam boot	Pressure sore prevention
Cherry GW, Powell SM, Ryan T. The efficacy of mupirocin in the management of venous leg ulcers. In: Harding KG, Cherry G, Dealey C, Turner TD, editors. Proceedings of the 2nd European Conference on Advances in Wound Management; 1992 Oct 20–23; Harrogate, UK. London: Macmillan Magazines, 1993:214.	Antibiotics – topical	Considered in the review of antimicrobials
Collier J. A moist, odour-free environment. A multicentred trial of a foamed gel and a hydrocolloid dressing. *Professional Nurse* 1992; **7**(12):804–8.	Hydrocolloid vs. foamed gel	No data on healing – mentions 'improved'
Cony M, Donatien PH, Beylot C, Geniaux M, Maleville J, Bezian JH, *et al.* Treatment of leg ulcers with an allogenic cultured-keratinocyte-collagen dressing. *Clin Exp Dermatol* 1990;**15**:410–14.	Cultured keratinocytes	No control group
Cooper R, Bale S, Harding KG. An improved cleansing regime for a modified foam cavity dressing. In: Harding KG, Dealey C, Cherry G, Gottrup F, editors. Proceedings of the 3rd European Conference on Advances in Wound Management; 1993 Oct 19–22, Harrogate, UK. London: Macmillan Magazines, 1994.		Comparison of methods of cleaning dressing
Cordts PR, Lawrence M, Hanrahan LM, Augustin A, Rodriguez AA, Woodson J, *et al.* A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. *J Vasc Surg* 1992;**15**(3):480–6.	Unna's Boot vs. hydrocolloid	Considered in compression review
Creese AL, Bale S, Harding KG, Hughes LE. Management of open granulating wounds. *Physician* 1986;February:637–9.	Silastic foam dressing vs. gauze dressing	No outcome of healing
Dale JJ, Ruckley CV, Harper DR, Gibson B, Nelson EA, Prescott RJ. A randomised, double-blind placebo controlled trial of oxpentifylline in the treatment of venous leg ulcers. In: Negus D, editor. Phlebology '95. *Phlebology* 1995;(Suppl 1):917–18.	Oxpentifylline	Trial of oral treatment not dressing
Danielson L, Madsen SM, Westh H. Rates of infection of chronic leg ulcers dressed with a hydrocolloid dressing or given an alternative treatment. In: Harding KG, Cherry G, Dealey C, Turner TD, editors. Proceedings of the 2nd European Conference on Advances in Wound Management; 1992 Oct 20–23; Harrogate, UK. London: Macmillan Magazines, 1993:97.	Hydrocolloids	Outcome not healing
Degreef H. Treatment of four arteriolar ulcers with topical 2% Ketanserin. *Curr Ther Res* 1988;**44**(1):100–4.	Ketanserin	No comparison group
Diem E. [Clinical trial of a new occlusive dressing in the management of venous stasis ulceration]. *Aktuel Dermatol* 1987;**13**(6):269–72.	Hydrocolloid	Not an RCT
Eriksson G. Bacterial growth in venous leg ulcers – its clinical significance in the healing process. In: Ryan TJ, editor. An environment for healing: the role of occlusion. *J R Soc Med* 1984:44–9.	Bacterial growth	Outcome bacterial growth
Fish FS, Katz I, Hien N, Briden ME, Johnson JA, Patt LM. Evaluation of glycyl-histidyl-L-lysine copper complex in acute wound healing. *Wounds* 1991;**3**:171–7.	Glycyl-histidyl–L–lysine vs. copper complex vs. PC1020	Mohs surgery
Fowler EM. New, once-daily pressure sore dressing speeds healing. *Registered Nurse* 1983;**46**(4):56–7.	Bard absorption dressing vs. wet-to-dry dressing	No outcome data

continued

TABLE 3 contd *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Freak L, Simon D, Kinsella A, McCollum C, Walsh J, Lane C. Leg ulcer care: an audit of cost-effectiveness. *Health Trends* 1995;**27**:133–6.	Leg ulcer costs	Not a trial of effectiveness of dressings
Friedman SJ, Su WP. Management of leg ulcers with hydrocolloid occlusive dressing. *Arch Dermatol* 1984;**120**(10):1329–36.	Hydrocolloid	Not an RCT
Genster HG, Oram V. [Arterial insufficiency in the lower extremities treated with drugs]. *Ugeskr Laeger* 1971;**133**(6):244–6.	Testosterone vs. steroids vs. callicreine vs. depot-padutin	Not randomised. Results of ulcer healing not presented separately from gangrene
Gibson B. A cost effectiveness comparison of two gels in the treatment of sloughy leg ulcers. Advanced Wound Care Symposium; 1995, April; San Diego. Wayne, PA: Health Management Publications, 1995.	Hydrogels vs. Intrasite	Included in debridement review
Gupta R, Foster ME, Miller E. Calcium alginate in the management of acute surgical wounds and abcesses. *J Tissue Viability* 1991;**1**(4):115–16.	Alginates vs. proflavine	Outcome measure not healing
Halbert AR, Stacey MC, Rohr JB, Jopp McKay A. The effect of bacterial colonization on venous ulcer healing. *J Dermatol* 1992;**33**(2):75–80.	Calcium alginate vs. bandages vs. viscopaste vs. acoband	Not a trial of effectiveness of dressings
Hall P. Prophylactic use of Op-Site on pressure sores. *Nurs Focus* 1983;Jan/Feb:148.	Pressure sore prevention vs. Opsite	Not an RCT
Hunyadi J, Farkas B, Bertenyi C, Olah J, Dobozy A. Keratinocyte grafting: a new means of transplantation for full-thickness wounds. *J Dermatol Surg Oncol* 1988;**14**(1):75–8.	Keratinocyte grafting	No appropriate outcome measures
Johnson A. Dressings for deep wounds. Allevyn cavity wound dressing. *Nurs Times* 1992;**88**(4):58.	Allevyn cavity wound dressing vs. Granuflex paste	No data on effectiveness (area of wounds or % healed)
Klostermann GF, Jakob H. [Comparative testing of a new cream-base against unguentum diachylon in ulcus cruris]. *Munchener Medizinische Wochenschrift* 1974;**116**(23):1169–70.	Topical applications	Crossover trial with no data on healing at crossover point
La Grenade L, Thomas PW, Serjeant GR. A randomized controlled trial of solcoseryl and duoderm in chronic sickle-cell ulcers. *West Indian Med J* 1993;**42**(3):121–3.	DuoDerm vs. solcoseryl	Sickle-cell ulcers
Leaper DJ, Cameron S, Hewitt H, Winter A, Lucarotti ME. A community- and hospital-based comparative evaluation of Comfeel Ulcer Dressings for chronic leg ulcers. *J Dermatol Treat* 1991;2:103–6.	Comfeel vs. jelonet	Crossover trial with no data on healing at crossover point
Lees V, Ilyas S, Reid CD. A comparison of the use of polythene sheet and Jelonet as temporary dressings for excised wounds. *Br J Plast Surg* 1991;**44**(8):612–4.	Polythene sheet vs. jelonet	Outcome pain not healing
Limova M, Mauro T. Treatment of leg ulcers with cultured epithelial autografts: clinical study and case reports. *Ostomy Wound Manag* 1995;**41**(8):48–50. **52**:54–60.	Cultured epithelial autografts applications	No control group
Lookingbill DP, Miller SH, Knowles RC. Bacteriology of chronic leg ulcers. *Arch Dermatol* 1978;**114**:1765–8.	Benzoyl peroxide	For consideration in review of antimicrobials
Mangete EDO, West KS, Blankson CD. Hypertonic saline solution: an effective wound dressing. *East African Med J* 1993;**70**(2):104–6.	Hypertonic saline solution	No data given on healing
Månsson T. Double bandage with ointment stocking as therapy for venous leg ulcers. elastic roller vs double bandage. *J Dermatol Treat* 1994;**5**(3):123–6.	Compression bandages	Not an RCT

continued

TABLE 3 contd *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Milward P, Siddle H, Johnson M, Bridgewater A. A user evaluation on the Triple Care cleanser and cream system examining impact on pressure ulcer incidence in a long term care centre. Poster presented at the 5th European Conference on Advances in Wound Management; 1995 Nov 21–24; Harrogate, UK.	Triple-care cleanser	Evaluation of a skin treatment rather than wound dressing
Mulder G, Jones R, Cederholm-Williams S, Cherry G, Ryan T. Fibrin cuff lysis in chronic venous ulcers treated with a hydrocolloid dressing. *Int J Dermatol* 1993;**32**(4):304–6.	Hydrocolloid	No data on healing
Müller K, Matzen E, Gottrup F. Treatment of incisional wound defects following laparotomy, in relation to treatment effect, time consumption and economy. A methodological description. Proceedings of the 3rd European Conference on Advances in Wound Management. 1994:30–2.	Hydrocolloids	No data on healing outcomes
Myers SA, Takiguchi S, Slavish S, Rose CL. Consistent wound care and nutritional support in treatment. *Decubitus* 1990;**3**(3):16–28.	Consistant wound care (cleansing povidone iodine solution, saline rinse, Opsite dressing) vs. controlled nutritional support vs. consistant wound care + nutritional support vs. standard hospital treatment (various dressings and support surfaces)	Not an evaluation of dressings or topical preparations
Nowak A, Bowszyc P, Blaszczyk M. A randomised, controlled, parallel group clinical trial of a new polyurethane foam dressings versus calcium alginate dressing in the treatment of moderately to heavily exuding venous ulcers. Lyofoam Extra dressing vs Sorbsan. Poster presented at the 5th European Conference on Advances in Wound Management. 1995 Nov.	Lyofoam extra dressing vs. Sorbsan	No data on healing
Petres *et al.* Alginates versus hydrocolloids in the treatment of venous leg ulcers. In: Harding KG, Dealey C, Cherry E, Gottrup F, editors. Proceeding of the 3rd European Conference on Advances in Wound Management; 1993 Oct 19–22, Harrogate, UK. London: Macmillan Magazines, 1994:165.	Kaltostat vs. Granuflex	Outcome measure 'complete or partial healing' with no breakdown or definition
Pierce GF, Tarpley JE, Allman RM, Goode PS, Serdar CM, Morris B, *et al.* Tissue repair processes in healing chronic pressure ulcers treated with recombinant platelet-derived growth factor BB. RPDGF-BB 100 µg/ml x rPDGF-BB 300 µg/ml x placebo. *Am J Pathol* 1994;**145**(6):1399–410.	r-PDGF-BB 100 µg/ml x r-PDGF-BB 300 µg/ml x placebo	Outcome electron microscopy
Pittl G, Milnes M, McMackin S, Boughey F, Fako W. A multi-phase, open label, randomized, parallel comparative study of two hydrocolloid dressings on patients with stage II and stage III exudating pressure ulcers. Comfeel Plus dressing vs Duoderm CGF. Poster presented at the Wound Ostomy and Continence Nurses annual conference.	Comfeel Plus dressing vs. DuoDerm CGF	Conflicting results. Coloplast contacted for clarification – no reply
Polous *et al.* [Local-action preparations in treating trophic ulcers in patients with vascular failure]. *Vrach Delo* 1985;**1**(10):57–9.	Chonsurid, solcoseryl, lyzozyme	Not an RCT. Preparations used preoperatively
Poole M, Milward P. A randomised prospective crossover trial to investigate the use of an odour-absorbing dressing with a four-layer bandage system. Principles, Progress and Practice in Wound Care; 1994 Nov 15–17; Harrogate, UK. London: Macmillan Magazines, 1995.	Melolin vs. carbonet	No data on healing
Resl V Jr. [Use of ion exchange in therapy of ulcer cruris]. *Dermatologische Monatsschrift* 1973;**159**(3):249–57.	Ion exchange	Not an RCT

continued

TABLE 3 contd *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Sashchikova VG, Vasil'ev MP, Pukhova ZI. [Use of a fibrous soluble collagen preparation in treating trophic ulcers of the lower extremities]. *Vestn Khir* 1980;**124**(1):131–2.	Collagen	Not an RCT
Shutler S, Stock J, Bale S, Harding KG, Squires D, Wilson I, *et al.* A multi-centre comparison of a hydrocellular adhesive dressing (Allevyn Adhesive) and a hydrocolloid dressing (Granuflex) in the management of stage 2 and 3 pressure sores. Allevyn Adhesive vs Granuflex hydrocolloid dressing. Poster presented at the 5th European Conference on Advances in Wound Management; 1995 Nov 21–24; Harrogate, UK.	Allevyn adhesive vs. Granuflex hydro-colloid dressing	No data on healing
Sironi G, Losa S, DiLuca G, Pezzoni F. Treatment of venous leg ulcers with Intrasite gel. OpSite Flexigrid, Allevyn hydrocellular dressing and Flexobande (elastic compression bandage) in vascular surgery. A protocol for clinical evaluations. In: Harding KG, Dealey C, Cherry G, Gottrup F, editors. Proceedings of the 3rd European Conference on Advances in Wound Management; 1993 Oct 19–22; Harrogate, UK. London: Macmillan Magazines, 1994:**164**.	Allevyn, Intrasite and Opsite	No data on healing or ulcer area
Stahl KW, Chastang C. Promotion healing of arterial and venous ulcers by TCDO. Insight in mechanisms of tissue repair. Tetrachloridecaoxygen anion complex (TCDO). *Fortschr Med* 1988;**106**(1):44–6.	Tetrachlorideca-oxygen anion complex	No objective measure of healing
Tarvainen K. Cadexomer iodine (Iodosorb) compared with dextranomer (Debrisan) in the treatment of chronic leg ulcers. *Acta Chir Scand Suppl* 1988;**544**:57–9.	Cadexomer iodine vs. dextranomer	Included in debridement review
Van-Den-Hoogenband HM. Treatment of leg ulcers with split-thickness skin grafts. Silver sulfadiazine pre-operatively + split thickness skin grafts vs split thickness skin grafts only. *J Dermatol Surg Oncol* 1984;**10**(8):605–8.	Silver sulfadiazine preoperatively + split thickness skin grafts vs. split thickness skin grafts only	Historical control
Vande Berg JS, Robson MC, Mikhail RJ. Extension of the life span of pressure ulcer fibroblasts with recombinant human interleukin-1β. Rhul1-1β 0.01μg/cm^2/day vs 0.1μg/cm^2/day vs 1μg/cm^2/day vs placebo. *Am J Pathol* 1995;**146**(5):1273–82.	Rhul1-1beta 0.01 μg/cm/day vs. 1 μg/cm/day vs. placebo	Outcome based on histology
Ward DJ, Bennett JP, Burgos H, Fabre J. The healing of chronic venous leg ulcers with prepared human amnion. Tissue-culture-maintained human amnion vs frozen human amnion vs fresh human amnion vs lyophilised human amnion. *Br J Plast Surg* 1989;**42**(4):463–7.	Tissue-culture-maintained human amnion vs. frozen human amnion vs. fresh human amnion vs. lyophilised human amnion	Compares four methods of preparing amnion. No control group, therefore effectiveness of amnion not assessed
Watts C, Lee S. Comparison of Allevyn Cavity Wound Dressing to saline-moistened gauze. In: Harding KG, Dealey C, Cherry G, Gottrup F, editors. Proceedings of the 3rd European Conference on Advances in Wound Management; 1993 Oct 19–22; Harrogate, UK. London: Macmillan Magazines, 1994.	Allevyn cavity wound dressing vs. saline-moistened gauze	No data on healing
Wethers DL, Ramirez GM, Koshy M, Steinberg MH, Phillips G Jr, Siegel RS, *et al.* Accelerated healing of chronic sickle-cell leg ulcers treated with RGD peptide matrix. RGD Study Group. RGD peptide matrix vs saline placebo. *Blood* 1994;**84**(6):1775–9.	RGD peptide matrix vs. saline placebo	Sickle-cell ulcers

continued

TABLE 3 contd *Studies excluded from the review and reasons for exclusion*

Reference	Comparison	Reason for exclusion
Winter A, Hewitt H. Testing a hydrocolloid. Comfeel dressing vs paraffin gauze. *Nurs Times* 1990; **86**; (50):59–62.	Comfeel dressing vs. paraffin gauze	Crossover design with no report of outcome at point of crossover
Wyszynska Z, Blonska B, Czaplicki J. [Trial use of embryonal and early-fetal thymus extractsin the treatment of non-healing skin defects. II. Crural ulcers in humans.] *Przegl Dermatol* 1987;**74**:309–15.	Growth factors	Not an RCT
Zeegelaar JE, Mekkes JR, Westerhof W. Evaluation of clinical wound healing trials using a CIA system. Iodosorb vs DuoDERM E vs Jelonet gauze. In: Cherry GW, Leaper DJ, Lawrence JC, Milward P, editors. Proceedings of the 4th European Conference on Advances in Wound Management; 1994 Sep 6–9; Copenhagen, Denmark. London: Macmillan Magazines, 1995:200.	Iodosorb vs. DuoDerm E vs. jelonet gauze	No data on healing

Appendix 4

Interpretation of forest plots

The figure below shows a forest plot as used in this review. The diagram represents a comparison between hydrocolloid dressings and foam dressings for the treatment of venous leg ulcers. For each individual trial the OR result is plotted as a single black square. The lines either side of the OR represent the 95% CI for that result. The ORs from the two trials have been combined in a meta-analysis, the result of which is represented by the black diamond towards the bottom of the figure. The horizontal width of this diamond represents the CI for the meta-analysis.

The horizontal axis at the bottom of the figure shows the numerical value of each OR and the vertical line in the centre represents the 'line of no effect', where the OR is 1 (i.e. treatment and control show equal benefit).

In order to extract useful information from a forest plot it is necessary to establish the following:

- the nature of the intervention under investigation (given in title)
- the outcomes being measured (stated in the study details on the left side of the figure)
- whether each outcome is good/positive (of benefit) or bad/negative (of harm)
- whether the OR (or mean difference for the meta-analysis) falls to the left or right of the line of no effect

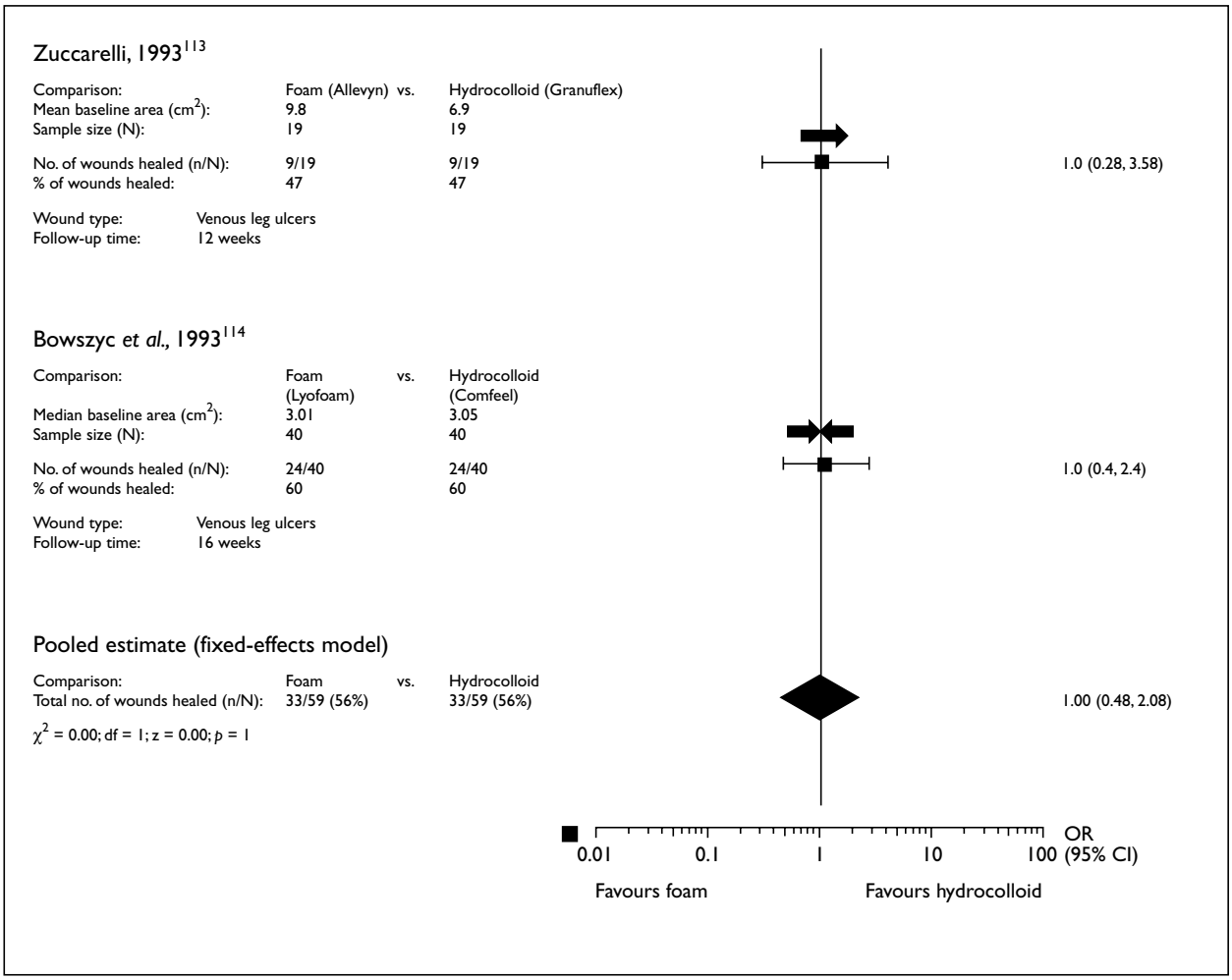

FIGURE 16 *Hydrocolloid compared with foam dressing for venous leg ulcer*

- whether the CIs cross the line of no effect
- whether the meta-analysis result 'looks' to be a fair representation of the individual trial results.

If a bad/negative outcome, such as recurrence of disease, is measured for a given intervention, then a beneficial result will be one in which the OR is less than one or to the left of the line of no effect (i.e. the intervention results in less of the outcome and the OR approximates to the proportion of the treatment group that experience the outcome compared with the control group). Similarly beneficial results for good/positive outcomes have ORs greater than one.

If the horizontal CI line crosses the vertical line of no effect then the result (shown by the OR square or diamond) does not show a clear or conclusive effect. In this systematic review we have used 95% CIs. The CI represents the range in which we are 95% confident that the true result of the study lies when the result from the individual trial or meta analysis is extrapolated to the whole of the population that was originally sampled in the study. Put another way, this means that, in theory, in 95 out of 100 trials we can be confident that the result will lie somewhere along the horizontal CI line. If the CI crosses the line of no effect then, because we can only be 95% certain that the result is somewhere along that line, it is possible that a result which looks beneficial may in fact be harmful or vice versa. In this situation, the result would be recorded as inconclusive or of uncertain benefit.

The visual appreciation of the results of a review would be the first step in using the review to guide a healthcare decision.

The plots used in this systematic review also show the difference in healing rates when expressed as a percentage or actual reduction in area, both of which are continuous variables. The difference between these values is described as the effect size (ES). With continuous variables the line of no effect falls at zero instead of 1 as when ORs are used. However, interpretation of the results is identical to that for OR results (e.g. a result lying to the left (less than zero) of the line of no effect means that the rate of ulcer healing in the intervention group is lower in the treatment group than in the control group).

Appendix 5

Quality assessment of RCTs

TABLE 4 *Quality assessment of RCTs of dressings and topical applications for surgical wounds*

Study	Inclusion and exclusion citeria stated	Overall sample size [arms]	*A priori* sample size calculation?	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment reported	Withdrawals stated†	ITT analysis
Schmidt & Greenspoon, 1991[38]	✔	40 patients [2]	+ (but fewer patients used than the analysis suggested)	✔	✔	✗	✔b	✗
Butterworth *et al.*, 1992[37]	✔	80 [2]	✗	✗	✔c	✗	✗	✗
Williams *et al.*, 1981[35]	✗	80 [2]	✗	✗	✔c	✗	✗	✗
Macfie & McMahon, 1980[34]	✔	50 [2]	✗	✗	✔c	✗	✔a	✗
Walker *et al.*, 1991[36]	✗	75 [2]	✗	✗	✔	✗	N/A	N/A

✔ = Yes; ✗ = No; N/A = not appropriate (no withdrawals)

** Baseline characteristics: ✔ = one or more appropriate characteristics stated (but not initial wound size); ✔c = initial wound size stated*

† Withdrawals: ✔a = reported by group and with reason; ✔b = withdrawals but not reported by group or reason not given; ✗ = withdrawals not reported

TABLE 5 *Quality assessment of RCTs of dressings and topical applications for pressure sores*

Study	Inclusion and exclusion citeria stated	Overall sample size [arms]	*A priori* sample size calculation?	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment reported	Withdrawals stated†	ITT analysis
Brod *et al.*, 1990[66]	✔	43 [2]	✗	✗	✔c	✗	✔a	✗
Colwell *et al.*, 1993[54]	✔	70 [2]	✗	✗	✔c	✗	✔a	✗
Barrois, 1993;[52] Huchon, 1992[53]	✔	76 [2]	✗	✗	✔c	✗	✔a	✗
Bale *et al.*, 1995[62]	✗	100 [2]	✗	✗	✔	✗	✔a	✗
Banks *et al.*, 1996[65]	✔	98 [2]	✗	✗	✔c	✗	N/A	N/A
Brown-Etris *et al.*, 1996[46]	✔	121 [2]	✗	✗	✔	✔	✔b	✗
Alm *et al.*, 1989[51]	✗	50 [2]	✗	✗	✔c	✔	✔b	✗
Hondé *et al.*, 1994[67]	✔	168 [2]	✗	✔	✔c	✗	✔a	✗
Banks *et al.*, 1994[64]	✔	40 [2]	✗	✔	✔c	✗	✔a	✗
Banks *et al.*, 1994[63]	✔	29 [2]	✗	✗	✔c	✗	✔a	✗
Banks *et al.*, 1994[68]	✔	50 [2]	✗	✔	✔c	✗	✔b	✗
Kraft *et al.*, 1993[61]	✔	38 [2]	✗	✗	✔	✗	✔a	✔
Xakellis & Chrischilles, 1992[55]	✔	39 [2]	✗	✗	✔c	✗	✔a	✔
Oleske *et al.*, 1986[57]	✔	15 [2]	✗	✗	✔c	✗	✔b	✗
Sebern, 1986;[58] 1989[59]	✔	200 [2]	✗	✔	✔c	✗	✔b	✗
Van Ort & Gerber, 1976[39]	✔	14 [2]	✗	✔	✔	✗	N/A	N/A
Mustoe *et al.*, 1994[43]	✔	41 [3]	✗	✗	✔c	✔	✔a	✗
Robson *et al.*, 1992[45]	✔	20 [4]	✗	✗	✔c	✔	N/A	N/A
Robson *et al.*, 1992[44]	✔	50 [3]	✗	✗	✔c	✔	✔a	✗
Robson *et al.*, 1994[42]	✔	26 [4]	✗	✗	✗	✗	✔b	✗
Saydak, 1990[60]	✔	16 lesions [2]	✗	✗	✔c	✗	N/A	N/A
LeVasseur & Helme, 1991[40]	✗	21 [2]	✗	✗	✔c	✗	N/A	N/A
Tytgat & Van Asch, 1988[41]	✗	16 [2]	✗	✗	✔c	✔	N/A	N/A
Gorse & Messner, 1987[56]	✔	52 [2]	✗	✗	✔	✗	N/A	N/A
Palmieri, 1992[50]	✔	48 [2]	✗	✗	✔	✗	N/A	N/A
Darkovich *et al.*, 1990[47]	✔	90 patients 129 wounds [2]	✗	✗	✔c	✗	✔a	✗
Mulder *et al.*, 1993[48]	✔	67 [3]	✗	✔	✔	✗	✔b	✗
Sayag *et al.*, 1996[49]	✔	92 [2]	✔	✔	✔c	✗	✔a	✔

✔ = Yes; ✗ = No; N/A = not appropriate (no withdrawals)

** Baseline characteristics: ✔ = one or more appropriate characteristics stated (but not initial wound size); ✔c = initial wound size stated*

† Withdrawals: ✔a = reported by group and with reason; ✔b = withdrawals but not reported by group or reason not given; ✗ = withdrawals not reported

TABLE 6 *Quality assessment of RCTs of dressings and topical agents for leg ulcers*

Study	Inclusion and exclusion citeria stated	Overall sample size [arms]	*A priori* sample size calculation?	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment reported	Withdrawals stated†	ITT analysis
Acosta *et al.*, 1992[86]	✔	12 [2]	✗	✔	✗	✗	✗	✗
Armstrong *et al.*, 1996[80]	✔	44 [2]	✗	✔	✗	✗	✔b	✗
Arnold *et al.*, 1994[99]	✔	70 patients [2] 90 ulcers	✗	✗	✔c	✗	✔a	✗
Backhouse *et al.*, 1987;[98] Blair *et al.*, 1988[104]	✔	56 [2]	✗	✗	✔c	✗	✗	✗
Bale *et al.*, 1995[62]	✗	30 [2]	✗	✗	✗	✗	✔a	✗
Bandrup *et al.*, 1990[79]	✔	43 [2]	✗	✗	✔ c	✗	✗	✔
Banerjee *et al.*, 1990[94]	✗	71 [2]	✗	✗	✔c	✗	✔b	✗
Banks *et al.*, 1996[65]	✔	100 [2]	✗	✔	✔c	✗	✗	✗
Bishop *et al.*, 1992[125]		68 [3]						
Bowszyc *et al.*, 1994[114]	✔	80 patients, 82 legs [2]	✗	✔	✔c	✗	✗	✔
Bulstrode *et al.*, 1988[135]	✔	48 [4]	✗	✔	✔c	✗	✗	N/A
Burgess & Robinson, 1993;[108] Robinson, 1993;[109] Burgess, 1993[110]	✔	121 [3]	✗	✗	✗	✗	✗	✗
Calabro *et al.*, 1995[85]	✗	80 [2]	✗	✗	✗	✗	✗	✗
Callam *et al.*, 1992[90]	✔	132 [2]	✗	✗	✔c	✗	✔a	✔
Caprio *et al.*, 1995[105]	✗	93 [2]	✗	✗	✗	✗	✔b	✗
Davis *et al.*, 1992[93]	✗	11 patients [2] 12 ulcers	✗	✗	✗	✗	✗	✗
Duhra *et al.*, 1992[119]	✔	22 patients [2] 30 ulcers	✗	✗	✔c	✗	✔a	✔
Falanga *et al.*, 1992[130]	✔	45 [2]	✗	✗	✔c	✔	✔b	✗
Freak *et al.*, 1994;[127] 1993[128]	✔	26 [4]	✗	✗	✔c	✔	✗	✔
Galasso *et al.*, 1978[116]	✗	62 [2]	✗	✗	✔c	✗	✔b	✔
Gibson *et al.*, 1986[69]	✗	22 [2]	✗	✔	✔c	✗	✔a	✗
Greguric *et al.*, 1994[133]	✔	110 [2]	✗	✔	✗	✗	✗	✗
Groenewald, 1984[103]	✗	72 [2]	✗	✗	✗	✔	✔a	✗
Holzinger *et al.*, 1994[70]	✗	63 [2]	✗	✗	✔	✗	✗	✗

✔ = Yes; ✗ = No; N/A = not appropriate (no withdrawals)

** Baseline characteristics: ✔ = one or more appropriate characteristics stated (but not initial wound size); ✔c = initial wound size stated*

† Withdrawals: ✔a = reported by group and with reason; ✔b = withdrawals but not reported by group or reason not given; ✗ = withdrawals not reported

continued

TABLE 6 contd *Quality assessment of RCTs of dressings and topical agents for leg ulcers*

Study	Inclusion and exclusion citeria stated	Overall sample size [arms]	*A priori* sample size calculation?	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment reported	Withdrawals stated†	ITT analysis
Knighton *et al.*, 1988[82]	✔	32 [2]	✗	✔	✔c	✗	✔a	✗
Limova *et al.*, 1996[111]	✗	20 [2]	✗	✗	✗	✗	✗	✗
Lindholm *et al.*, 1993;[73] Lindholm, 1995;[74] Lindholm, 1994;[75] Ohlsson *et al.*, 1994[72]	✗	28 [2]	✗	✗	✗	✗	✗	✗
Mansson, 1996[101]	✗	153 [3]	✗	✗	✔c	✗	✔a	✔
Meredith & Gray, 1988[100]	✗	49 [2]	✗	✔	✔c	✗	✔a	✗
Mian *et al.*, 1991;[76] 1992[77]	✗	50 [2]	✗	✗	✔c	✗	✗	✗
Milward, 1991[102]	✗	38 [2]	✗	✗	✗	✗	✗	✗
Moffatt *et al.*, 1992[88]	✔	60 [2]	✗	✗	✔c	✗	✗	✗
Moffatt *et al.*, 1992[97]	✔	60 [2]	✔	✔	✔c	✗	✔b	✗
Nelson *et al.*, 1995[96]	✔	200 [2]	✔	✔	✔c	✗	✗	✔
Nyfors *et al.*, 1982[78]	✔	34 [2]	✗	✗	✗	✗	✗	✗
Palmieri, 1992[50]	✗	48 [2]	✗	✗	✗	✗	✗	N/A
Passarini *et al.*, 1982[115]	✗	48 [2]	✗	✗	✗	✗	✗	✗
Pessenhoffer & Stangl, 1989;[91] 1992[92]	✗	48 [2]	✗	✗	✔c	✗	✔b	✗
Rasmussen *et al.*, 1991;[129] 1994[126]	✔	102 [4]	✔	✗	✔c	✗	✔	✔
Rundle *et al.*, 1981[117]	✗	26 patients [2] 48 ulcers	✗	✗	✔c	✗	✔	✗
Sabolinski *et al.*, 1996[118]	✗	233 [2]	✗	✗	✗	✗	✗	✗
Salim, 1991[123]	✔	153 [3]	✔	✔	✔c	✗	✔a	✔
Salim, 1992[124]	✔	168 [3]	✔	✔	✔c	✗	✔a	✔
Smith, 1994[106]	✔	40 [2]	✗	✗	✔c	✗	✔a	✗
Smith *et al.*, 1992[95]	✔	200 [2]	✗	✔	✔c	✗	✔a	✗
Stacey *et al.*, 1992;[89] 1997	✔	113 patients [3] 133 limbs	✗	✗	✔c	✗	✔a	✗
Stromberg *et al.*, 1984[83]	✔	37 [2]	N/A	✔	✔c	✔	✔b	✗

✔ = Yes; ✗ = No; N/A = not appropriate (no withdrawals)

** Baseline characteristics: ✔ = one or more appropriate characteristics stated (but not initial wound size); ✔c = initial wound size stated*

† Withdrawals: ✔a = reported by group and with reason; ✔b = withdrawals but not reported by group or reason not given; ✗ = withdrawals not reported

continued

TABLE 6 contd *Quality assessment of RCTs of dressings and topical agents for leg ulcers*

Study	Inclusion and exclusion citeria stated	Overall sample size [arms]	*A priori* sample size calculation?	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment reported	Withdrawals stated†	ITT analysis
Teepe *et al.*, 1993[131]	✔	43 patients [2] 47 ulcers	✔	✗	✔c	✗	✔	✗
Torregrossa & Caroti, 1983[84]	✗	43 [2]	✗	✗	✔	✗	✗	✔
Tosti & Veronesi, 1983[132]	✗	22 [2]	✗	✗	✔c	✗	✔	✗
Tsakayannis *et al.*, 1994[122]	✔	9 patients [2] 10 wounds	✗	✗	✗	✗	✗	✗
Veraart *et al.*, 1994[107]	✔	38 [2]	✗	✔	✗	✗	✔a	✗
Werner-Schlenzka & Kuhlmann, 1994[121]	✔	148 [3]	✗	✗	✔c	✗	✗	✗
Werner-Schlenzka & Lehnert, 1994[120]	✔	99 [2]	✗	✗	✔c	✗	✔a	✔
Whipps Cross,[112]	✗	29 [2]	✗	✗	✔c	✗	✔b	✗
Wilson *et al.*, 1979[134]	✗	36 [2]	✗	✗	✗	✗	✔a	✗
Wunderlich & Orfanos, 1991[87]	✔	40 [2]	✗	✗	✔c	✗	✗	✗
Zuccarelli, 1993[113]	✔	40 [2]	✗	✗	✔c	✗	✔b	✗

✔ = Yes; ✗ = No; N/A = not appropriate (no withdrawals)

* *Baseline characteristics: ✔ = one or more appropriate characteristics stated (but not initial wound size); ✔c = initial wound size stated*

† *Withdrawals: ✔a = reported by group and with reason; ✔b = withdrawals but not reported by group or reason not given; ✗ = withdrawals not reported*

Appendix 6

Studies of treating non-healing surgical wounds

TABLE 7 *Dressings compared with traditional treatments for the management of surgical wounds healing by secondary intention*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Macfie & McMahon, 1980[34] UK Wound type: Perineal wounds (surgery). Method of randomisation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Community-based trial with assessment undertaken at an outpatient clinic. Treatment continued until all wounds had healed.	Inclusion criteria: Patients who had undergone either proctocolectomy or rectal excisions. Exclusion criteria: No exclusion.	Treatment: I: Silicone foam cavity dressing (Silastic Foam®) applied to the wound cavity by a syringe. After expansion and setting it was removed, reshaped and then replaced. The foam was covered with a dry dressing. Patients removed the foam twice a day and took a salt bath. The foam was washed in water and soaked in cetrimide before drying and replacing, *n* = 30. C: A gauze dressing soaked in mercuric chloride was loosely packed into the wound. The pack was removed at least once a day and patients took a salt bath while the pack was out, *n* = 30. Patients were allowed to change and dress their own wounds if they felt comfortable doing so. Otherwise dressing changes were managed by a visiting nurse.	Mean wound volume (cm^3): I: 55.5 (4.5 SEM) C: 61.5 (5.3 SEM) Other characteristics: I C Mean age (years): 54 59 M:F 1:1.3 1:1.8 Reason for surgery: Ulcerative colitis 8 6 Crohn's disease 5 3 Carcinoma rectum 10 13 Villous papilloma 1 0 Irradiation colitis 1 1 Colloid carcinoma 0 1 Diverticulitis 0 1 Data are only given for those 50 patients, 25 per group, completing the trial.	Complete healing: I: 20/25 (80%) C: 20/25 (80%) Mean time to healing (days) for all wounds: I: 60.3 (3.0 SEM) C: 69.5 (7.3 SEM) ($p > 0.05$, NS; Student's *t*-test)	I: Three deaths; two patients failed to heal for reasons related to the nature of their illness. C: Three deaths; two patients failed to heal for reasons related to the nature of their illness. Withdrawals were not included in the baseline data or results.	Less analgesia and fewer district nurse visits appeared necessary for patients treated with Silastic Foam (I).
Walker *et al.*, 1991[36] UK Wound type: Surgical (pilonidal sinus and abscesses). Method of randomisation: Not stated. Objective outcome: Time to healing. Assessments were made twice weekly by the surgical team. Setting and length of treatment: Outpatients treated in hospital and later in the community. Treatment was continued until the wound healed. A maximum treatment time was not specified.	Inclusion criteria: Patients with pilonidal sinuses or abscesses. Exclusion criteria: Not stated.	Treatment: I: Silicone foam cavity dressing (Silastic Foam). The foam was constructed in the wound and then removed. Patients were instructed on how to remove and replace the dressing. Dressing were removed and washed twice daily. A new sponge was made when the original no longer fitted the cavity, *n* = 34. C: Eusol-soaked gauze at half strength. The dressing was laid in the cavity twice daily and then once daily when considered clean enough by nursing staff, *n* = 41. After surgery, and prior to randomisation, all wounds were dressed with ribbon gauze soaked in half strength Eusol. This dressing was removed after 48 hours and patients randomised to a treatment group.	Wound size: Not stated. Other characteristics: All groups Male patients: Sample size 72 Mean age (years) 25 Female patients: Sample size 3 Mean age (years) 19 I C Wound type: Pilonidal sinus 17 21 Abscess 17 20	Mean time to healing for pilonidal sinuses (days): I: 30 (range, 21–39) C: 33 (range, 20–46) Mean time to healing for abscesses (days): I: 39.8 (range, 26–54) C: 39.6 (range, 27–53)	No withdrawals.	Patients receiving I treatment required only two or three visits to refashion the dressing, while those treated with C required daily visits.

I, intervention; C, comparator; SEM, standard error of the mean; SD, standard deviation; M, male; F, female

continued

TABLE 7 contd *Dressings compared with traditional treatments for the management of surgical wounds healing by secondary intention*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Williams, *et al.*, 1981[35] UK Wound type: Surgical (pilonidal sinus). Method of randomisation: Not stated. Objective outcome: Time to healing, defined as when the wound surface was completely epithelialised. Assessments were made weekly. Setting and length of treatment: A multicentre trial of outpatients treated in the community. Treatment was continued until the wound healed.	Inclusion criteria: Patients with a pilonidal sinus. Exclusion criteria: Not stated.	Treatment: I: Silicone foam cavity dressing (Silastic Foam). The dressing was refashioned at weekly intervals, *n* = 44. C: Gauze soaked in 0.5% aqueous solution of chlorhexidine (Hibitane). The dressing was changed daily, *n* = 36.	Mean wound volume (ml): I: 59 (57.7 SD) C: 64 (74.5 SD) Other characteristics: Not stated.	Mean time to healing (days): I: 66.2 (26.1 SD) C: 57.7 (19.6 SD)	Not stated.	The foam dressing (I) was associated with fewer nurse visits per patient (I: 4.6 visits; C: 35.1 visits). Changing the foam dressing (I) caused mild discomfort, while the gauze dressing (C) was associated with moderate-to-severe discomfort. Length of hospital stay and time lost from work were similar in both groups.

I, intervention; C, comparator; SEM, standard error of the mean; SD, standard deviation; M, male; F, female

TABLE 8 *Comparison of dressings for the treatment of surgical wounds healing by secondary intention*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Butterworth *et al.*, 1992[37] UK Wound type: Surgical (pilonidal sinus). Method of randomisation: Not stated. Objective outcome: Time to healing. Length, width and depth were measured and the wound photographed at weekly assessments. Setting and length of treatment: Outpatients treated in the community. Treatment was continued until the wound healed. A maximum treatment time was not specified.	Inclusion criteria: Patients with a cavity wound that had resulted from either pilonidal sinus excision or abdominal surgery. Exclusion criteria: Clinical wound infection; immunosuppression; pregnancy; receiving cytotoxic therapy or radiotherapy.	Treatment: I: Polyurethane foam dressing (Allevyn). The dressing was applied directly to the cavity. Where the wound was deep more than one dressing was used as appropriate. The dressings were changed when saturated or at least every 3 days. At dressing changes the wound was washed for at least 20 seconds in tap water before applying the fresh dressing and securing with surgical tape, *n* = 40. C: Silicone foam cavity dressing (Silastic Foam). The foam mixture was poured into the wound and allowed to set for 3 minutes before the dressing was removed. Dressings were cleansed and sterilised twice daily (method of sterilisation not stated). Dressings were held in place by surgical tape and covered with an absorbent pad, *n* = 40. Patients were responsible for changing their own dressings.	Wound size (mm (range)): I C Length: 63 (23–148) 62 (25–160) Width: 20 (0–59) 19 (0–51) Depth: 26 (8–82) 27 (5–65) Other characteristics: I C Mean age (years): 30.4 28.2 Wound type: Pilonidal sinus 30 32 Abdominal 10 8	Number of pilonidal wounds healed (days to healing): I: 29/30 (51.4; 20.9 SD) C: 29/32 (61.9; 26.1 SD) Number of abdominal wounds healed (days to healing): I: 8/10 (51.9; 20.5 SD) C: 8/8 (56.6; 37.6 SD)	Not stated.	90% of patients from both groups reported that the dressings were painless.

TABLE 9 *Topical agents compared with traditional treatments for the management of surgical wounds healing by secondary intention*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Schmidt & Greenspoon, 1991[38] USA Wound type: Surgical Method of randomisation: Stratified randomisation by computer allocation. Objective outcome: Time to healing. Method of assessment not stated. Setting and length of treatment: Outpatients treated in the community. Patients were treated until the wound was completely epithelialised.	Inclusion criteria: Outpatients with surgical wounds requiring healing by secondary intention after either Caesarean delivery or laparotomy for gynaecological surgery. All wounds had opened spontaneously or had been drained to treat a seroma, haematoma, or wound abscess before referral. Exclusion criteria: Diabetes mellitus; cancer; use of glucocorticoids or immunosuppressive drugs; history of abdominal irradiation; a chronic debilitating disease. At commencement no patient had cellulitis at the wound site or required antibiotic therapy.	Treatment: I: Aloe vera gel. Traditional treatment was supplemented by the addition of aloe vera (Carrington Dermal wound gel formulation) to the granulating area, *n* = 20. C: Traditional treatment. The wound was debrided with either a gauze pad or a scalpel as required and irrigated with high-volume, high pressure irrigations. A wet-to-dry dressing was applied. This was repeated every 8 hours until the commencement of granulation, after which treatment was repeated every 12 hours, *n* = 20. A visiting home nurse performed all the treatment changes for both groups.	Wound size: Not stated. Other characteristics: All groups Mean age (years): 28.3 M:F All female Ethnic origin: Hispanic Weight (kg): 73.7 I C Abdominal wound types: Vertical incision 10 11 Transverse incision 10 9 Note: the mean surface area of transverse incisions was statistically larger in the I group at baseline. This will invalidate comparisons between the two groups.	Mean time to healing for vertical incision only (days): I: 84 (± 27; *n* = 8) C: 47 (± 18; *n* = 5) ($p < 0.05$; NS) Mean time to healing for transverse incision only (days): I: 83 (± 35; *n* = 5) C: 53 (± 24; *n* = 3) (NS) Mean time to healing all wound types (days): I: 83 (± 28; *n* = 13) C: 53 (± 24; *n* = 8) ($p < 0.03$) (Student's *t*-test was used for normally distributed data while the Wilcoxon non-paired rank sum was used to compare non-normally distributed data).	I: Two with a vertical incision and five with a transverse incision. C: Six with a vertical incision and six with a transverse incision.	No adverse effects were recorded in either group.

Appendix 7

Studies of healing pressure sores

TABLE 10 *Topical agents compared with no direct wound management*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Van Ort & Gerber, 1976[39] UK Method of randomisation: Random number list. Objective outcome: Rate of healing of wound, defined as decrease in diameter per day assessed by photograph. Setting and length of treatment: Nursing home. Treatment continued for 15 days.	Inclusion criteria: Decubitus ulcers; skin break due to pressure, evidence by epidermal injury involving erythema, pallor, cyanosis and superficial erosion. Size of sore between 1.0 cm and 7.0 cm. Skin breakdown in existence 14 days or less prior to admission to study. Exclusion criteria: Not stated.	I: Topical application of ten units of U-40 regular insulin (USP) twice a day for 5 days. Insulin was dropped from a syringe and exposed to the air to dry. No dressing was applied, *n* = 6. C: All participants received routine supportive nursing care including position changes, increased fluid intake, high protein diet, and local massage. Only patients in the treatment group received insulin therapy, *n* = 8.	Area of wound: Not stated. Other characteristics: I C Mean age (years): 72.5 (all groups) M:F 1:5 1:7 Authors state no statistically significant differences on a range of other variables, including body build, blood glucose, fluid and protein intake, number and location of ulcers, mobility, incontinence, diabetes mellitus, endocrine, circulatory, digestive, genito-urinary or musculoskeletal disease, use of antibiotics, anticoagulants, parenteral insulin, oral hypoglycaernic, steroids or vitamins.	Healing rate: Statistical analysis between the healing rate of the two groups favoured treatment with I. $t = 7.71$ ($p = 0.05$) Student's *t*-test. Number of days of treatment required: Statistical analysis between the two groups again favoured treatment with I. $t = 2.65$ ($p = 0.05$). Note: Primary data were not available in this study.	None.	Time to healing appeared to depend on age, number of pressure sores, respiratory, nervous system and musculo-skeletal disease and mental disorder, and antibiotic therapy, but the results of significance tests are not presented.

TABLE 11 *Topical agents (including concentration comparisons) compared with placebo formulations*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Le Vasseur & Helme, 1991[40] Australia Method of randomisation: Not randomised. Objective outcome: Ulcer area assessed by weekly photography. Time to healing. Setting and length of treatment: Hospital and nursing home patients. Treatment continued for 6 weeks.	Inclusion criteria: Grade I and II pressure ulcers. Exclusion criteria: Not stated.	Treatment: I: Active cream F14001 (extract of barley plant at 1% concentration in cetomacrogol cream base), *n* = 8. C: Placebo cream (not stated), *n* = 13.	Ulcer size (cm^2): I: 9.6 (3.9 SD) C: 9.0 (2.0 SD) Other characteristics: I C Age (years): 82.5 81.5 Norton score: 10.9 12.9 Duration (months): 7.6 3.5	Wound size: No significant main effect found by ANOVA for treatment, though patients in the active group showed a significantly greater reduction in size at week 4, but not week 6. Healing time (days): I: 18.4 (4.4 SD) C: 29.1 (3.6 SD)	None.	
Mustoe *et al.*, 1994[43] USA Method of randomisation: Not stated. Objective outcome: Wound volume and area assessed by alginate moulding and planimetry; time to healing Setting and length of treatment: Nursing homes or hospitals. Treatment for 28 days, follow-up of 5 months.	Inclusion criteria: Clinical confirmation of grade III or IV pressure sore in adult, with total surface area between 4 and 100 cm^2 and no evidence of surrounding cellulitis or malignant neoplasms in the area of the ulcer or elsewhere. Exclusion criteria: Venous or arterial ulcer implicated in the cause of the ulcer; existence of significant endocrine disease or malignant neoplasms in past 5 years; use of immunotherapy, cytotoxic chemotherapy or an investigational drug or drugs.	Treatment: I1: r-PDGF-BB, 100 mg/ml, *n* = 15. I2: r-PDGF-BB, 300 mg/ml, *n* = 12. C1: Placebo, *n* = 14. Treatments applied daily as a topical spray, at a volume of 10 ml/cm^2. All wounds dressed daily with moist saline gauze dressings and mechanically debrided as necessary during treatment period. Intermittent pressure relief was obtained through turning regimens according to nursing home and hospital routines. Pressure-reducing mattresses were not used.	Mean wound volume (cm^3): C1: 10.8 ± 13.2 I1: 5.5 ± 6.1 I2: 7.1 ± 8.8 Other characteristics: C1 I1 I2 Mean age: 73.4 73.5 67.5 M:F 1:1.8 1:2.8 1:1.4 Duration (months): 2 5.2 3.9 % of patients at grade: III 21.4 26.7 25 IV 78.6 73.3 75 Location (%): Ischium 29 20 17 Sacrum 43 33 42 Trochanter 21 27 17 Other 7 20 25 Groups were also comparable on baseline laboratory values e.g. blood albumin, haemoglobin and protein.	Complete healing at 28 days: C1: 3 I1: 2 I2: 0 % reduction in sore volume at 28 days: C1: 20 I1: 71 I2: 60 No significant differences after adjustment for differences in initial volume using ANCOVA ($p = 0.06$). For the two treatment groups combined mean volume was less than with placebo ($p = 0.009$). Reduction in wound area at 28 days: After ANCOVA adjustment for initial area, no significant group differences ($p = 0.08$). Time to achieve 50% healing: No significant differences ($p = 0.22$) 5-month follow-up: majority of ulcers remained unhealed, suggesting that treatment effects were transient.	None reported.	After 5 months follow-up, the majority of ulcers remained unhealed and static in size.

ANOVA, analysis of variance; ANCOVA, analysis of covariance

continued

TABLE 11 contd *Topical agents (including concentration comparisons) compared with placebo formulations*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Robson *et al.*, 1992[45] USA Method of randomisation: Not stated. Objective outcome: % change in wound depth and volume using wound gauge, mould weight. Setting and length of treatment: Inpatient setting. Treatment continued for 28 days; follow-up for up to 5 months.	Inclusion criteria: Sores between 25 and 95 cm^2 with full-thickness skin loss (grade III or IV) or penetrating to bony prominence (grade IV), with no past or present evidence of malignancy, with mechanical debridement of necrotic tissue at least 2 days prior, and normal or clinically insignificant results on pre-treatment blood count, and coagulation, chemistry and urinalysis. Exclusion criteria: Arterial or venous disorder resulting in ulcerated wounds; clinically significant disease; significant malnutrition; recent use of steroidal therapy; immunotherapy or cytotoxic chemotherapy; diabetes.	Treatment: r-PDGF-BB at three concentrations: I1: 1 µg/ml, *n* = 4 I2: 10 µg/ml, *n* = 4 I3: 100 µg/ml, *n* = 5. Treatment given daily for 4 weeks at a dose of 0.01 ml/cm^2 of sore surface. After treatment the wound was left open to allow absorption. Each sore was packed with sterile gauze and closed with Biobrane. C1: Placebo (not stated), *n* = 7.	Mean wound depth (cm): C1: 2.8 ± 0.4 (range, 1.5–5.2) I1: 1.7 ± 0.5 (range, 0.5–2.7) I2: 1.6 ± 0.6 (range, 0.8–3.5) I3: 2.8 ± 1.0 (range, 1.6–6.8) (Comparison of means by ANOVA: NS.) Mean wound volume (cm^3): C1: 12.9 ± 3.8 (range, 5–33) I1: 13.8 ± 4.8 (range, 5–26) I2: 15.8 ± 4.0 (range, 9–28) I3: 11.6 ± 5.5 (range, 4–33) (Comparison of means by ANOVA: NS.) Wound duration (months): C1: 14.2 ± 6.2 (range, 1–37) I1: 11.6 ± 5.5 (range, 3–27) I2: 16 ± 7.1 (range, 4–36) I3: 17.3 ± 12.4 (range, 4–67) (Comparison of means by ANOVA: NS.) Other characteristics: Age (years): C1: 27 ± 2 (range, 22–35) I1: 40 ± 8 (range, 21–56) I2: 43 ± 5 (range, 32–54) I3: 29 ± 4 (range, 21–45) (Comparison of means by ANOVA: NS.)	% reduction in wound volume at 28 days: C1: 78.2% (5.6 SEM) I1: 63% (15 SEM) I2: 55% (15 SEM) I3: 93.5% (4 SEM) No clinically significant differences between patients treated with 1 or 10 µg of r-PDGF-BB.	None reported.	Histological evaluation of the tissue biopsies found no treatment-related group differences in cellular influx or extracellular matrix deposition. The 100 µg/ml "tended to have greater fibroblastic and endothelial cell influx", but no data presented.
Robson *et al.*, 1992[44] USA Method of randomisation: Not stated. Objective outcome: Change in diameter and volume of wound, measured by planimetry and alginate moulding. Setting and length of treatment: Multicentre trial of hospitalised patients. Treatment continued for 22 days.	Inclusion criteria: Hospitalised patients aged 18–65 years, grade III or IV pressure sores between 10 and 200 cm^2 extending from bone to subcutaneous tissue. Mechanical debridement > 24 hours before treatment. Normal or clinically insignificant abnormalities in complete blood count, coagulation, blood chemistry, and urinalysis. Exclusion criteria: Arterial or venous disorder, or wound due to vasculitis; clinically significant systemic disease or malnutrition; recent steroidal therapy; penicillin allergy.	r-bFGF at three concentrations: I1: 100 µg/ml, *n* = 11 I2: 500 µg/ml, *n* = 11 I3: 1000 µg/ml, *n* = 12. Treatments given at different application schedules, at a dose volume of 1.01 ml/cm^2. Wound packed with saline-moistened sterile gauze changed after 12 hours. (note: 35 patients entered this arm of the trial, but data were only provided for 34). C1: Placebo (not stated), *n* = 14. All patients were denervated in the area of ulceration because of congenital or acquired spinal cord pathology. Standard pressure-relieving devices were used as appropriate.	Baseline data are only present for all r-bFGF groups combined (I1, I2, I3) Initial ulcer size: Not stated, but reported that there were no significant group differences. Other characteristics: Age (years): I1, I2, I3: 37.8 C1: 37.9 Duration (months): I1, I2, I3: 17.7 C1: 25.9 M:F I1, I2, I3: 3.9:1 (all groups) No statistically significant differences were found between baseline characteristics (Wilcoxon test). No group differences in ethnicity.	Number of patients achieving 70% volume reduction: I1, I2, I3: 21/35 (60%) C1: 4/14 (29%) (p = 0.047) % reduction in wound volume: I1, I2, I3: 69% C1: 59%	One patient in placebo group removed from trial because of possible neoplasm.	Blinded observers reported significant differences in visual improvement of overall healing, favouring r-bFGF (I1, I2, I3). No statistical tests reported. Fibroblast and capillary counts appear from a histogram to favour r-bFGF but the differences appear small and no statistical tests are reported.

continued

TABLE 11 contd *Topical agents (including concentration comparisons) compared with placebo formulations*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Robson *et al.*, 1994[42] USA Method of randomisation: Not stated. Objective outcome: % decrease in wound volume from baseline. Setting and length of treatment: Inpatients. Treatment until healing or maximum of 28 days.	Inclusion criteria: Pressure sores extending from the bone to the subcutaneous tissue (grade III/IV sores). Exclusion criteria: Significant renal, hepatic, cardiac, endocrine or haematologic disease, or neoplastic disease producing ulcerated wounds; arterial or venous disorders resulting in ulcerated wounds; systemic sepsis from the pressure ulcer; lack of cooperation; 'unsuitability', inability to provide informed consent; whirlpool therapy requirements; HIV+; use of investigational drugs within 1 month before study entry; or treatment of the target ulcer with cytokines within 3 months of entry.	Treatment: Interleukin 1-beta, a cytokine given in a single treatment per day at three different concentrations: I1: 0.01 μg/cm^2 I2: 0.1 μg/cm^2 I3: 1.0 μg/cm^2. 0.01 ml/cm^2 was delivered by spray after saline cleansing. Wounds were then air-dried and dressed with saline-moistened dressing, changed 12 hours later. Treatment applied at three different dosages of 0.01, 0.1 and 1.0 to six patients per group (total *n* = 18). C1: Placebo (not stated), *n* = 6. All patients were denervated in the area of ulceration because of congenital or acquired spinal cord pathology. Pressure-relieving devices were used as appropriate. Patients on non-air-fluidised beds re-positioned every 2 hours.	No statistically significant differences were reported between groups in race, gender, tobacco use, ulcer location, age, height, weight, or ulcer stage or size at baseline. No data are presented. All pressure sores were located on the sacrum, ischium or trochanter.	% reduction in wound volume: I1: 68% I2: 75% I3: 58% C1: 25%	I1: 1 I2: 0 I3: 1 C1: 0 Of the two withdrawals, one left hospital before completion of study and one was withdrawn because of osteomyelitis at base of ulcer. These were replaced; unclear how this was done.	Effect of treatment on fibroblasts assessed but not reported in detail.
Tytgat & Van Asch, 1988[41] Belgium Method of allocation: Not randomised. Objective outcome: Wound area. Setting and length of treatment: Setting not stated. Treatment was continued for 3 weeks.	Inclusion criteria: Multiple sclerosis patients with decubitus ulcers. No other information. Exclusion criteria: Not stated.	Treatment: I1: 2% Ketanserin ointment, *n* = 8 C1: Placebo ointment (not stated), *n* = 8 Each was applied twice daily for 3 weeks.	Median wound area (mm^2): I: 1150 C: 860 Other characteristics: I1 C1 Mean age (years): 58 60 M: F 1:1 (all groups) Duration (weeks): 17 24 Diabetes: 1 0	% reduction in wound area at 3 weeks: I1: 81% C1: 16% ($p < 0.05$, Wilcoxon matched-pairs signed ranks test).	None reported.	No side-effects in either group.

TABLE 12 *Topical agents compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Brown-Etris *et al.*, 1996[46] USA Method of randomisation: Method not stated; stratification occurred according to surface area and stage. Objective outcome: Area reduction assessed by gravimetric planimetry with wound tracing onto plastic film and photography. Independent analysis by biostatistical analysis firm. Change in level of wound margin undermining assessed. Setting and length of treatment: Hospital, long-term care, home or outpatients. Medical centres (no other details). Trial participation was until 10 weeks, or treatment change was indicated or the wound healed, whichever came first.	Inclusion criteria: Patients > 18 years with one or more pressure ulcers. Grade II, III or IV only. Wound size between 2 and 80 cm^2 and < 1 cm deep, clinically non-infected, eschar-free, with ≥ 75% granulation base with fixed wound margins. Adequate nutritional intake by mouth tube or hyperalimentation. Exclusion criteria: Grade I ulcers or grade IV ulcers with exposed tendon or bone; wound size < 2 cm^2 or > 80 cm^2, or > 1 cm deep; wounds covered with necrotic eschar or necrotic wound base containing > 25% slough; diagnosis or suspicion of osteomyelitis at study wound site; carcinomatosis, or signs or symptoms of wound clinical infection; inadequate nutritional intake; sinus tract, tunnelling or > 0.5 cm of wound margin undermining.	Treatment: I1: Topical hydrogel (Transorbent), *n* = 66. I2: Hydrocolloid dressing (Duoderm CGF, Granuflex CGF), *n* = 55. Evaluation took place weekly, dressing changes occurred every 7 days or more frequently.	Mean surface area of wound: Not stated. Other characteristics: All groups Mean age (years): 70 M:F 1:1 I1 I2 Duration (months): < 1 23% 31% 1–3 38% 49% 4–6 10% 14% 7–12 13% 2% > 12 16% 4% Location: Sacrum 33% 37% Trochanter 17% 26% Heel 16% 18% Ischium 16% 13% Malleolus 10% 4% Spine 6% 2% Knee 2% 0%	Surface area reduction at 10 weeks (cm^2): Grade II ulcers (2–30 cm^2): I1: 3.6, *n* = 12 I2: 2.3, *n* = 12 (NS) Grade III ulcers (2–30 cm^2): I1: 6.3, *n* = 42 I2: 5.2, *n* = 36 (NS) Grade III ulcers (31–80 cm^2): I1: 24.5, *n* = 3 I2: 4.3, *n* = 2 (NS) Insufficient data were available for analysis of the following subgroupings: Grade II (31–80 cm^2) Grade IV (2–30 cm^2) Grade IV (31–80 cm^2)	19 randomised patients were not included in the analysis as they did not complete the first 3 weeks of the study, or missed two or more sequential weekly visits.	No significant differences in clinical wound infection, odour, or dressing changes/week.
Darkovich *et al.*, 1990[47] USA Method of randomisation: Not stated. Objective outcome: Perimeter of ulcer traced and in some cases photographed to determine the size of the ulcer. Number of ulcers healed. Setting and length of treatment: Maximum 60 day trial unless wound healed, patient discharged or withdrawn by clinician. Measurements taken at each dressing change or at least weekly intervals.	Inclusion criteria: Patients in acute care facilities and nursing homes with grade I or II pressure sores ulcers (size > 2 cm^2). Exclusion criteria: Receiving radiation therapy; infection, sinus tracts or fistulae in the wound; a blood sugar level > 180 mg/dl; no improved nutritional status.	Treatment: I1: Hydrogel (Biofilm), *n* = 62. I2: Hydrocolloid (DuoDerm; Granuflex), *n* = 67. All wounds were initially cleansed with hydrogen peroxide and saline. Patients with an oily skin were degreased to allow for a 1.25 inch adhesion belt around the wound. Although this was not maintained where the wound was > 20 cm^2, instead utilising 4 x 4 inch dressings. Dressings were usually changed every 3–4 days and washed in saline before reapplication. All patients lay on pressure-reducing mattresses.	Mean area of wound (cm^2): Biofilm: 11.0 (range, 0.2–100) DuoDerm: 9.2 (range, 0.4–64) Other characteristics: All groups Mean age (years): 75 M:F 1:1.6 I1 I2 Ratio of grade I:II ulcers: 1:1.3 1:1.6 Serum albumin (g/dl): 2.8 2.7 No. of grade I wounds: 27 31 No. of grade II wounds: 35 67 There was a significant difference between the age of patients in the acute care setting (69) and the extended care facilities (83).	Mean area of pressure sore at 60 days (cm^2): I1: 3.5 C1: 5.5 Mean reduction (absolute and relative) in pressure sore area at 60 days (cm^2): I1: 7.5 (68%) I2: 3.7 (40%) Complete healing at 60 days: I1: 26/60 (43%) I2: 15/24 (24%) Mean treatment days: I1: 12 I2: 11.3	Six extreme results were exempt from the analysis to make it more meaningful. Three patients in the I1 group and one in the I2 group had wounds that enlarged by > 10% per day. One patient in each group was excluded because their wounds decreased by more than 25% per day.	Hydrogels such as Biofilm (I1) offered the ability to absorb excess fluid without degradation and maintain a moist environment. Patients appeared to prefer I1 too because of the lack of odour, cushioning and lightness. The gel layer in I2 was found to degrade easily, which necessitated mechanical cleansing of the wound, which damaged the healing tissue layers.

continued

TABLE 12 contd *Topical agents compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Mulder *et al.*, 1993[48] USA Method of randomisation: Computer allocation. Objective outcomes: Perimeter of ulcer traced on to a transparency and area determined by computer. Largest length, width and depth of the wound was measured and a photograph was taken at each assessment. Setting and length of treatment: A multicentre trial (three independent sites). Assessments of ulcer size made weekly for 8 weeks or until the ulcer was healed. Where possible, each patient evaluated by same investigator throughout the trial.	Inclusion criteria: Grade II and III pressure sores ≥ 1.5 cm x 0.5 cm, but ≤ 10 cm x 10 cm. All patients had to be >18 years and have a life expectancy of at least 2 months. Exclusion criteria: Grade IV wounds or those with tendon, bone, capsule, or fascia exposure; pregnancy; chemotherapy; prior wound infection; extensive undermining of the ulcer (> 1 cm); AIDS; patients receiving > 10 mg of corticosteroids.	Treatment: I1: Hydrogel (Clearsite), changed twice a week, *n* = 23. I2: Hydrocolloid dressing (DuoDerm, Granuflex) changed twice a week, *n* = 20. C1: Saline solution and moistened gauze, changed three times a day, *n* = 21. Dressings were changed either by the patient or the care giver, after they had received appropriate instructions. 67 patients were enrolled in to the trial – data analysed for only 64 patients.	Area of wound (cm^2): Not stated. Other characteristics: I1 / I2 / C1 Mean age (years): 56.7 / 63.1 / 57.2 M:F 1:3.6 / 1:5.6 / 1:9.5 Ulcer stage: Grade II 8 / 9 / 5 Grade III 14 / 13 / 18 Race (patients): Black 4 / 3 / 6 White 17 / 16 / 14 Hispanic 1 / 1 / 0 No statistically significant differences between the three groups.	Mean % reduction in wound area per week: I1: 8 (14.8 SD) I2: 3.3 (32.7 SD) C1: 5.1 (14.8 SD) ($p > 0.05$; non-parametric test) Median % reduction in wound area per week: I1: 5.6 I2: 7.4 C1: 7.0 ($p > 0.05$; non-parametric test)	I1: Three patients were omitted from the final analysis. No reasons are given for these withdrawals. I2: 0 C1: 0 Three patients were not evaluable and their data are not presented in the baseline characteristics.	One patient treated with I2 had mild irritation, another showed minor sensitivity. One case of inflammation occurred in the I1 group, and another patient had excoriation, which was possibly related to I1 treatment. There were no adverse reactions to C1 treatment.
Palmieri, 1992[50] Italy Method of allocation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Wound clinic. Treatment was continued until all wounds had healed.	Inclusion criteria: Venous leg ulcers; pressure sores; diabetic gangrene; pressure sores; post-traumatic wounds; burns and radioactive ulcers. Note: Data are only given here for leg ulcers and pressure sores. Exclusion criteria: Additional treatments with drugs (with the exception of digitalis).	Treatment: I1: Collagen sponge applied directly to the wound after saline nebulisation. The dressing was checked every day and if the collagen sponge was swollen or partially reabsorbed more sponge was applied without removing the previous one. Greasy sponge and regular non-allergenic tape completed the dressing, *n* = 24. Polysaccharide beads (Debrisan) were applied directly to the wound bead and replaced daily, *n* = 24. All wounds were sharp debrided prior to randomisation. In addition all wounds were treated to ensure negative bacterial cultures at baseline.	Wound area: Not stated. Other characteristics: All groups Age range (years): 58–75 M:F 1: 0.6 Wound type: Leg ulcers 12 Diabetic gangrene 12 Pressure sores 12 Post traumatic 12	Mean time to healing (days): Leg ulcers: I1: 36 I2: 60 ($p < 0.005$; Student's *t*-test) Pressure sores: I1: 20 I2: 47 ($p < 0.001$; Student's *t*-test)	No withdrawals.	

continued

TABLE 12 contd *Topical agents compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Sayag *et al.*, 1996[49] France Method of randomisation: Sealed envelopes. Objective outcome: Area of ulcer measured by planimetry, digitised twice and the area calculated by computer. The mean of the two values was used to determine individual ulcer area. A photograph was taken of each wound at every evaluation. Setting and length of treatment: A multicentre trial based at 20 centres (17 specialising in the care of elderly people and three in dermatology). Assessments were made on a weekly basis by the same.	Inclusion criteria: Patients aged ≥ 60 years hospitalised for ≥ 8 weeks, with a pressure sore graded III or IV and surface area from 5–100 cm^2. Sores were located on the sacrum, ischium, trochanters and heels. Exclusion criteria: More than half the total ulcer area had granulating tissue; ulcer covered by necrotic plaque; active infection requiring local or systemic antibiotic therapy; severe renal failure.	Treatment: I1: Polysaccharide beads (Debrisan paste) applied to a depth of 3 mm over the wound surface, *n* = 45. I2: Calcium alginate dressings (Algosteril) applied directly on to wound to cover the entire area, *n* = 47. In both groups a sterile gauze was applied as a secondary dressing. No other local treatments were used except for saline solution the use of which was not restricted. Dressings were inspected and changed daily or at least every 4 days depending on the degree of exudate.	Mean area of wound (cm^2): I1: 16.1 ± 12.5 SD I2: 20.1 ± 12.9 SD Other characteristics: I1 / I2 Mean age (years): 80.4 (9.1) / 81.9 (8.9) M:F 1:2.8 / 1:2.9 Mean (SD) duration (months): 3.0 (3.2) / 3.5 (3.8) Wound grade: III 30 / 33 IV 15 / 14 No significant difference between the two groups. Where patients had multiple wounds only one was selected for study.	Mean wound area reduction per week (cm^2): I1: 0.27 ± 3.21 SD I2: 2.39 ± 3.54 SD (p = 0.0001; Student's t-test) Mean wound area reduction per week using the data from only those patients reaching ≥ 40% (cm^2): I1: 2.15 ± 3.60 SD I2: 3.55 ± 2.18 SD (p = 0.0004; Student's t-test) Number of wounds with > 75% reduction in area: I1: 6 (13%) I2: 15 (32%) Number of pressure sores with > 40% reduction in area: I1: 19 (42%) I2: 35 (74%) (p = 0.002 exact)	I1: 22 I2: 10 All withdrawals were included in the analysis and few were considered to have improved at the last evaluation. End point data were not available for one patient in the I2 group due to admission to a special care unit. Reasons for withdrawals: I1: death (6); adverse event (1); deterioration or stagnation of ulcer after 4 week (15). I2: death (5); transfer (2); deterioration of health (1); deterioration or stagnation of ulcer after 4 week (2).	On average the number of dressing changes per week was similar: 4.28 (1.49 SD) for I2 and 4.52 (1.42 SD) for I1. 8% of I2 and 33% of I1 patients experienced adverse effects.

TABLE 13 *Dressings compared with traditional therapy*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Alm *et al.*, 1989[51] Sweden Method of randomisation: Method not stated. Stratification used. Randomisation of sores, not patients, took place. Objective outcome: Weekly photography of ulcer, evaluated by dermatologist blinded to treatment. Setting and length of treatment: Long-stay wards (multicentre). Treatment was initially for 6 weeks; if healing not complete, treatment continued for 3–6 weeks.	Inclusion criteria: Patients on long-term wards with pressure sores. Exclusion criteria: Patients with a Norton score < 7.	Treatment: I1: Hydrocolloid dressings (Comfeel) changed when necessary. This included Comfeel Ulcus sheet, paste and powder. Sheet: sodium carboxymethylcellulose particles embedded in an adhesive elastic mass. Paste: sodium carboxymethylcellulose, guar cellulose and xanthan cellulose (25 ulcers). C1: Wet saline gauze changed routinely twice daily (31 ulcers). 50 patients with 56 pressure sores were randomised.	Wound size: I1 C1 Median depth (mm): 1.75 2.00 Median area (cm^2): 2.02 2.44 Other characteristics I1 C1 Mean age (years): 84 83 M:F approx. 1:3 (all groups) Duration (months): 4.6 4.8 Norton score: 12 13 Body weight (kg): 50 50 About one-third of sores were on the heel, and one third on the sacral region.	Complete healing at 6 weeks: I1: 11/25 (44%) C2: 5/31 (16%) Median reduction in wound area at 6 weeks (cm^2): I1: 2 (100% reduction) C1: 1.8 (70% reduction) ($p = 0.006$) Wound depth: Median depth only significant at week 4 ($p = 0.047$) Detailed analysis of results for granulated tissue not reported, but stated that hydrocolloid dressing filled with granulation tissue more quickly.	I1: 2 C1: 3 Drop-outs occurred because of death for reasons unrelated to treatment, or violation of protocol or unknown reasons. One patient was lost because data were incomplete.	Patients in the hydrocolloid (I1) group were reported to have the most favourable healing distribution function, though the overall difference was non-significant. No difference in pain at dressing changes.
Barrois, 1992;[52] Huchon, 1992[53] France Method of randomisation: Not stated. Objective outcome: Sores improved (totally or partially healed). Decrease in surface area/ week. Tracing took place every 7 days, with photograph at days 0, 28, 56. Setting and length of treatment: 56 days or earlier if sore healed.	Inclusion criteria: Patients with open necrotic pressure sores or ulceration. Exclusion criteria: Not stated.	Treatment: I1: Hydrocolloid dressing (Granuflex standard), $n = 38$. C1: Standard dressing (Tulle gauze) impregnated with povidone-iodine antiseptic, $n = 38$. Cleansing was carried out with saline, and debridement with forceps if necessary.	Mean surface area of wound: 15 cm^2 (all patients). Surface area of sores reported as comparable between treatment groups, no details presented. No other baseline details of patients.	Complete healing at 8 weeks: I1: 10/38 (26%) C1: 9/38 (24%) ($p = 0.16$) (partial healing: 22 vs. 18) Overall improvement at 8 weeks: Granuflex: 32 (84%) Standard: 27 (71%) Reduction in area: I1: 10%/week C1: 7%/week	I1: Two patients due to deterioration in pressure sore. C1: Five patients due to deterioration in pressure sore.	No adverse effects observed, but no data are reported. Mean dressings used: Granuflex: 2.4/week Standard: 5.1/week ($p < 0.0001$).

continued

TABLE 13 contd *Dressings compared with traditional therapy*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Colwell *et al.*, 1993[54] USA Method of randomisation: Not stated. Objective outcome: Decrease in wound size and area, measured by tracing every 4th day on acetate film and measuring with electronic planimeter. Width and length recorded. % of pressure ulcers completely healed calculated. Setting and length of treatment: Academic tertiary-care centre. Average length of time in study = 17 days, range 6–56 days.	Inclusion criteria: Patients with pressure sores. Exclusion criteria: Underlying condition or treatment likely to affect healing. Clinically infected sores, grade I or IV pressure sores, or pressure ulcer that could not be accurately graded. Patients were excluded if they did not remain in the study for ≥ 8 days, or were receiving other sore therapy likely to confound results (e.g. hydrotherapy).	Treatment: I1: Hydrocolloid dressing (DuoDerm; Granuflex) extending at least 2.5 cm beyond sore margins, changed every 4 days or as needed, *n* = 33. C1: Moist gauze dressings with 0.9% sodium chloride solution, loosely applied and covered with sterile dry gauze dressing and a secondary dressing to keep inner dressing moist, secured with hypoallergenic tape. Changed every 6 hours, or as needed, *n* = 37. All patients were placed on pressure-reducing surface (foam overlay or low air-loss bed), and in both groups ulcers and surrounding skin were cleansed with warm tap water and dried.	C1 I1 No. of ulcers: 48 (49%) 49 (51%) Sore location: Sacrum/coccyx 29 (60%) 27 (55%) Other 19 (40%) 22 (45%) Duration of sore: < 1 month 25 (60%) 27 (59%) 1–3 months 21 (45%) 19 (41%) Ulcer grade: II 33 (69%) 21 (44%) III 15 (31%) 28 (56%) Initial ulcer Length (cm): 1–21 1–12 Width (cm): 0.4–10 1–10 Area (cm): 2.3 2.4 Total : 70 patients with 97 pressure ulcers Other characteristics: C1 I1 Mean age (years): 68 68 M:F 1:1.1 (all groups) No significant differences in continence or general health; typical patient had poor health, nutritional status, and was confused and debilitated. Significantly more grade II ulcers in I1 group, hence groups were stratified by ulcer grade for analysis. Significantly fewer I1 patients with diabetes.	Complete healing at 8 weeks: I1: 11/49 (22%) C1: 1/18 (2%) (p = 0.04) No statistically significant group difference in total sore surface area at end of study, controlling for initial surface area, stage of sore, and length of time in study (F = 2.03, p > 0.05). No significant group differences in change in sore length or width, either between or within groups.	Of 94 patients initially enrolled, 24 did not complete 8 days of treatment for reasons not given, five were discharged prior to completion of 8 days of treatment, 12 died of unrelated causes, five were lost to follow-up. Two dropped out because of colonisation with methicillin-resistant *Staphylococcus aureus*, one because ulcer progressed to grade IV.	No other outcomes reported, though a major focus of the paper was cost-effectiveness. Total cost per case was much lower with I1 than C1.
Gorse & Messner, 1987[56] USA Method of randomisation: Not randomised. One treatment used on each of two wards; patients were allocated to wards to give a balance of surgical and medical patients. Objective outcome: % of sores improved; decrease in ulcer area. Setting and length of treatment: Hospital. Maximum of 75 days follow-up.	Inclusion criteria: Pressure sores of grade II, III or IV pressure sores. Exclusion criteria: Adjacent osteomyelitis or extension of pressure sore into fascia, bone and/or joint space; venous stasis and ischaemic ulcers of the extremities; rapidly fatal underlying disease; and planned hospital discharge within 7 days of treatment initiation.	Treatment: I1: Dakin's solution (wet-to-dry dressing) changed every 48 hours, *n* = 25 patients with 52 pressure sores. I2: Hydrocolloid dressing changed every 4 days or more frequently if contaminated or if systematic infection developed, *n* = 27 patients with 76 pressure sores.	Mean area of wound: Not stated. Other characteristics: I1 I2 Mean age (years): 72 68.4 % of sores among patients > 65 years: 75% 56% Distribution of underlying disease, distribution of pressure sores by site, proportion of grade II sores, and nutritional status all reported to be similar in the two groups. A greater % of pressure sores was present in the ambulatory wet-to-dry group, and a greater % of sores in this group were infected (p = 0.021).	Complete healing at 75 days: I1: 26/52 (50%) I2: 54/76 (71%) Rate of decrease in wound area (cm^2/day): I1: 0.55 I2: 0.72 (NS) Mean days to healing: I1: 8.7 I2: 10.0 (NS). Results based on those wounds that did heal.	None.	

continued

TABLE 13 contd *Dressings compared with traditional therapy*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Kraft *et al.*, 1993[61] USA Method of randomisation: Not stated. Objective outcome: Number of pressure sores at weeks 3, 6, 12, and 24. Setting and length of treatment: Tertiary care veteran's hospital. Patients treated for 24 weeks.	Inclusion criteria: Patients with pressure sores Exclusions criteria: Grade I and IV pressure sores; infected ulcers; patients on special beds; unstable insulin-dependent diabetes; serum albumin < 2 g; haemoglobin < 12 g; Class IV congestive heart failure; chronic renal failure; severe peripheral vascular disease; severe chronic obstructive pulmonary disease.	Treatment: I1: Non-adherent semi-occlusive foam wound dressing with an adhesive cover (Epi-Lock), *n* = 24. C1: Saline-moistened gauze, changed once every 8 hours, *n* = 14. Standardised dressing procedures applied in both groups.	Wound area: Not stated. Other characteristics: Mean age: 56 years (all groups) Geriatric but mainly spinal cord injured patients. Duration of sores: ranged from new to 5 years. Ulcers in existence 2 months or less in 53% of subjects. Previous hospitalisation for pressure ulcer treatment (usually saline) reported in 53% of patients. Grade II sores were present on 22 patients and grade III were found on 16 patients.	Number of patients healed by week 12: I1: 10/24 (42%) C1: 2/14 (14%) (p = 0.1) Number of patients healed by week 12: I1: 10/24 (42%) C1: 3/14 (21%) (p = 0.26)	I1: 11 (five where staff requested removal, and four because of reactions to treatment) C1: Six (two deaths, one reaction to saline, three other reasons).	Grade II ulcers showed most healing by 6 weeks. Grade III ulcers healed more slowly. Epi-lock (I1) dressing required fewer dressings per week and less nursing time, so that the overall weekly dressing cost for Epi-lock was US$21 vs. US$75 for saline.
Oleske *et al.*, 1986[57] USA Method of randomisation: Quasi-experimental, random assignment of treatment protocol and random assignment of patients. Objective outcome: Reduction in wound area. Setting and length of treatment: University hospital. Treatment was continued for 10 days.	Inclusion criteria: > 21 years, afebrile, confined to bed, wheelchair or chair and expected to be so for at least 2 weeks, expected to be hospitalised for at least 2 weeks, patient or next of kin English speaking. Ulcer with skin break not expending to muscle (grade I or II only), in an area not currently being irradiated with no evidence of infection. Haemoglobin level at least 10 g/dl. Exclusion criteria: Patients with skin breakdown due to non-pressure related causes; ulcer too small for reliable measurement (< 2 cm).	Treatment: I1: Self-adhesive polyurethane dressing (Opsite) applied for approximately 2 days otherwise changed only if dislodged from the sore, *n* = 7. C1: Normal saline-moistened gauze cut to size and covered with a plastic pad held in place by paper tape. Dressing changed every 4 hours around the clock during study period, or more frequently if soiled, *n* = 6. Pretreatment in both groups consisted of rinsing with normal saline before application of dressing.	Mean area of wound (cm^2): I1: 3.9 (0.73 SD) C1: 12.67 (11.28 SD) (NS) Mean longest axis (cm): I1: 3.1 C1: 3.1 (NS) Other characteristics: Mean age: 69 years (all groups). Sex ratio not reported, but groups reported not to be different. All sores treated were in gluteal or coccyx areas.	Mean decrease in wound surface area at 10 days (cm^2): I1: 1.8 (1.30 SD) C1: 2.5 (5.54 SD) % reduction in wound area at 10 days: I1: 49 (37.31 SD) C1: 26.67 (44.3 SD)	One patient transferred to a nursing home. No details on which group they belonged to.	No other outcomes.
Saydak, 1990[60] USA Method of randomisation: Not randomised. Alternate allocation of wounds was used. Objective outcome: Length of greatest axis and depth, measured with sterile calipers. Setting and length of treatment: Veterans medical centre. Treatment for 2–8 weeks depending on length of stay.	Inclusion: Patients with at least two pressure sores of comparable length and depth. Exclusion: Known sensitivity to povidone-iodine.	Treatment: I1: Absorption dressing. The dressing was changed daily. C1: Povidone-iodine solution (1%) with normal saline rinse. Total of 11 patients included in study, with each patient acting as his own control.	Wound size: Mean depth (cm): I1: 1.27 (1.16 SD) C1: 1.23 (1.05 SD) (NS) Mean length (cm): I1: 7.5 (4.95 SD) C1: 5.7 (4.6 SD) (NS) Other characteristics: All subjects were male, mean age 64 years. Ten had some neurological disorder; nine were confined to bed; six were on a water mattress; four on an air-fluidised bed or mattress; one was on an eggcrate mattress. Location of sores: Five patients had sores on their hip, three had hip and sacral sores.	Mean % reduction in depth of wound: I1: 54.2 (26.5 SD) C1: 5.5 (68 SD) (NS) Mean % reduction in length of wound: I1: 13.5 (22.9 SD) C1: 4.9 (21.1 SD) (NS)	None.	Odour control improved more with absorption dressing.

continued

TABLE 13 contd *Dressings compared with traditional therapy*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Sebern, 1986;[58] 1989[59] USA Method of randomisation: Random number list used to assign ulcers to treatments. Objective outcome: Healing status; final grade of pressure sore; decrease in wound area. Setting and length of treatment: Home care setting. Treatment continued for 8 weeks.	Inclusion criteria: Patients with grade II or grade III pressure ulcers receiving visits from nursing service. Exclusion criteria: Wound containing eschar, grade I or IV ulcer, patient had terminal illness, white cell count < 4000, or patient had three or more existing ulcers; necrotic ulcers; pressure ulcers > 50 cm^2.	Treatment: I1: Polyurethane sterile dressing (moisture vapour permeable). Changed daily to three times a week depending on adherence of dressing, *n* = 100 sores. C1: Wet-to-dry gauze dressing, with saline on the contact layer, covered with dry gauze and pad. Changed every 24 hours, with saline used to loosen dressing, and irrigation with half-strength hydrogen peroxide and saline. If wound was contaminated, povidone iodine was applied for 2 minutes and rinsed away with saline, *n* = 100 sores. Study protocol included a turning schedule and wheelchair push-ups. Wheelchair-dependent patients were given a silicone gel pad or dense foam cushion, or an alternating pressure pad for patients in bed. The same protocol for pressure relief and wound irrigation was used in both groups.	Median area of wound (cm^2): Grade II: I1: 1.9 C1: 3.4 Grade III: I1: 6.1 C1: 4.5 Other characteristics: I1 C1 Mean age (years): 76.3 72.4 Grade II: 59% 30% Grade III: 41% 70% No statistically significant group differences in height, weight and PULSES score. All participants had a chronic illness, and according to PULSES score were very severely disabled. All patients had chronic illness (mostly focal cerebral disorders, spinal cord disorders, neurological disorders, and miscellaneous chronic conditions, e.g. cardiac causes) and poor nutrition. 5–9% of ulcers were on the foot.	Median decrease in wound area at 8 weeks: Grade II ulcers: I1: 100% C1: 52% ($p < 0.01$) Grade III ulcers: I1: 67% C1: 44% ($p = 0.15$) (NS) Healing status at 8 weeks: (Four-point scale: healed, progress, no change, deteriorated/ discontinued) Grade II ulcers: none of the gauze-treated group healed vs. 64% of MVP-treated ulcers. Chi-squared test: ($p < 0.01$). Grade III ulcers: no significant group differences. Final grade: I1 dressing had lower final grade ($p < 0.01$, chi-square).	23 drop-outs in less than 3 weeks; most frequently due to death, hospitalisation, and inability to comply with the study protocol for pressure relief.	No differences in supply costs, but costs of treatment (including nursing visits) for grade II ulcers significantly lower with I1 ($p < 0.05$). Less pain with I1, though no data presented.
Xakellis & Chrischilles, 1992[55] USA Method of randomisation: Not stated. Objective outcome: Number of wounds healed (i.e. with epithelial covering by inspection and absence of moist surface by palpation). Time to healing. Setting and length of treatment: Intermediate-level long-term care facility. Treatment period 6 months maximum.	Inclusion criteria: Patients with skin break over a bony prominence. Exclusion criteria: Grade I or IV pressure sores; rapidly fatal disease, or anticipated discharge within one week; skin ulcers from cause other than pressure, e.g. venous stasis ulcers.	Treatment: I1: Hydrocolloid dressing rimmed with tape, changed if non-occlusive and changed twice weekly to allow wound assessment. Cleaned with normal saline at this time, *n* = 18. C1: Saline gauze (non-sterile 8-ply 4 x 4-inch gauze dressing moistened with saline covered with two non-sterile gauze dressing rimmed with tape), *n* = 21. Routine care to all participants included repositioning every 2 hours and cleaning of incontinence with warm water as required. Necrotic tissue was debrided using sharp debridement at enrolment and during treatment as necessary. All patients were placed on an air mattress and an air-filled wheelchair cushion.	Median wound surface area (cm^2): I1: 0.66 C1: 0.38 (NS) Other characteristics: I1 C1 Age (years): 77 84 M:F 1:12 (all groups) Norton score: 11 13 No statistically significant group differences in other baseline measures, including comorbidities (diabetes, stroke, cancer, dementia, urinary tract infection, Foley catheterisation, other mobility limiting condition), incontinence, nutritional status, % with exudate, erythema, necrotic tissue, maceration, sore grade II or III, location of ulcer, or history of ulcer at same site.	Complete healing at 6 months: I1: 16/18 (89%) C1: 18/21 (86%) (NS) Median time to healing (days): I1: 9 C1: 11 ($p = 0.12$) 75% of I1 group healed within 14 days vs. 26 days in C1. Healing rate was significantly reduced when exudate was present at baseline, and after adjustment for this variable, healing rates did not differ significantly between the two groups.	I1: Two withdrawals C1: Three deaths.	Median nursing cost (including cost of nursing time) was significantly lower for the hydrocolloid group (I1), though total nursing costs using local nursing wages were not significantly different, though at national wage rates hydrocolloid treatment was cheaper.

PULSES score, a measure of severity of illness; MVP, moisture vapour permeable

TABLE 14 *Comparisons of modern dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Bale *et al.*, 1995[62] UK Method of randomisation: Not stated. Objective outcome: Total healing rates and % reduction in wound area. Setting and length of treatment: Community-based trial with patients followed until wound healed up to maximum of 8 weeks.	Inclusion criteria: Pressure sores, leg ulcers and other wounds were included. No other inclusion/exclusion criteria given. Exclusion criteria: Not stated.	Treatment: I1: Hydrocellular dressing (Allevyn), *n* = 51; 17 with pressure sores. I2: 'Improved formulation' hydrocolloid dressing, Trade name not stated (ConvaTec), *n* = 49; 15 with pressure sores.	Mean surface area of wound: Not stated. Other characteristics: I1 I2 Mean age (years): 76 78 M:F 1:3.3 (all groups)	Complete healing at 8 weeks: Pressure sores: I1: 10/17 (59%) I2: 4/15 (27%); $p = 0.07$ Leg ulcers: I1: 2/16 (13%) I2: 1/14 (7%) Other wounds: I1: 11/17 (65%) I2: 10/17 (59%) All wounds: I1: 23/50 (46%) I2: 15/46 (33%) No stratified results for reduction in wound area.	14 patients withdrawn due to adverse incidents, of which seven (maceration, overgranulation and pain), were related to dressings. Four patients excluded from analysis: one due to lost case report forms, two patients spent < 7 days in study, so insufficient data; and one protocol violation.	Patient-assessed comfort of dressings was also analysed. Hydrocellular dressings (I1) were more comfortable, but results not stratified by wound type.
Banks *et al.*, 1994[64] UK Method of randomisation: Computer-generated random order. Objective outcome: Healing. Setting and length of treatment: Patients resident in the community treated for 6 weeks unless the pressure sore had healed.	Inclusion criteria: Aged > 16 years, with shallow, moist sores of grade II or III that could be covered adequately with a single 10 cm x 10 cm dressing, who could be managed to prevent further lesions developing. Exclusion criteria: Patients with lesions involving tissues other than skin and subcutaneous fat, grade I, IV or V pressure sores, dry or necrotic lesions (included once debrided); patients taking systemic corticosteroids; patients whose sores had been dressed with either of the treatments in the previous 2 weeks, or who had previously reacted to either dressing; infected pressure sores; patients incapable of giving an opinion about the dressing; patients incontinent of urine or faeces with sacral pressure sores or site likely to be soiled.	Treatment: I1: Hydrocolloid dressing (Granuflex E), *n* = 20. I2: Polyurethane dressing (Spyrosorb), *n* = 20. Patients in both groups were provided with pressure-relieving mattresses and cushions. Dressings were changed when the area discoloured by exudate was < 1 cm from edge. Cleansing with warmed saline was undertaken if necessary. No topical applications were allowed.	Mean wound area (cm^2): I1: 1.51 I2: 1.47 Other characteristics I1 I2 Median age (years): 73 71 M:F 1.1:1 (all groups) Median duration (days): 21 56 Wound location: Buttock 45% 50% Sacrum 5% 20% Other 50% 30%	Complete healing at 6 weeks: I1: 10/20 (50%) I2: 12/20 (60%) (NS)	I2: Two withdrawals for reasons unrelated to wound I1: Two for wound deterioration; two for overgranulation; two for discomfort; four for reasons unrelated to the wound.	Spyrosorb (I2) reported to be easier to remove ($p < 0.005$). No significant differences in reported pain on removal, or comfort, or mean number of days which dressing remained in place.

continued

TABLE 14 contd *Comparisons of modern dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Banks *et al.*, 1994[63] UK Method of randomisation: Not stated. Objective outcome: Healing within study period. Time to healing. Setting and length of treatment: Hospital based. Final assessment was after 6 weeks of treatment or sooner if wound healed.	Inclusion criteria: Aged > 16 years, with shallow, moist sores of grade II or III that could be covered adequately with a single 10 cm x 10 cm dressing, who could be managed to prevent further lesions developing. Exclusion criteria: Patients with lesions involving tissues other than skin and subcutaneous fat; dry or necrotic lesions (included once debrided); patients taking systemic cortico-steroids; patients whose sores had been dressed with either treatment in past 2 weeks, or who had previously shown sensitivity to either dressing; infected sores; patients incapable of giving an opinion about the dressing; patients incontinent of urine or faeces with sacral pressure sores or site likely to be soiled.	Treatment: I1: Hydrocolloid dressing (Granuflex E), *n* = 16. I2: Polyurethane dressing (Spyrosorb), *n* = 13.	Mean wound area (cm^2): I1: 2.4 I2: 1.4 Other characteristics: I1 I2 Median age (years): 74 73 M:F 1.1:6 (all groups) Median duration (days): 6.5 7 Wound location: Buttock 56% 62% Sacrum 38% 31% Other 6% 8%	Complete healing at 6 weeks: I1: 11/16 (69%) I2: 10/13 (77%) (NS) Median time to healing (days): I1: 12.7 (*n* = 12) I2: 13.4 (*n* = 10) (NS)	I1: Four all due to wound- or dressing-related problems. I2: Three withdrawals (two due to wound- or dressing-related problems).	No differences in comfort, or length of time dressings remained *in situ.* Spyrosorb significantly easier to remove and associated with significantly less pain at dressing changes ($p < 0.005$). No difference in appearance or odour.
Banks *et al.*, 1994[68] UK Method of randomisation: Independently, by sealed envelope. Objective outcome: Healing rate and time to healing. Setting and length of treatment: Hospital and community. 12 weeks, or until wound healed.	Inclusion criteria: Grade II or III pressure sores. Exclusion criteria: Terminal illness, necrotic or infected sores, sores > 6–7 cm in any direction, or patient unavailable for full 12 weeks.	Treatment: I1: Polyurethane foam dressing (Lyofoam A), *n* = 26. I2: Low-adherence dressing (N-A) secured with vapour-permeable film (Tegaderm), *n* = 24. Dressing changed when necessary. Patients also had access to pressure-relieving equipment.	Mean area of wound (no. of patients): I1 I2 < 1 cm^2: 11 12 > 1 cm^2, < 2.5 cm^2: 2 2 > 2.5 cm^2: 6 1 Other characteristics: 68% of patients aged > 75 years M:F 1:1.8 36% had body mass index < 19 kg/m^2. Most common wound was sacral site (53%) followed by buttocks (32%), trochanter and foot, not heels (both 6%), and heels (3%). Duration of sore not known for 28% of patients. Not reported by group.	Complete healing at 12 weeks: I1: 19/26 (73%) I2: 15/24 (63%) (NS)	I1: 7 I2: 9 12 withdrawals (no other information) and four patients died.	No significant group differences in pain on removal or comfort, or nurse-assessed ease of application or removal.

continued

TABLE 14 contd *Comparisons of modern dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Banks *et al.*, 1996[65] UK Method of randomisation: Not stated. Objective outcome: Relative change in wound area. Number of ulcers healed. Improvement in wound condition. Setting and length of treatment: Community setting. Up to 13 weeks (leg ulcers). 4–6 weeks (pressure sores).	Inclusion criteria: Patients with grade II and III pressure sores, or venous leg ulcers. Exclusion criteria: Not stated.	Treatment: I1: Hydrocolloid dressing (Granuflex improved formulation) leg ulcers, *n* = 50; pressure sores, *n* = 49. I2: Hydropolymer dressing (Tielle), leg ulcers, *n* = 50; pressure sores, *n* = 50. Dressings were changed every 7th day.	Mean surface area of wound (mm^2): Leg ulcers: I1: 334.7 I2: 431.3 Pressure sores: I1: 286.24.7 I2: 263.6 Other characteristics: I1 I2 Leg ulcers: Mean age 75.3 73.4 M:F 1:2.5 (all groups) Pressure sores: Mean age 78.6 80.1 M:F 1:2.2 (all groups) No significant differences in ulcer duration, wound area, visual appearance, exudate, odour, or pain at baseline. For pressure sores there was also no difference in baseline grade distribution. Approximately half of the pressure sores in each group were on the heels. Both wound types were free of clinical infection, and had a maximum dimension of 8 cm.	Number of ulcers healed at 6 weeks: Leg ulcers: I1: 19/50 (38%) I2: 18/50 (36%) (p = 0.84) Pressure sores: I1: 15/49 (31%) I2: 12/49 (24%) (p = 0.5) Relative change in mean wound area at 6 weeks: Leg ulcers: I1: 31.5% I2: 49.3% (p = 0.6) Pressure sores: I1: 115.4% I2: 105% (p = 0.9)	I1: 4 I2: 4	No difference in comfort or ease of removal between the two treatments
Brod *et al.*, 1990[66] USA Method of randomisation: Stratified by lesion grade and randomised, method not stated. Patients were randomised in the ratio 60:40 to two treatments. Objective outcome: % with complete healing; time to complete healing; absolute healing rate (area/week). Setting and length of treatment: Academic skilled nursing facility caring for the elderly. Treatment continued to complete ulcer healing (maximum treatment length approx. 100 days)	Inclusion criteria: Grade II or III pressure sores as assessed by inspection, and estimated life expectancy of ≥ 6 months. Normal marrow, hepatic and renal functioning. Exclusion criteria: Not stated.	Treatment: I1: Polyhydroxyethyl methacrylate (Poly-hema) dissolved in polyethylene glycol, applied as a paste which solidified to a flexible dressing, *n* = 27. I2: Hydrocolloid dressing (DuoDerm, Granuflex) applied as a sheet with adhesive backing, *n* = 16. Surgical debridement took place before randomisation in three patients. Dressing were changed routinely twice weekly, with additional dressings if dressing came off or became contaminated or disrupted.	Median area of wound (cm^2): I1: 2.5 I2: 1.9 (p = 0.09) Other characteristics: All groups Mean age (years): 84.5 M:F Not stated Wound duration (months): Not stated	Complete healing at final assessment: I1: 52% I2: 62% (p = 0.54) Median time to healing (days): I1: 32 I2: 42 (p = 0.56) Absolute healing rate to week 6 (cm^2/week): I1: 0.18 I2: 0.1 (p = 0.005)	I1: Two deaths. I2: One death (due to concurrent illness); two patients (7.4%) discontinued treatment because of adverse effects or poor response.	DuoDerm easier to apply, being a paste. Complications were uncommon, but no data presented.

continued

TABLE 14 contd *Comparisons of modern dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Hondé *et al.*, 1994[67] France Method of randomisation: Randomisation list prepared by biometry group using SAS software. Objective outcome: Number of patients healed; median healing time. Setting and length of treatment: Hospital, multi-centre. Either 8 weeks or until ulcer healing, whichever occurred first.	Inclusion criteria: Hospitalised patients > 65 years old, with grade II to IV pressure sore < 10 cm diameter. Exclusion criteria: Signs and symptoms of clinical infection (treated before entry); necrotic pressure sores with black crust (removed before entry); pressure sores on irradiated skin; sores requiring surgery; deep ulcers extending to bone with risk of osteitis complications; patients on air-fluidised beds.	Treatment: I1: Amino acid copolymer membrane (Inerpan), *n* = 80. I2: Standard hydrocolloid dressing (Comfeel), *n* = 88.	Mean surface area (cm^2): I1: 8.99 I2: 6.85 (NS) Other characteristics: I1 I2 Age (years): 80 84 M:F 1:2.6 (all groups) Grade distribution: Grade II 64% 54% Grade III 30% 40% Grade IV 6% 6% No significant differences in weight, height, systolic or diastolic blood pressure, Norton score or range of plasma measures assessing nutritional status.	Complete healing at 8 weeks: I1: 31/80 (39%) I2: 23/88 (26%) (p = 0.089) Median healing time at 8 weeks (days): I1: 32 I2: 38 Analysis adjusted for initial wound depth found difference in favour of Inerpan (p = 0.044). % change in area from baseline: Reported to be higher with Inerpan (p = 0.09) but no data presented.	38 withdrawals. I1: Four for emergent reasons (mainly necrosis); ten for reasons unrelated to treatment (mainly death, transfer or discharge). I2: Six for emergent reasons (mainly necrosis); 18 for reasons unrelated to treatment (mainly death, transfer or discharge).	Investigators' unblinded assessment at completion of study favoured Inerpan. Unclear what this assessment was based on. Ease of care similar in each group. Trial sponsored by company producing Inerpan.

Appendix 8

Studies of healing arterial leg ulcers

TABLE 15 *Dressings compared with control/traditional treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Gibson *et al.*, 1995[69] UK Wound type: Arterial ulcers Method of randomisation: Sequentially numbered, sealed, opaque envelopes. Objective outcome: Ulcer area determined by tracing ulcer outline onto acetate and subsequent planimetry by operator blind to treatment. Setting and length of treatment: Multicentred, multifactorial trial in outpatient leg ulcer clinics. 6 months.	22 patients with arterial leg ulcers or diabetes. Inclusion criteria: ABPI < 0.8 or diabetic ulcer > 2 months' duration. Ulcer > 10 mm in length. Exclusion criteria: Severe concurrent disease; steroid therapy; warfarin; vasoactive drugs; infected leg ulcer.	Treatment: I1: Knitted viscose dressing (N-A), *n* = 10. I2: Hydrocolloid dressing (Granuflex), *n* = 12. Concurrent treatment: Orthopaedic wool bandage and crepe bandage. Patients also randomised to oxpentifylline (Trental®) or placebo.	Mean age (years): I1: 72.5 (range, 58–83) I2: 73.1 (range, 61–81) Mean ulcer duration (months): I1: 10.8 I2: 13.3 Mean ulcer size (mm^2): I1: 1489.4 (range, 89–7440) I2: 1005.1 (range, 193–2038)	Number healed in trial: I1: 0 I2: 3	I1: Nine due to dressing. I2: Five (four due to dressing). Mean time to withdrawal: I1: 18.8 days I2: 104 days	Sponsored by ConvaTec Ltd.

ABPI, ankle brachial pressure index

TABLE 16 *Topical preparations compared with control/traditional treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Janssen *et al.*, 1989[71] Belgium Wound type: Arterial and arteriolar ulcers. Method of randomisation: Not reported. Objective outcome: Wound surface area measured by planimetry. Also 'scored' on basis of granulation tissue. Setting and length of treatment: Multicentre trial. 2–8 weeks.	299 patients with decubitus ulcers, venous insufficiency, inoperable arterial insufficiency, arteriolar insufficiency, and chronic ulcers in diabetics were recruited. 40 patients had arterial or arteriolar ulcers. Exclusion criteria: Life expectancy of < 6 weeks.	Treatment: I1: 2% Formulation of ketanserin base microfine in polyethylene glycol, *n* = 19. I2: Polyethylene glycol, *n* = 21. Both were applied twice daily. Concurrent interventions: Surgical or mechanical debridement plus cleansing with antiseptics.	Mean wound area: No data.	Number completely healed at 8 weeks: No data. Final wound area as % of initial at 5 weeks: I1: 11% I2: 62% Stated that wound area was less in treated group (Mann-Whitney U test, $p < 0.05$).		
Holzinger *et al.*, 1994[70] Austria Wound type: Leg ulcers (arterial and venous). Method of randomisation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Setting not stated. Patients were treated until healing or for a maximum of 75 days.	Patients with leg ulcers arising from chronic arterial occulsive disease (CAOD) or venous post-thrombotic syndrome (PTS). All patients had previously been unsuccessfully treated with alternative therapies. Exclusion criteria: Not stated.	Treatment: I1: Autologous activated mononuclear cells in suspension were applied to the wound by dripping from a syringe and allowed to dry. After 20 minutes the wound was covered with a paraffin dressing. Prior to treatment wounds were cleansed with sterile saline. Dressings and topical agents were changed twice a week, *n* = 33. I2: Placebo of tissue culture medium alone. Treatment was otherwise as stated for I1, *n* = 30.	Mean wound area (cm^2): I1: 5.14 (2.7 SD) I2: 5.26 (2.9 SD) Other characteristics: I1 / I2 Mean age (years): 65.3 / 63.6 M:F 1:0.6 / 1:0.5 Pretreatment (months): 9.2 / 9.4 CAOD 21 / 20 PTS 12 / 10 Diabetes 9 / 5	Mean time to healing at 75 days (weeks) for all wounds: I1: 4.7 (1.9 SD) I2: 8.1 (1.2 SD) ($p < 0.01$, Student's *t*-test) 3.4% (2.34, 4.56) Mean time to healing at 75 days (weeks) for CAOD wounds: I1: 5.0 (2.0 SD) *n* = 18 I2: 8.4 (2.1 SD) *n* = 10 ($p < 0.01$, Student's *t*-test) 3.4% (1.75, 5.05) Mean time to healing at 75 days (weeks) for PTS wounds: I1: 3.9 (1.4 SD) *n* = 11 I2: 7.7 (3.5 SD) *n* = 7 ($p < 0.01$, Student's *t*-test) 3.8 (1.328, 6.272) All the above results do not include the non-responders after 75 days. Number of wounds healed at 60 days: I1: 30 I2: 16 OR = 8.75 (2.186, 35.027)	No withdrawals, but three patients in the treatment group and 14 in the placebo group were classed as non-responders at 75 days and not included in the time to healing analysis.	

Appendix 9

Studies of healing arterial leg ulcers not differentiated by aetiology

TABLE 17 *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Mian *et al.*, 1991;[76] 1992[77] Italy Wound type: Mixed leg ulcers. Method of randomisation: Not apparently randomised. Objective outcome: Area of ulcer; no details on method. Setting and length of treatment: No information.	Patients with angiodermatitis of the lower limb (*n* = 30), chronic disepithelialisation (*n* = 5) or a homogeneous series who acted as controls (*n* = 15). Exclusion criteria: No information.	Treatment: I1: Lyophilised collagen sponges applied to foci of exuding wounds, *n* = 35. I2: Standard pressure dressing, *n* = 15.	Mean wound area (mm^2): I1: 5675 (814 SD) I2: 5510 (630 SD) Other characteristics: Age (years): I1: 72.8 (12.5) I2: 69.0 (11.7)	Wound area at end of trial: (mm^2): I1: 3434 (416) I2: 4180 (240) % reduction in area at end of trial: I1: 39.5% I2: 24.1%	No data presented.	Also presents results as a regeneration index. No information on time of trial, randomisation, concurrent therapies, setting.
Nyfors *et al.*, 1982[78] Wound type: Leg ulcers – mixed aetiology. Method of randomisation: Not stated. Objective outcome: Ulcer area estimation using planimetry. Setting and length of treatment: Policlinic (outpatient clinic).	31 patients with venous, arteriosclerotic or mixed ulcer aetiology. 22 women and nine men, age 35–89 years. 20 varicose ulcers, seven post-thrombotic or varicose, two mixed aetiology (arterial and venous) and two arterial ulcers. Three patients had ulcers on both limbs. 34 ulcers – 17 in each group. Exclusion criteria: Ulcer infection; erysipelas.	Treatment: I1: Film dressing (Synthaderm), *n* = 17 ulcers I2: Saline gauze (5%), *n* = 17 ulcers. Concurrent treatments: Elastic compression bandage.	Mean wound area (cm^2): All groups: 0.5–78	Number completely healed at 8 weeks: I1: 8/17 (47%) I2: 9/17 (53%)	No data.	

continued

TABLE 17 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Ohlsson *et al.*, 1994;[72] Lindholm *et al.*, 1993;[73] Lindholm, 1994;[75] 1995[74] Sweden Wound type: Leg ulcers of venous or arterio-venous aetiology. Method of randomisation: 'Randomly allocated to treatment'. Objective outcome: Photograph of ulcer with fixed scale frame. No. of patients healing ulcer. Setting and length of treatment: Community setting. 6 weeks.	30 consecutive patients with venous or arterial and venous leg ulcers. Exclusion criteria: None stated.	Treatment: I1: Saline-soaked gauze changed twice a day, *n* = 15. I2: Hydrocolloid dressing changed once a week or sooner if exudate leakage, *n* = 15. Concurrent treatments: Ulcers cleansed with soap and tap water. Low stretch compression bandage applied to all limbs.	Mean wound area (mm^2): I1: 857 (range, 80–3808) I2: 1387 (range, 25–6795) Other characteristics: Venous:mixed aetiology: I1: 12:2 I2: 10:4 Age (median): I1: 73.5 I2: 77.6	Number completely healed at 6 weeks: I1: 2/15 (13%) I2: 7/15 (47%) Wound area after 6 weeks (mm^2): I1: 696 I2: 678 Mean % area change: I1: 19% I2: 51% ($p < 0.13$, Wilcoxon test) Mean treatment costs (SEK): Dressing materials only: I1: 608 (range, 169–2423) I2: 653 (range, 53–2423) Mean staff costs (SEK): I1: 3518 I2: 1565 Total treatment costs (SEK): I1: 4126 (range, 341–13,156) I2: 1565 (range, 102–6196) Statistical analysis of healing, costs and pain by Wilcoxon's test.	I1: One patient withdrew due to erysipelas. I2: One patient withdrew for social reasons.	Pain also assessed using a visual analogue scale. Patients in hydrocolloid group reported less pain at dressing changes.

TABLE 18 *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Armstrong *et al.*, 1996[80] UK and France Wound type: Leg ulcers. Method of randomisation: Randomised by numbered, sealed envelopes. Stratified according to wound exudate; moderate or high. Moderate exudate defined as requiring a change of dressing every 24–48 hours with a conventional dressing, or 48–72 days with a modern absorbent dressing. Heavy exudate defined as: requiring changes every 24 hours or less with a conventional dressings or every 48 hours with a modern absorbent dressing. Objective outcome: Ulcer area assessed by measurement and photography at baseline, at days 14, 28 42. Setting and length of treatment: Multicentre trial, Scotland, France and England. 6 weeks follow-up.	44 patients with leg ulcers described as moderately or heavily exuding. Inclusion criteria: Moderately or heavily exuding ulcer. Age > 18 years. < 7.5 cm in any one dimension.	Treatment: I1: Aquacel®, a hydrocolloid fibrous dressing, *n* = 21 I2: Kaltostat®, an alginate, fibrous dressing, *n* = 23. Concurrent treatments: Secondary dressing was a thin hydrocolloid. A bandaging regimen appropriate for the ulcer aetiology was applied. Dressings changed as required.	Limited mobility or were immobile: I1: 62% I2: 52%	Median percentage change in ulcer area: I1: 30.5% I2: 28.1% (NS) Complete healing: I1: 6/21 (29%) I2: 2/23 (9%) Mean wear time (days): I1: 4.11 I2: 3.05 difference = 1.03 (95% CI, 0.385–1.672) Pain at dressing change: I1 I2 None 144 186 Mild 38 29 Moderate 6 8 Severe 2 0 Excruciating 0 0 No analysis of pain.	I1: 5 I2: 7	Sponsored by ConvaTec Ltd.
Bandrup *et al.*, 1990[79] Denmark Wound type: Leg ulcers (venous and arterial). Method of randomisation: Patients were matched in pairs before randomisation to avoid time associated variables and the influence of ulcer type. Sealed envelopes were used for randomisation. Objective outcome: Ulcer size traced on to plastic foil and area measured by planimetry. Setting and length of treatment: Outpatients treated at a wound clinic by a district nurse. Patients treated for 8 weeks with assessment at 2, 4 and 8 weeks.	Outpatients with venous and arterial leg ulcers between 1 and 100 cm^2. Multiple ulcers were included but only the largest was monitored. Exclusion criteria: Chemotherapy; glucocorticosteriods; antibiotics; positive patch tests to the dressings.	Treatment: I1: DuoDerm applied to the ulcer and 5 cm of surrounding skin, *n* = 21. I2: Mezinc® applied to the ulcer and 0.5 cm of surrounding skin, *n* = 22. Prior to dressing all ulcers were debrided and cleaned with 0.9% sodium chloride. This was repeated at each dressing change. Absorbent material was applied on top of the dressings and a compression bandage was allowed for venous ulcers. Dressings were changed once a day for the first 14 days and thereafter every third day.	Mean wound area (cm^2): I1: 11.1 (9.1 SD) I2: 13.7 (15.9 SD) Other characteristics: I1 I2 Mean age (years): 77 73 M:F 1:6.5 1:2.2 Median duration (months): 5 8 Wound type: Venous/arterial 14/1 14/2 Baseline results are only available for the 31 patients completing the trial.	Mean % reduction in ulcer area at 8 weeks: I1: 48% I2: 64% Number of ulcers healed at 8 weeks: I1: 4 I2: 4 % reduction in size (I1 vs. I2): 16% OR healed (I1 vs. I2): 1:059 (95% CI, 0.228; 4.922)	I1: Two due to skin irritation; one developed erysipelas; three due to ulcer deterioration. I2: Two due to positive patch test; one due to recurring erysipelas; one due to pain; two were lost to follow-up (one death, one transferred).	Spearman correlation coefficient suggested that ulcer healing was related to systolic blood pressure (*r* = 0.63), but not patient age, ulcer duration or initial ulcer area.

Aquacel®, Kaltostat®, ConvaTec Ltd; Mezinc®, Molnlycke Healthcare

continued

TABLE 18 contd *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Palmieri, 1992[50] Italy Wound type: Leg ulcers, diabetic ulcers, pressure sores, post-traumatic ulcers. Method of randomisation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Wound clinic based trial. Treatment was continued until all wounds were considered healed.	Patients with venous leg ulcers; pressure sores; burns and radio-active ulcers. Data will only be given for leg ulcers. Exclusion criteria: Additional treat-ment with drugs (with the exception of digitalis).	Treatment: I1: Collagen sponge applied directly to the wound after saline nebulisation. The dressing was checked every day and if the collagen was swollen or partially reabsorbed by collagenases or lysosomal enzymes more of the product was added without removing the previous one. Greasy sponge and regular non-allergenic tape com-pleted the dressing, $n = 6$. I2: Dextranomer beads applied directly to the wound bed and replaced daily, $n = 6$. Prior to randomisation all wounds underwent sharp debridement to remove all necrotic tissue. In addition all wounds were treated to ensure negative bacterial cultures at baseline.	Mean area of wounds: Not stated. Other characteristics: All groups Age range (years): 58–75 M:F 1:0.6 Wound type: Leg ulcers 12 Diabetic gangrene 12 Pressure sores 12 Post-traumatic 12	Mean time to healing (days): I1: 36 I2: 60 ($^{*}p < 0.005$, Student's *t*-test). ES: I1 vs. I2 leg ulcers = 24	No withdrawals.	

TABLE 19 *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Stromberg & Agren, 1984[83] Sweden Wound type: Venous ulcers and arterial ulcers. Method of randomisation: Not stated but patients matched for ulcer type and time of admission before allocation. Objective outcome: Ulcer tracings at weekly intervals – then planimetry. (Trial period 8 weeks). Outcome was assessed blind to treatment. Setting and length of treatment: Community trial – patients attended clinic.	37 patients attending a hospital clinic, 18 with venous leg ulcers, 19 with arterial leg ulcers. 24 females, 13 males. Inclusion criteria: Ulcer area 0.5–100 cm^2. Exclusion criteria: Symptoms indicated more than one cause of the ulcer. Systemic zinc or antibiotic therapy. Diagnostic criteria: Venous ulcers: ABPI ≥ 0.9 or 0.5–0.9 plus clinical signs. Arterial ulcers: ABPI ≤ 0.5 or 0.5–0.9 plus clinical signs.	Treatment: I1: Sterile dry cotton compress with zinc oxide (400 µg/cm^2), *n* = 18. I2: Sterile dry cotton compress, *n* = 18. Concurrent treatments: Wound cleansing with sterile normal saline. Dressed once a day. Patients with venous leg ulcers had compression. Antibiotics given as required.	Median ulcer area (cm^2): I1: 3.6 (range, 0.5–14.4) I2: 4.2 (range, 1.4–85.4) Ulcer sizes not evenly distributed between groups: two largest ulcers to the placebo group, (range, 1.4–85.4 cm^2); three smallest to the zinc group (range, 0.5–14.4). Other characteristics: I1 / I2 Median age (years): 78 (66–95) (all groups) M:F: 1:1.1 / 1:3.5 Diabetes: 3 / 5 Ulcer type: Venous: 4 / 8 Arterial: 4 / 7	Ulcers healed in 8 weeks: I1: 6 I2: 4 Ulcers healed in 12 weeks: I1: 11 I2: 4 Ulcer area at end of 8 weeks mean (cm^2): I1: 0.4 (range, 0–17.1) I2: 2.7 (range, 0–65.0) Number of pain complaints: I1: 1 I2: 2 No data on healing of ulcers by aetiology. Sequential analysis was used 'to demonstrate that the treatment was superior ($p < 0.05$)'.	I1: Patient developed an ulcer infection during treatment. Another patient appears to have been withdrawn due to ulcer enlarging I2: Six developed ulcer infections and were withdrawn; one discontinued treatment as dressing adhered to wound.	Also measured serum zinc levels at end of trial: median values (µmol/l): I1: 10.6 (range, 5.9–14.8) I2: 10.1 (range, 7.7–12.3)
Torregrossa & Caroti, 1983[84] Italy Wound type: Mixed aetiologies, post-traumatic and vascular insufficiency ulcers. Method of randomisation: Not clear if random. Objective outcome: Ulcer area as traced onto a transparent sheet and digitised using a computer. Setting and length of treatment: 30 days.	Patients with venous, arterial, pressure or traumatic leg ulcers. Exclusion criteria: Cellulitis or necrotic ischaemia.	Treatment: I1: Twice-daily application of gauze impregnated with hyaluronic acid, *n* = 27. I2: Control group with various treatment, *n* = 16. Concurrent treatments: Antibiotics.	Mean wound area (mm^2): I1: 417 I2: 568 Other characteristics: I1 / I2 Ulcers: Venous: 20 / 9 Arterial: 1 / 1 Traumatic: 6 / 5 Pressure: 0 / 1 Duration of ulcer (months): I1: 3.7 I2: 3.1 Mean age (years): I1: 69 I2: 69	Healed in 30 days: I1: 9/27 (33%) I2: 0/16 (0%)	No data.	

continued

TABLE 19 contd *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Calabro *et al.*, 1995[85] Italy Wound type: Venous, traumatic, arterial and diabetic leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area as traced onto a transparent sheet and digitised using a computer. Setting and length of treatment: Outpatient clinic.	80 patients with ulcers of mixed aetiologies; 59 women and 21 men. Exclusion criteria: None stated.	Treatment: I1: Fibrin glue applied weekly. I2: 'Traditional' treatments (paraffin gauze, povidone iodine gauze, Duoderm, Biofilm, Cutinova®). Concurrent treatments: All non-arterial ulcers had elastic compression.	Mean wound area: No data. Ulcer aetiology: 69 venous disease, three trauma, two arterial, six diabetic. Other characteristics: Age: 35–80 years.	Healed in trial: I1: 20/26 (77%) I2: 48/54 (89%) Time to heal: I1: 15 days–3 months I2: 3–9 months.	No data.	
Knighton *et al.*, 1990;[81] 1988[82] USA Wound type: Leg ulcers due to venous disease, diabetes, peripheral vascular disease and vasculitis. Method of randomisation: Blinded card selection process. Objective outcome: Not stated. Setting and length of treatment: Wound-healing clinic of hospital; outpatients visited clinic every 2–3 weeks.	32 patients with a chronically non-healing, full-thickness, cutaneous ulcer of a lower extremity of at least 8 weeks' duration. Normal peripheral blood platelet. Exclusion criteria: Failure to follow protocol instructions on two or more visits; amputation of the extremity before completion of the trial; any extensive surgical intervention after randomisation.	Treatment: I1: Platelet-derived wound healing formula added to platelet buffer solution and microcrytstalline collagen, *n* =16 patients. I2: Platelet buffer solution and microcrytstalline collagen, *n* = 16 patients. Concurrent treatments: sharply debrided in the clinic to remove all fibrin, infected, foreign or necrotic tissue.	Mean wound area (cm^2): I1: 11.6 (24.5 SD) I2: 22.0 (19.2 SD) Other characteristics: Wound duration (weeks): I1: 119 (114 SD) I2: 47 (63 SD) Diagnosis (I1:I2): Diabetes 5:4 Peripheral vascular disease 1:3 Venous stasis 6:4 Vasculitis 1:0 Age (years): I1: 64 (8 SD) I2: 62 (10 SD)	Number completely healed at 8 weeks: I1: 17/21 (81%) I2: 2/13 (15%) At termination 13 patients with 21 wounds remained in I1, while 11 patients with 13 wounds remained in group I2:	I1: Three: one for non-compliance; one due to amputation; one incomplete data. I2: Five: two non-compliance; two amputation; one incomplete data analysis.	

TABLE 20 *Topical preparations compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Acosta *et al.*, 1992[86] Spain Wound type: Chronic leg ulcers (arterial and venous). Method of randomisation: Not stated. Objective outcome: Ulcer area as traced onto a transparent sheet and digitised using a computer. Setting and length of treatment: Appear to be in outpatients department, 4 weeks.	12 patients with venous or arterial leg ulcers: eight women and four men. Nine venous ulcers, two arterial ulcers and one neuropathic ulcer. Exclusion criteria: Cellulitis or necrotic ischaemia.	Treatment: I1: Growth hormone mixed with paraffin, covered with a hydrocolloid dressing (Comfeel). I2: Hydrocolloid dressing. (Comfeel). Concurrent treatments: Swabs were taken for microbiological culture and sensitivity. If the result was positive, antibiotics were commenced. No mention of compression for venous leg ulcers.	Mean wound area: No data. Other characteristics: No data.	Percentage reduction in wound area: I1: 82% I2: 77% Not significantly different (MANOVA).	No data.	

MANOVA, multiple analysis of variance

Appendix 10

Studies of healing venous leg ulcers

TABLE 21 *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Arnold *et al.*, 1994[99] UK and USA Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer healing and ulcer area. Setting and length of treatment: Outpatient, hospital clinic, multicentre study; 10 weeks.	70 patients with 90 venous ulcers attending clinic. Exclusion criteria: Arterial insufficiency; vasculitis; rheumatoid arthritis; deep dermal involvement; exposure of tendon; muscle or bone.	Treatment: I1: Hydrocolloid dressing, *n* = 35. I2: Conventional dressing (paraffin gauze in USA, povidone iodine gauze in UK), *n* = 35. Compression: Unna's Boot.	Mean wound area (mm^2): I1: 2100 (685 SEM) I2: 1983 (659 SEM) Mean wound duration (weeks): I1: 46.2 I2: 47.8	Number completely healed at 8 weeks: I1: 11/35 (31%) I2: 14/35 (40%) Reduction in wound area: I1: 71% (4.3 SD) I2: 43% (7.1 SD) Time to healing (weeks): I1: 7.1 (0.2 SEM) I2: 8.2 (0.4 SEM)	I1: Nine: two infection; one discomfort; six unrelated to dressing. I2: Seven: three pain/discomfort; one cellulitis; one infection; two unrelated to dressing.	
Backhouse *et al.*, 1987[98] UK Method of randomisation: 'Randomised'. Outcome measure: Ulcer traced on cellophane, this was transferred onto card and the area derived from the weight of the card. Setting and length of treatment: Venous ulcer clinic. Follow-up 12 week.	56 patients with chronic venous leg ulcers smaller than 10 cm^2. Exclusion criteria: Arterial disease as indicated by Doppler assessment.	I1: Hydrocolloid (Granuflex), *n* = 30. I2: Non-adherent dressing (N-A), *n* = 30. Concurrent treatments: All ulcers were washed with saline and had all loose slough removed. All patients received compression bandaging (four-layer). Antibacterials permitted only for spreading cellulitis. Dressed weekly unless exude was excessive.	Mean ulcer area (cm^2): I1: 3.4 (0.4) I2: 3.1 (0.4) Mean age (years): I1: 69.9 I2: 67.5 Median duration of present ulcer (months): I1: 22 I2: 21	Number healed at 12 weeks: I1: 21/30 (70%) I2: 22/30 (73%)	Not stated.	Sponsored by Johnson & Johnson, 3M, Sigvaris, Zyma, and Squibb. Streptococcal cellulitis was seen in seven cases: I1: 4 I2: 3.
Banerjee *et al.*, 1990[94] Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area: tracings of ulcer outline and photographs taken at weeks 0, 4, 8, 12 and 17. Setting and length of treatment: Inpatients or attending a day hospital for the elderly; 17 weeks.	71 elderly patients with venous leg ulcers. Exclusion criteria: Significant peripheral vascular disease (assessed using Doppler ultrasound). Ulcers were assessed and dressed by one person.	Treatment: I1: Polyurethane film (Synthaderm), *n* = 36. I2: Paraffin-impregnated tulle (Paratulle®), *n* = 35. Concurrent treatments: Cleansed by pouring warm saline over ulcers. Treatment applied, then a pad placed on top. Support bandage (K-band®) applied from toes to knee.	Median wound area (cm^2): I1: 12.2 (range, 1.1–138) I2: 11.4 (range, 1.3–134) Other characteristics: Mean age (years): I1: 75.9 (7.7 SD) I2: 81.2 (7.3 SD) Ulcer duration (years): I1: 2 I2: 2 Number of recurrent ulcers: I1: 14 I2: 14 Number treated by a district nurse: I1: 30 I2: 26 Locomotor problems: I1: 26 I2: 30 All groups: 50% of patients lived alone. 1/3 were on diuretics.	Number completely healed at 17 weeks: I1: 11/36 (30%) I2: 8/35 (23%) (NS)	I1: Eight: one withdrawn; seven deaths. I2: 11: eight withdrawn; three deaths.	
Paratulle®, Seton Scholl Healthcare Ltd						

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Callam *et al.*, 1992[90] UK Wound type: Venous leg ulcers. Method of randomisation: 'Randomly allocated'. Objective outcome: Complete ulcer healing, change in ulcer area. Setting and length of treatment: Multicentre trial. Outpatients – treatment provided by experienced research nurses. Factorial design of trial with compression also compared; 12 weeks.	132 patients with venous leg ulcers attending trial leg ulcer clinics. Exclusion criteria: Diabetes mellitus; rheumatoid arthritis; ABPI < 0.8.	Treatment: I1: Knitted viscose dressing (Tricotex®), *n* = 66. I2: Polyurethane foam (Allevyn), *n* = 66. Concurrent treatments: Compression applied by multilayer compression, either long-stretch or short stretch. The dressings and bandages had separate effects (interaction test: *p* = 0.87) and therefore comparisons could be made between dressings. Treatment provided by specialist nurses.	Mean wound area (cm^2): I1: 8.35 I2: 10.87 Other characteristics: I1 / I2 Duration of ulcer: < 6 months 31 / 33 6–11 months 18 / 18 1–2 years 11 / 14 3+ years 6 / 1 Mean duration of ulcer (months): 11.2 / 11.7 Mean age (years): 63 / 64 M:F 30:36 / 29:37	Number completely healed at 12 weeks: I1: 23 I2: 31 (NS; *p* = 0.08, stepwise Cox model) Primary outcome of complete ulcer healing was assessed using Cox survival analysis. Secondary outcome measure of change in ulcer area was examined using a stratified two-sample Wilcoxon test (the four strata having been chosen on the basis of pre-specified levels of initial ulcer size). Forward stepwise selection of baseline covariate ensured that any potentially influential imbalances in baseline characteristics were taken into account. Patients withdrawn from treatment were considered failures of treatment rather than lost to follow-up.	I1: 15 after a mean of 5.5 weeks: two sensitivity; six exudate; 12 deterioration; one social reasons; six other (including bandage slippage). I2: 13 after a mean of 4.6 weeks: eight sensitivity; seven exudate; 12 deterioration; one social reasons; four other (including bandage slippage). Note: More than one reason could be given for each patient.	Funded by Smith & Nephew (manufacture both dressings). Also assessed dressing influence on pain.
Davis *et al.*, 1992[93] USA Wound type: Venous leg ulcers. Method of randomisation: 'Randomly assigned'. Objective outcome: Ulcer traced. Setting and length of treatment: 6 months.	11 patients with 12 ulcerated legs; ulcers diagnosed as being secondary to venous insufficiency. Exclusion criteria: Arterial pathology.	Treatment: I1: Polyurethane film and Unna's Boot (*n* = 5 legs); (Tegaderm or Bioclusive according to availability). I2: Unna's Boot alone (Unna's Boot = wide mesh gauze impregnated with zinc oxide, calamine and gelatine, all covered with an elastic bandage to keep in place and apply compression), *n* = 7. Concurrent treatments: Cleansed by scrubbing lower leg with a washcloth, mild soap and water. Wound was then irrigated with saline. All patients received 1 hour of intermittent pneumatic compression therapy. Ulcers redressed twice weekly.	Mean wound area: No data, but 'larger wounds were placed in the experimental group'. Other characteristics: No details.	Number completely healed at 6 months: No data. Reduction in wound area (cm^2/day): I1: 0.30 (five ulcers) I2: 0.12 (seven ulcers) (Excluding bilateral ulcerated leg: I1: 0.27 (*n* = 4) I2: 0.13 (*n* = 6)) Mean reduction in wound area (cm^2): I1: 39.26 (25.56 SD) I2: 7.11 (6.11 SD)	None stated.	Unit of randomisation was patient but results are presented as per ulcer.

Tricotex®, Smith & Nephew Healthcare Ltd

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Groenewald, 1984[103] South Africa Wound type: Venous ulceration. Method of randomisation: Randomised but method not stated. Objective outcome: Reduction in ulcer size – ulcer outline traced onto acetate (area measurement by person not involved in trial). Average of three area tracings was used. Setting and length of treatment: Setting unclear; 8 weeks.	72 patients suffering from venous leg ulcers, the majority were of > 6 months duration.	Treatment: I1: Conventional treatment, *n* = 36. I2: Hydrocolloid dressing, *n* = 36. Concurrent treatments: I1: Ulcer and surrounding skin washed with a soft brush and solution of povidone iodine. Povidone iodine placed onto ulcer. Foam pad, zinc paste bandage and an elastic compression bandage. I2: Skin cleansed with soft brush and povidone iodine solution.	No data on ulcer size or distribution of sizes in two groups. All groups M:F approx. 1:3	Reduction in ulcer size: I1: 22.62% I2: 67.64% $p < 0.0001$, pooled SEM 3.51.	I1: Six: over-whelming sepsis and increase in ulcer size. I2: Seven: two non-compliant; five treatments had to be stopped (two pain and irri-tation, three overwhelming sepsis).	Appears as though the control group had compression whereas the trial group did not. Without baseline data it is not possible to determine the significance of the results.
Mansson, 1996[101] Sweden, Denmark, The Netherlands and UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area – method of measurement not stated. Setting and length of treatment: Multicentre trial; 12 weeks.	153 patients with venous leg ulcers attending trial centres. Inclusion criteria: None. Exclusion criteria: None.	Treatment: I1: Cadexomer iodine (Iodosorb), *n* = 56. I2: Hydrocolloid (Duoderm E, Granuflex E), *n* = 48. I3. Paraffin-impregnated gauze (Jelonet), *n* = 49. Concurrent treatment: Compression bandages (Comprilan®).	Mean duration of ulcer (years): I1: 8.4 (14.4 SD) I2: 3.9 (8.4 SD) I3. 7.8 (12.8 SD) Mean initial ulcer area (median): I1: 9.6 (5.1) (13.4 SD) I2: 10.0 (5.8) (19.1 SD) I3. 7.8 (5.1) (8.6 SD) Other characteristics: I1 I2 I3 M:F 15:41 15:33 18:31 Mean age (years): I1: 74(13.6 SD) I2: 74 (12.7 SD) I3. 72 (12.8 SD)	Number healed in 12 weeks: I1: 8/56 (14%) I2: 5/48 (10%) I3. 7/49 (14%) Number with wound infection: I1: 1 I2: 5 I3. 4 Mean reduction in wound area (%): I1: 62 I2: 41 I3. 24 Mean ulcer area at 12 weeks (cm^2): I1: 5.2 (8.6 SD), *n* = 56 I2: 6.0 (9.8 SD), *n* = 46 I3. 6.1 (9.6 SD), *n* = 49 ITT analysis: Median ulcer area at 12 weeks: I1: 1.8 (range, 0–46.6) I2: 1.9 (range, 0–53.2) I3. 3.2 (range, 0–48.4)	I1: Seven: one wound infection; six pain. I2: 13: three increases in ulcer size; five wound infec-tions; five dermatitis on peri-ulcer skin. I3. Ten: six increase in ulcer area; four wound infection.	Sponsored by Perstorp Pharma. Pain gradually decreased in frequency throughout the trial, except for the Duoderm E group at 8 and 12 weeks. There was no difference between the groups in the use of analgesics (no data presented).

Comprilan®, Beiersdorf

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Meredith *et al.*, 1988[100] UK Wound type: Venous leg ulcers. Method of randomisation: Random number table. Objective outcome: Ulcer area determined by tracing ulcer outline onto acetate film, subsequent scanning and digitisation. Ulcers < 1 cm^2 were also measured by using 1 mm^2 graph paper. Setting and length of treatment: Leg ulcer clinic; 6 weeks.	50 patients attending the leg ulcer clinics with an ulcer deemed to be due to venous insufficiency, irrespective of whether patients was diabetic or not. Exclusion criteria: None stated.	Treatment: I1: Hydrocolloid (Granuflex), *n* = 25. I2: One layer of paraffin-impregnated paraffin gauze (Jelonet) covered with a cotton dressing pad, *n* = 25. Concurrent treatments: Ulcers cleansed using normal saline, or in a few cases, povidone iodine. Support provided by Elastocrepe® or straight Tubigrip®. Dressings were changed at least weekly or when required due to exudate leakage. Patients in the hydrocolloid group were permitted to remove the Tubigrip and bathe or shower. This was not permitted for the control group.	Mean wound area (cm^2): I1: 1.1 I2: 4.7 (three very large ulcers were allocated to the I2 group: 29.9, 25.5 and 14.7 cm^2) Other characteristics: Both groups Mean age (years): 70.4 (range, 32–92)	Number completely healed at 6 weeks: I1: 19/25 (76%) I2: 6/25 (24%) No inferential statistics presented. Mean reduction in wound area (cm^2): I1: 0.84 I2: 0.32 Cost of dressings (£) (including non-drug tariff items): I1: 436.86 I2: 855.87	One from control group – admitted to hospital for an unrelated condition. This patient is omitted from data presented. No adverse reactions to either dressing.	
Milward, 1991[102] UK Wound type: Not stated. Method of randomisation: Not stated. Objective outcome: Ulcer healed. Setting and length of treatment: Community trial; 12 weeks.	38 patients with wounds in the community. Exclusion criteria:	Treatment: I1: Traditional dressing, *n* = 19. I2: Hydrocolloid (Comfeel), *n* = 19.	Mean wound area: No data.	Number completely healed at 12 weeks: I1: 0 I2: 3 Median decrease in ulcer area (%): I1: 7.66 I2: 63.3 Cost of dressings (£): I1: 2815.35 I2: 2541.02 Number of visits: I1: 1056 I2: 436	No data.	
Moffatt *et al.*, 1992[97] UK Wound type: Venous leg ulcers. Method of randomisation: Assigning sequential numbers to each patient and relating this to a randomisation group. Objective outcome: Ulcer area measured using computerised planimetry. Setting and length of treatment: Community leg ulcer clinics; 12 weeks.	60 patients form community leg ulcer clinics with non-healing ulcers. Inclusion criteria: Failure to reduce by 20% of original size in 12 weeks; or failure to heal in 24 weeks of four-layer bandaging; or ABPI ≥ 0.8. Exclusion criteria: Known allergy or contraindication to one of the trial treatments.	Treatment: I1: Knitted viscose dressing (N-A), *n* = 30. I2: Hydrocolloid (Comfeel), *n* = 30. Concurrent treatment: Four-layer compression bandaging applied.	Median ulcer size (cm^2): I1: 6.7 (range, 2.6–14.9) I2: 7.3 (range, 1.3–66.3) No data on duration of ulcer. Other characteristics: I1 I2 Female: 18 15 Median age (years): 71 74 Diabetes: 3 0 Hypertension: 4 3 All groups Age range (years): 26–89 Ulcer size (cm^2): 1.3–66.3 M:F 27:33	Number healed after 12 weeks: I1: Seven healed (23%) I2: 13 healed (43%) Cumulative healing rate in the trial: I1: 17% I2: 46% (relative risk = 2.25, 95% CI, 0.88, 5.75)	Four withdrew: two refused to continue; two died in trial period.	*A priori* power calculation: 10% vs. 40% healing in 12 weeks (power = 80%, at 5% significance). Comparison of life tables up to 12 weeks of treatment was made using the log-rank method. Comparisons were made using the chi-square and Mann–Whitney *U* test. Funded by Coloplast (Comfeel).

Elastocrepe®, Smith & Nephew Healthcare Ltd; Tubigrip®, SSL Ltd

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Moffatt *et al.*, 1992[88] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area – not stated how this was measured. Setting and length of treatment: Community clinics; 12 week follow-up.	60 patients with venous ulcers from community leg ulcer clinics. Inclusion criteria: ABPI ≥ 0.8; surface area < 10 cm^2. Exclusion criteria: Known allergy to the products in the trial.	Treatment: I1: Tegagel, *n* = 30. I2: N-A, *n* = 30. Concurrent treatments: Four-layer compression bandaging. Cleansed and redressed weekly or according to excessive exudate or infection.	Median ulcer size (cm^2): I1: 3.6 (range, 0.9–9.8) I2: 6.4 (range, 1.1–9.9) Median ulcer duration (months): I1: 2 (range, 1–192) I2: 3 (range, 1–20) Other characteristics: I1 I2 Male: 10 13 Hypertension: 8 4 Diabetes: 0 0 All patients Age (years): range, 38–88	Ulcers healed at 12 weeks: I1: Tegagel, 26/30 (87%) I2: N-A, 24/30 (80%) No difference. Analysis by life table for time to complete healing.	No data.	Sponsored by 3M.
Nelson *et al.*, 1995[96] UK Wound type: Venous leg ulcers (confirmed by presence of multi-centre, factorial study of dressing; bandage and drug (oxpentifylline). Method of randomisation: Sequentially numbered, sealed, opaque envelopes. Objective outcome: Ulcer area determined by tracing ulcer outline onto acetate. Subjected to planimetry by someone blind to treatment. Setting and length of treatment: Outpatients; 24 weeks. Dressings done by experienced research nurses.	200 patients attending leg ulcer clinics with ulcers of minimum 8 weeks duration and 1 cm diameter. Inclusion criteria: Age >18 years; consent; clinical signs of venous disease and confirmation of venous pathology by hand-held Doppler examination. Exclusion criteria: ABPI < 0.8; severe concurrent disease; diabetes; rheumatoid arthritis; taking warfarin, steroids, or vasoactive drugs.	Treatment: I1: Knitted viscose dressing (N-A), *n* = 98. I2: Hydrocolloid (Granuflex E), *n* = 102. Concurrent treatments: Also randomised to bandages: four-layer or Granuflex adhesive compression bandage, and 1200 mg oxpentifylline daily or placebo.	Ulcer size (mm^2): I1: 1124, *n* = 94 I2: 914, *n* = 98	Healed in trial: I1: 44/98 (45%) I2: 49/102 (48%)	No data.	Sponsored by Convatec UK and Hoechst Marion Roussel.

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Pessenhoffer & Stangl, 1989;[91] 1992[92] Austria Wound type: Venous leg ulcers. Method of randomisation: 'Allocated by lot'. Objective outcome: Area, circumference and maximum diameter of ulcer. Measured by photography using a Polaroid camera and then digitisation. Setting and length of treatment: Outpatients; follow-up period is up to 281 days.	48 patients with venous leg ulcers. Inclusion criteria: None. Exclusion criteria: None.	Treatment: I1: Polyurethane foam (Lyomousse), *n* = 25. I2: Sterile gauze compress, *n* = 23. Concurrent treatments: Cleansing with normal saline, compression bandage by Fischer method. Fibrolan® cream (enzymatic wound cleanser) applied if required.	Mean area of ulcers (mm^2): I1: 1078.3 (1743.6 SD) I2: 1170.2 (2424.5 SD) Mean circumference of ulcers (mm^2): I1: 130.8 (106.2 SD) I2: 121.5 (103.9 SD) Other characteristics: I1 I2 M:F 4:21 3:20 Mean age (years): I1: 65.7 (12.6 SD) I2: 66.7 (9.3 SD)	% change in ulcer area: I1: –65.6 (47.0 SD) I2: +78.3 (215.8 SD) (negative value indicates a reduction in area).	I1: One. I2: Six. Reasons for withdrawal: patients did not re-attend or were admitted to hospital for further treatment.	Complete healing not reported.
Smith *et al.*, 1992[95] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated but stratified by initial maximum ulcer diameter, 2–4 cm or > 4 cm. Objective outcome: Ulcer area measured monthly by tracing onto acetate and subsequent planimetry. Average of three area measurements was taken for each assessment. Pain and comfort measured monthly on a five-point scale. Setting and length of treatment: Patients attended hospital for initial assessment and monthly thereafter; the community nurses carried out all other treatments. Trial period 4 months.	200 patients with venous leg ulcers, minimum diameter 2 cm, attending an outpatient clinic. Assessed by continuous wave ultrasound and photoplethysmography. In those patients with bilateral ulceration data were recorded for the right leg only. Exclusion criteria: Diabetes; rheumatoid arthritis; infected ulcers; known intolerance to iodine; neurological impairment; lymphoedema; intolerance to compression; malignant disease in ulcer; ABPI < 0.75.	Treatment: I1: Biofilm applied with a 2 cm overlap all around the ulcer. In deep ulcers Biofilm powder was used to fill the cavity and then the Biofilm dressing was applied over this (*n* = 64 small ulcers, *n* = 35 large ulcers, 99 in total). I2: Jelonet and Betadine®, cut to the shape of the ulcer, absorbent pad placed over this (*n* = 62 small ulcers, *n* = 30 large ulcers, 101 in total). Two patients who were randomised to Jelonet received Biofilm instead; three patients received Jelonet instead of Biofilm (due to administrative error). Concurrent interventions: Cleansed with isotonic, sterile saline. Compression (two shaped support bandages (shaped Tubigrip) or compression stocking - Venosan® 2002). Dressings done by district nurses. Patients in the I1 group were allowed to remove their stocking and bathe or shower. Patients in the control group were not able to do this.	Age (years): I1: Small ulcer = 74 I1: Large ulcer = 76 I2: Small ulcer = 72 I2: Large ulcer = 73 Median ulcer duration (months): I1: Small ulcer = 5 I1: Large ulcer = 4 I2: Small ulcer = 3 I2: Large ulcer = 17 Median ulcer area (cm^2): I1: Small ulcer = 3.1 I1: Large ulcer = 13.3 I2: Small ulcer = 2.6 I2: Large ulcer = 17.6 Analysed by treatment received rather than ITT.	Median healing rate in 1st month (cm^2/day) (*n* = 153): I1: Small 0.056 (*n* = 50) I1: Large 0.184 (*n* = 25) I2: Small 0.062 (*n* = 52) I2: Large 0.017 (*n* = 26) (*p* = 0.09 for large ulcers; *p* = 0.4 for small ulcers) Number healed in 4 months: I1: Small 38/64 (59%) I1: Large 12/35 (34%) I2: Small 43/62 (69%) I2: Large 4/39 (10%) All ulcers healed in trial: I1: 50/99 (50.5%) I2: 47/101 (46.5%) The association between whether the ulcer healed and the treatment received was examined using Fisher's exact test. Biofilm and control dressings were not significantly different in healing ulcers sized 2–4 cm (*p* = 0.27). In the ulcers sized > 4 cm, Biofilm did result in a higher proportion of ulcers healing (*p* = 0.02). Relative risks and 95% CI from proportional hazards model: Ulcer area (cm^2) (halving initial area) = 1.92 (1.58, 2.33) Duration of ulceration (months) (halving this) = 1.35 (1.17, 1.56) Age (years) (10-year decrease) = 1.34 (1.12, 1.59) Biofilm treatment = 1.16 (0.77, 1.77) No deep vein involvement (determined by PPG) = 1.80 (1.19, 2.78).	I1: 21: nine refused; five were admitted to hospital; six had suspected allergic reaction; one moved away. I1: Six: three refused; one infection; two admitted to hospital. I2: 14: four refused; one infection; five admitted to hospital; two had suspected allergic reaction; two died. I2: 19: seven refused; 11 infection; one moved away. Note: None of the suspected allergic reactions were confirmed by patch testing. Rate of infection was significantly higher in the large ulcer/ Betadine group (*p* = 0.004, Fisher's exact test).	Pain: in first months for 123 patients: less pain in Biofilm group (*p* = 0.02), no difference for comfort. Sponsored by Clinimed Ltd.

Fibrolan®, Parke-Davis; Betadine®, SSL Ltd; Venosan®, Credenhill

continued

TABLE 21 contd *Dressings compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Stacey *et al.*, 1991[89] Australia Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area – method of assessment not stated. Setting and length of treatment: Outpatient foot and leg ulcer clinic. Follow-up period 9 months.	113 patients with 133 ulcerated limbs, suffering from proven venous ulceration. Inclusion criteria: Proven venous ulceration (plethysmography); ABPI (cut-off point not stated); ulcer diameter 0.5–10 cm. Exclusion criteria: Diabetes; rheumatoid arthritis; arterial disease; cellulitis.	Treatment: I1: Zinc-impregnated bandage (Viscopaste®) in a spiral fashion, *n* = 43. I2: Zinc oxide-impregnated stockinet (Acoband®), *n* = 44. I3: Alginate dressing (Kaltostat), *n* = 46. Concurrent treatments: Leg and foot washed in a soap and water bath. Standard compression used over dressing (two Elastocrepe bandages) plus Tubigrip. Dressings changed twice or three times a week in early stages of treatment, reducing to weekly once the exudate had reduced.	Mean ulcer area (cm^2): I1: 10.8 (range, 1.5–57.5) I2: 9.9 (range, 3.6–61.3) I3: 10.7 (range, 2.4–75.4) All patients Median age (years): 74 (range, 31–92) M:F 46:67	% totally healed in 3 months: I1: 66% I2: 50% I3: 45% (numerator and denominator not given). Time to total healing compared using a log rank analysis: Viscopaste was better than either the zinc-impregnated stockinette ($p < 0.05$) or the Kaltostat ($p < 0.05$). There was no difference in the healing between the alginate and the stockinette group.	I1: Five: two allergy; one pain; two medical/ personal. I2: Six: one allergy; one pain; one cellulitis; three medical/ personal. I3: Ten: one allergy; three pain; three cellulitis; three medical/ personal.	
Wunderlich & Orfanos, 1992[87] Germany Wound type: Venous leg ulcers. Method of randomisation: No details. Objective outcome: Ulcer size – tracing subjected top planimetry every 2 weeks. Setting and length of treatment: 6 weeks.	40 patients with venous leg ulcers of whom 38 produced evaluable data. Exclusion criteria: Diabetes mellitus, steroid therapy, drugs which affect wound healing.	Treatment: I1: 5 days cleaning with mechanical and enzymatic debridement and then application of a polyamide, activated charcoal dressing with 0.15% silver. I2: 5 days cleaning with mechanical and enzymatic debridement then dressing according to stage of healing Granulation: paraffin oil or PVI cream; epithelialisation: Fettgaze or oil in water emulsion. Concurrent treatments: Mechanical debridement at least every 4 days.	Mean wound area (mm^2): I1: 3 I2: 2 Other characteristics: I1 I2 M:F 7:12 4:15 Age (years): 74.3 72.9 Duration of ulcer (years): 7.6 7.9	Number completely healed at 6 weeks: I1: 6/19 (32%) I2: 2/19 (11%) Wound area at end of 6 weeks (change) (mm^2): I1: 1 (2) I2: 1 (1) % reduction in ulcer size: I1: 75% I2: 65%	No data.	

Viscopaste®, Smith & Nephew Healthcare Ltd; Acoband®, Auspharm

TABLE 22 *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Caprio *et al.*, 1995[105] Italy Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Tracings and photographs of ulcer outlines made on days 0, 28 and 56. Setting and length of treatment: Five centres, 8 weeks.	93 patients with 98 clean ulcers of venous origin. Exclusion criteria: None.	Treatment: I1: Hydrocolloid (Granuflex E). I2: Lyophilised collagen covered with gauze and cotton bandage.	Mean wound area: No data.	Number completely healed at 8 weeks: I1: 25 I2: 20 Unable to calculate % healed as numbers in each group not given. Reduction in wound area (mm^2/week): I1: 152.7 I2: 103.66 Total mean cost of dressing materials (lira): I1: 102,607 I2: 142,527	No data.	Product-related adverse events: I1: 0 I2: 5
Palmieri, 1992[50] Italy Wound type: Mixed (leg ulcers; diabetic; pressure sores; post-traumatic). Method of randomisation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Wound clinic based trial. Treatment was continued until all wounds were considered healed.	48 patients with venous leg ulcers (12); pressure sores (12); burns (12) and radioactive ulcers (12). Data will only be given for leg ulcers. Exclusion criteria: Additional treatment with drugs (with the exception of digitalis).	Treatment: I1: Collagen sponge applied directly to the wound after saline nebulisation. The dressing was checked everyday and if the collagen was swollen or partially reabsorbed by collagenases or lysosomal enzymes more of the product was added without removing the previous one. Greasy sponge and regular non allergenic tape completed the dressing (24). I2: Dextranomer beads applied directly to the wound bed and replaced daily (24). Prior to randomisation all wounds underwent sharp debridement to remove all necrotic tissue. In addition all wounds were treated to ensure negative bacterial cultures at baseline.	Mean area of wounds: Not stated. Other characteristics: All patients (n = 48) Age range (years): 58–75 M:F 1:0.6	Mean time to healing (days): I1: 36 I2: 60 ($^*p < 0.005$: = $p < 0.001$: Student's t-test).	No withdrawals.	
Banks *et al.*, 1996[65] UK Wound type: Leg ulcers and pressure sores. Method of randomisation: Not stated. Objective outcome: Not stated. Setting and length of treatment: 13 weeks. Multicentre study in the community.	200 patients: 100 with venous leg ulcers and 100 with grade II or III pressure sores. Inclusion criteria: I1: Pressure sores: grade II or III. I2: Venous leg ulcers: ABPI > 0.8. Exclusion criteria: Clinical infection.	Treatment: Leg ulcers: n = 100. I1: Hydrocolloid (Granuflex), n = 50. I2: Hydropolymer (Tielle), n = 50.	Leg ulcers: Median age (years): I1: 80 I2: 77 Ulcer duration (months): I1 I2 < 1 3 2 1–3 13 9 > 3 34 39 Ulcer area (mean/median; mm^2): I1: 334.7/243.5 (range, 10–2758) I2: 431.3/417.5 (range, 16–1876)	Leg ulcers: Ulcers healed in 13 weeks: I1: 19/47 (40%) I2: 18/49 (37%) Mean % change in ulcer area: I1: 31.5 I2: 49.3 Change in mean ulcer area (mm^2): I1: 334.7–157.6 I2: 431.3–238.3	No data.	No details of the concurrent treatments.

continued

TABLE 22 contd *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Smith, 1994[106] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area measured by tracing ulcer outline onto acetate sheet and calculating area using image analyser. Setting and length of treatment: Dermatology outpatients clinic. 6 weeks.	40 patients with venous ulcers greater than 2.5 cm in diameter. Exclusion criteria: Wound infection; immune deficiency; steroid therapy; malignant disease.	Treatment: I1: Alginate (not named), *n* = 18. I2: Hydrocolloid (Granuflex), *n* = 22. Concurrent treatments: Wound cleansed with physiological saline, compression applied. N.B. gauze used as a secondary dressing over alginate.	Mean baseline ulcer area (cm^2): I1: 12.74 I2: 22.17	Number healed in 6 weeks: I1: 2/18 (11%) I2: 4/22 (18%) % change in ulcer size: I1: 34.9 I2: 57.1 (NS) Cost of treatment materials: I1: £364.08 I2: £431.73	I1: Six: four for pain, two for infection. I2: Six: one for pain, one for infection, one for possible allergy, one dressing leakage, one misdiagnosis, one subject defaulted.	Also measured pain, sleep disturbance, convenience, ease of application and removal. Pain levels fell during trial with both treatments.
Veraart *et al.*, 1994[107] The Netherlands Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Tracing of ulcer outline on transparent foil for later computerised planimetry. Setting and length of treatment: Two centre trial; outpatients; 8 weeks. Dressings done by hospital nurses only.	38 patients. Inclusion criteria: Signs of venous insufficiency ABPI > 0.9. Refilling time by LRR > 25 seconds. Exclusion criteria: Acute skin disease around the ulcer; severe concurrent illness (high blood pressure, diabetes, cardiopulmonary disease); steroids/ immunosuppressants.	Treatment: Both hydrocolloids. I1: Comfeel Extra Absorbing dressing, *n* = 19. I2: Granuflex (DuoDerm) CGF, *n* = 19. Concurrent treatments: Cleansed with normal saline, short-stretch bandages (Elco Rosidal®) applied twice weekly for the first 4 weeks and weekly thereafter. If there was more than one ulcer per patient the largest ulcer was monitored.	Mean age (years): I1: 70.5 (range, 53–85) I2: 67.5 (range, 42–85) No data on baseline area/ duration.	Healed in 8 weeks: I1: 12/19 (63%) I2: 10/19 (53%) Numbers healed and time to healing were similar in the two groups.	I1: Three: one patient did not want to continue/DNA; two worsening of peri-wound eczema. I2: Seven: three did not want to continue/DNA; three injury of peri-ulcer skin; one extensive exudate and odour leakage.	Also measured pain and pH.
Burgess & Robinson, 1993[108] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Traced onto acetate fortnightly. Setting and length of treatment: Multicentre, community study; follow-up 13 weeks.	79 patients with venous leg ulcers. Exclusion criteria: ABPI < 0.8.	Treatment: I1: Standard Granuflex. I2: Improved formulation Granuflex. Concurrent treatments: Class 2 graduated compression hosiery – removed at night if wished.	Mean wound area: Not stated. Other characteristics: Not reported.	Reduction in wound area (mm^2/day): I1: 7 I2: 8.17	No data presented.	Sponsored by ConvaTec. Difference between two formulations of Granuflex is that the improved formulation does not form a liquid gel upon hydration, rather a gelatinous mass is retained within the body of the dressing. This may make the dressing less prone to leakage.

continued

TABLE 22 contd *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Robinson, 1993[109] UK Wound type: Venous leg ulcers. Method of randomisation: 'Randomly assigned'. Objective outcome: Ulcer size recorded by tracing onto acetate fortnightly, this was digitised. Setting and length of treatment: Multicentre, community trial. 13 weeks.	121 patients living at home, with venous leg ulcers. Exclusion criteria: ABPI < 0.8.	Treatment: I1: Granuflex. I2: Comfeel. I3: Improved formulation Granuflex. Concurrent treatments: Class 2 graduated compression hosiery.	Mean wound area: Not stated. Other characteristics: Total ulcer area (mm^2): 77,923.	Reduction in wound area (mm^2/day): I1: 7.06 I2: 6.07 I3: 8.17 Labour and material costs: I1: Not stated I2: £4.15 per day I3: £3.39 per day Cost-effectiveness (cost per day/area healed per day): I1: Not stated I2: £0.68 per mm^2 per day I3: £0.41 per mm^2 per day Mean duration of visit was 17 minutes.	Not stated.	Sponsored by ConvaTec. Have requested a copy of final report — not received. This is the same trail as Burgess, reference number 108.
Zuccarelli, 1993[113] France Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Wounds assessed weekly and outlines traced at 0, 4, 8 and 12 weeks. Setting and length of treatment: 12 weeks, setting unclear.	40 patients with venous leg ulcers of at least 4 weeks duration. 38 patients were evaluable. Inclusion criteria: Age >18 years; duration > 4 weeks; venous insufficiency confirmed by Doppler. Exclusion criteria: ABPI < 0.8; pregnancy; myocardial infarction < 6 months previously; uncontrolled hypertension; unstable diabetes or rheumatoid arthritis; necrotic or infected ulcers.	Treatment: I1: Hydrocellular dressing (Allevyn), *n* = 19. I2: Hydrocolloid (Granuflex), *n* = 19. Concurrent treatments: Compression bandages. (Nylex® and Biflex®). Dressings and bandages changed weekly or more often if required due to irritation, excess exudate, or pain. Steroids for eczematous peri-ulcer skin as required. In the case of multiple ulcers the largest ulcer was monitored.	Mean ulcer area (cm^2): I1: 9.8 I2: 6.9 Mean ulcer duration (weeks): I1: 48.9 I2: 37.4 Mean age (years): I1: 70.1 I2: 77.3 M:F I1: 6:13 I2: 2:17 Previous ulceration: I1: 14 I2: 17 Baseline data only available for those completing the trial.	Number healed at 12 weeks: I1: 9 /19 (47%) I2: 9 /19 (47%)	I1: None. I2: Two allergic reaction, and one intolerance of peri-ulcer skin. One patient lost to follow-up and one record book lost.	
Bowszyc *et al.*, 1993[114] Poland Wound type: Venous leg ulcers. Method of randomisation: Allocated to treatment according to a pre-prepared randomisation listing. Objective outcome: Area of ulcer measured at baseline and weekly thereafter by tracing ulcer outline onto a transparent grid and by measurement of the length and breadth of the ulcer. Setting and length of treatment: Dermatology clinic. 16 weeks follow-up.	80 patients (82 affected legs; 27 men; 53 women) with venous leg ulcers attending a dermatology clinic. Inclusion criteria: Age > 18 years; ABPI ≥ 0.8. Exclusion criteria: Diabetes; heavily exuding wound; necrotic ulcer, clinically infected; poor state of health; immunocompromised; corticosteroid treatment.	Treatment: I1: Polyurethane foam dressing (Lyofoam), *n* = 40. I2: Hydrocolloid dressing (Granuflex), *n* = 40. Concurrent treatments: Sloughy wounds treated with sodium chloride solution containing 0.3–0.4% available chlorine before entry to the study. Setopress high compression bandage applied. Dressings and bandages changed weekly or according to exudate level.	Mean area of largest ulcer (cm^2): I1: 3.01 (4.88 SD) I2: 3.05 (6.77 SD) Mean pre-trial duration (weeks): I1: 26.2 (37.6 SD) I2: 36.1 (70.9 SD) Mean age (years): I1: 64.2 I2: 55.5 Other characteristics: I1 I2 Completely mobile: 28 35 Initial number of ulcers ($\bar{x}$): 83 12	Number of legs where ulcers completely healed in 16 weeks: I1: 24 (60%) I2: 24 (60%)	I1: Four. I2: Four. Three for personal reasons; two for localised infection; one required steroids for an allergy; one had very high exudate levels and the dressing would not adhere; one complained of severe pain in the leg.	Five were excluded because they had heavily exuding wounds; unclear if this was pre-randomisation. Mean pain score on removal: I1: 3.72 (0.55 SD) I2. 3.63 (0.83 SD) (NS) (scale = 1–4; very painful – no pain).

continued

TABLE 22 contd *Comparisons of dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Limova, 1996[111] USA Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area. Setting and length of treatment: 8 weeks.	20 patients with venous leg ulcers. Inclusion criteria: Not stated. Exclusion criteria: Not stated.	Treatment: I1: DuoDerm CGF hydrocolloid dressing, *n* = 10. I2: Tegasorb hydrocolloid dressing, *n* = 10. Concurrent treatments: All had Medicopaste® and Coban® bandages, changed weekly.	Mean wound area: No data.	Number of ulcers healed in trial period: I1: 2/10 (20%) I2: 6/10 (60%)	No data.	The Tegasorb dressing was 'preferred in terms of ease of application to skin, adhesion to skin, conformability, exudate absorption, barrier properties, transparency and patient comfort'. No data presented for these parameters.
Whipps Cross[112] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area. Setting and length of treatment: 6 weeks.	29 outpatients with venous leg ulcers. Inclusion criteria: Not stated. Exclusion criteria: Not stated.	Treatment: I1: DuoDerm CGF hydrocolloid dressing, *n* = 16. I2: Comfeel Plus, *n* = 13. Concurrent treatments: Class II (UK) stockings – Venosan.	Median wound area (cm^2): I1: 4.9 (range, 1.9–10.1) I2: 6.4 (range, 5.5–19.23) Other characteristics: I1 I2 M:F 3:13 5:8 Mean age (years): I1: 71.4 (16.5 SD) I2: 70.3 (10.75 SD) Median duration of ulcer (months) (interquartile range): I1: 13 (5.5–28.5) I2: 12 (4–18)	Reduction in wound area during trial: I1: 45% I2: 57% Median wear time (days): I1: 7 I2: 7 Stated that the healing rates in the two groups were similar whether analysed by ulcer area or perimeter.	Two withdrawals due to reactions to dressing but not clear whether from I1 or I2:	Dressings were also assessed in terms of condition of dressing after 1 week, wear time, ease of removal of dressing, amount of exudate, and ease of application of new dressing. Ease of dressing removal and comfort score said to be higher for Comfeel Plus, though no analysis presented.

TABLE 23 *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Passarini *et al.*, 1982[115] Italy Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Ulcer area and healing index (% healed). Setting and length of treatment: Outpatients; 20 days.	48 patients with venous leg ulcers (26 women and 22 men). Exclusion criteria: No data.	Treatment: I1: Hyaluronic acid on gauze 2 mg in glycerine on a 10 x 10 cm gauze pad; changed daily, *n* = 23. I2: Control: various treatments (e.g. local antibiotics, zinc cream), *n* = 25. Concurrent treatments: All had surgical or enzymatic cleansing.	Mean wound area: No data. Other characteristics: I1 I2 M:F 9:14 13:12 Age (years): 61 67	Reduction in wound area: I1: 78% I2: 44%	No data.	
Galasso *et al.*, 1978[116] Italy Wound type: Venous ulcer. Method of randomisation: Not clear if randomly allocated. Objective outcome: Ulcer healed. Setting and length of treatment:	62 patients with venous disease. Exclusion criteria: Extending infection < 2 cm.	Treatment: I1: Hyaluronic acid on gauze, *n* = 27. I2: Gauze, *n* = 35. Ulcers cleaned elastic compression during day and elevation at night. Zinc oxide paste bandage used on 12 control patients.	Ulcer duration (months): I1: 23.1 (33.67 SD) I2: 7.4 (7.0 SD) Ulcer length (cm): I1 I2 2 5 9 2–4.9 11 16 5.0 2 1 5.1–9.9 3 8 ≥ 10 6 1 Deep:superficial venous disease: I1: 17:10 I2: 24:11 Deep:superficial ulcer: I1: 11:16 I2: 12:23	Number healed: I1: 21/27 I2: 29/35 OR healing: 0.72 (0.2, 2.56)	I1: Three. I2: Four.	
Rundle *et al.*, 1981[117] UK Wound type: Venous leg ulcers. Method of randomisation: 'Randomly allocated'. Objective outcome: Tracing of ulcer on acetate. This tracing was transferred to card of known density and this was weighed. Hence the area could be calculated. Setting and length of treatment: Two hospital outpatient departments; no data on trial period; applied by experienced physiotherapists.	26 ambulatory patients with 48 ulcers. Patients with multiple ulcers received only one type of therapy. Exclusion criteria: No data.	Treatment: I1: Application of porcine dermis (after reconstitution in isotonic saline). Then paste bandage and self-adhesive elastic compression bandage (15 patients with 23 ulcers). I2: Paste bandage and self-adhesive elastic compression (11 patients with 20 ulcers). Concurrent treatments: Ulcer cleaned with isotonic saline. Dressings changed twice weekly as long as there was frank exudate and thereafter weekly.	Mean wound area (cm^2): I1: 0.2–47.8 (median, 2.0) I2: 0.5–45.0 (median, 3.0) Other characteristics: Age (years): I1: 45–88 (median, 62) I2: 56–80 (median, 73)	Number completely healed in trial: Not stated. Median duration of healing: (weeks): I1: 6 (range, 1–16) I2: 9 (range, 3–63) Difference = 21 days.	I1: Four (five ulcers): two admitted due to failure to heal; one patient (with two ulcers) failed to attend; one suffered a sensitivity reaction and was admitted to hospital. I2: One patient failed to heal and was admitted to hospital.	

continued

TABLE 23 contd *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Sabolinski *et al.*, 1996[118] USA Wound type: Leg ulcers (venous). Method of randomisation: Not stated. Objective outcome: Time to healing. Setting and length of treatment: Outpatients treated in the community. The trial was continued until all ulcers had healed.	Patients with venous leg ulcers. Exclusion criteria: Not stated.	Treatment: I1: Living Skin Equivalent® was applied directly to the ulcer and dressed with a three-layer wrap composed of a primary non-adherent dressing, a cotton bolster, and a high-stretch compression bandage. The dressing was changed weekly. The living skin equivalent was applied generally only twice, subsequent treatment only involved application of the three-layer wrap dressing. I2: Graduated, multi-layered compression (CMP) therapy entailing weekly applications of a four-layer wrap consisting of a primary non-adherent dressing, a secondary bolster dressing, a zinc gelatin-impregnated gauze, and a high-stretch compression bandage. 233 patients were randomised to one of the two groups. The number of patients in each group is not stated.	Mean wound area (cm^2): Not stated. Other characteristics: Not stated.	Median time to healing (days): I1: 57 I2: 181 ES: I1 vs. I2 124	Not stated.	I1 costs US$2601 per patient, while I2 costs US$3257 per patient.
Duhra *et al.*, 1992[119] UK Wound type: Leg ulcers (venous). Method of randomisation: Not stated, but randomisation was by ulcer not patient. Objective outcome: Reduction in ulcer size assessed by tracing the wound shape and then transferring it to graph paper to calculate the area. A photograph was taken at each assessment. Setting and length of treatment: Outpatients attending a leg ulcer clinic. Treatment was continued until the wound healed or for a maximum of 6 weeks. Assessments were made every 2 weeks by the same investigator.	Patients with venous ulcers of < 30 cm^2 and present for at least 6 months.	Treatment: I1: Keratinocyte allografts released with 0.25% Dispase® and backed with a non-adherent dressing (Jelonet) several layers of gauze and an absorbent pad. Tubigrip and a compression bandage. Dressings were changed every 5 days by a qualified nurse (I1 patients with 15 wounds). I2: Placebo of an identical dressing soaked in culture medium (I1 patients with 15 wounds). Concurrent treatments: All ulcers were treated with conventional therapy until they were suitable for grafting. Wounds in both groups were cleansed with sterile saline before application of the dressing. Patients were instructed to rest at home with their feet elevated for 48 hours.	Mean wound area (cm^2): I1: 9.1 (1.6 SEM) I2: 10.7 (1.7 SEM) Other characteristics: I1 / I2 Mean age (years): 70.6 / 63.7 M:F 1:1.2 / 1:1.8 Mean duration (years): 4.8 / 4.5 OR no healed (I1 vs. I2): 0.3118 (0.0117, 8292) ES absolute (I1 vs. I2): 0.6.	Reduction in mean ulcer area (cm^2) at 6 weeks: I1: 2.7 I2: 3.3 ($p < 0.001$ between baseline size: $p > 0.05$. NS between groups at final assessment). Number of wounds healed at 6 weeks: I1: 0 I2: 1	Three patients with a total of four ulcers were withdrawn: three ulcers were in the allograft (I1) group and one in the placebo (I2) group. All these ulcers became clinically infected.	There was no significant difference in pain relief between the two groups throughout the study period.

Living Skin Equivalent®, Organogenesis Inc.

continued

TABLE 23 contd *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Tsakayannis *et al.*, 1994[122] USA Wound type: Venous leg ulcers. Method of randomisation: Not clear that patients were randomly allocated. Objective outcome: Ulcers examined biweekly for ulcer contraction. Area quantified using photoplanimetry. Setting and length of treatment: Setting not stated. 8 weeks.	Nine patients with ten full-thickness wounds, open at least 8 weeks. Exclusion criteria: Infection, surgery indicated.	Treatment: I1: Sucralfate ointment (four patients with five wounds). I2: Vehicle alone (five patients with five wounds). Concurrent interventions: No data.	No data.	Number completely healed in 8 weeks: I1: 2/4 patients healed (= 2/5 ulcers) 50% I2: 0/5 ulcers healed (= 0/5 patients) 0%	No withdrawals.	Letter to *Vasa*, very limited information. No adverse events or withdrawals reported.
Salim, 1992[124] Iraq Wound type: Venous ulcers. Method of randomisation: Sealed envelopes. Objective outcome: Not stated. Setting and length of treatment: Outpatients.	168 patients in three groups (90 women and 78 men). Inclusion criteria: Non-circumferential ulcers; on medial aspect of the leg; < 10 cm^2 area; first ulcer; gross leg oedema. Exclusion criteria: Alcoholism; ulcer infection; pregnancy; diabetes; hypertension; steroids; non-steroidal anti-inflammatory drugs; regular medication use; hepatic or renal disorders; rheumatoid arthritis; collagen diseases; venous ulceration confirmed by history, examination and ABPI.	Treatment: I1: DL-cysteine powder, *n* = 57. I2: DL-methionine-methyl sulphonium chloride, *n* = 56. I3: Placebo powder, *n* = 55. Concurrent treatments: Ulcer cleansed with normal saline, skin treated with olive oil. Non-adherent dressing + four-layer compression bandage. Dressed every day for 7 days and then weekly.	I1 I2 I3 M:F 29:28 25:31 24:31 Mean age (years): I1: 58 (range, 30–69) I2: 59 (range, 29–71) I3: 56 (range, 28–72) Mean ulcer duration (months): I1: 20 I2: 24 I3: 22 Mean (± SEM) ulcer size (cm^2): I1: 5.3 ± 0.3 I2: 5.5 ± 0.1 I3: 4.6 ± 0.2	Ulcer size at 12 weeks (cm^2): I1: 0.4 ± 0.1 I2: 0.5 ± 0.1 I3: 1.1 ± 0.2 Number healed at 12 weeks (not ITT): I1: 43 (93% of 46) I2: 42 (93% of 45) I3: 32 (70% of 46) ITT analysis: I1: 43/57 (75%) I2: 42/56 (75%) I3: 32/55 (58%) (p = 0.078)	I1: 11: three infection; three adverse events; one concomitant treatment; four non-compliant. I2: 11: four infection; two adverse events; two concomitant treatment; three non-compliant. I3: None: four infection; two adverse events; three non-compliant.	When all patients who were excluded from the study and the analysis repeated with all the excluded ulcers assumed to be healed or unhealed, then the placebo remained significantly worse than the other two treatments. (p < 0.01). However if the analysis assumes that the placebo exclusions healed, and none of the other exclusions healed, then the difference is no longer statistically significant. Calculations not presented. Did do an *a priori* power calculation (80% power to predict difference of 30% between two groups, p < 0.05).

continued

TABLE 23 contd *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Salim, 1991[123] Iraq Wound type: Venous ulcers. Method of randomisation: Alternating sequence sealed envelopes. Objective outcome: Ulcer size determined by tracing the ulcer margin onto cellophane and then transferring the outline to card with a known weight to area ratio. Setting and length of treatment: Outpatients.	153 patients in three groups (n = 51; n = 50; n = 52). Inclusion criteria: Non-circumferential ulcers; on medial side of the leg, < 10 cm^2 area; first ulcer; gross leg oedema; no evidence of surgery or injection sclerotherapy for varicose veins; venous ulceration confirmed by history; clinical and Doppler examination and ABPI. Exclusion criteria: Alcoholism; ulcer infection; pregnancy; diabetes; hypertension; steroids; non-steroidal anti-inflammatory drugs; regular medication use; hepatic or renal disorders; serious underlying disease; rheumatoid arthritis; collagen diseases.	Treatment: I1: Allopurinol powder, n = 51. I2: DMSO powder (pharmaceutical grade BP), n = 50. I3: Placebo (inert powder), n = 52. Concurrent treatments: Ulcer cleansed with normal saline, devitalised skin removed with olive oil. Skin treated with propylene glycol monostearate. Non-adherent dressing + layered (crepe, Elset® and Coban) compression bandage. Dressed every day for 7 days and then weekly.	Presents data only for patients 'fully evaluable'. I1 I2 I3 M:F 29:28 25:31 24:31 Mean age (years): I1: 56 (range, 31–68), n = 45 I2: 57 (range, 29–71), n = 44 I3: 58 (range, 28–71), n = 44 Mean ulcer duration (months): I1: 24, n = 45 I2: 23, n = 44 I3: 20, n = 44 Mean ulcer size (± SEM; cm^2): I1: 4.4 ± 0.5 I2: 4.6 ± 0.7 I3: 4.1 ± 0.2	Ulcer size at 12 weeks (cm^2): I1: 0.3 ± 0.1 I2: 0.2 ± 0.1 I3: 1.3 ± 0.3 Reduction in ulcer area in 12 weeks (cm^2): I1: 4.1 I2: 4.4 I3: 2.8 Number healed at 12 weeks (not ITT): I1: 42 (93% of 45) I2: 42 (95% of 44) I3: 31 (70% of 44) ITT analysis: I1: 42/51 (82%) I2: 42/50 (84%) I3: 31/52 (60%)	I1: Six: three infection; one adverse events; one concomitant treatment; one non-compliant. I2: Six: two infection; two adverse events; two non-compliant. I3: Eight: four infection; one adverse events; three non-compliant.	When all patients who were excluded from the study and the analysis repeated with all the excluded ulcers assumed to be healed or unhealed, then the placebo remained significantly worse than the other two treatments (p < 0.01). However if the analysis assumes that the placebo exclusions healed, and none of the other exclusions healed, then the difference is no longer statistically significant. Calculations not presented. Did do an *a priori* power calculation (80% power to predict difference of 30% between groups, p < 0.05).
Bishop *et al.*, 1992[125] USA Wound type: Venous ulcer. Method of randomisation: Not stated but ulcers were stratified by lesion size: 3–20 cm^2 or 21–50 cm^2. Objective outcome: Ulcer traced and area determined by digitised planimetry weekly. Evaluator was blind to treatment. Setting and length of treatment: Multicentre trial; 4 weeks.	93 patients admitted to the plastic surgery clinics with lower extremity ulceration caused by venous insufficiency. Inclusion criteria: Age 21–90 years; ulcer duration ≥ 3 months; ulcer surface area 3–50 cm^2. Exclusion criteria: Women of childbearing potential who are, or are likely to become pregnant; > 105 bacteria/g of tissue in the wound; systemic sepsis of presence of bone infection; ABPI < 0.5; hypercupraemia; systemic immunosuppressive or cytotoxic therapy; insulin-dependent diabetes mellitus.	Treatment: I1: 0.4% tripeptide copper complex in petrolatum based cream (Unibase®), n = 31 (29). I2: 1% silver sulphadiazine cream, n = 29 (28). I3: Petrolatum-based cream (Unibase), n = 30 (29). Numbers in brackets refer to the 86 patients for whom data are presented. Treatments dispensed by a third party. Patient instructed on daily application of cream. Concurrent treatments: Ulcers cleansed by rinsing with normal saline. After application of cream, a non-adherent dressing and elastic bandage was applied.	Mean ulcer area [median] (cm^2): I1: 9.9 (8.5 SD) [6.5] I2: 11.9 (11.2 SD) [6.9] I3: 9.6 (8.1 SD) [6.2] Mean ulcer duration [median] (months): I1: 57.1 (94.9 SD) [11.0] I2: 44.1 (58.0 SD) [19.0] I3: 38.0 (88.7 SD) [12.0] Number of ulcers > 20 cm^2: I1: 5 I2: 5 I3: 4 Other characteristics: Mean age (years): I1: 58.2 (14.6 SD) I2: 58.2 (14.5 SD) I3: 51.6 (17.3 SD) M:F I1: 14:15 I2: 9:19 I3: 20:9 Weight (kg): I1: 92.1 (26.1 SD) I2: 92.2 (35.6 SD) I3: 103.2 (34.7 SD)	Number completely healed at 4 weeks: I1: 0/31 (0%) I2: 6/29 (21%) I3: 1/30 (3%) % reduction in wound area at week 4: I1: 18.7 (9.07 SEM) I2: 44.0 (8.21 SEM) I3: 22.5 (10.2 SEM) Comparisons (analysed by method of least square means) + Fisher's exact test: I1 vs. I2, p = 0.03 I1 vs. I3, p = 0.82 I2 vs. I3, p = 0.05 Silver sulphadiazine cream was better than the other two preparations. There was no difference in efficacy between the other two preparations. Comparing reduction in wound area using Tukey–Kramer, I1 vs. I2, I1 vs. I3 and I2 vs. I3, all have p > 0.05.	Immediate withdrawals: I1: One I2: Two	

continued

TABLE 23 contd *Topical preparations compared with traditional/control treatments*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Werner-Schlenzka & Lehnert, 1994[120] Germany Wound type: Leg ulcers (venous). Method of randomisation: Not stated. Objective outcome: Ulcer size. Wounds were measured each week by taking a tracing and determining the area by computer-aided planimetery. A photograph was taken on the 1st, 2nd and 8th week of treatment. Setting and length of treatment: A multicentre trial at 14 sites; treatment was continued for 8 weeks.	Both out- and inpatients with leg ulcers thought to be of venous origin in the size range 3–100 cm^2. Multiple ulcers were included but only the largest was monitored. Exclusion criteria: Ulcers present for less than 2 months; ABPI < 0.9.	Treatment: I1: Iloprost, 10 µg/ml for the first 3 days and then at 40 µg/ml for the rest of the treatment period if tolerated well, otherwise patients were returned to the lower concentration. The Iloprost was incorporated into a hydrogel to aid application, *n* = 65. I2: Placebo: hydrogel only. The increase in treatment concentration in the Iloprost group was simulated in the placebo group, *n* = 34. Systemic medication of concomitant disease was continued and documented. Compression was obligatory.	Mean wound area (cm^2): I1: 26.6 I2: 16.2 Wound dimensions are only available for valid cases (i.e. those completing the trial). Other characteristics: I1 I2 Mean age (years): 64.6 63.4 M:F 1:4 1:5.8 Ankle index: 1.09 1.14 Duration: 2–6 months 10 7 6–12 months 14 4 1–5 years 17 11 > 5 years 24 12 Diabetes: 14 5	Mean % reduction in ulcer area (cm^2) at 8 weeks: I1: 44% I2: 43% Absolute reduction in mean ulcer area (cm^2) at 8 weeks: I1: 9.4 I2: 6 Difference 3.4 ($p > 0.05$, NS; ANCOVA). Results by ITT analysis were also insignificant. Number of ulcers healed at 8 weeks: I1: 4 I2: 3 OR 0.6776 (0.143, 3.22)	I1: 12: one refusal of compression; one progression; one no regular visit; one pain; one further treatment refused; seven violations of the study protocol. I2: Six: one bleeding from ulcer; one new ulcer; two progression; two violations of the study protocol.	Larger number of diabetics in the Iloprost group may have influenced the healing rates. 83% of Iloprost patients tolerated the higher concentration. 88% of patients in the placebo group tolerate the simulated increase in concentration. Forty-seven (72%) patients on Iloprost and 21 (62%%) on placebo complained of adverse events (i.e. burning, itching, stinging and pain).
Werner-Schlenzka & Kuhlmann, 1994[121] Germany Wound type: Leg ulcers (venous). Method of randomisation: Not stated. Objective outcome: Reduction in ulcer size determined by tracing the ulcer and measuring the area by computer-aided planimetry. Photographs were taken at intervals throughout the study. Setting and length of treatment: Clinic-based trial. Treatment was continued until the wound healed or for a maximum of 8 weeks.	Patients with ulcers thought to be of venous origin and no larger than 2 cm^2. Multiple ulcers were included but only the largest was monitored. Exclusion criteria: ABPI index measured by Doppler ultrasound < 0.9; antibiotics; creams containing antiphogistics or corticoids.	Treatment: I1: Iloprost solution, 0.0005%, *n* = 49. I2: Iloprost solution, 0.002%, *n* = 49. I3: Placebo, *n* = 50. All treatments were prepared by an independent person prior to application. 1.5 ml of the treatment was applied twice weekly with a cotton stick to the ulcer edge and ulcer surrounding. Treatment of the ulcer base was continued in the usual way. Systemic medication of concomitant disease was continued and documented. Compression was obligatory with lastobind.	Mean ulcer area (cm^2): I1: 25.8 I2: 26.5 I3: 35.1 Other characteristics: I1 I2 I3 Mean age (years): Male 53.9 59.8 55.4 Female 61.4 56.8 60.0 M:F 1:3.5 1:3.1 1:1.8 ABPI: 1.1 1.1 1.1 Duration: < 6 months 12 14 13 6–12 months 9 8 2 1–5 years 15 12 22 > 5 years 13 12 13 Unknown 0 0 0	Number of wounds healed after 8 weeks: I1: 2 I2: 5 I3: 2 Mean % reduction in ulcer area at 8 weeks: I1: 15.9 I2: 32.9 I3: 14.6 OR healed I1 vs. I2: 0.3745 (0.069, 2.031) I1 vs. I3: 1.021 (0.138, 7.556) I2 vs. I3: 2.727 (0.503, 14.788) % reduction (difference): I1 vs. I2: –17% I1 vs. I3: 1.3% I2 vs. I3: 18.3%	Not stated.	90% of patients for both groups reported that the dressings were painless.

TABLE 24 *Topical preparations compared with placebo*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Rasmussen *et al.*, 1991;[129] 1994[126] Denmark Wound type: Venous leg ulcers. Method of randomisation: Randomised in blocks of four. Stratified according to initial ulcer area. Objective outcome: Ulcer tracing and area determined by point counting. Setting and length of treatment: Multicentre trial; treated at home by a research unit nurse; 6 weeks, (2 weeks run-in period of treatment with compression and a hydrocolloid).	102 patients with venous ulceration of more than 3 months duration; aged > 18 years; ulcer area > 1.5 cm^2; able to tolerate compression. Exclusion criteria: ABPI < 0.8; diabetes; haemoglobin < 6 mmol/l; systemic corticosteroid or cytotoxic therapy; cellulitis and history of evidence of peripheral arterial disease.	Treatment: I1: Human growth hormone, 0.17 IU/l, *n* = 20. I2: Human growth hormone, 1.0 IU/l, *n* = 22. I3: Human growth hormone, 11.2 IU/l, *n* = 23. I4: Saline solution, *n* = 22. (all 0.1 ml/cm^2/day 5 days a week). Sandwich technique of administration was used: one piece of hydrocolloid was placed around the ulcer margins and a second placed over this to form a fluid tight seal which incorporated a connecting piece through which fluids could be administered. Concurrent treatment: Ulcers washed in sterile water through the dressing before treatment, 1 ml/cm^2. Treatment fluid administered and left for 30 minutes. Double layer of compression bandages applied, reapplied daily. Dressings changed 1–5 times weekly (mean = three times a week).	Mean wound area (cm^2): I1: 14 (26 SEM) I2: 11 (27 SEM) I3: 12 (30 SEM) I4: 12 (26 SEM) Average duration of ulcer (months): I1: 24 (6 SEM) I2: 56 (19 SEM) I3: 36 (12 SEM) I4: 26 (6 SEM) Other characteristics: I1 I2 I3 I4 Age (years): 78 (20) 75 (21) 78 (17) 77 (24) M:F 3:21 7:16 8:15 13:9 Baseline details are only for patients completing the trial.	Number completely healed at 6 weeks: I1: 3/20 (15%) I2: 2/22 (9%) I3: 2/23 (9%) I4: 3/22 (14%) Number completely healed at 3 months: Incomplete follow-up: I1: 7/20 (35%) I2: 3/22 (14%) I3: 3/23 (13%) I4: 3/22 (14%) Healing rate % per week: I1: 17.9 (13.0) I2: 7.6 (5.5) I3: 9.6 (4.5) I4: 7.9 (4.0)	I1: Three infection. I2: One infection. I3: None. I4: Two: one infection; one vasculitis. There were a futher nine withdrawals but all were included in the analysis. (Nine patients withdrew during the run-in period due to reasons of dressing intolerance, infectious disease, inability to tolerate compression, and unwillingness to participate. Four patients were excluded from the analyses because of cellulitis necessitating antibiotic treatment, and need for a change in therapy (three in I1 and one in I2). One patient was excluded because of severe peripheral vascular disease, and another was hospitalised during the first week of treatment for pneumonia. This left 87 for analysis of healing rates.)	Performed an *a priori* power calculation. Adverse reactions: I1: Three infection; one ulcer worsening. I2: Two infection; one non-compliance. I3: Two infection; one ulcer worsening; one eczema; one vasculitis; one hospitalisation. I4: One infection.

continued

TABLE 24 contd *Topical preparations compared with placebo*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Freak *et al.*, 1993;[132] 1994[131] UK Wound type: Chronic venous leg ulcers. Method of randomisation: Stratified according to ulcer size (above or below 10 cm^2). Traced onto acetate film, computerised planimetry. Setting and length of treatment: Ulcer clinic at weekly intervals; visited at home by research nurse 5 days a week; treatment for 6 weeks initially – if not achieved 50% healing at this point then continued for a further 6 weeks.	29 Patients with a venous ulcer of at least three months' duration, ulcer size greater than 1.5 cm^2. Exclusion criteria: ABPI < 0.8; insulin-dependent diabetes mellitus; haemoglobin < 9 g/dl; oral or parenteral corticosteroids or cytotoxic therapy within the previous 6 months; with cellulitis; deep tissue infection; gangrene; amputation for peripheral vascular disease; intermittent claudication; unreliable contraception. Three patients who consented to enter the study failed to complete the 2 week run-in period so 26 received trial medication.	Treatment: I1: Biosynthetic human growth hormone, 0.17 IU/ml, *n* = 7. I2: Biosynthetic human growth hormone, 1.0 IU/ml, *n* = 6. I3: Biosynthetic human growth hormone, 11.2 IU/ml, *n* = 6. I4: Placebo, *n* = 7. 0.1 ml/cm^2 ulcer area. Concurrent treatments: Ulcers cleansed with saline. Sandwich dressing of two layers of hydrocolloid, the bottom layer covered the peri-ulcer skin only, the top layer contained a port for the introduction of the trial fluid. Four-layer compression bandaging renewed weekly.	Mean wound area (cm^2): I1: 10.24 I2: 9.83 I3: 7.90 I4: 10.58 Other characteristics: Duration of ulcer (months): I1: 44.14 I2: 98.33 I3: 20.5 I4: 54.57 Age (years): I1: 73.42 I2: 65.33 I3: 75.83 I4: 70.42	Number completely healed at 8 weeks: No data. Reduction in wound area, % per week: I1: 33 (11% SEM) I2: 25 (14% SEM) I3: 11 (3.3% SEM) I4: 22 (6.8% SEM) Comparisons (SEM): I1 vs. I4: +11% I2 vs. I4: +3% I3 vs. I4: –11%.	No data.	Compliance with the trial dressing was poor mainly because of the damage to the surrounding skin. In these circumstances a non-adherent dressing was applied to allow the peri-ulcer to recover. Therefore a large number of patients did not receive five doses per week. Problems with the surrounding skin were reported in 104/201 visits (maceration, inflammation, and new ulcers). Trial abandoned after recruitment of 29 patients (< 30% of those originally planned). Sponsored by Coloplast and Novo Nordisk.
Falanga *et al.*, 1992[130] USA Wound type: Venous ulcers. Method of randomisation: Objective outcome: Length, width of ulcer; double-blind evaluation. Setting and length of treatment: 10 weeks.	45 patients with ulcers of < 2 years duration; no recent sign of re-epithelialisation, or granulation tissue covering < 50% of ulcer area. Exclusion criteria: Atypical location of ulcer; ulcer involving gangrene; tendon; ABPI < 0.8; history of systemic malignancy; uncontrolled diabetes; medication known to interfere with healing such as corticosteroids or immunosuppressive agents.	Treatment: I1: Reconstituted lyophilised human recombinant epidermal growth factor (h-EGF), 7.5 ml on a non-adherent pad left in place for 30 minutes, *n* = 23. I2: Diluent used to reconstitute h-EGF alone, 7.5 ml on a non-adherent pad left in place for 30 minutes, *n* = 22. Concurrent treatments: Legs were dressed with a gauze bandage and a compression bandage. The patient administered treatment twice daily. A new batch was supplied to the patient weekly. Systemic antibiotics were allowed if necessary to treat cellulitis.	Mean wound area (cm^2): I1: 12.8 I2: 19.2 Other characteristics: All groups Age (years): 60 M:F 20:26 Ethnic origin: White 11 Black 21 Hispanic 12 Baseline data omit one patient who never received the treatment.	Number completely healed at 10 weeks: I1: 6/17 (35%) I2: 2/18 (11%) Mean (median) reduction in wound area: I1: 48% (73%) I2: 13% (33%) Difference = 35%, $p = 0.32$. Adverse events: I1: One severe burning sensation and erythema; one patient with a history of epilepsy had seizures during two application of the treatment. I2: One moderate pain around the ulcer; two patients developed cellulitis.	Ten in total: four lost to follow-up; three protocol violations; two cellulitis; one patient was never treated. (One patient never received the treatment and was excluded from the analysis. Nine further patients withdrew from the trial and therefore 35 patients were included in the analysis.)	Sponsored by Ethicon Inc.

TABLE 25 *Topical preparations compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Tosti & Veronesi, 1983[132] Italy Wound type: Venous leg ulcers. Method of randomisation: Not stated; not clear if randomly allocated (CCT). Objective outcome: Ulcer area as traced onto a transparent sheet and digitised using a computer. Setting and length of treatment: 26 days.	22 patients with venous leg ulcers (11 men and 11 women); age 65–80 years.	Treatment: I1: Collagen dressing at day 2, and day 8 and thereafter weekly, *n* = 11. I2: Control (local antiseptic) applied daily, *n* = 11.	Mean wound area (cm^2): I1: 19.6 I2: 19.7 Other characteristics: I1 I2 Age (years): 71.9 72.5 M:F 5:6 6:5	Number healed in 26 days: I1: 8/11 (73%) I2: 1/11 (9%)	I1: None. I2: One lost to follow-up.	
Greguric *et al.*, 1994[133] Croatia Wound type: Venous leg ulcers. Method of randomisation: Consecutively numbered, sealed envelope. Objective outcome: Ulcer traced at enrolment and subsequently area measured by computerised planimetry. Photograph taken. Setting and length of treatment: Multicentre trial. Inpatients and outpatients; treatment was for a maximum of ten dressing changes.	110 patients with venous leg ulcers. Exclusion criteria: Ulcer size < 2.5 cm in length or > 5 cm; ABPI < 0.9; rheumatoid arthritis; sickle-cell disease; patients with sensitivity to any of the interventions used; malignant ulcers; malignant disease; patients taking anti-neoplastic drugs or > 5 mg prednisolone per day; immune deficiency or immunosuppressive drug therapy; pregnancy; patients with abnormal wound healing; and those who would be better treated by an alternative regimen.	Treatment: I1: 10 x 10 cm piece of hydrocolloid (Varihesive), *n* = 55. Compression applied by use of two shaped tubular bandages, changed on average every 2 days. I2: Magnesium sulphate paste (approx. 15 g), applied to ulcer using a spatula. Bland petroleum jelly applied to surrounding skin and then approximately six pieces of sterile gauze applied on top. Dressing changed on average every day, *n* = 55. Ulcers cleaned with normal saline and hydrogen peroxide. Double layer of elastic bandage applied to provide compression.	Mean wound area: Not stated. Other characteristics: Mean age (years): I1: 61 (15 SD) I2: 61 (13 SD) Median ulcer duration (days): I1: 1737 (15,902*) I2: 1987 (12,218*) * 95% central range Deep ulcer:superficial ulcer I1: 11:44 I2: 10:45	Number completely healed at ten dressing changes: I1: 3/55 (5%) I2: 0/55 (0%) Reduction in wound area (mm^2/day): I1: 32 I2: 21	No data.	Adverse events: I1: 12 adverse events in 11 patients (five thought not related to dressing). Events possibly due to dressing were pain in leg (1), itching of peri-ulcer skin (1), erythema of surrounding skin (1), bullous reaction (1), erysiplelas cruis (1). Events probably due to dressing were 1 cm^2 erosion of skin under the dressing Varihesive E = Granuflex E = Improved Formulation Granuflex = Duoderm E. I2: No data. Trial duration in two groups is dissimilar (approx. 21 days in hydrocolloid and 10 days in conventional treatment).

continued

TABLE 25 contd *Topical preparations compared with dressings*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Teepe *et al.*, 1993[131] The Netherlands and Belgium Wound type: Venous leg ulcers. Method of randomisation: Not stated. Both centres were randomised separately. Objective outcome: Computerised planimetric analysis of cellophane tracings taken weekly. Setting and length of treatment: Multicentre trial; outpatient treatment; 6 weeks then cross-over.	43 consecutive patients with 47 unilateral or bilateral ulcers. Inclusion criteria: Ulcer duration at least 3 months; evidence of venous insufficiency as demonstrated by clinical findings or LRR.	Treatment: I1: Hydrocolloid (Granuflex/DuoDerm) (21 patients with 23 ulcers). I2: Cryopreserved cultured allografts (22 patients with 24 ulcers). Concurrent treatments: Saline dressings and debridement for 2 weeks pre-trial. At each dressing change, ulcer cleansed with saline, debrided if necessary, and short-stretch compression bandage applied (Elko).	Mean ulcer area (cm^2): I1: 1.4 (0.4 SD) I2: 2.3 (0.95 SD) Median ulcer area (cm^2): I1: 6.1 (range, 0.99–21.37) I2: 9.0 (range, 1.09–40.35) Other characteristics: Mean age (years): I1: 69 (range, 39–85) I2: 74 (range, 60–90) Mean ulcer duration (months): I1: 26 (range, 3–360) I2: 25 (range, 3–40) M:F I1: 6:16 I2: 5:16	Number healed at 6 weeks: I1: 5/25 (20%) I2: 6/24 (25%) Ulcer area after 6 weeks; % of initial ulcer area (from graph): I1: 38 I2: 18 ($p = 0.01$) Absolute change in ulcer area: I1: 0.9 I2: 1.4 Healing rate in first 6 weeks was higher with I2 ($p = 0.03$). Cross-over at 6 weeks if not healed. Also measured pain (no difference between study groups).	I1: Four: three due to wound infection; one non-compliance. I2: Five: four due to wound infection; one due to treatment failure.	Performed an *a priori* power calculation; 90% vs. 50% healing in 6 weeks = 20 in each arm, 80% power, a + 0.05.

TABLE 26 *Comparisons of topical preparations*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Wilson *et al.*, 1979[134] Eire Wound type: Varicose ulcers. Method of randomisation: Method not stated – 'randomly separated'. Objective outcome: Ulcer area determined by planimetry. Setting and length of treatment: Outpatient clinic. Trial period is unclear.	36 patients with varicose ulcer attending a varicose ulcer clinic. Inclusion criteria: None stated. Exclusion criteria: Diabetes mellitus Group I1 had larger mean ulcer area at baseline – no data provided.	Treatment: I1: Buffered acidifying ointment (M/15 phosphate buffer in emulsifying ointment), pH 6, *n* = 18. I2: Emulsifying ointment, pH 7.3, *n* = 18. Concurrent treatments: Covered with gauze, crepe bandage and elastic stocking. Dressings done twice a week.	I1 had larger mean ulcer area at baseline – no data provided.	Mean healing rate (cm^2/day): I1: 22.6 (15.2 SD) I2: 3.3 (7.4 SD) Number healed in trial: I1: 16/16 (16/18) I2: 11/13 (11/18) Figures in brackets indicate proportion healing including withdrawals.	I1: Two: one found to be diabetic and therefore excluded; one poor response and withdrawn. I2: Five poor response and withdrawn.	Authors selected seven patients with equal ulcer areas and compared the healing rate (cm^2/day). The treatment group had a higher rate (16.3/5.8) compared with the control (6.3/3.3), $p < 0.005$.
Bishop *et al.*, 1992[125] USA Wound type: Venous ulcer. Method of randomisation: Not stated but ulcers were stratified by lesion size: 3–20 cm^2 or 21–50 cm^2. Objective outcome: Ulcer traced and area determined by digitised planimetry weekly. Evaluator was blind to treatment. Setting and length of treatment: Multicentre trial; 4 weeks.	93 patients admitted to the plastic surgery clinics with lower extremity ulceration caused by venous insufficiency. Inclusion criteria: Age 21–90 years; ulcer duration ≥ 3 months; ulcer surface area 3–50 cm^2. Exclusion criteria: Women of childbearing potential who are, or are likely to become pregnant; > 105 bacteria/g of tissue in the wound; systemic sepsis of presence of bone infection; ABPI < 0.5; hypercupraemia; systemic immunosuppressive or cytotoxic therapy; insulin-dependent diabetes mellitus.	Treatment: I1: 0.4% tripeptide copper complex in petrolatum-based cream (Unibase), *n* = 31 (29). I2: 1% silver sulphadiazine cream, *n* = 29 (28). I3: Control (petrolatum-based cream; Unibase), *n* = 30 (29). Numbers in brackets refer to the 86 patients for whom data are presented. Treatments dispensed by a third party. Patient instructed on daily application of cream. Concurrent treatments: Ulcers cleansed by rinsing with normal saline. After application of cream, a non-adherent dressing and elastic bandage was applied.	Mean wound area: Mean ulcer area [median] (cm^2): I1: 9.9 (8.5 SD) [6.5] I2: 11.9 (11.2 SD) [6.9] I3: 9.6 (8.1 SD) [6.2] Mean ulcer duration [median] (months): I1: 57.1 (94.9 SD) [11.0] I2: 44.1 (58.0 SD) [19.0] I3: 38.0 (88.7 SD) [12.0] Number of ulcers > 20 cm^2: I1: 5 I2: 5 I3: 4 Other characteristics: Mean age (years): I1: 58.2 (14.5 SD) I2: 58.2 (17.3 SD) I3: 51.6 (14.6 SD) M:F I1: 14:15 I2: 9:19 I3: 20:9 Weight (kg): I1: 92.1 (26.1 SD) I2: 92.2 (35.6 SD) I3: 103.2 (34.7 SD)	Number completely healed at 4 weeks: I1: 0/31 (0%) I2: 6/29 (21%) I3: 1/30 (3%) % Reduction in wound area at week 4: I1: 18.7 (9.07 SEM) I2: 44.0 (8.21 SEM) I3: 22.5 (10.2 SEM) Comparisons: (analysed by method of least square means) + Fisher's exact test. I1 vs. I2, $p = 0.03$ I1 vs. I3, $p = 0.82$ I2 vs. I3, $p = 0.05$ Silver sulphadiazine cream was better than the other two preparations. There was no difference in efficacy between the other two preparations. Comparing reduction in wound area using Tukey–Kramer, I1 vs. I2, I1 vs. I3 and I2 vs. I3, all have $p > 0.05$.	Immediate withdrawals: I1: One I2: Two	

continued

TABLE 26 contd *Comparisons of topical preparations*

Study and design	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Bulstrode, 1988;[135] 1987[136] UK Wound type: Leg ulcers. Method of randomisation: Drawing cards from a sealed box. Objective outcome: Time to healing. Ulcer size was determined by direct computer planimetry. A photograph was taken weekly. Setting and length of treatment: Hospital-based trial. Treatment was continued until the wound healed or for a maximum of 6 weeks.	Patients with chronic leg ulcers present for more than 2 years with no major underlying disease. Patients had to agree to be admitted to hospital for a minimum period of 6 weeks' bed rest or until complete ulcer healing. Exclusion criteria: Haemoglobin < 10 g; active arthritis; diabetes; cardiac insufficiency: peripheral vascular index of < 0.9; diastolic blood pressure > 100 mmHg.	Treatment: I1: Saline 0.9% NaCl (osmolarity 150 mosmol/l), *n* = 12. I2: Electrolyte free amino acid (osmolarity 150 mosmol/l), *n* = 12. I3: Hypertonic saline 5% NaCl (osmolarity 850 mosmol/l), *n* = 12. I4: Electrolyte free amino acid (osmolarity 850 mosmol/l), *n* = 12. On admission to hospital the ulcers were cleaned with Eusol mixed with liquid paraffin until the ulcer base consisted of clean, granulating tissue. Ulcers were dressed daily after a bath with a simple sterile gauze into which a flexible polythene tube was tucked. The dressing was covered with a backing of waterproof plaster tape, while the tube was attached to a syringe loaded with irrigation solution. The rate of irrigation kept the dressing moist and non-adherent without flooding. Bed rest was compulsory and at no time were patients allowed to sit with their legs dependent. Daily physiotherapy was performed. The manufacturers standard method of application was followed for both treatments.	Mean wound area (mm^2): I1: 32.5 I2: 31.3 I3: 47.8 I4: 38.4 Other characteristics: Mean age (years): I1: 73 I2: 74 I3: 72 I4: 77 M:F I1: 1:11 I2: 1:5 I3: 0:12 I4: 1:5 OR healing: I1 vs. I2 0.7 (0.13, 3.79) I1 vs. I3 5.5 (0.51, 59.1) I1 vs. I4 0.167 (0.03, 0.98) I2 vs. I3 7.86 (0.75, 82.18) I2 vs. I4 0.24 (0.042, 1.36) I4 vs. I3 33 (2.91, 374.5) OR combined: I1 + I3 vs. I2 + I4 0.188 (0.0524, 0.6738) I3 + I4 vs. I1 + I2 1.19 (0.3738, 3.792) % difference combined: I1 + I3 vs. I2 + I4 49% I3 + I4 vs. I1 + I2 15%	Number of wounds healed after 6 weeks: I1: 4 I2: 5 I3: 1 I4: 9 I1 and I3 vs. I2 and I4, $p > 0.05$ (saline vs. amino acid) I3 and I4 vs. I1 and I2, $p > 0.5$ (concentrated vs. dilute) (Chi-square test) Mean % reduction in ulcer area at 3 weeks: I1: 25 I2: 32 I3: 0 I4: 42 Change in area at the third week has been strongly correlated with final healing ($r > 0.85$, $p < 0.05$) and so was used by the authors for evaluation purposes. % difference: I1 vs. I2 –7% I1 vs. I3 25% I1 vs. I4 –17% I2 vs. I3 32% I2 vs. I4 –10% I4 vs. I3 42%	No withdrawals.	Using only the 3-week data weekly healing rates can be determined. This shows that the reductions are: I1 = 25% I2 = 32% I3 = 0% I4 = 42% Using these data I1 and I3 vs. I2 and I4 is significant $p < 0.005$, but I3 and I4 vs. I1 and I2 is not significant ($p > 0.15$).

Appendix 11

Studies of cost-effectiveness

TABLE 27 *Summary of cost-effectiveness data*

Study	Treatment	Variable cost of control (per patient)	Variable cost of intervention (per patient)	Incremental variable cost (per patient)	Semi-fixed cost of control (per patient) (units and price)	Semi-fixed cost of intervention per patient (units and price)	Incremental difference	ICERs	Comment
Milward, 1990 UK pounds sterling	Control: Gauze, *n* = 19 (none healed). I: Hydrocolloid, *n* = 19 (three healed).	£2815 (£148)	£2541 (£134)	£274 (–£14)	1056 nurse visits (56 visits) Five per week over 12 weeks (0.7 per day)	436 nurse visits (23 visits) 1.9 per week over 12 weeks (0.27 per day)	–620 nurse visits (–33 visits)	Dominated	Data stochastic no indication of variance and no significance testing.
Ohlsson, 1994 Swedish kronor	Control: Saline gauze, *n* = 14 (two healed). I: Hydrocolloid, *n* = 14 (seven healed).	(SEK 608; range, 169–970)	(SEK 653; range, 53–2423)	(SEK 45)	1053 dressing changes (mean, 75; range 21–94) 12.5 per week over 6 weeks (1.8 per day)	181 dressing changes (mean, 13; range 2–33) 2.2 per week 0.31 per day (over 6 weeks)	–872 dressing changes (–62 per patient)	Variable K 8 per ulcer; semi-fixed, dominated	Statistical testing of total costs indicate hydrocolloid significantly cheaper than gauze.
Meridith, 1988 UK pounds sterling	Control: Paraffin gauze, *n* = 24 (six healed). I: Hydrocolloid, *n* = 25 (19 healed).	£856 (£36)	£437 (£17)	–£419 (–£19)	Not possible to estimate	Not possible to estimate	Not possible to estimate	Dominated	Data stochastic, no indication of variance and no significance testing.
Smith, 1994 UK pounds sterling	Control: Alginate, *n* = 18 (two healed). I: Hydrocolloid, *n* = 22 (four healed).	£364 (£20)	£432 (£20)	£0	Not possible to estimate	Not possible to estimate	Not possible to estimate	Dominated	Data stochastic, no indication of variance and no significance testing.
Sebern, 1986, 1989 US dollars (1986)	Control: Gauze and tape, *n* = 100. I: Vapour-permeable dressing, *n* =100.	(Grade II ulcers $99; grade III ulcers $140)	(Grade II ulcers $97; grade III ulcers $179)	(–$2) ($39)	(Grade II ulcers $1260; grade III ulcers $1272)	(Grade II ulcers $758; grade III ulcers $1373)	(–$502) ($101)	II ulcers dominated. III ulcers dominated in other direction	For grade II ulcers MVP more cost-effective; no difference in outcome for grade III ulcers therefore gauze dominates; however, possible type 2 error.
Xakellis, 1992 US dollars (1990)	Control: saline gauze, *n* = 21 (18 healed). I: Hydrocolloid dressing, *n* = 18 (16 healed).	Median $4; mean $6; interquartile range, $3–9)	Median $13; mean $18; interquartile range, $10–26.	($12)	28 dressing changes; 17.8 per week; 2.5 per day (over 11 days)	3.5 dressing changes; 2.7 per week; 0.39 per day (over 9 days)	25 changes	$15 for variable Dominated for semi-fixed	Study reported medians which are difficult to interpret. Data were tested for statistical significance using tests of medians; hydrocolloid significantly cheaper depending on price assumptions of nurse time.
Kraft *et al.*, 1993 US dollars	Control: Saline gauze, *n* = 14. I: Foam dressing, *n* = 24.	$5.25 per week	$12.18 per week	$6.93 per week	21 dressing changes per week; 3 per day (over 24 weeks)	2.5 dressing changes per week; 0.34 per day (over 24 weeks)	–18.5 dressing changes	$24.75 per week for variable dominated for semi-fixed	Foam dressing higher initial acquisition costs but reduced used of nursing time and was more effective. Data were stochastic but were not subject to statistical analysis therefore it is not clear whether reduction in dressing changes is statistically significant.

continued

TABLE 27 contd *Summary of cost-effectiveness data*

Study	Treatment	Variable cost of control (per patient)	Variable cost of intervention (per patient)	Incremental variable cost (per patient)	Semi-fixed cost of control (per patient) (units and price)	Semi-fixed cost of intervention per patient (units and price)	Incremental difference	ICERs	Comment
Bale *et al.*, 1995 UK pound sterling	Control: Hydrocolloid, *n* = 46. I: Hydrocellular, *n* = 50.	8 weeks of treatment: Material costs £15; other dressing costs £44 (95% CI, £20, £68) (£59 per patient)	8 weeks of treatment: Material costs £29; other dressing costs £31 (95% CI, £27, £35) (£60 per patient)	£1	1.7 dressing changes per week (95% CI, 1, 7); 0.24 per day (over 8 weeks)	1.9 dressing changes per week (95% CI, 1, 15); 0.27 per day (over 8 weeks)	0.2	£8 per healed patient in dressing costs 0.12 dressing visits per patient	No evidence that costs were different statistically between two groups. Paper presented average cost-effectiveness ratios (£179 and £130 for hydrocolloid and hydro-cellular, respectively), which underestimates the potential cost-effectiveness of hydrocellular dressing.
Colwell *et al.*, 1993 US dollars	Control: Moist gauze dressing, *n* = 49. I: Hydrocolloid, *n* = 48.	$1.93 per day	$2.58 per day	$0.65	4.1 dressing changes per day (over 17 days)	0.42 dressing changes per day (over 17 days)	–3.68	$3.25 per healed patient Dominated for semi-fixed	Materials cost higher for hydrocolloid dressings due to greater acquisition costs; however, number of dressing changes reduced. No statistical testing of cost differences which would have been appropriate.

TABLE 28 *Differences in dressing frequency between hydrocolloid and gauze dressings*

	Dressing type		Difference (95% CI)	Significance
	Hydrocolloid	Gauze		
Average no. of dressing changes per day[a]	0.43	2.58	2.15 (0.93, 3.37)	$p = 0.01$
Summary statistics				
Number of studies[b]	5	5		
Mean	0.34	2.42		
Median	0.31	2.5		
Minimum	0.24	0.7		
Maximum	0.42	4.1		

[a] *After adjusting for length of study*
[b] *Five studies not common to both groups*

TABLE 29 *Incremental variable costs of hydrocolloid dressings compared with gauze*

Study	Incremental variable cost per patient	1997 £UK[a]
Milward, 1991[102]	–£14 (1990)	17.49
Ohlssen, *et al.*, 1994[72]	45 SEK (1994)	3.19
Meridith & Gray, 1988[100]	–£19 (1988)	27.99
Xakellis & Chrischilles, 1992[55]	$12 (1990)	9.02
Colwell, *et al.*, 1993[54]	$0.65 (1993)	0.46

[a] *Converted using GNP purchasing power parities and inflated using retail prices index*

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