Health Technology Assessment 1999; Vol. 3: No. 17 (Pt 1)

Review

The debridement of chronic wounds: a systematic review

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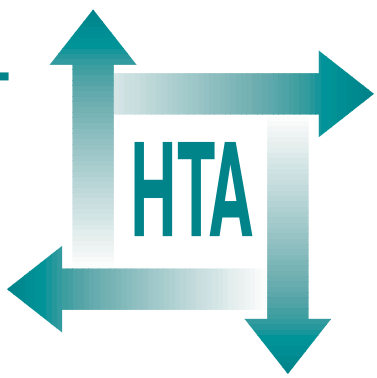
Health Technology Assessment
NHS R&D HTA Programme



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The debridement of chronic wounds: a systematic review

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Competing interests:
none declared

Published September 1999

This report should be referenced as follows:

Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999;**3**(17 Pt 1).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA web site (see overleaf).

NHS R&D HTA Programme

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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.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

Copies of this report can be obtained from:

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Contents

List of abbreviations

C	comparator*
I	intervention*
CI	confidence interval
CRD	Centre for Reviews and Dissemination
ES	effect size
F	female*
HTA	Health Technology Assessment
ITT	intention-to-treat
M	male*
NS	not significant*
OR	odds ratio
RCT	randomised controlled trial
SD	standard deviation*
SEM	standard error of the mean*

* Used only in tables and figures

Executive summary

Background

A wide variety of debridement methods and products are available, all of which have diverse properties, costs and levels of acceptability. There is currently wide variation in their use and a lack of consensus on how to treat specific wound types.

Objectives

- To summarise the evidence for the relative effectiveness and cost-effectiveness of different debriding agents on wound healing.
- To identify areas for future research.

Methods

Data sources

A range of electronic databases and several wound care journals were searched; 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

Studies were considered for inclusion if they were randomised controlled trials (RCTs), published or unpublished, that assessed the effectiveness of a recognised debriding agent as identified by an expert panel, and assessed patients with chronic non-healing wounds (pressure sores, leg ulcers, sinuses and surgical wounds healing by secondary intention). Studies were only included if they used a quantifiable and objective measure of healing rate.

Data synthesis

For each trial an odds ratio and/or effect size was calculated for all objective outcomes. Where possible the analysis was performed on an intention-to-treat basis, and 95% confidence intervals were included when sufficient detail to allow their calculation was provided.

Results

Forty-seven reports describing 35 RCTs were identified that met the inclusion criteria.

Interventions

The following interventions were identified as agents that would be used primarily for wound debridement.

- Dextranomer polysaccharide beads or paste
- Cadexomer iodine polysaccharide beads or paste
- Hydrogels
- Enzymatic agents
- Adhesive zinc oxide tape
- Surgery or sharp debridement
- Larval (maggot) therapy.

Other interventions that are believed to have a debriding function, such as hydrocolloid dressings and antibiotics/antiseptics, were not included in this review as debridement was not the primary reason for their application.

No RCTs were found that evaluated the effectiveness of surgical debridement, larval therapy, or that compared debridement with no debridement.

Dextranomer polysaccharide beads or paste versus traditional or control treatment

Nine trials met the inclusion criteria, five of which found a statistically significant difference between treatments: three favoured dextranomer polysaccharide, and two favoured traditional treatment.

Cadexomer iodine polysaccharide versus traditional or control treatment

Nine trials met the inclusion criteria, of which three had a statistically significant result that favoured cadexomer iodine polysaccharide.

Hydrogels versus traditional or control treatment

Only one trial out of four that compared a hydrogel with a traditional or control treatment found a statistically significant difference between treatments, which suggested a small benefit from treatment with a hydrogel dressing compared with a hydrocolloid dressing.

Enzymatic agents versus traditional or control treatment

None of the five trials in this category showed a statistically significant outcome in favour of either treatment for wound closure. In fact, one trial

showed an increase in wound size with both the enzyme collagenase and the control treatment; however, the increase was significantly less in the enzyme-treated group.

Adhesive zinc oxide tape versus traditional treatment

A single trial meeting the inclusion criteria showed that adhesive zinc oxide tape was more effective in eradicating or reducing by more than 50% the necrotic area of diabetic foot ulcers than a hydrocolloid dressing.

Cadexomer iodine polysaccharide versus other debriding agents

Two trials were comparisons with dextranomer polysaccharide and one trial was a comparison with a hydrogel. None of the trials had statistically significant results.

Dextranomer versus other debriding agents

Four RCTs comparing dextranomer polysaccharide with another debriding agent included two trials with enzyme formulations, namely collagenase and streptokinase/streptodornase, and two trials using a hydrogel as the comparator. Only one of the two comparisons with a hydrogel showed a statistically significant benefit associated with the hydrogel.

Hydrogel versus hydrogel

A single trial was found. There was no statistically significant difference between the two treatments.

Enzymatic agent versus enzymatic agent

One trial that compared the enzyme preparation streptokinase/streptodornase with the enzyme trypsin was included in the review. No statistically significant difference between the two treatments was found.

Cost-effectiveness

Cost-effectiveness has not been thoroughly assessed in studies of debriding agents. The unit cost for each treatment is stated in some studies, and a few contain further details on other important variables, such as nursing time or number of dressing changes. However, no study provides sufficient detail from which a reliable cost-effectiveness analysis can be constructed.

Conclusions

No studies were found that compared debridement with no debridement and without these studies it is unclear whether wound debridement is a beneficial process that expedites healing.

There is insufficient evidence to promote the use of one debriding agent over another. There was only a single comparison between two debriding agents that produced a significant result (hydrogel significantly reduced necrotic wound area compared with dextranomer polysaccharide paste).

Implications for policy

There is little evidence to identify which agents are the most effective. Pending the availability of improved data on relative effectiveness, other considerations, such as cost-minimisation, may reasonably guide decisions on the use of debriding agents.

Recommendations for research

Much of the research is of poor quality, and direct comparisons are few. In the trials reviewed, sample sizes were rarely sufficient to detect clinically important effects, and poor baseline comparability frequently confounded outcome measures. Several important messages can be identified for future studies.

- Recruitment numbers should be based on a sample size calculation.
- The proportion of wounds healed should be used as an objective outcome measure. Where healing rates are based on wound area, both the percentage and absolute change in area should be given.
- Experimental groups should be comparable at baseline.
- Baseline data and intervention details should always include a thorough description of how the patients were nursed and report the use of concurrent treatments, including secondary dressings.
- Comparisons between debriding agents are required and should use agents that are recommended for wounds of a similar nature.
- Assessment should be blind to treatment.
- Survival rate analysis should be adopted for all studies that assess wound healing.
- All RCTs should be published.
- Detailed cost-effectiveness analyses should be seen as a priority for future trials.
- The frequent use of surgical debridement and the increasing interest in larval therapy indicate that RCTs in these areas are needed.

Chapter 1
Introduction

Wound healing is an efficient and natural process that normally requires no special treatment. However, chronic non-healing wounds can occur when there is some underlying factor preventing healing, and in such cases intervention is considered necessary. For example, pressure sores are initially acute wounds caused by ischaemic death of tissue due to excessive pressure and will usually heal readily when pressure is relieved and the blood supply restored. However, in certain patients, particularly the elderly and persons with low mobility, it may not be easy to resolve these causative factors and chronic wounds can develop.

A characteristic of most chronic wounds is an accumulation of devitalised tissue and cellular exudate at the outer surface. These products result from a restriction of nutrients to the damaged epithelium and form either a dry, hard eschar or, as in the case of deep moist wounds, a slough that frequently hardens on the outside with exposure to the air. The accumulation of these products in the wound bed is generally regarded, though not experimentally proven, to prevent or delay granulation and epithelialisation. The removal of this tissue by a process termed debridement is therefore thought to facilitate healing.[1]

Although the clinical evidence in support of debridement is lacking, treatment is regarded as a necessity for patient acceptability and for the prevention of infection:[2] moist slough is malodorous and visually repugnant, and provides an ideal culture medium for pathological organisms. The treatment of infection with topical prophylactic antibiotics is often unsuccessful in sloughy wounds as the active agent is unable to penetrate and diffuse through the necrotic debris. Debridement will remove this barrier and may thereby assist in the treatment of infection.

Although many products used during the treatment of a wound may have a debriding function, only a few are commonly used specifically for this purpose. Despite having diverse properties, costs and levels of acceptability, these specific debriding agents can broadly be classified as mechanical or non-mechanical interventions (*Table 1*).

TABLE 1 *Classification of debriding agents*[2]

Mechanical debridement	Non-mechanical debridement
Surgery (scalpel)	Polysaccharide beads or paste (dextranomer, cadexomer iodine)
Wet-to-dry dressings (saline gauze)	Enzymatic agents (streptokinase/ streptodornase, trypsin, collagenase)
Bio-surgery (maggot larvae)	Hydrogels

Mechanical debridement

Surgical or sharp debridement has been practised for several centuries and is still commonplace today. The technique is simple, requiring only the use of sterile scissors or a scalpel, but it does require some degree of skill to avoid aggravating the wound. It is considered that sharp debridement is best suited to wounds where there is a clear distinction between healthy and devitalised tissue and where a patient is unlikely to experience significant pain.[2]

Bio-surgery, which exploits the feeding behaviour of certain insect larvae, has an equally long medical history and is presently enjoying a resurgence of interest.[3] Sterile maggots (fly larvae) are considered ideal debriders, having a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue.[4] Maggots are placed directly onto the affected area and held in place by a close-net-dressing.[5] These animals may also perform an antimicrobial role that is beneficial for wound healing, as the antibacterial agent allotoxin is actively excreted from the maggot's body.[2] Evidence for clinical effectiveness is restricted to case reports and expert opinion; it remains untested by randomised controlled trials (RCTs).

Wet-to-dry debridement is used infrequently in the UK but is common in many European countries and the USA. The wound is soaked in saline to moisten hard material before the application of a moist gauze pad over the affected area. As the devitalised tissue drys it re-hardens and becomes

attached to the gauze, when the dressing is changed the adhered material is pulled free.[6] This method is less discriminating than those previously discussed, removing both healthy and granulating tissue from the wound bed. Patients are known to experience pain, and newly formed epithelial tissue may be significantly damaged.[7]

Non-mechanical debridement

Non-mechanical techniques have become increasingly popular for wound cleansing. These treatments are usually easy to apply and may have additional properties that are beneficial for wound healing. Such interventions include enzymes, hydrogels and specific chemical formulations, such as cadexomer iodine and dextranomer.

Several different enzyme preparations are available that digest slough and necrotic tissue. In the UK, only the formulation containing streptokinase and streptodornase (Varidase Topical®, Wyeth Laboratories) is licensed for use.[8] This enzyme aggressively digests the proteins fibrin, collagen and elastin which are commonly found in the necrotic exudate of a wound.[9] Other enzymatic debriding agents are available and used internationally; these include trypsin and collagenase.

Dextranomer polysaccharide is supplied as anhydrous, porous beads with a diameter of 0.1–0.3 mm or as a paste. The beads are highly hydrophilic and rapidly absorb exudate from a necrotic sloughy mass. Prostaglandins, hormones and other relatively small molecules enter the matrix of the beads, while larger particles such as bacteria and wound debris become concentrated at the surface of the dextranomer layer. When the beads are changed by washing with saline the absorbed and trapped necrotic material is removed.[10]

Cadexomer iodine is similar to dextranomer, consisting of small spherical beads that are hydrophilic in nature. The beads are made from a modified starch infused with iodine at a concentration of 0.9%. Absorption of fluid from the wound results in a slow controlled displacement of iodine from the matrix, which acts as a bactericidal agent.[10] The slow and consistent release of iodine overcomes the problem of iodine inactivation by protein absorption in the wound. The antibacterial property, biodegradability and high rate of fluid absorption distinguish cadexomer iodine from dextranomer.

Hydrogels are a group of agents that were primarily developed as debriding agents. These gels are biologically inert and have a significant water content. They complement the body's natural debriding process by providing an advantageous environment for autolysis, while still acting to preserve living healthy tissue.[2] The hydrogel is usually applied directly into the wound bed and held in place by a non-adherent dressing. Once the gel is fully hydrated it is unable to absorb the copious quantities of exudate that are released by some wounds. For this reason hydrogels are often used in conjunction with a highly absorbent dressing. In addition to the amorphous gel, hydrogels are also available in a sheet form. Several types of hydrogel are available manufactured under different trade names (Intrasite® Gel, Smith & Nephew Healthcare Ltd; Sterigel®, Seton Healthcare Group plc; Granugel®, CovaTec UK Ltd).

In clinical practice there is wide variation in the use of debriding agents and no consensus on which agent is most appropriate for each type of wound.[11] As a result, many clinicians combine debriding agents in a dual or triple therapy in an attempt to maximise healing rates, but such measures are untested and are not endorsed by manufacturers. This review, commissioned by the NHS Health Technology Assessment (HTA) Programme, attempts to summarise the evidence to date for the relative effectiveness and cost-effectiveness of these different interventions and to identify the gaps in our research knowledge. In this way it is hoped that clinical practice may better reflect the results of scientific research.

Chapter 2
Methods

Literature search

A systematic review of primary research was undertaken using the NHS Centre for Reviews and Dissemination (CRD) structured guidelines.[12] Nineteen electronic databases of medical literature were searched up to October 1997 using a sensitive search strategy designed in collaboration with an information specialist in CRD (appendices 1–3). This was supplemented by a handsearch of five specialist wound care journals, twelve conference proceedings and 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 4). Relevant economic studies 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 trial-based economic evaluations.

Study selection and data extraction

Retrieved studies were assessed by a single reviewer for relevance to this review, and decisions on final inclusion were checked by a second reviewer; disagreements were resolved through discussion. Trials, irrespective of date, language and publication status, were included if they were human-based RCTs, which evaluated the efficacy of a recognised debriding 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.

Many treatments commonly used in wound management may have a debriding function; only a few, however, are specifically used for this purpose. An expert panel was consulted to identify those treatments that they believed were primarily used for debridement. The panel identified the following interventions as debriding agents: dextranomer polysaccharide, cadexomer iodine polysaccharide, hydrogels, various enzymatic agents, adhesive zinc oxide tape, surgery and larval therapy. Other interventions such as hydrocolloid dressings and antibiotics/antiseptics were not considered by the panel to be debriding agents as debridement may occur only as a secondary function following their application rather than being the primary reason for their use.

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

Data synthesis

For each trial an odds ratio (OR) and/or effect size (ES) was calculated for all objective outcomes. Where possible the analysis was performed on an intention-to-treat (ITT) basis and 95% confidence intervals (CIs) were included when sufficient detail to allow their calculation was provided. The results from each study were plotted onto graphs, and individual study details are presented in structured tables containing information relevant to study validity. Heterogeneity between studies indicated that pooling of results would be inappropriate. Studies varied in duration of follow-up, nature of the comparator treatment, wound types, setting and baseline comparability of patient groups.

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 these measurements.

Most subjective outcomes, such as estimates of oedema, erythema, granulation, pus and debris, are unlikely to be measured consistently between wounds. Unless assessment is blinded to treatment allocation, subjective outcomes are likely to result in significant biases. For example, in one trial cadexomer iodine was judged by visual assessment to be more effective than dextranomer, but a later

assessment of quantitative planimetric results indicated that there was no difference between the two treatments.[13] This appears to be a characteristic feature of research in this area; subjective measurements almost invariably overestimate the relative effectiveness of the experimental treatment compared with objective measures in the same trial.

Objective measures of debridement are usually based on wound area. Planimetry, often aided by computer assessment, is the most frequently used tool for calculating wound area, though other methods, such as the measurement of wound diameter or the weight of a celluloid 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 sufficiently demonstrated.[14] 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.[15]

However, 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 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 2*.

In large trials, random allocation should ensure that the mean wound size and variance in each group are 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 3*.

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

The change in area of a wound also assumes a linear rate of healing or at least a predictable rate. However, this may not always be the case, with some wounds enlarging prior to healing while others initially decrease rapidly in size before experiencing a slower rate of healing. For this reason complete healing is seen as the most valuable outcome in studies of wound healing. Unfortunately, to follow all wounds to complete healing can require an extended period of follow-up that is not ideal for most studies, where financial resources and time are limited. For this reason many studies

TABLE 2 *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 3 *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

in the literature report changes in wound size rather than complete healing.

Despite the potential for the objective outcomes discussed to be biased by differences in wound size at baseline or by the variability of healing rate between wounds, they remain the most reliable assessment of wound healing as they reduce the bias of the assessor, which cannot be estimated.

Chapter 3
Results

A total of 47 RCTs met the review inclusion criteria. Twelve studies (26%) had a shared data set with another publication, and of these: two contained interim results later published in full,[16,17] three were reproduced as papers presented at international conferences,[18–20] one was presented at an international conference and later published as a drug company bulletin,[21] six studies were repeat publications of results previously published in other journals,[22–27] two of which[22,23] were identical to a previously published paper,[28] except for a change in the first author. Where duplication occurred and sufficient detail could not be extracted from a single publication, the studies were pooled and incorporated to represent a single trial entry. In total, 35 individual trials from the 47 relevant publications were identified for inclusion.

The majority of trials had methodological weaknesses (appendix 5, *Table 4*). Fewer than 10% of studies reported an *a priori* estimate of the number of participants required to have sufficient power to detect a clinically important effect as statistically significant. It was rare for a trial to have more than 50 patients in each arm, and typically fewer than 30 were included. Twenty-six per cent reported that the outcome had been assessed by someone blind to treatment allocation. Appropriate patient characteristics were recorded by treatment group in 90% of studies, but ulcer size at baseline was reported in only 62%. Withdrawals occurred in most trials and were recorded by group and cause in 72% of trials where it was appropriate, but less than one fifth performed an ITT analysis. Seventy-four per cent of trials clearly stated the inclusion criteria for patients to the trial, but information that indicated whether or not that participants had been truly randomised to alternative treatments was given in only 37%.

Figures 1–7 show the OR and/or ES calculated from the results for each of the included studies. Where possible, ITT analysis has been used; where such analysis was inappropriate the sample size used in the calculation is given in parentheses.

Debriding agents versus traditional or control therapy

Twenty-eight trials compared a recognised debriding agent with a traditional or control therapy. The definition and nature of traditional therapy varied widely between trials. In many trials, a single traditional treatment was not used in the comparative group, in extreme cases a different treatment regimen was used for each patient in the control group. The absence of a single standard comparator makes interpretation of the results across studies difficult.

Dextranomer polysaccharide versus traditional or control treatment

Nine RCTs met the inclusion criteria (*Figure 1;* appendix 6, *Table 5*). Four trials showed a statistically significant result, three of which favoured treatment with dextranomer polysaccharide,[29–31] and one which favoured treatment with calcium alginate dressings.[32] In an additional trial, the author's own statistical analysis indicated a significant improvement for those wounds treated with a collagen sponge dressing when compared with dextranomer.[33] However, insufficient data were available to test the analysis further. The remaining four trials had statistically insignificant results.[34–37]

Trials of dextranomer polysaccharide versus traditional or control treatment can be grouped into categories which are defined by the nature of the comparative therapy.

Dextranomer polysaccharide versus Eusol

Two small studies compared dextranomer polysaccharide with Eusol; both were unable to detect a statistical difference between the treatments.[35,36] The study by Nasar and Morley[36] was confounded by the switching of treatment for three wounds that were considered to be healing slowly from the Eusol group to the dextranomer group. These patients were excluded from the analysis because of the bias that was hence introduced. In this same study, the cost of materials for average treatment time was calculated, and showed that Eusol was 1.6 times more costly than dextranomer.

Dextranomer polysaccharide versus saline soaks

Saline soaks were evaluated against dextranomer polysaccharide in two trials, which were both conducted over a 2-week period.[31,34]

The trial by Eriksson and co-workers[34] found no statistically significant difference between the treatments for the percentage of ulcers healed by 50% or 25%. The trial by Sawyer and co-workers,[31] however, found a statistically significant effect in favour of dextranomer beads for the healing of venous leg ulcers. Despite the absence of baseline data in this latter trial it is unlikely that such a large difference in healing rates between the two treatments could be explained merely in terms of poor group matching at baseline.

Dextranomer polysaccharide versus other traditional or control therapies

One study found that dextranomer polysaccharide beads were significantly more effective than povidone-iodine for the treatment of venous leg ulcers.[29] However, high dropout rates were reported, which could have introduced a bias. Dextranomer polysaccharide beads have also been found to be more effective when compared with antiseptic/antibiotic treatments.[30] This is in contrast to a small study comparing dextranomer polysaccharide beads with an air dried combination of sugar and egg white, which did not find a statistically significant difference between the two treatments.[37]

Dextranomer polysaccharide paste was outperformed by calcium alginate dressings for the healing of pressure sores over an 8-week period.[32] These results were statistically significant despite a bias that favoured the smaller sores in the dextranomer polysaccharide group.

Insufficient data were provided to determine the CIs required to test statistical significance in a study that compared dextranomer beads with a collagen sponge dressing.[33] However, the author's own analysis suggested a statistically significant reduction in healing time occurred with the collagen sponge dressings.

Cadexomer iodine polysaccharide versus traditional or control treatment

Nine RCTs compared cadexomer iodine polysaccharide with a traditional or control therapy (*Figure 2*; appendix 6, *Table 6*). Three trials (five papers) had a statistically significant result favouring treatment with cadexomer iodine polysaccharide when compared with hydrogen peroxide and zinc paste,[38] hydrogen peroxide or potassium permanganate,[22,23,28] and mechanical debridement by wet-to-dry dressings.[39] However, high withdrawal rates[22,23,28] and inappropriate movement of some patients between groups during the trial[39] may have introduced confounding factors, which would have implications for the validity of these results.

In two trials the authors own statistical analysis indicated that cadexomer iodine resulted in a significant reduction in wound size when compared to traditional dressing regimes.[40,41] However, in both studies the papers provided insufficient information for CIs to be calculated which prevented further analysis in this review.

The remaining trials comparing a traditional treatment with cadexomer iodine polysaccharide were unable to detect a statistically significant effect in favour of either treatment.[42–45] This may have been a consequence of small sample size or a reflection of the diversity of traditional therapies evaluated in a single trial. In one trial, 12 of the 13 patients in the traditional group were treated with a variant on the basic standard therapy.[41]

Hydrogels versus traditional or control treatment

Four trials were included that compared a hydrogel with a traditional or control treatment (*Figure 3*; appendix 6, *Table 7*).[46–49] Only one of these trials showed a statistically significant difference between treatments. In this comparison a hydrogel dressing showed a small improvement in the number of wounds healed when compared with a hydrocolloid dressing.[46]

Enzyme treatments versus traditional or control treatment

Only one of the five trials included in the review showed a statistically significant difference between an enzymatic debriding agent (collagenase) and a control treatment (*Figure 4*; appendix 6, *Table 8*).[50] However, the wounds in this trial actually increased in size and the predicted bias was in the direction of enzymatic treatment. Despite the majority of trials showing a trend in favour of enzyme treatment, statistical significance could not be demonstrated. All the trials in this category suffered from small sample size;[9,37,51,52] only one of the included studies had more than 15 patients in each arm.[52]

Adhesive zinc oxide tape versus traditional treatment

In a single trial an adhesive zinc oxide tape was compared with a hydrocolloid dressing for the treatment of necrotic diabetic foot ulcers (appendix 6, *Table 9*).[53] The adhesive zinc oxide tape was more effective in eradicating or reducing necrotic area than the hydrocolloid dressing (OR = 4.44; 95% CI: 1.34, 14.70). Treatment was discontinued in nine patients (four from the adhesive zinc oxide tape group and five from the hydrocolloid dressing group) due to a significant increase in necrotic area (> 100%). Common adverse effects seen in both groups were maceration of skin edges, pain and oedema.

Comparisons between debriding agents

Nine trials were identified that directly compared two debriding agents. Seven trials compared either dextranomer polysaccharide or cadexomer iodine polysaccharide with another debriding agent, one trial compared two enzyme treatments, and a further trial was a comparison between hydrogels.

Cadexomer iodine polysaccharide versus other debriding agents

Three RCTs were included that compared cadexomer iodine polysaccharide with another debriding agent (*Figure 5*; appendix 6, *Table 10*). Dextranomer polysaccharide[13,54] was the comparator in two trials and a hydrogel was used in the third trial.[55] None of the trials showed a statistically significant effect, and in two the point estimate of relative effectiveness was close to the line of no effect.[13,55]

Dextranomer polysaccharide versus other debriding agents

Four RCTs were included that compared dextranomer polysaccharide with another debriding agent (*Figure 6*; appendix 6, *Table 11*). Two trials were comparisons with enzyme formulations (collagenase or streptokinase/streptodornase), and two were comparisons with a hydrogel.

Both hydrogel trials attempted to record debridement directly by employing an outcome measure based on wound cleansing (the reduction in area of necrotic tissue covering the wound bed).[56,57] The study by Colin and co-workers[56] failed to find a statistically significant effect for 100% cleansing. However, the smaller study by Thomas and Fear[57] found a large statistically significant effect in favour of the hydrogel. Although the treatments used in both studies appear to have been similar, it is likely that the formulation of Intrasite used by Colin was a modification of that employed by Thomas and Fear. Interestingly, in the latter study, treatment was continued beyond the 14-day follow-up period in a selected group of patients. After 28 days, a further four wounds were fully cleansed in the dextranomer polysaccharide group, compared with no additional successes in the hydrogel group. This may suggest that over a longer period the results in this trial would have reflected those reported by Colin and co-workers.

A non-significant benefit was found in favour of dextranomer polysaccharide when compared with the enzyme collagenase, this benefit was recorded against the direction of wound size bias.[37] In the only other trial to compare dextranomer polysaccharide with an enzyme preparation (streptokinase/streptodornase), no difference between the treatments was found.[58]

Hydrogel versus hydrogel

Only one study made a direct comparison between two hydrogels (Intrasite Gel and Granugel) (*Figure 7*; appendix 6, *Table 12*).[59] This trial found no statistically significant difference between the groups after 21 days treatment. The total cost for treatment per person from baseline to final assessment was calculated to be £43.25 for Granugel and £40.25 for Intrasite, while the average cost per 10 cm^2 reduction in area was £8.59 and £13.38, respectively. The data appear to indicate that treatment with Granugel may be more cost-effective than with Intrasite. However, this is misleading as the analysis is based on absolute changes in ulcer size. The Granugel group had larger ulcers at baseline, suggesting that this group was more likely to experience larger changes in absolute ulcer area.

Enzyme versus enzyme

Only one RCT directly compared two enzymatic agents (*Figure 8*; appendix 6, *Table 13*).[60] No statistically significant difference was found between wounds treated with streptokinase/streptodornase and those treated with trypsin.

Cost-effectiveness

Cost-effectiveness has not been thoroughly assessed in studies of debriding agents. The unit cost for each treatment is stated in some studies, and a few contain further details on other important variables, such as nursing time or number of dressing changes. However, no study provides sufficient detail for a reliable cost-effectiveness analysis to be constructed.

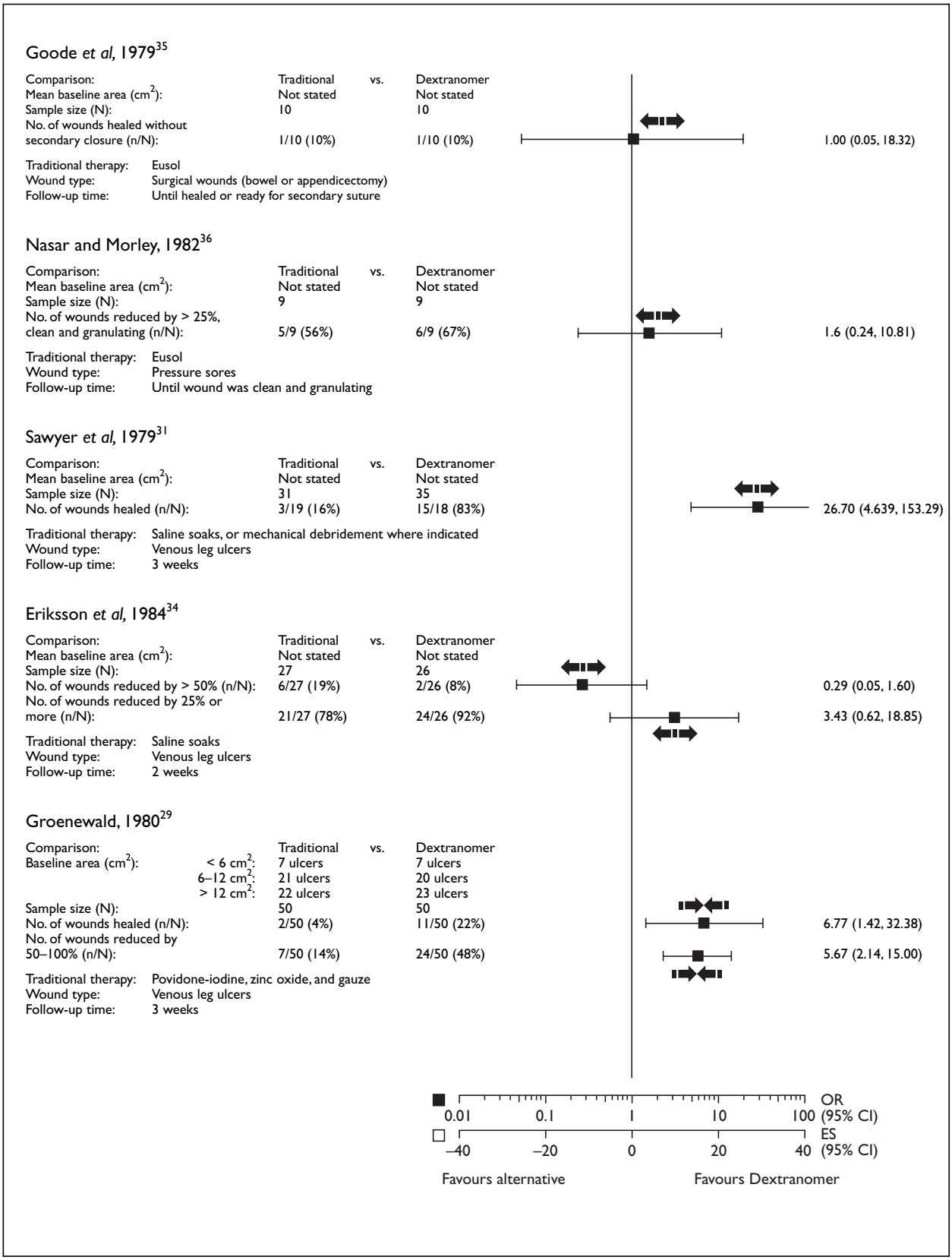

FIGURE 1 *Dextranomer polysaccharide compared with traditional or control treatments. Study results are presented as OR and/or ES enclosed by their 95% CI. An arrow by a trial indicates that the results were biased by poor comparability between groups for wound size at baseline; the direction of the arrow suggests which intervention was favoured by this 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*

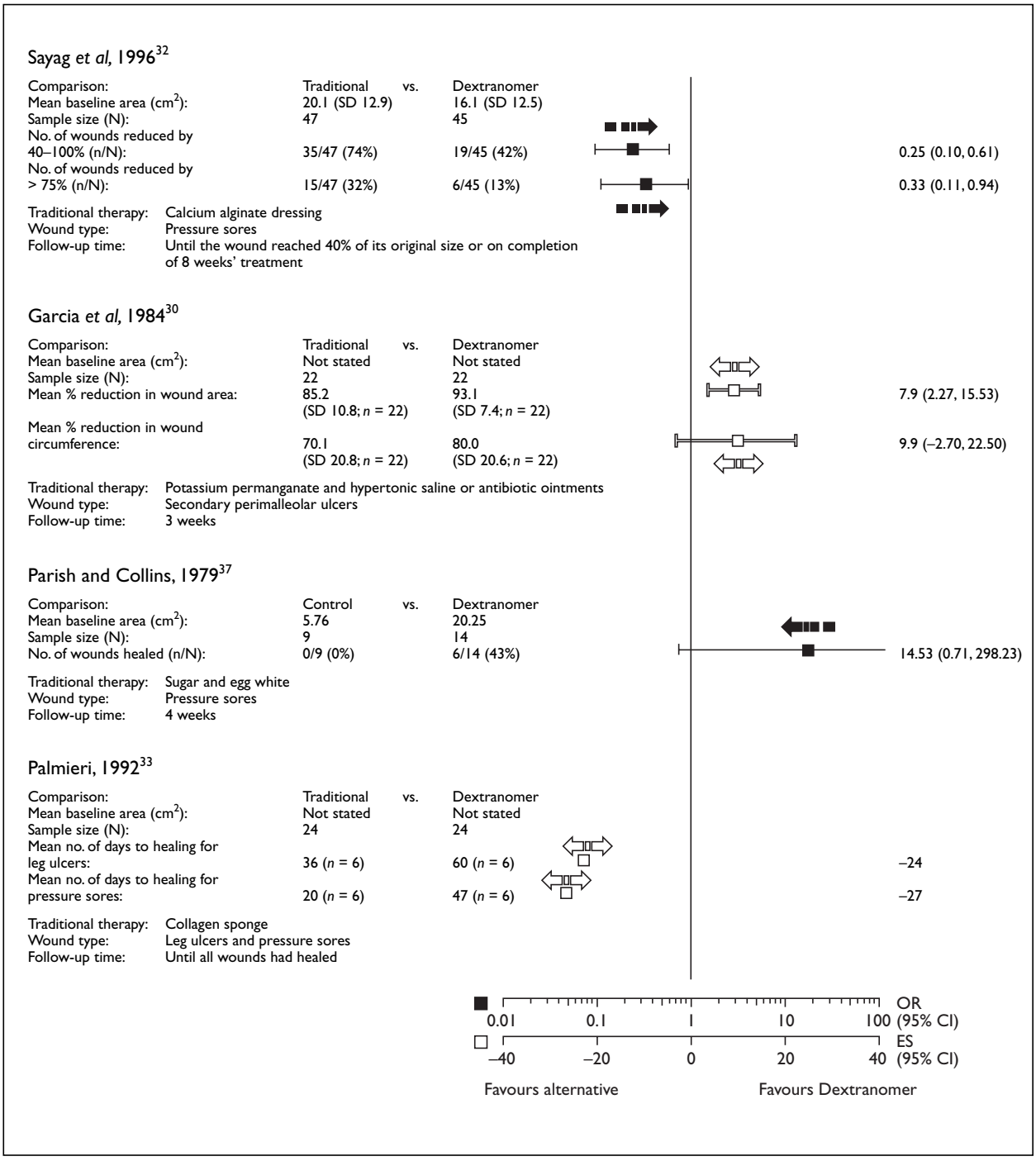

FIGURE 1 contd *Dextranomer polysaccharide compared with traditional or control treatments. Study results are presented as OR and/or ES enclosed by their 95% CI. An arrow by a trial indicates that the results were biased by poor comparability between groups for wound size at baseline; the direction of the arrow suggests which intervention was favoured by this 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*

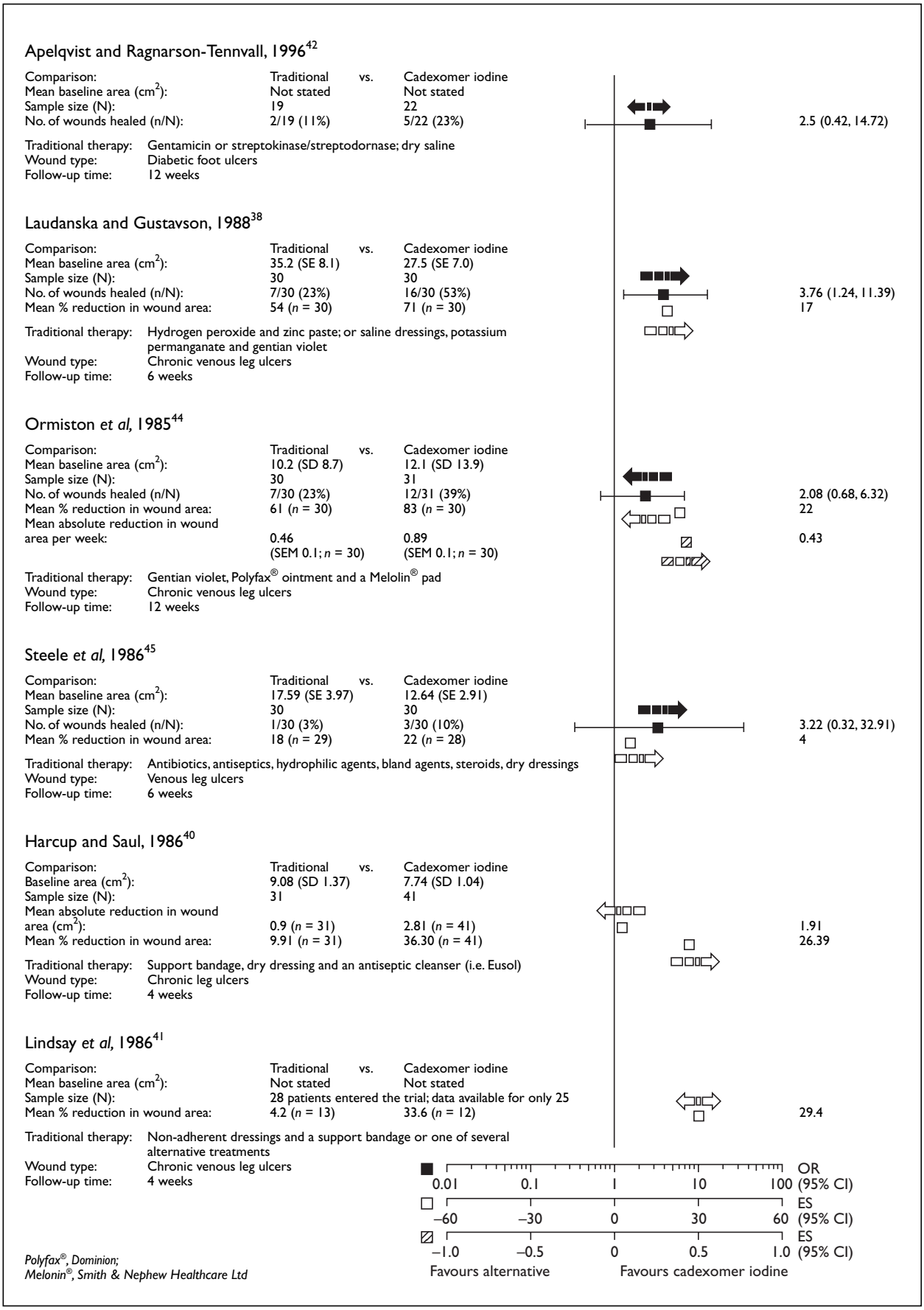

FIGURE 2 *Cadexomer iodine polysaccharide compared with traditional or control treatments*

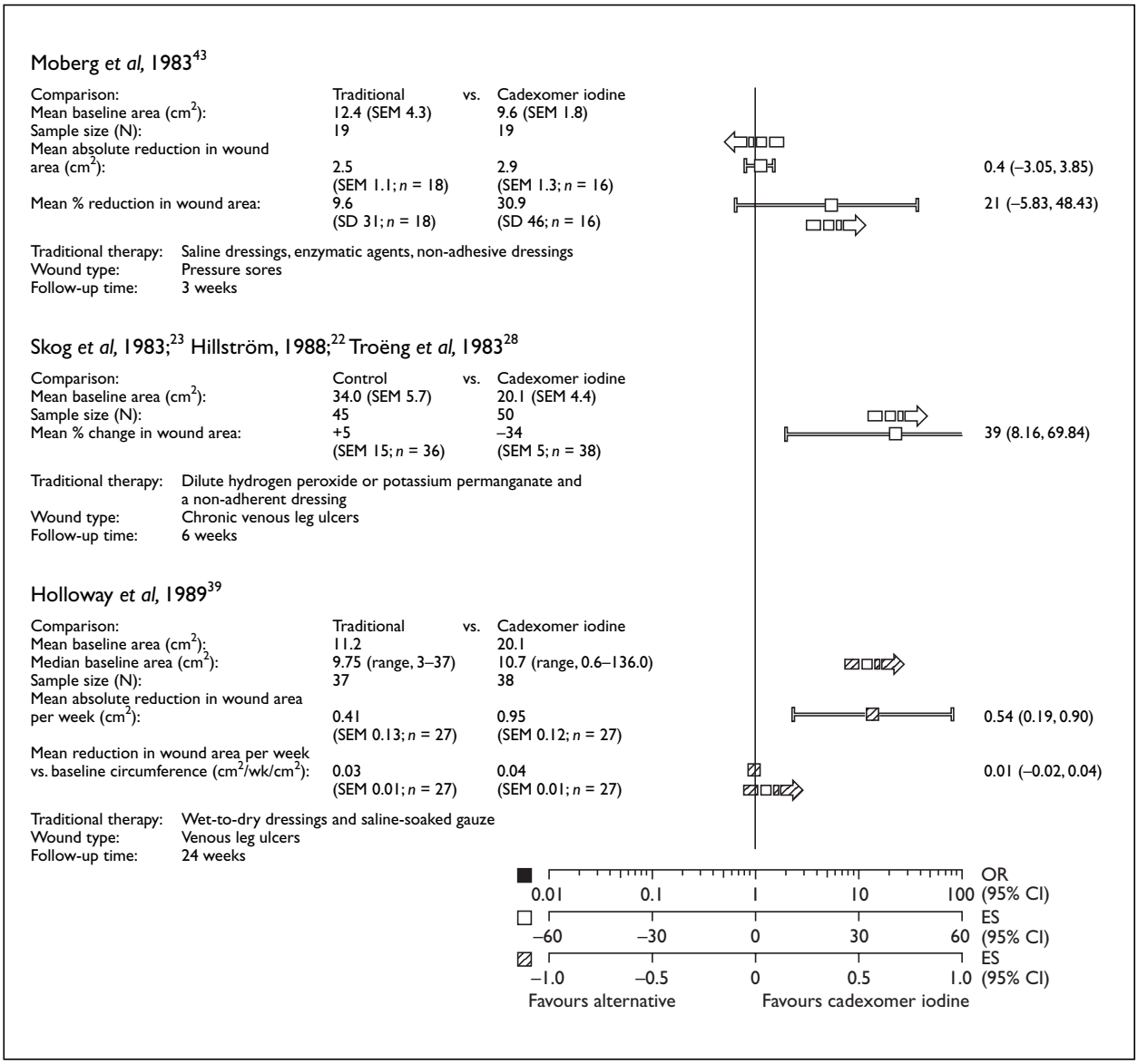

FIGURE 2 contd *Cadexomer iodine polysaccharide compared with traditional or control treatments*

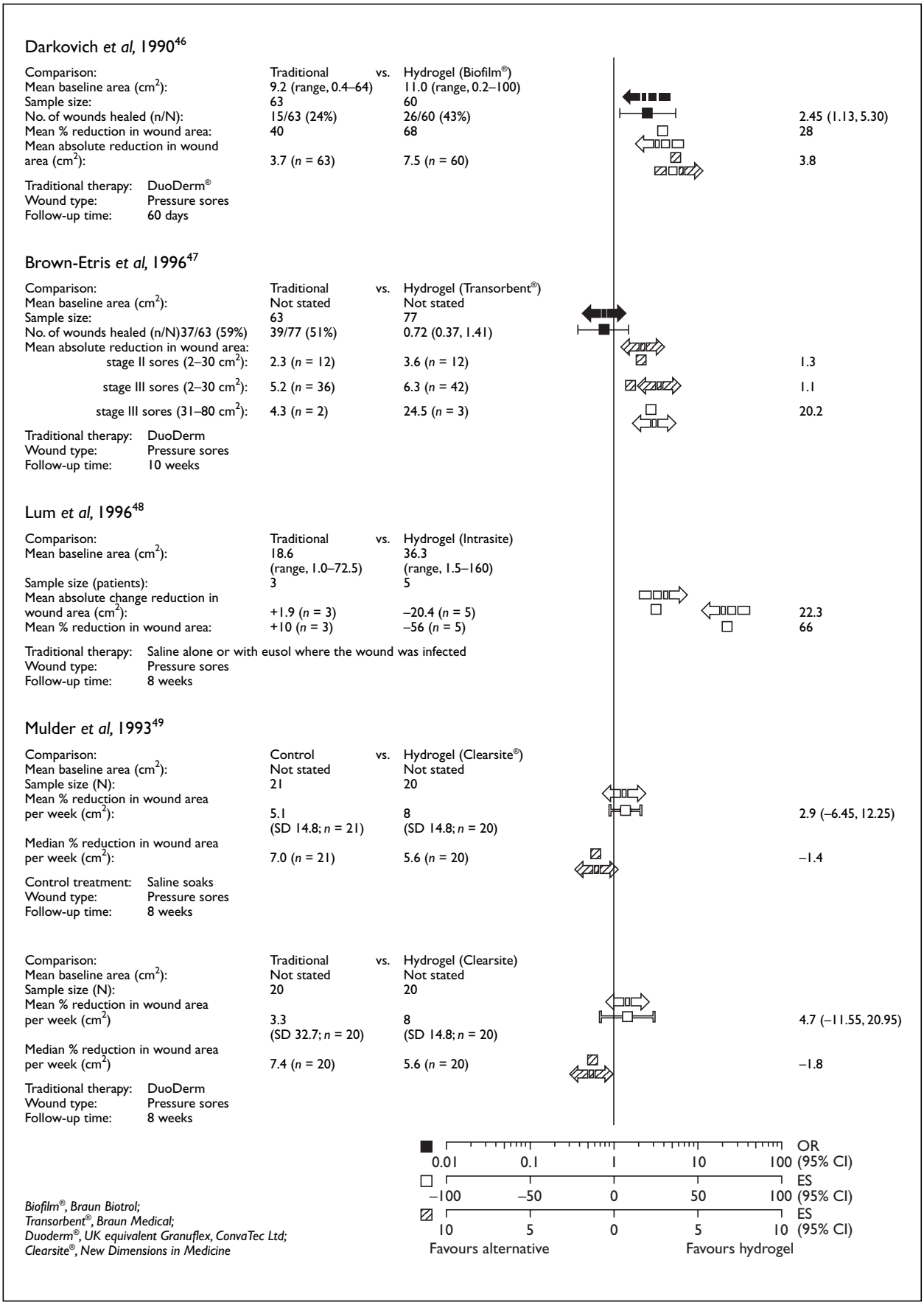

FIGURE 3 *Hydrogels compared with traditional or control treatments*

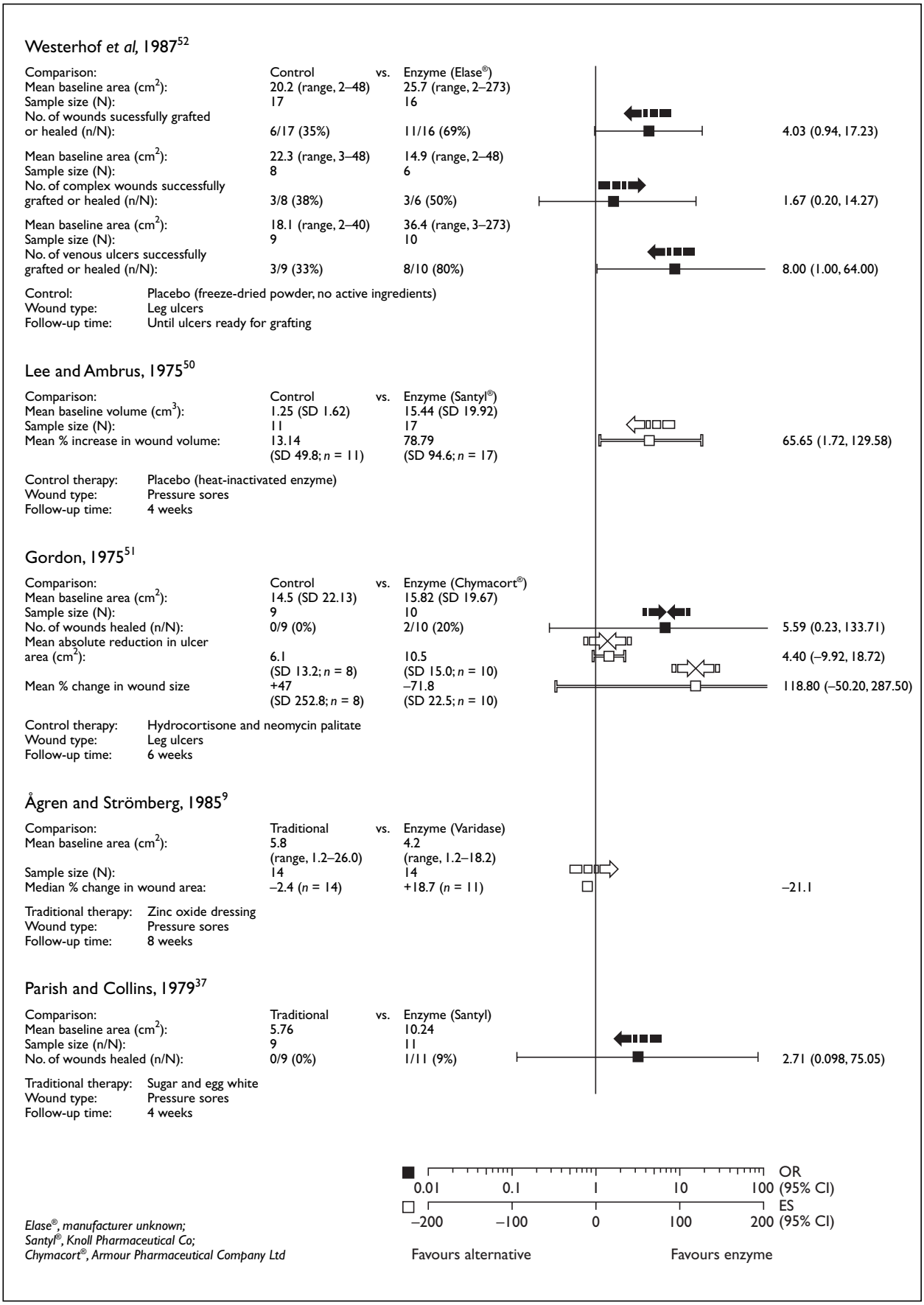

FIGURE 4 *Enzymatic agents compared with traditional or control treatments*

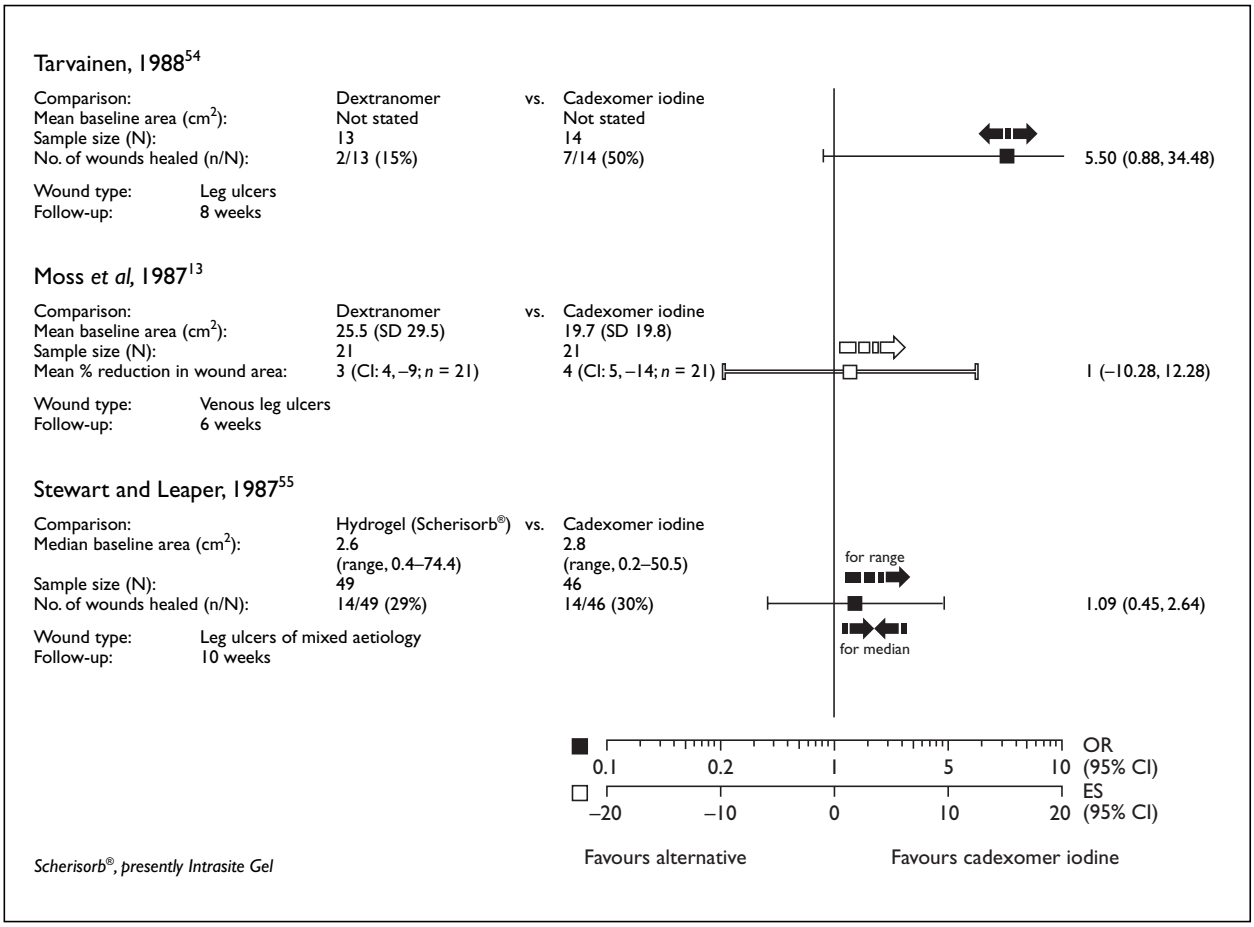

FIGURE 5 *Cadexomer iodine polysaccharide compared with other debriding agents*

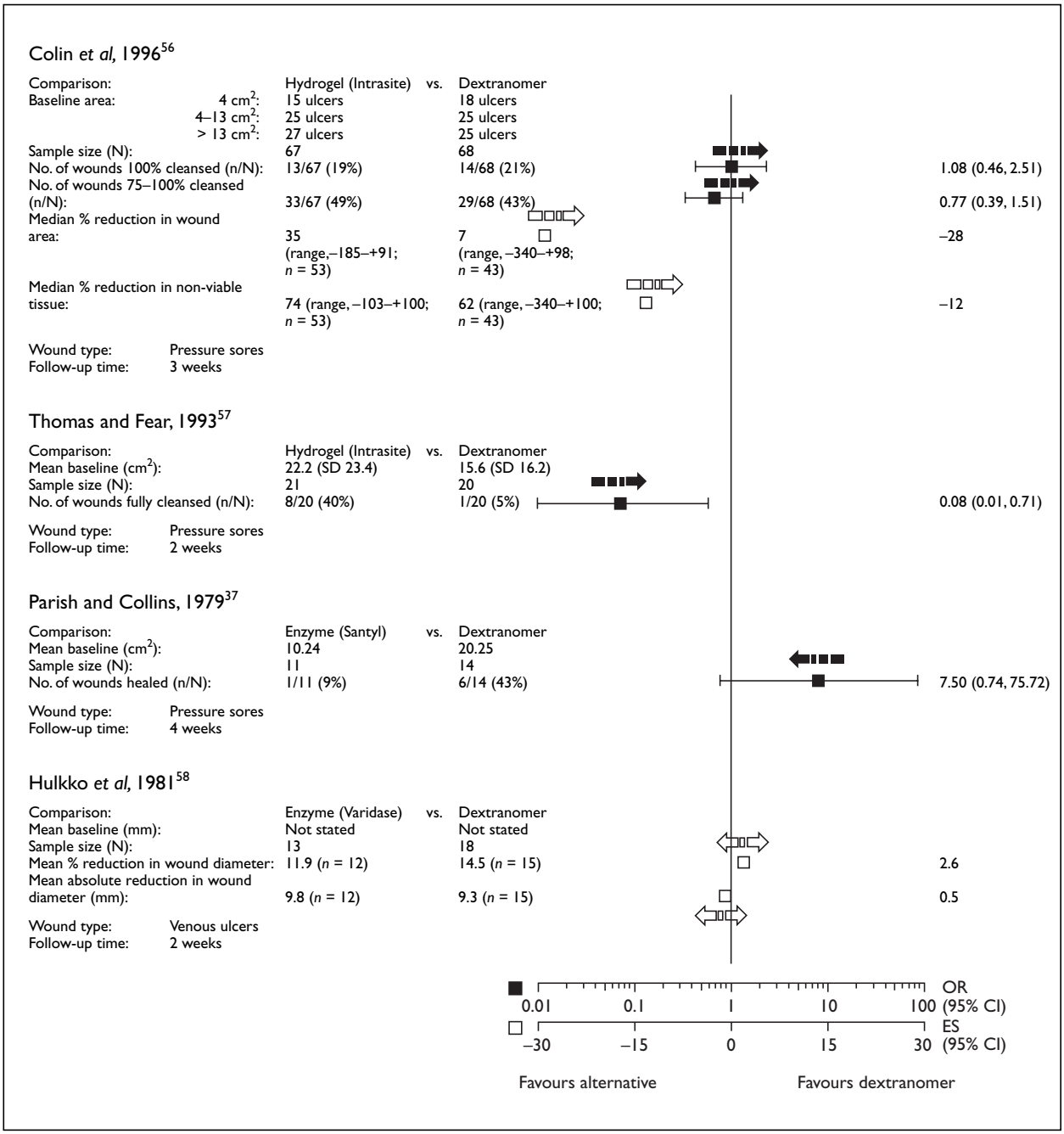

FIGURE 6 *Dextranomer polysaccharide compared with other debriding agents*

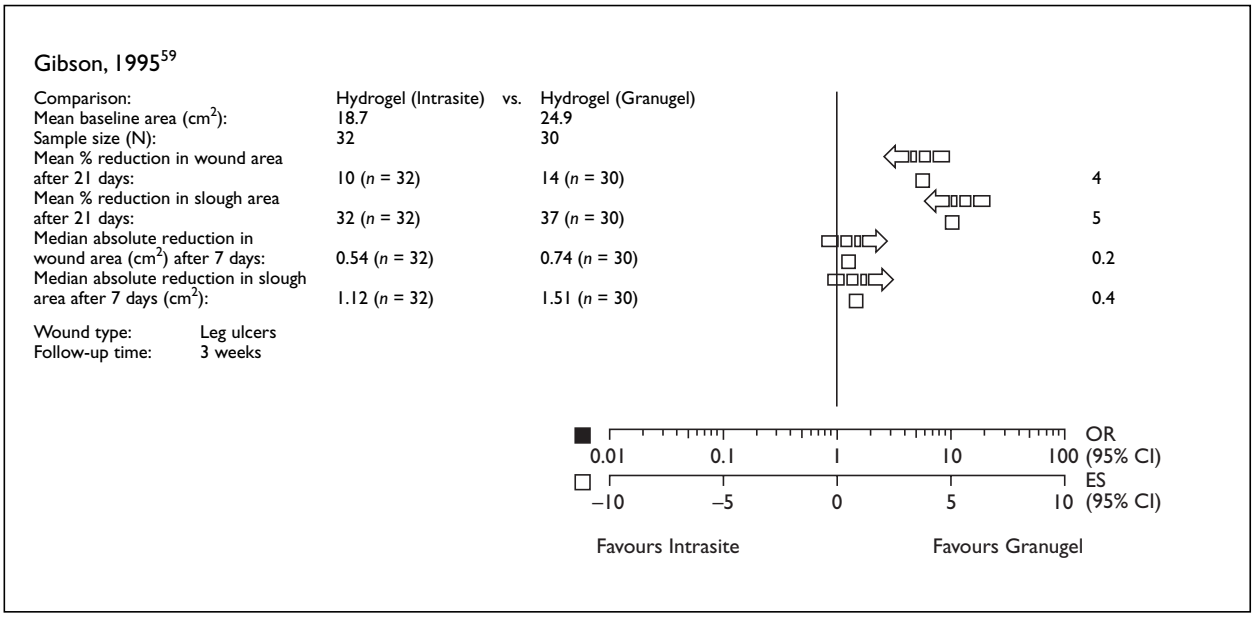

FIGURE 7 *Comparison between hydrogels*

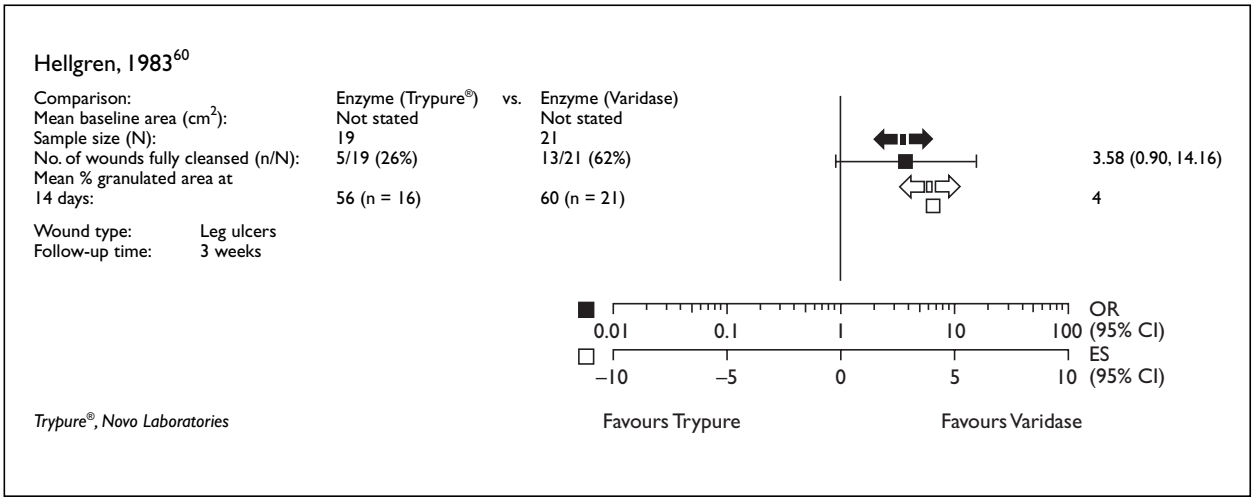

FIGURE 8 *Comparison between enzyme treatments*

Chapter 4
Discussion

There are no RCTs comparing debridement with no debridement. A limited number of trials have employed an inert or placebo comparison, but the extent to which even secondary dressings contribute to wound healing is unclear. Given the multi-faceted way that topical debriding agents are thought to work, the obvious study to answer the question of whether debridement is a necessity for wound healing would be a comparative evaluation of surgical, or sharp debridement with no debridement.

The majority of trials investigated debridement of either pressure sores or venous ulcers and for these wounds the debriding agent generally showed a benefit over traditional or control treatments. However, without conclusive evidence that debridement is an important procedure for wound healing, it is not possible to determine whether the benefit over traditional treatment is a true assessment of effectiveness, or a consequence of harm induced by the traditional therapies.

Although evidence in the form of RCTs is lacking, many clinicians believe that debridement facilitates wound closure by removing necrotic tissue that acts as a barrier to new tissue growth. This suggests that if debridement really does aid wound closure then the effectiveness of a debriding agent should be measured by an outcome based on wound healing. Even though the debriding agent is not necessarily used throughout the entire healing process an outcome measure based on healing remains valid as long as both comparison groups follow a similar schedule of nursing care after the debridement period. In this way, any difference in healing rates between groups can be attributed to the debriding agent used. Some researchers however, have attempted to estimate the effectiveness of these agents by measuring the degree of debridement expressed as the percentage area of wound covered in necrotic material. This measurement may not be a reliable indication of treatment effect as the extent of debridement does not appear to have been scientifically validated as a surrogate or proxy measure of wound healing.

The results reported in many of the included studies are biased by a lack of comparability between the groups for wound size at baseline. The underlying bias is frequently in the direction of the treatment effect, suggesting that the study results should be viewed cautiously. A statistically significant study result favouring one treatment over another 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. When baseline data are not given for wound size it is not possible to estimate the degree of bias, and in the absence of other indicators, validity of the trial result should be considered doubtful.

Analysis of studies where patients received a traditional or control therapy in the comparison arm indicates that the validity of the outcome measure, according to baseline comparability, was doubtful in about 70% of the trials. In the remaining 30%, where wound size bias was unlikely to have affected the outcome measure, the OR or ES was in the direction of the debriding agent in over 88% of cases, though only two studies obtained statistical significance. In other words those studies with the most reliable results indicate that treatment with a known debriding agent is favourable to traditional or control therapy.

Analysis by intervention type suggests that both dextranomer polysaccharide and cadexomer iodine polysaccharide may improve wound healing when compared with a traditional or control therapy. However, evidence for the use of hydrogels or enzymatic agents in preference to traditional or control treatment is less convincing as, with the exception of one trial,[46] these debriding agents did not show a statistically significant improvement in wound closure. The lack of evidence for the effectiveness of enzymatic agents suggests that careful consideration should be given to the continued use of streptokinase/streptodornase, given that its topical application is known to induce the production of anti-streptokinase antibodies, which could theoretically put patients at risk if given streptokinase immediately following a myocardial infarction.[61]

In drawing these conclusions on effectiveness it is necessary to bear in mind that many of the traditional treatments employed as comparators

are no longer used in clinical practice, and some may even have a detrimental effect on healing. This implies that relative effectiveness, as recorded in many of the trials, may be an over-estimate of what we might expect to obtain in a similar trial today.

Recently, there have been several non-systematic narrative reviews in nursing-orientated publications, which have suggested that hydrogels are the non-mechanical debridement agent of choice.[2,62] In terms of scientific evidence, such a statement can only be supported by trials that directly compare two or more debriding agents; such trials, however, are relatively rare in the literature and are generally of poor quality. Using the criteria previously described, around 40% of comparisons between debriding agents had a valid result, but only one trial found a statistically significant difference between treatments.[57] The small number of reliable trials and the diversity of comparisons implies that there is insufficient evidence to promote the use of one debriding agent over another on the basis of effectiveness alone.

In wound care research it is not uncommon for trials to be associated with funding from the pharmaceutical industry. This may in part explain the lack of direct comparisons between different, commercially important debriding agents. A pharmaceutical company is unlikely to be willing to compare its product with that of a competitor if the product has only shown marginal benefits over traditional or control treatments.

A pooled estimate of effectiveness for each debriding agent has not been calculated; to do so would be inappropriate considering the heterogeneous nature of the studies and the potential biases due to differences in wound size at baseline. Pooling would compound these biases and result in an over-estimate of effectiveness, particularly considering the likely influence of publication bias favouring positive outcomes. If similar trials reported both absolute and percentage reductions in ulcer size then a pooled estimate could be calculated for each of the outcomes, which would provide a reasonable estimate of effectiveness. Unfortunately, this is rarely the case and where sufficient details are provided there are other differences between studies, such as wound type, follow-up time, the presence of other underlying conditions such as ischaemia, and the variability of traditional treatments within a single comparison group which make combining results inappropriate.

A multiplicity of traditional therapies are frequently employed in the same trial to act as a comparator with a single debriding agent. Although it could be argued that this reflects typical clinical practice it makes interpretation of the results very difficult. It is likely that within such a varied group of traditional treatments there will be considerable variation in effectiveness. It is possible also that one of these treatments may be equally, if not more effective, than the debriding agent under evaluation, but that its beneficial effect is masked by the other less effective treatments within the group. It is also possible that treatment care may vary depending on the care givers familiarity with each of the traditional treatments employed. This is less likely to be an issue in the application of a homogeneous debriding agent.

Different debriding agents may be more appropriate for different types of wound because the mode of action employed by each agent to facilitate wound healing differs. For example, two studies compared the same hydrogel with dextranomer polysaccharide for the treatment of pressure sores.[56,57] Dextranomer polysaccharide is thought to actively absorb water and necrotic material from the wound bed, whereas the hydrogel is believed to liquefy the wound and maintain a moist environment that facilitates auto-debridement.[57] Clearly these two agents work in very different ways and their effectiveness is likely to depend on the type of wound to which they are applied. Dextranomer polysaccharide is then recommended for the treatment of moist, yellow sloughy wounds, while a hydrogel, although a generalist agent, is recommended particularly for dry necrotic wounds.[10] Comparisons between debriding agents should then take into account the local nature of the wound under examination when assessing effectiveness.

The categories used in this review to group debridement interventions could be misleading because they may mask pharmaceutical developments. For example, the formulation of Intrasite Gel has changed over time, and that used in a trial in the late 1980s is unlikely to be the same as that used in the early 1990s. The vehicle used for a treatment may also vary. For example, dextranomer polysaccharide can be applied as either beads or as a paste with polyethylene glycol, and the nature of this vehicle may have consequences for effectiveness. Considering all dextranomer polysaccharide trials together does not take into account these potential differences. However, only by grouping these interventions under broad categories can a general overview of effectiveness be gained, and as the data are not statistically pooled erroneous interpretations are avoided. In addition, both

clinicians and patients alike are primarily concerned with whether a treatment works rather than its mode of action. If the subtle differences identified between products in the laboratory do not translate into improved wound healing rates in clinical practice, then there is little benefit in discussing differences in product formulation.

Quality assessment indicates that most studies included in the review have methodological flaws that affect their validity. In general, the RCTs are too small to ensure that wounds of different sizes are equally allocated to both experimental groups. This suggests that most trials will be subject to a bias at baseline. Most trials had a short follow-up, which mitigates against the outcome of the number of wounds healed. Studies that employ such an outcome measure should analyse the data using 'survival analysis', which takes into account both whether and when a wound healed; in this way it is a more efficient method for estimating the rate of healing. Many of the studies also excluded sick, debilitated or confused patients and those with diseases that affect healing, such as diabetes and rheumatoid arthritis. These are the very patients whose wounds tend to be chronic and are therefore the most likely to be prescribed debriding agents in practice. In general then, the patients enrolled into a trial are a highly selected group and are unlikely to be representative of the those encountered in clinical practice.

Subjective outcome measures such as degrees of oedema, erythema, granulation, pus and debris are frequently recorded by authors, but are not considered in this review. These outcomes are more susceptible to bias as the assessor may have an unconscious preference for one of the treatments. Analysis of subjective outcomes nearly always produced a statistically significant result in favour of the experimental treatment. Similarly, other variables that are likely to influence treatment choice such as pain, comfort and quality of life issues, are not addressed in this review because the outcome measures employed had not been validated and were likely to result in misleading information.

Larval (maggot) therapy has had a long history, and is enjoying a resurgence of interest in the UK.[4] However, evidence for effectiveness remains restricted to case reports and anecdotal articles; there is presently no research evidence to support claims of effectiveness. Considering the high profile of this intervention, clinical trials, particularly RCTs, are urgently required.

Publication bias appears to be present in debridement studies with the majority of trials favouring the debriding agent under evaluation. This may be a reflection of commercial interests in many of the included trials. Even if a debriding agent was effective, one would expect by chance to get occasional results from studies that found in favour of the alternative treatment, particularly because of the small sample size of the RCTs, giving more opportunity for chance variation.

Future trials that assess wound healing need to be larger in terms of patient numbers than the majority of those reviewed here. The design of smaller trials could be improved by the use of matched or stratified randomisation to ensure comparability between treatment groups at baseline: patients should be stratified based on wound type and size at baseline and these groupings should then be randomised to treatment. If patients have been matched for wound size and type then matched pairs analysis should be used to analyse the data. But even with this type of design the trial still needs to be large enough to ensure comparability for other features and confounding factors, such as age or duration of the wound.

Planned and future studies would also benefit from the inclusion of a detailed cost-effectiveness analysis. Several reports included in this review detailed the costs incurred during the trial period, but unfortunately none of the studies provided sufficient detail for a reliable cost-effectiveness analysis to be constructed.

Chapter 5
Conclusions

There is some, if limited, evidence to suggest that the use of a specific debriding agent is beneficial for wound healing when compared with certain traditional or control treatments. In contrast, there is little or no evidence to suggest that one debriding agent is more effective than any other.

Implications for policy

As the benefits shown over traditional or control treatments are at best marginal, the choice of which debriding process to adopt should perhaps be based on the relative cost of the treatments, unless clinical experience suggests otherwise. There is little reliable research evidence to suggest that the more expensive agents should be used in preference to some of the less costly ones. However, this decision should not be based on the net cost of each treatment as this does not take into account important variables, such as the number of dressing changes required, coverage of the wound area, or nursing time. The financial cost of a treatment can only be determined from studies designed specifically to address this issue and this should be seen as a priority for future research.

Recommendations for research

Much of the research into wound debridement is of poor quality and direct comparisons are few. In those trials reviewed, sample sizes were rarely sufficient to detect clinically important effects, and poor baseline comparability frequently confounded outcome measures. Several important messages can be identified for future studies.

- Recruitment numbers should be based on an *a priori* sample size calculation, though this may be complicated by the lack of trials on which to base such a calculation.
- The proportion of wounds healed should be used as an objective outcome measure. Where healing rates are based on wound area both the percentage and absolute change in area should be given.
- Experimental groups should be comparable at baseline. In small RCTs, randomisation alone will not achieve comparability; in such situations patients should be paired by baseline characteristics and then the individuals of each pair randomised to treatment. However, with particularly small groups, pairing of patients is still unlikely to ensure that all risk factors (known and unknown) are distributed equally between the groups, and hence, large sample size should still be the ultimate goal.
- Baseline data and intervention details should always include a thorough description of how the patients were nursed and the use of concurrent treatments including secondary dressings.
- Comparisons between debriding agents are required and should use agents that are recommended for wounds of a similar nature.
- Assessment should be blind to treatment.
- Survival rate analysis should be adopted for all studies that assess wound healing.
- All RCTs should be published.
- Detailed cost-effectiveness analyses should be seen as a priority for future trials.
- RCTs of both surgical and larval debridement have not been performed. The frequent use of surgical debridement and the increasing interest in the larval therapy indicate that these trials are needed.

Acknowledgements

This review was commissioned by the NHS R&D HTA programme. The authors are indebted to Julie Glanville and Alison Fletcher for assistance with the search, location and collection of literature. We are also grateful to our expert panel (appendix 4) for their helpful comments on the review protocol and draft report. The report also benefited greatly from comments received from the HTA referees.

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Appendix 1

MEDLINE search strategy

MEDLINE has been searched for RCTs from 1966 to October 1997 using a mixture of free text terms and MEDLINE search headings:

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

The MEDLINE search strategy used is as follows:

decubitus ulcer/ or foot ulcer/
leg ulcer/ or varicose ulcer/
pilonidal cyst/
skin ulcer/
diabetic foot/
((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer$).tw.
((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer$).tw.
((pressure or bed) adj sore$).tw.
((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore$).tw.
((diabetic adj foot) or (cavity adj wound)).tw.
((varicose or leg or skin) adj ulcer$).tw.
(decubitus or (chronic adj wound$)).tw.
((sinus adj wound$) or (cavity adj wound$)).tw.

or/1-13

debridement/ or biological dressings/ or bandages/
occlusive dressings/ or clothing/ or wound healing/
antibiotics/ or growth substances/ or platelet-derived growth factor/
fibroblast growth factor/ or electrical stimulation therapy.ti,ab,sh.
lasers/ or nutrition/ or surgery/ or surgery, plastic/
surgical flaps/ or skin transplantations/ or homeopathy/ or homeopathic/
acupuncture therapy/ or acupuncture/ or alternative medicine/
alternative medicine/ or massage/ or iloprost/ or alginates/
zinc/ or zinc oxide/ or ointments/ or anti-infective agents/
dermatologic agents/ or colloids/ or cushions/ or wheelchairs/
beds/ or wound dressings/
(debridement or dressing$ or compress$ or cream$ or (growth adj factor$)).tw.
(pressure-relie$ or (recombinant adj protein$) or bandag$ or stocking$).tw.
(antibiotic$ or (electric adj therapy) or laser$ or nutrition$ or surg$).tw.
(homeopath$ or acupunture or massage or reflexology or ultrasound).tw.
(iloprost or alginate$ or zinc or paste$ or ointment$ or hydrocolloid$).tw.
((compression adj therapy) or (compression adj bandag$) or wrap$).tw.
(bed$ or mattress$ or wheelchair$ or (wheel adj chair) or cushion$).tw.
((wound adj dressing$) or vitamin$ or bind$ or gauze$ or heals or healing).tw.
(diet or lotion$ or infect$ or reduc$ or (wound adj healing)).tw.
(treat$ or prevent$ or epidemiol$ or aetiol$ or etiol$ or therap$ or prevalence or incidence).tw.

or/15–35
14 and 36

random allocation/ or randomized controlled trials/
controlled clinical trials/ or clinical trials phase I/ or clinical trials phase II/
clinical trials phase III/ or clinical trials phase IV/ or clinical trials overviews/
single-blind method/ or double-blind method/
publication bias/ or review/ or review, academic/
review tutorial/ or meta-analysis/ or systematic review/
((random$ adj controlled adj trial$) or (prospective adj random$)).tw.
((random adj allocation) or random$ or (clinical adj trial$) or control$).tw.
((standard adj treatment) or compar$ or single-blind$ or double-blind$).tw.
(blind$ or placebo$ or systematic$ or (systematic adj review)).tw.
(randomized controlled trial or clinical trial).pt. or comparative
study.sh.

or/38-48
37 and 49
limit 50 to human

burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
peptic ulcer/ or duodenal ulcer/ or stomach ulcer/
((peptic adj ulcer) or (duodenal adj ulcer) or traum$).tw.
((aortocaval adj fistula) or (arteriovenous adj fistula)).tw.
(bite adj wound$).tw.

or/52–56
51 not 57

Appendix 2

CINAHL and EMBASE search strategy

Other databases that have been searched for RCTs are:

EMBASE [to October 1997]
CINAHL (Cumulative Index of Nursing and Allied Health Literature) [to April 1997]

The CINAHL search strategy used is as follows:

pressure ulcer/ or foot ulcer/ or leg ulcer/ or skin ulcer/
diabetic foot/ or diabetic neuropathies/
diabetic angiopathies/ or diabetes mellitus/co
pilonidal cyst/ or surgical wound infection/
((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer$).tw.
((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer$).tw.
((pressure or bed) adj sore$).tw.
((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore).tw.
((diabetic adj foot) or (cavity adj wound)).tw.
((varicose or leg or skin) adj ulcer$).tw.
(decubitus or (chronic adj wound$)).tw.
((sinus adj wound$) or (cavity adj wound$)).tw.

or/1–12

debridement/ or biological dressings/ or occlusive dressings/
(bandages.ti,sh,ab,it. and "Bandages and Dressings"/) or
compression garments/ or antibiotics/
electric stimulation/ or Laser Surgery/ or lasers/th lasers/ or Nutrition Care (Saba HHCC)/ or diet therapy/ or Nutrition
Therapy (Iowa NIC)/
surgery, reconstructive/ or surgery, plastic/ or surgical flaps/
surgical stapling/ or skin transplantation/ or alternative therapies/
acupuncture/ or massage/ or zinc/ or ointments/
antiinfective agents, local/ or antibiotics/ or dermatologic agents/
dermatology nursing/ or colloids/ or beds nad mattresses/
flotation beds/ or wheelchairs/ or positioning:wheelchair/ or positioning:therapy/
patient positioning/ or positioning/ or wound care/ or wound healing/
(debridement or dressing$ or compress$ or cream$).tw.
((growth adj factor$) or pressure relie$ or (recombinant adj protein$) or bandag$).tw.
(stocking$ or antibiotic$ or (electric adj therapy) or laser$ or nutrition$ or surg$).tw.
(iloprost or alginate$ or zinc or paste$ or ointment$ or hydrocolloid$).tw.
((compression adj therapy) or (compression adj bandag$) or wrap$).tw.
(bed$ or mattress$ or wheelchair$ or (wheel adj chair) or cushion$).tw.
((wound adj dressing$) or vitamin$ or bind$ or gauze$ or heals or healing).tw.
(diet or lotion$ or infect$ or reduc$ or etiol$ or (wound adj healing)).tw.
(treat$ or prevent$ or epidemiol$ or aetiol$ or therap$ or prevalence or incidence).tw.
"Bandages and dressings"/ or skin transplantation/ or homeopathy/ or ointments/ or "beds and mattresses"/

or/14–34
13 and 35

clinical trials/ or single-blind studies/ or double-blind studies/
control group/ or placebos/ or meta analysis/
((random$ adj clinical adj trial$) or (prospective adj random$)).tw.
((random adj allocation) or random$ or controlled clinical trial$ or control).tw.
(comparison group$ or (standard adj treatment) or compar$).tw.
(single-blind$ or (single adj blind) or double-blind or (double adj blind)).tw.
(blind$ or placebo$ or systematic or (systematic adj review)).tw.
(meta analysis or meta-analysis).tw. or (trials or trial or prospective).tw.
(clinical trials).sh. or (comparative studies).sh .

or/37–45
36 and 46

burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
peptic ulcer/ or duodenal ulcer/
((peptic adj ulcer) or (duodenal adj ulcer) or trauma).tw.

(burn$ or (gunshot adj wound$) or (corneal adj ulcer) or dentist$ or (bite adj wound)).tw.
or/48–51

47 not 52

Appendix 3

Additional databases searched

ISI Science Citation Index (on BIDS)

BIOSIS (on Silver Platter)

British Diabetic Association Database

CINAHL (on OVID CD-ROM)

CISCOM, the database of the Reseach Council for Complementary Medicine

Cochrane Database of Systematic Reviews (CDSR)

Cochrane Wounds Group Specialised Trials Register

Current Research in Britain (CRIB)

Database of Abstract of Reviews of Effectiveness (DARE)

Dissertation Abstracts

DHSS Data (on Knight-Ridder Datastar)

EconLit

EMBASE (on Knight-Ridder Datastar)

Index to Scientific and Technical Proceedings (searched on BIDS)

MEDLINE (on OVID CD-ROM)

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 4

Expert advisory panel

Dr Mary Bliss, Consultant Geriatrician, Department of Medicine for the Elderly, Homerton Hospital, Homerton Row, London E9 6SR, UK.

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Dr Raj Mani, Southampton University Hospitals Trust, Medical Physics Department, Level D, Centre Block, Southampton SO9 4XY, UK.

Andrea Nelson, Department of Health Studies, University of York, Heslington, York YO1 5DD, UK.

Dr Steve Thomas, Director, Surgical Materials Testing Laboratory, Bridgend General Hospital, Bridgend, Mid Glamorgan, UK.

Dr Ewan Wilkinson, Liverpool Health Authority, Hamilton House, 24 Pall Mall, Liverpool L3 6AL, UK.

Appendix 5

Quality assessment

TABLE 4 *Quality assessment of RCTs of debridement*

Study	Inclusion and exclusion criteria stated	Total no. of wounds [arms]	*A priori* sample size calculation	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment	Appropriate outcome measures	Withdrawals†	ITT analysis
Ågren and Strömberg, 1985[9]	✗	28 patients [2]	✗	✔	✔c	✗	✔	✔a	✗
Apelqvist *et al,* 1990[53]	✔	44 patients [2]	✗	✗	✔c	✔	✔	✔a	✗
Apelqvist and Tennvall, 1996[42]	✔	41 [2]	✗	✔	✗	✔	✔	✔b	✗
Brown-Etris *et al,* 1996[47]	✔	140 [2]	✗	✗	✔	✔	✔	✔b	✗
Colin *et al,* 1996[56]	✔	135 [2]	✔	✗	✔c	✗	✔	✔a	✔
Darkovich *et al,* 1990[46]	✔	123[2]	✗	✗	✔c	✗	✔	✔a	✗
Eriksson *et al,* 1984[34]	✔	53 [2]	✗	✗	✔	✗	✔	N/A	N/A
Garcia *et al,* 1984[30]	✔	44 [2]	✗	✗	✔	✗	✔	N/A	N/A
Gibson, 1995[59]	✗	62 [2]	✗	✗	✔c	✗	✔	✗	✗
Goode *et al,* 1979[35]	✗	20 [2]	✗	✔	✔	✗	✔	N/A	N/A
Gordon, 1975[51]	✗	19 [2]	✔	✗	✔c	✔	✔	✔a	✗
Groenewald, 1980[29]	✗	100 [2]	✗	✗	✔c	✗	✔	✔a	✗
Harcup and Saul, 1986[40]	✔	72 [2]	✗	✗	✔c	✗	✔	✔a	✔
Hellgren, 1983[60]	✔	40 [2]	✗	✗	✔	✔	✔	✔a	✗
Holloway *et al,* 1989[39]	✔	75 [2]	✗	✗	✔c	✗	✔	✔a	✗
Hulkko *et al,* 1981[58]	✗	31 [2]	✗	✗	✔	✗	✔	✔b	✗
Laudanska and Gustavson, 1988[38]	✔	60 [2]	✗	✗	✔c	✗	✔	✔b	✗
Lee and Ambrus, 1975[50]	✗	28 [2]	✗	✗	✔c	✗	✔	✔a	✗
Lindsay *et al,* 1986[41]	✔	28 [2]	✗	✗	✔	✗	✔	✔a	✗
Lum *et al,* 1996[48]	✔	20 [2]	✗	✔	✔c	✗	✔	✔a	✗
Moberg *et al,* 1983[43]	✔	38 patients [2]	✗	✗	✔c	✔	✔	✔a	✗
Moss *et al,* 1987[13]	✔	42 [2]	✗	✗	✔c	✗	✔	✔b	✗
Mulder *et al,* 1993[49]	✔	64 patients [3]	✗	✔	✔	✗	✔	✔b	✗
Nasar and Morley, 1982[36]	✔	18 [2]	✗	✗	✗	✔	✔	✔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*

continued

TABLE 4 contd *Quality assessment of RCTs of debridement*

Study	Inclusion and exclusion criteria stated	Total no. of wounds [arms]	*A priori* sample size calculation	Randomisation procedure stated	Appropriate baseline characteristics reported*	Blinded outcome assessment	Appropriate outcome measures	Withdrawals†	ITT analysis
Ormiston *et al*, 1985[44]	✔	61 [2]	✗	✔	✔c	✔	✔	✔a	✔
Palmieri, 1992[33]	✔	48 [2]	✗	✗	✔	✗	✔	N/A	N/A
Parish and Collins, 1979[37]	✗	34 [3]	✗	✗	✔c	✗	✔	N/A	N/A
Sawyer *et al*, 1979[31]	✗	37 [2]	✗	✔	✗	✗	✔	N/A	N/A
Sayag *et al*, 1996[32]	✔	92 [2]	✔	✔	✔c	✗	✔	✔a	✔
Skog *et al*, 1983;[23] Hillström, 1988;[22] Troëng *et al*, 1983[28]	✔	95 [2]	✗	✗	✔c	✗	✔	✔a	✗
Steele *et al*, 1986[45]	✔	60 [2]	✗	✔	✔c	✗	✔	✔a	✗
Stewart and Leaper, 1987[55]	✔	95 [2]	✗	✔	✔c	✗	✔	✔a	✗
Tarvainen, 1988[54]	✔	27 [2]	✗	✔	✔	✗	✔	✔a	✗
Thomas and Fear, 1993[57]	✔	40 patients [2]	✗	✔	✔c	✗	✔	✔a	✔
Westerhof *et al*, 1987[52]	✔	33 [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

Summary of studies

TABLE 5 *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Eriksson *et al*, 1984[34] Sweden Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Area and volume measured by stereophotogrammetric examination. Setting and length of treatment: Treated over a 2-week period.	Inclusion criteria: Outpatients with venous leg ulcers. Exclusion criteria: Diabetes mellitus; manifest arterial insufficiency; clinical picture of erysipelas or cellulitis. Before commencement the general health of all participants and the state of venous and arterial peripheral circulation were evaluated. A pressure index ankle/arm of less than 0.75 was considered pathological and as such an exclusion criteria.	Treatment: I: Dextranomer polysaccharide beads (Debrisan®) mixed with sterilised glycerol and covered with gauze. The dressing was changed every day for the first week and every second day for the second week, *n* = 26. C: Sterilised gauze soaked in 0.9% (w/v) sodium chloride in water. The gauze was moistened regularly through the day, *n* = 27. Prior to the initial treatment and at the start of the second week of treatment, all ulcers were bathed for 15 min in water containing 1 ml/l of 3% (w/v) potassium permanganate. Crust and debris were removed.	Mean wound area (cm^2): Not stated. Other characteristics: All groups Mean age (years): 70.1 M:F ratio: 1:3.1 Mean duration (months): No details Both groups comparable for all background characteristics except elevated blood glucose levels and a history of previous thrombosis (both these factors are negatively correlated with ulcer healing): High glucose levels / History of thrombosis I: 8% / 16% C: 30% / 38%	Number of wounds decreased in % area: > 50 / 50 / 25 I: 2 / 8 / 14 C: 6 / 5 / 10 Number of wounds increased in % area: > 50 / 50 / 25 I: 0 / 1 / 1 C: 0 / 3 / 3 Number of wounds decreased in % volume: > 50 / 50 / 25 I: 4 / 6 / 11 C: 9 / 1 / 6 Number of wounds increased in % volume: > 50 / 50 / 25 I: 0 / 2 / 3 C: 0 / 5 / 6 No statistical difference between the two treatments was found.	No withdrawals.	Pain as judged by the patient showed a reduction in the I (dextranomer) group ($p < 0.05$). Changes in area were found to be highly correlated with background variables: elevated glucose levels resulted in slower healing as did a history of previous thrombosis. Bacterial flora remained unchanged throughout the study irrespective of treatment.
Garcia *et al*, 1984[30] Spain Wound type: Secondary perimalleolar ulcers. Method of randomisation: Not stated. Objective outcome: Area and circumference of the wound measured by planimetry. Setting and length of treatment: Hospital and community-based trial over a 3-week period.	Inclusion criteria: Patients with secondary perimalleolar ulcers and chronic venous insufficiency Exclusion criteria: Patients not submitted for surgical treatment.	Treatment: I: Dextranomer polysaccharide beads (Debrisan), *n* = 22. C: Potassium permanganate 1/5000 and hypertonic saline or antibiotic ointments, *n* = 22.	Mean wound area: Not stated. Other characteristics: All groups Mean age (years): 56.5 M:F ratio: 2.2:1 Mean duration (months): 164 33 patients required hospitalisation while the remaining nine could be treated as out-patients.	% reduction in mean area of wound after 3 weeks: I: 93.1% (7.4 SD; *n* = 22) C: 85.2% (10.8 SD; *n* = 22) ($p < 0.01$; Student's *t*-test) % reduction in mean circumference after 3 weeks: I: 80.0% (20.6 SD; *n* = 22) C: 70.1% (20.8 SD; *n* = 22) ($p > 0.05$, NS; Student's *t*-test)	No withdrawals reported.	I (dextranomer) does not induce contact dermatitis, eczema or allergic reactions. Statistical significance is greater 1 and 2 weeks after the initiation of treatment (for area $p < 0.001$; for circumference $p < 0.05$).

Debrisan®, Pharmacia Upjohn

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Goode *et al*, 1979[35] UK Wound type: Surgical wounds. Method of randomisation: Sealed envelopes. Objective outcome: Time to secondary wound closure. Each wound was photographed at the start, during and at the end of treatment. Setting and length of treatment: Hospitalised surgical patients. Treatment was continued until it was considered appropriate to close the wound.	Inclusion criteria: Patients who developed wound infections after an appendicectomy or bowel surgery. Exclusion criteria: Not stated.	Treatment: I: Dextranomer polysaccharide beads (Debrisan) were applied directly into the wound to a depth of 0.5 cm, followed by a light pack. Dextranomer was applied twice daily, $n = 10$. C: Eusol and paraffin soaked ribbon gauze dressings changed twice daily, $n = 10$. All other nursing procedures were identical for both groups.	Mean wound area (cm^2): Not stated. Other characteristics: I / C Mean age (years): 52.9 / 50.9 M:F ratio: 1:0.4 / 1:0.7 Wounds: Appendicectomy 6 / 7 Paramedian 4 / 3 Delayed primary suture 4 / 6 Wound abscess 6 / 4 All wounds were either heavily contaminated at operation and left open for delayed primary suture (ten patients), or those which were closed primarily and subsequently developed an abscess that required the removal of sutures and drainage (ten patients).	Number of wounds healed without secondary closure: I: 1/10 (10%) C: 1/10 (10%) Mean time and range (days) to secondary closure: I: 8.1 (range, 5–28; $n = 10$) C: 1.6 (range, 6–22; $n = 10$) ($p < 0.05$; Mann-Whitney U-Test)	There were no withdrawals.	Three patients in the C group (Eusol) continued to have serious discharges for up to 5 days after wound closure. This did not occur in the I (dextranomer) group. Wound healing was the principal factor preventing discharge from hospital; those treated with I had a shorter hospital stay by a median of 2.2 days. The author states that the high cost of I is compensated by the saving from shorter hospital stay.

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Groenewald, 1980[29] South Africa Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: The circumference of the wound was measured by a millimetre overlay. A photograph was taken at each visit. Setting and length of treatment: Hospital clinic. Patients treated for 21 days and assessed daily by two independent investigators.	Inclusion criteria: Outpatients with post-phlebitic stasis leg ulcers. Exclusion criteria: Not stated.	Treatment: I: Dextranomer polysaccharide (Debrisan) beads were poured directly onto the ulcer surface to form a layer at least 2–3 mm thick. A multilayer gauze pad was used to cover the ulcer and kept in place by a standard gauze bandage, *n* = 50. C: Povidone-iodine ointment was swabbed onto the ulcer and a pressure bandage applied. The whole foot and lower leg were bound with a zinc oxide-impregnated gauze bandage, *n* = 50. The ulcers and surrounding leg area in both groups were initially washed with a soft brush in a povidone-iodine solution, before being temporarily covered with gauze swabs soaked in Eusol solution. In the presence of *Pseudomonas* infection 0.25% acetic acid solution was applied. The surrounding skin was painted with tincture of methiolate. In the presence of commonly occurring fungal infections of the surrounding skin area, an appropriate antifungal agent was applied. Where the surrounding skin was eczematous, flucinoline ointment was applied.	Wound size: I C < 6 cm: 7 7 6–12 cm: 20 21 > 12 cm: 23 22 Other characteristics: I C Mean age (years): Not stated M:F ratio: 1:3.5 1:4.6 Mean duration (months): Not stated Depth of ulcer: Shallow 20 29 Deep 30 21 Racial distribution (%): White 23 22 Coloured 26 25 Black 1 3 The number of affected right and left legs were almost equal in each of the two groups. The samples were shown to be representative of the overall clinic population.	Reduction in wound size at 21 days: I C 0%: 8 26 10%: 2 1 25%: 1 1 50%: 6 2 75%: 7 3 100%: 11 2 Mean time to healing: I: 4.44 weeks (*n* = 35) C: 5.32 weeks (*n* = 35) ($p < 0.05$)	30 patients, 15 in each group were not included in the final analysis. These patients were treated surgically after the wound was deemed to be clean (e.g. by skin grafting). Five additional patients dropped out of the trial and were replaced to keep the group number at 50. (Reasons for these withdrawals are not stated.)	Of 30 I (dextranomer) patients complaining of pain, 20 showed improvement within 24 hr, one after 3 days and one after 10 days. In the remaining eight patients the pain initially worsened before improving. Of the 35 C patients complaining of pain, seven improved after 24 hr, three after 3 days, and six after 7 days. In 13 the pain worsened before improving, in two patients the pain level remained unchanged, and in four the pain worsened without improving later.

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Nasar and Morley, 1982[36] UK Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Wound area was measured using celluloid squares and the entire wound photographed. End point was reached when the wound was clean and granulating and appeared to be less than 25% its original size (= healed). Setting and length of treatment: Hospital-based trial. Assessments were made every 3 days by an independent observer and a photograph taken once a week. Treatment was continued until the wound reached the end point, or for a maximum of 94 days.	Inclusion criteria: Patients with deep pressure sores of approximately similar size. Exclusion criteria: Urinary tract infection.	Treatment: I: Dextranomer polysaccharide (Debrisan) applied as a stiff paste twice daily for the first 3 days and daily thereafter, *n* = 9. C: Eusol and paraffin packs were applied to the wound and dressings were changed three times daily for the first 3 days and thereafter twice daily. Melolin dressings were used throughout held in place by micropore tape. A savlon sachet was used each time the dressing was changed, *n* = 9. Prior to initiation of the trial all hardened sloughs were cut off and all patients were nursed on a large cell ripple mattress. The only concurrent therapy was ultraviolet light applied to 12 square inches of skin to produce first degree erythema with the sore masked from the ultraviolet rays.	Mean wound area: Not stated. Other characteristics: I C Mean age (years): 83.2 77.4 M:F ratio: Not stated Mean duration (months): Not stated Anaemia, hypoalbuminaemia, hypovitaminosis, and high blood urea were corrected if present. Scrupulous control of diabetic patients was ensured. Patients with urinary incontinence were catheterised. Pressure sores were mostly on the foot or heel in both groups.	Number of wounds attaining the end point: I: 6/9 (67%) C: 5/9 (56%) Mean time to reach end point: I: 39.3 days C: 62 days	I: Three wounds. Two due to patient death; one as a result of patient discomfort. C: Four wounds. One due to patient death; three switched to dextranomer (two after 16 days and one after 48 days).	Wounds treated with C (Eusol) were observed to be associated with a rise in blood urea to 11 mmol/l. Cost of materials calculated for each treatment for average treatment time in that group. C treatment was 1.6 times more costly than I.

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Palmieri, 1992[33] Italy Wound type: Leg ulcers and pressure sores. 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 given here for leg ulcers and pressure sores only. Exclusion criteria: Additional treatments with drugs (with the exception of digitalis).	I: Dextranomer polysaccharide beads (Debrisan) were applied directly to the wound bead and replaced daily, *n* = 24. C: 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. 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 ratio: 1:0.6 Mean duration (months): Not stated Wound type: Leg ulcers: 12 Diabetic gangrene: 12 Pressure sores: 12 Post traumatic: 12	Mean time to healing (days): Leg ulcers: I: 60 (*n* = 6) C: 36 (*n* = 6) ($p < 0.005$; Student's *t*-test) Pressure sores: I: 47 (*n* = 6) C: 20 (*n* = 6) ($p < 0.001$; Student's *t*-test)	No withdrawals.	
Parish and Collins, 1979[37] USA Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Number of ulcers healed. Setting and length of treatment: Community (nursing home) 4-week trial.	Inclusion criteria: Patients with pressure sores, residing in a nursing home. Exclusion criteria: Not stated.	I: Dextranomer polysaccharide beads (Debrisan) applied to a depth of at least 3 mm covered with a dry dressing. Changed 1–3 times daily depending on exudate, *n* = 14 wounds from seven patients. C: Sugar and egg white applied after a saline wash. Changed four times a day. Allowed to dry and not covered, *n* = 9 wounds from five patients.	Mean wound size = √ of surface area (cm): I: 4.5 C: 2.4 No statistical difference between the groups for ulcer size Other characteristics: I C Age range (years): 29–57 32–70 M:F ratio: Not stated Mean duration (months): Not stated	Number of wounds healed at 4 weeks: I: 6/14 (43%) C: 0/9 (0%) ($p < 0.05$; Fisher's test) Number of patients with healed wounds at 4 weeks: I: 4/7 (57%) C: 0/5 (0%)	No withdrawals.	No side-effects reported by patients with any of the treatments.

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Sawyer *et al*, 1979[31] USA Wound type: Venous leg ulcers. Method of randomisation: Sealed envelopes. Objective outcome: % increase in epithelised area. Method of measurement not stated. Setting and length of treatment: Hospital and medical centre clinic. Assessments were performed a minimum of once a week (daily for hospitalised patients) for 3 weeks.	Inclusion criteria: Outpatients or hospitalised patients with cutaneous ulcers of mixed origin. Note: only the results for venous ulcers are presented here. Exclusion criteria: Not stated.	Treatment: I: Dextranomer polysaccharide beads (Debrisan) applied to a depth of 2–3 mm. For convex wounds the beads were mixed with glycerol to form a paste. Fresh dextranomer applied once or twice daily, unless heavy exudate required more frequent changing, *n* = 18. C: Soaks only. Repeated twice daily, *n* = 19. Both treatments were covered with gauze and a cling bandage. Legs were elevated above the heart as frequently as possible. All wounds soaked in pHiso Hex® for 30 min prior to treatment.	Mean wound area: Not stated Other characteristics: Mean age (years): Not stated M:F ratio: Not stated Mean duration (months): Not stated	Number of wounds healed at 3 weeks: I: 15/18 (77%) C: 3/19 (16%) ($p < 0.05$; chi-squared test)	I: No withdrawals C: No withdrawals.	Pain from the wound improved in 31 patients treated with I (dextranomer) and in five patients treated with C (saline). The pain worsened in two patients treated with I and in 14 patients treated with C.

pHiso Hex®; manufacturer unknown

continued

TABLE 5 contd *Dextranomer polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Sayag *et al*, 1996[32] France Wound type: Pressure sores. Method of randomisation: Sealed envelopes. Objective outcome: Area of wound measured by planimetry, digitised twice and the area calculated by computer. The mean of the two values was used to determine individual wound 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 researcher at each centre. Treatment was terminated when the wound reached 40% of the initial area, or after a maximum of 8 weeks.	Inclusion criteria: Patients aged ≥ 60 hospitalised for ≥ 8 weeks, with a pressure sore graded III or IV (*Yarkony's classification) and surface area from 5–100 cm^2. Exclusion criteria: More than half the total ulcer area had granulating tissue; wound covered by necrotic plaque; active infection requiring local or systemic antibiotic therapy; severe renal failure; heel ulcers when combined with end-stage arteriopathy of the lower limbs; receiving radiotherapy or cytotoxic therapy.	Treatment: I: Dextranomer polysaccharide paste (Debrisan) applied to a depth of 3 mm over the wound surface, *n* = 45. C: 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 wound area (cm^2): I: 16.1 (12.5 SD) C: 20.1 (12.9 SD) Other characteristics: I C Mean (SD) age (years): 80.4 (9.1) 81.9 (8.9) M:F ratio: 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 (Student's *t*-test). Where patients had multiple wounds only one was selected for study. Pressure sores were located on the sacrum, ischium, trochanter and heels.	Mean wound area reduction per week (cm^2): I: 0.27 (3.21 SD) C: 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): I: 2.15 (3.60 SD) C: 3.55 (2.18 SD) (*p* = 0.0004; Student's *t*-test) Number of wounds with > 75% reduction in area: I: 6/45 (13%) C: 15/47 (32%) Number of pressure sores with ≥ 40% reduction in area: I: 19/45 (42%) C: 35/47 (74%) (*p* = 0.002; Fisher's exact test) Cumulative curves of the number of patients reaching 40% reduction differed significantly (*p* = 0.0002 Logrank test) between the groups, with a median of 4 weeks in C and 8 weeks in I.	I: 22 Withdrawals: death (*n* = 6); adverse event (*n* = 1); deterioration or stagnation of ulcer after 4 week (*n* = 15). C: Ten withdrawals: death (*n* = 5); transfer (*n* = 2); deterioration of health (*n* = 1); deterioration or stagnation of ulcer after 4 week (*n* = 2). All 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 C due to admission to a special care unit.	On average the number of dressing changes per week was similar: 4.28 (1.49 SD) for C and 4.52 (1.42 SD) for I. 8% of the C patients and 33% of I patients experienced adverse effects.

Algosteril®, Les Laboratories Brothier (now manufactured by Beiersdorf UK Ltd)

* *Yarkony GM*, et al. *Classification of pressure ulcers*. Arch Dermatol *1990;**126**:1218–19*.

TABLE 6 *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Apelqvist and Tennvall, 1996[42] Sweden Wound type: Diabetic foot ulcers. Method of randomisation: Computer allocation. Stratification was performed on size and type of wound (Wagner grade I–II). Objective outcome: Area of wound determined by photographing wounds against a graduated scale. The maximum length and maximum width were multiplied together to calculate the area. In addition the number of wounds healed was recorded. Setting and length of treatment: Open controlled trial with blinded photo-evaluation. Patients were treated either at home or on visiting an outpatient clinic. Assessments were made at 1, 4, 8 and 12 weeks.	Inclusion criteria: Caucasian outpatients > 40 years old with previously known diabetes mellitus. All wounds were exudating and below the ankle (Wagner grade I–II*) with an ulcer area > 1 cm^2 and a systolic toe pressure > 30 mmHg or a systolic ankle pressure > 80 mmHg. Exclusion criteria: Wounds > 25 cm^2; patients with a deep abscess; osteomyelitis or gangrene (Wagner grade III–IV); patients undergoing thyroid gland investigation; patients unlikely to adhere to the study protocol. In patients with several wounds, only the largest wound meeting the selection criteria was chosen.	Treatment: I: Cadexomer iodine polysaccharide ointment (Iodosorb®) was changed once daily for the first week and then daily or every second or third day thereafter according to the degree of exudation, *n* = 22. C: Gentamicin solution (80 mg/ml) was given twice daily where cellulitis was present. Streptodornase/ streptokinase (Varidase Topical) was used for moist necrotic lesions and changed twice daily. Dry saline gauze was used as an absorptive dressing and changed once or twice daily according to exudation, *n* = 19. Wounds were cleaned with sterile saline prior to dressing in accordance with the manufacturers guidelines. Dressings were applied by regular healthcare nurses. For both treatments when the ulcers had stopped exudating, Vaseline gauze (Jelonet®) was used. Footwear of patients was corrected or special footwear provided to relieve pressure. Oral antibiotics were given in case of signs of infection.	Mean wound area (cm^2): Not stated. Other characteristics: Mean age (years): Not stated M:F ratio: Not stated Mean duration (months): Not stated	Number of wounds healed: I: 5/22 (23%) C: 2/19 (11%)	I: Five withdrawals C: One withdrawal Two patients were excluded from the analysis due to violation of inclusion criteria (size > 25 cm^2 and/or ulcer type, Wagner III). Two patients were excluded because of hospitalisation (one for myocardial infarction, one became febrile and later died), these hospitalisations were not associated with treatment. One patient was excluded for non-compliance with treatment. One other patient was excluded because of insufficient data. 35 patients remained for clinical evaluation.	Mean weekly cost was 903 SEK for I and 1421 SEK for C, of which the major part was costs for staff and transportation related to frequency of dressing changes. No adverse reactions were recorded with either treatment.

Iodosorb®, Smith & Nephew Healthcare Ltd; Jelonet®, Smith & Nephew Healthcare Ltd

* *Wagner FW. The dysvascular foot: a system for diagnosis and treatment.* Foot Ankle *1981;***2***:64–122.*

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Harcup and Saul, 1986[40] UK Wound type: Chronic leg ulcers. Method of randomisation: Not stated. Objective outcome: Area of wound was measured by tracing the outline on to a plastic sheet. Setting and length of treatment: Patients were treated at home under the guidance of a general practitioner. Patients or carers were responsible for changing dressings. Assessments were made every 2 weeks and 4 weeks.	Inclusion criteria: Out-patients with exuding chronic leg ulcers not responding to existing treatment. Exclusion criteria: Concomitant, serious or life-threatening disease; a suspected malignant ulcer; insulin-requiring diabetes; pregnancy; iodine sensitivity; psychiatric disease; low intelligence; dementia; or other conditions likely to affect the patient's ability to comply with the trial.	Treatment: I: Cadexomer iodine polysaccharide beads (Iodosorb) applied to a depth of 3 mm after cleansing with sterile saline swabs or a gentle stream of water or saline. Covered with a dry sterile dressing and secured by bandaging or stocking. Cadexomer iodine was changed daily, $n = 41$. C: Primarily a support bandaging or stocking and a dry dressing. 21 of the participants received a variant on this treatment which included amongst others: Crêpe bandaging (Elastocrepe®), absorbent dressings (Melolin), topical antibiotics (Polyfax®) and medicated dressings (Sofra-Tulle®), $n = 31$.	Mean area of wound (cm^2): I: 7.74 (1.04 SD) C: 9.08 (1.37 SD) Other characteristics: All groups Mean age (years): 67.8 M:F ratio: 1:2.2 Mean duration (months): 16.9 Additional wounds (%): 26	Mean wound area at 4 weeks: I: 2.81 ($n = 41$) C: 0.90 ($n = 31$) % reduction in mean area of wound at 4 weeks: I: 36.30 ($n = 41$) C: 9.91 ($n = 31$) $p < 0.01$ I vs. C (analysis of covariance)	I: Three patients were withdrawn after 2 weeks due to various reasons, including diarrhoea, erythema, oedema, ulcer irritation and unhappiness with treatment. These patients were included in the analysis at 4 weeks.	During the 4-week treatment period those patients receiving C reported a 27% decrease in pain, while those treated with I reported a 66% reduction.
Holloway *et al*, 1989[39] USA Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Area of the wound was measured by planimetry on transparent tracings. A colour photograph was taken at each evaluation. Setting and length of treatment: A multicentre trial conducted for 24 weeks or until the wound was considered to be healed. Measurements were taken at 2-week intervals for the first 8 weeks and then at monthly intervals.	Inclusion criteria: Out-patients with venous stasis ulcers present for a minimum of 3 months and otherwise in good health. Exclusion criteria: Initially wounds < 2 cm in diameter; proven or suspected non-venous cause of wounds; inability to comply with the treatment; major medical disorders; iodine allergy; clinically significant arterial disease.	Treatment: I: Cadexomer iodine polysaccharide powder (Iodosorb) sprinkled onto the wound after irrigation with saline, and covered with a dry gauze dressing, $n = 38$. C: Wet-to-dry dressings with saline-soaked sterile 4 x 4 inch gauze pads, $n = 37$. Patients in both groups were responsible for changing their own dressings once a day. Both treatments were covered with a toe-to-knee elastic compression bandage.	Mean wound area (cm^2): I: 20.1 C: 11.2 Other characteristics: I / C Mean age (years): 63.0 / 61.5 M:F ratio: 1:0.8 / 1:1.5 Mean duration (months): 29.5 / 11.4 No statistical differences between the two groups reported. Although the mean duration and initial mean area are greater in the I group.	Mean reduction in wound size per week after 24 weeks (cm^2): I: 0.95 (0.12 SEM; $n = 27$) C: 0.41 (0.13 SEM; $n = 27$) ($p = 0.0025$; analysis of covariance) Mean reduction in wound size vs. baseline circumference after 24 weeks (cm^2/wk/cm^2): I: 0.04 (0.01 SEM; $n = 27$) C: 0.03 (0.01 SEM; $n = 27$) ($p = 0.0720$; analysis of covariance) The reduction in wound area was significantly different from baseline in both groups ($p < 0.001$; analysis of covariance).	15 patients did not complete the treatment: four failed to respond to treatment; two died from causes unrelated to their ulcers; nine dropped out and failed to return for follow-up. Six patients were not included in the analysis: two were felt to have been inappropriately admitted to the study because their ulcers were too small; four lacked adequate follow-up information. Withdrawals were in equivalent proportions from both groups.	Six patients treated with I experienced mild transient burning, pain, or itching. No adverse effects were reported in the C group.

Elastocrepe, Smith & Nephew Healthcare Ltd; Sofra-Tulle, Hoechst Marion Roussel

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Laudanska and Gustavson, 1988[38] Poland Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcomes: The wound perimeter was drawn onto a transparency and the area calculated by planimetry. The number of wounds healed was recorded. Setting and length of treatment: 6-week trial. Measurements taken at 0, 1, 2, 4 and 6 weeks.	Inclusion criteria: Hospitalised patients with chronic venous ulcers that had resisted outpatient treatment for more than 3 months. Exclusion criteria: Wounds < 2 cm; iodine sensitivity; severe peripheral arterial disease.	Treatment: I: Cadexomer iodine powder (Iodosorb) applied daily in a 3–4 mm layer, covered with a light elastic bandage, *n* = 30. C: Dilute hydrogen peroxide and zinc paste (in addition saline dressings, dilute potassium permanganate and Gentian violet were applied) covered with a light elastic bandage, *n* = 30. All patients were given complete bed rest for 6 weeks.	Mean wound area (cm^2): I: 27.5 (7.0 SE) C: 35.2 (8.1 SE) ($p > 0.05$; Student's *t*-test) Other characteristics: I C Mean age (years): 64.8 63.5 M:F ratio: 1:0.8 1:1.5 Mean duration (months): 19.1 15.0 No statistical difference between the two groups. Details are only available for 60 of the 67 participants initially randomised to treatment.	Mean % reduction in wound area at 6 weeks: I: 71% (*n* = 30) C: 54% (*n* = 30) ($p < 0.01$; Student's *t*-test) Both treatments were significantly different from baseline. ($p < 0.05$; Wilcoxon matched pairs) Number of ulcers healed or shallow at 6 weeks: I: 16/30 (53%) C: 7 / 30 (7%)	Four withdrawals before the first assessment: three due to social reasons and one due to cardiac failure. Three patients were withdrawn after completing the trial. One in each group was excluded due to large ulcer area (ten times that of the mean ulcer area). The third patient had rheumatoid arthritis which interfered with assessment. 30 patients in each group completed the trial.	Application of I resulted in more pain than with C. Serum concentrations of protein-bound iodine increase with I treatment. But there is no disturbance of thyroid function. Five patients on I complained of stinging.

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Lindsay *et al*, 1986[41] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Area of the wound was traced onto a plastic sheet and measured. Setting and length of treatment: Patients treated at home under the guidance of a general practitioner. Patients or carers were responsible for changing dressings. Assessments were made every 2 weeks for 4 weeks.	Inclusion criteria: Out-patients with chronic venous leg ulcers and not responding to existing treatment. Exclusion criteria: Concomitant serious or life-threatening disease, suspected malignant change in the ulcer; insulin-dependent diabetes; pregnancy; iodine sensitivity; psychiatric disease; very low intelligence; dementia; any other condition that might affect the patients ability to comply with the conditions of the trial.	Treatment: 28 patients entered the trial, but allocation between the groups was not stated. I: Cadexomer iodine powder (Iodosorb) applied to a depth of not less than 3 mm after cleansing with sterile saline swabs, or a gentle stream of water or saline. Covered with a dry sterile dressing and secured by bandaging or stocking. The dressing was changed on alternate days. C: Primarily a non-adherent dressing plus support bandaging or stocking. The dressing was changed on alternate days. Twelve of the participants received a variant on this treatment which included amongst others: Crêpe bandaging (Elastocrepe), absorbent dressings (Melolin), Povidone iodine and medicated dressings (Sofra-Tulle).	Mean wound area: Not stated. Other characteristics: All groups Mean age (years): 66.7 M:F ratio: All female Mean duration (months): 20.1 No. of patients with additional ulcers: 11	Mean % reduction in wound area at 4 weeks: I: 33.6 (n = 12) C: 4.2 (n = 13) (p < 0.005 I vs. C; analysis of variance).	I: One patient was withdrawn after 2 weeks due to an allergic reaction. C: One patient was withdrawn after 4 weeks on the discovery of peripheral vascular disease. The results are based on 25 patients suggesting there was a further withdrawal, probably in the I group.	Mean wound duration was 20 months so a reduction of 33% in only 4 weeks on I is impressive. However, no data are given of other measures that may have been employed to reduce wound size.
Moberg *et al*, 1983[43] Sweden Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Perimeter of the wound was traced and the area calculated by planimetry or measurement of the longest diameter. Setting and length of treatment: 3-week trial.	Inclusion criteria: Hospitalised patients with pressure sores. Exclusion criteria: Confirmed or suspected malignancies, moribund, iodine sensitivity, psychiatric illness, severe psoriasis, any other criteria that might make a patient unsuitable for a clinical trial or unable to give informed consent.	Treatment: I: Cadexomer iodine polysaccharide powder (Iodosorb) applied daily to a depth of 3 mm. Removed by running water saline or wet swab, n = 19. C: Standard treatment was variable. It included: saline dressings, enzyme-based debriding agents, and non-adhesive dressings, n = 19. All patients were subject to: attention to nutrition; improvement of hygiene; removal of pressure by using decubitus mattresses, turning the patient every 2 or 3 hrs, and optimal mobilisation.	Mean wound area (cm^2): I: 9.6 (1.8 SEM) C: 12.4 (4.3 SEM) Other characteristics: I C Mean age (years): 72.6 80.1 M:F ratio: 1:4.3 1:2.6 Mean duration (months): 6.2 6.2 Values are only available for the patients not withdrawn from the study.	Mean decrease in area of wound at 3 weeks: I: 2.9 (1.3 SEM; n = 16) C: 2.5 (1.1 SEM; n = 18) (p < 0.05 for both treatments when compared with baseline; correlated t-test or Fisher's exact test). % reduction in mean area of wound at 3 weeks: I: 30.9% (46 SD; n = 16) C: 19.6% (31 SD; n = 18) (p < 0.02; correlated t-test or Fisher's exact test)	I: Three withdrawals. Two patients felt they were getting worse and one had skin irritation and oedema around a sacral ulcer and chose not to continue. C: One withdrawal where the wound had grown and the patient was moved to another hospital.	I caused three patients to experience smarting after application, one patient had minor skin irritation and another had an exacerbation of psoriasis. Overall pain as a result of the wound was significantly less in patients treated with I. I was easy to apply and remove.

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Ormiston *et al*, 1985[44] UK Wound type: Venous leg ulcers. Method of randomisation: Sealed envelopes. Objective outcomes: Perimeter of the wound was drawn onto a transparency and the area calculated by planimetry. The wound was also photographed. The number of wounds healed was recorded. Setting and length of treatment: 12-week trial. Patients were assessed at regular intervals. After 12 weeks patients were allowed to cross-over.	Inclusion criteria: Out-patients with chronic venous leg ulcers persisting for at least 3 months. Exclusion criteria: Ulcers of non-venous aetiology, peripheral vascular disease (ABPI < 0.7), poor compliance expected due to concomitant physical or mental disability, travelling problems. Almost all patients selected were able to dress and bandage their own ulcers.	I: Cadexomer iodine polysaccharide powder (Iodosorb), 3–5 mm deep and covered with a gauze pad, *n* = 31. C: Gentian violet, followed by topical antibiotics (Polyfax) applied in a generous layer, and covered with a non-adherent pad (Melolin), *n* = 30. Each dressing was covered with a crêpe bandage and a cotton crêpe bandage.	Mean wound area (cm^2): I: 12.1 (13.9 SD) C: 10.2 (8.7 SD) Other characteristics: I / C Mean age (years): 67.3 / 70.3 M:F ratio: 1:1.3 / 1:2.6 Mean duration (months): 45.9 / 15.9 Baseline data was only given for 30 of the 31 patients treated with I (see withdrawals).	% reduction in mean area of wound at 12 weeks: I: 83% (*n* = 30) C: 61% (*n* = 30) ($p < 0.02$; Student's *t*-test). Reduction in mean area per week over 12 weeks (cm^2): I: 0.89 (0.1 SEM; *n* = 30) C: 0.46 (0.1 SEM; *n* = 30) ($p < 0.0001$; Student's *t*-test). Both treatments are statistically different from baseline ($p < 0.001$; analysis of covariance). Number of ulcers healed after 12 weeks: I: 12/31 (39%) C: 7/30 (23%) ($p > 0.05$; chi-squared analysis)	I: One patient was admitted to hospital for surgery, and had inappropriately dressed ulcers (this patient was excluded from the baseline data set). Two further patients were withdrawn: one died of a perforated ulcer and the other had difficulty in removing I from the ulcer. These two patients were included in the analysis. C: No withdrawals.	Patients were able to adequately bandage their own wounds. Two patients had difficulty removing I and three patients complained of stinging and itching. Pain was assessed on a scale of 0–100 by the individual patient. Pain was perceived to be similar in both groups. Two patients on C and five on I developed eczema, puritis or a rash.

ABPI, ankle brachial pressure index

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Skog *et al*, 1983;[23] Hillström, 1988;[22] Troëng *et al*, 1983[28] Sweden Wound type: Leg ulcers. Method of randomisation: Not stated. Objective outcome: Area of the wound was measured by planimetry, or by measuring the greatest diameters. All wounds were photographed against a ruler scale at each assessment. Setting and length of treatment: A multicentre trial in ten centres. Assessments were made after 1, 2, 4 and 6 weeks at which point the trial was terminated.	Inclusion criteria: Out-patients with chronic infected leg ulcers that failed to respond to current treatments. Exclusion criteria: Ulcers with diameters smaller than 2 cm and areas less than 3 cm^2; history of iodine sensitivity; peripheral arterial disease.	Treatment: I: Cadexomer iodine polysaccharide powder (Iodosorb) applied to a depth of approx. 3 mm after washing in running water, and covered with a dry dressing, $n = 50$. C: Each day ulcers were cleaned with dilute hydrogen peroxide or dilute potassium permanganate and non-adherent dressings were applied. Paraffin-impregnated dressings were most commonly used, but saline dressings and bland ointments were occasionally used. In case of difficulties the physician was able to modify the treatment. Other therapies used included: Salvstrumpa®, merbromine and systemic antibiotics, $n = 45$. In both groups during the first few days when exudate was heavy the dressings could be changed twice daily, but for the remainder of the trial this was seldom necessary and dressings were changed daily. All patients were treated with compression bandages applied by a nurse either at the clinic or at home. Some patients were trained to change their own bandages (*n*-values given are for patients remaining after withdrawals).	Mean wound area (cm^2): I: 20.1 (4.4 SEM) C: 34.0 (5.7 SEM) Other characteristics: I / C Mean (SEM) age (years): 68.1 (1.99) / 72.1 (3.54) M:F ratio: 1:2.8 / 1:3.5 Mean (SEM) duration (months): 26.5 (18.3) / 22.2 (14.3) Wound type: Venous 37 / 30 Other 1 / 6 Depth of ulcer: Deep 11 / 12 Superficial 26 / 23 Very superficial 1 / 1 No significant difference between the two groups. Baseline details are only available for the 74 patients completing the trial from the original 95 randomised.	Mean % change in wound area after 6 weeks (cm^2): I: –34% (5 SEM; $n = 38$) C: +5% (15 SEM; $n = 36$) ($p < 0.02$; Wilcoxon matched pairs signed-ranks test, two-sided).	I: Four patients did not meet the selection criteria; one developed a rash; two took holidays; two had beta-haemolytic Streptococcus infection; two had missing information; and one experienced recurrence of ulcer pain. C: Three patients did not meet the selection criteria; four had beta-haemolytic Streptococcus infection; one developed squamous cell carcinoma ; and one experienced a dramatic increase in ulcer size.	One patient on C and four on I complained of pain on application of the dressing. This subsided 30–60 min later. One patient developed a rash in the I group, but tests showed that this was due to coal tar derivatives and not the treatment. Another patient in this group acquired an itch around the ulcer which subsided after 2 weeks. Thyroxine, tri-iodothyronine, serum thyroxine binding protein and thyroid index did not change significantly over the study period.

Salvstrumpa®, manufacturer unknown

continued

TABLE 6 contd *Cadexomer iodine polysaccharide versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Steele *et al*, 1986[45] UK Wound type: Venous leg ulcers. Method of randomisation: Random number table. Objective outcomes: The wound perimeter was drawn onto a transparency and the area calculated by computer planimetry. Number of wounds healed was also recorded. Setting and length of treatment: Patients recruited from primary care practices. Six-week trial. Measurements taken at 0, 2, 4 and 6 weeks.	Inclusion criteria: Out-patients with venous leg ulcers present for more than 3 months, and larger than 2 cm^2. Exclusion criteria: Arterial disease, diabetes, rheumatoid arthritis, neurological disease, connective tissue disease, and ongoing hospital treatment.	Treatment: I: Cadexomer iodine polysaccharide powder (Iodosorb), covered with gauze, $n = 30$. C: A variety of agents were used including: antibiotics, antiseptics, hydrophilic agents, bland agents, steroids and dry dressings. All treatments were covered with gauze, $n = 30$. Dressings changed three times a week. All patients wore crêpe bandages.	Mean wound area (mm^2): I: 1264 (291 SEM) C: 1759 (397 SEM) ($p = 0.32$; statistical method not stated). Other characteristics: I C Mean age (years): 69.5 73.4 M:F ratio: 1:2.5 1:2.6 Mean duration (months): 16.6 16.3 No statistical differences between the two groups. Data are only available for 57 of the 60 participants.	% reduction in mean area of wounds at 6 weeks: I: 22% ($n = 28$) C: 18% ($n = 29$) ($p = 0.31$; chi-squared analysis) Number of wounds healed at 6 weeks: I: 3/30 (10%) C: 1/30 (3%)	I: 2 C: 1 Withdrawals due to hospital admission and lack of cooperation.	Pain directly after application was more common for I. Day-to-day pain was similar in both groups after 6 weeks' treatment.

TABLE 7 *Hydrogel dressings versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Brown-Etris *et al*, 1996[47] USA Wound type: Pressure sores. Method of randomisation: 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: A multicentre trial. Participation was until 10 weeks, or when treatment change was indicated or the wound healed, whichever came first.	Inclusion criteria: Patients > 18 years with one or more pressure sores. Stage II, III or IV only. Wound size between 2 cm 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: Stage I sores or Stage IV sores 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.	I: Hydrogel dressing (Transorbent), *n* = 77. C: Hydrocolloid dressing (Duoderm CGF), *n* = 63. Evaluation took place weekly, dressing changes occurred every 7 days or more frequently.	Mean wound area: Not stated Other characteristics: All groups Mean age (years): 70 M:F ratio 1:1 I C 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 0% 2%	Number of wounds healed at 10 weeks: I: 39/77 (51%) C: 37/63 (59%) Reduction in mean area of wounds at 10 weeks: Stage II sores (2–30 cm^2): I: 3.6 cm^2 (*n* = 12) C: 2.3 cm^2 (*n* = 12) (NS) Stage II sores (2–30 cm^2): I: 6.3 cm^2 (*n* = 42) C: 5.2 cm^2 (*n* = 36) (NS) Stage III sores (31–80 cm^2): I: 24.5 cm^2 (*n* = 3) C: 4.3 cm^2 (*n* = 2) (NS) Insufficient data were available for analysis of the subgroupings: Stage II (31–80 cm^2) Stage IV (2–30 cm^2) Stage 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.

continued

TABLE 7 contd *Hydrogel dressings versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Darkovich *et al*, 1990[46] USA Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcomes: Perimeter of the wound was traced and in some cases photographed to determine size. The number of wounds healed was also recorded. 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 stage I or II pressure sores ulcers (size > 2 cm^2). Exclusion criteria: Receiving radiation therapy; infection, sinus tracts or fistulas in the wound; a blood sugar level > 180 mg/dl; no improved nutritional status.	I: Hydrogel dressing (Biofilm), *n* = 60 wounds. C: Hydrocolloid dressings (Duoderm), *n* = 63 wounds. 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 the same type of pressure-reducing mattresses.	Mean area of pressure sore (cm^2): I: 11.0 (0.2–100 range) C: 9.2 (0.4– 64 range) Other characteristics: All groups Mean age (years): 75 (range, 30–98) M:F ratio: 1:1.6 I C Ratio of grade I:II ulcers: 1:1.3 1:1.6 Serum albumin (gm/dl): 2.8 2.7 No. of stage I wounds: 27 31 No. of stage II wounds: 35 36 There was a significant difference between the age of patients in the acute care setting (69 years) and the extended care facilities (83 years).	Mean wound area at 60 days (cm^2): I: 3.5 C: 5.5 Mean reduction in wound area at 60 days (cm^2): I: 7.5 (68% reduction) C: 3.7 (40% reduction) Number of wounds healed at 60 days: I: 26/60 (43%) C: 15/63 (24%) Mean treatment days: I: 12 C: 11.3	I: One patient was excluded because the wound enlarged by > 10% per day. One patient was excluded because the wound decreased by > 25% per day. C: Three patients were excluded because their wounds enlarged by > 10% per day. One patient was excluded because the wound decreased by > 25% per day.	Patients appeared to prefer I (hydrogel) because of the lack of odour, cushioning and lightness. The gel layer in C (hydrocolloid) was found to degrade easily which necessitated mechanical cleansing of the wound, which damaged the healing tissue layers.

continued

TABLE 7 contd *Hydrogel dressings versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Lum *et al*, 1996 (unpublished)[48] Hong Kong Wound type: Pressure sores. Method of randomisation: Patients with an odd admission number were assigned to the control group, those with an even number were assigned to the treatment group. Objective outcome: Wound size was measured. In addition the time spent by nursing staff and cost of pharmaceuticals was monitored. Setting and length of treatment: Post-acute hospital. Treatment progression was monitored weekly and a final assessment was made after 8 weeks, complete healing, discharge or death.	Inclusion criteria: Hospitalised post acute patients aged ≥ 65 years with pressure sores. Exclusion criteria: Pressure sores ≤ 1 cm^2; grade 1 sores; patients considered for supportive care only; patients requiring antimicrobial agents for management of systemic infection from pressure sores; patients (or carers) did not give consent for the study.	Treatment: I: Hydrogel dressing (Intrasite Gel) covered with a hydrophilic polyurethane foam dressing (Allevyn®), *n* = 12 wounds from five patients. C: The sore was cleansed with a frequency dependent on the amount of discharge (for uninfected sores cleansing was performed by saline only while for infected sores cleansing was performed with 1/2 Eusol for at most three times a day followed by rinsing with saline), *n* = 8 wounds from five patients. All patients received the same general treatment which included: bathing at least on alternate days; turning every 2 hrs (7 am–11 pm) and every 3 hrs (11 pm–7 am); given at least 1.5 litres of fluid per day unless contraindications existed; nutritional support and monitoring; vitamins only to be given if evidence of deficiency; anti-microbial agents only to be given with evidence of systemic sepsis.	Mean wound area (cm2): I: 36.3 (range, 1.5–160) C: 18.6 (range, 1.0–72.5) Other characteristics: I / C Mean age (years): 80 / 78.4 M:F ratio: 1:4 / 1:1.5 Mean duration (months): Not stated No statistically significant difference between the two groups was reported.	Mean size of pressure sore at final assessment (cm^2): I: 15.9 (p = 0.02) C: 20.5 (p = 0.87) (p = 0.94; Wilcoxon sign test or Mann-Whitney rank sum test were used for statistical analysis) Mean % change in wound area at final assessment: I: –56% C: +10% Cost of local treatment (HK$): I / C Nursing time: 785 / 1658 Pharmaceutical items: 1884 / 280 Treatment with I was statistically less expensive than treatment with C.	I: No withdrawals. C: Two patients died from pneumonia.	Estimated manpower required for general care was 5.8 and 2.72 hr/day/patient, with less time used in the treatment arm (p = 0.046). The average duration of stay was 4.8 days in the I (Hydrogel) group and 6.4 days in the C (standard treatment) group (p = 0.15; NS).

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continued

TABLE 7 contd *Hydrogel dressings versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Mulder *et al*, 1993[49] USA Wound type: Pressure sores. Method of randomisation: Computer allocation. Objective outcomes: The wound perimeter was traced on to a transparency and the area determined by computer analysis. In addition the largest length, width and depth of each wound was measured and a photograph taken at each assessment. Setting and length of treatment: A multicentre trial at three independent sites. Assessments of wound size were made weekly for 8 weeks or until the wound was healed. Where possible, each patient was evaluated by the same investigator throughout the trial. Efforts were made to standardise observations between investigators.	Inclusion criteria: In-patients and out-patients with stage II and III pressure sores. Sores ≥ 1.5 cm x 0.5 cm and ≥ 10 cm x 10 cm were included. Patients were ≥ 18 years and had a life expectancy of at least 2 months. Exclusion criteria: Stage 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: I: Hydrogel dressing (Clearsite), changed twice a week, *n* = 23. C1: Hydrocolloid dressing (DuoDerm), changed twice a week, *n* = 20. C2: 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 were analysed for only 64.	Mean wound area (cm^2): Not stated. Other characteristics: I C1 C2 Mean age (years): 56.7 63.1 57.2 M:F ratio: 1:3.6 1:5.6 1:9.5 Wound stage: II: 8 9 5 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 was reported.	Mean % reduction in wound area per week: I: 8 (14.8 SD) C1: 3.3 (32.7 SD) C2: 5.1 (14.8 SD) ($p > 0.05$; non-parametric test) Median % reduction in wound area per week: I: 5.6 C1: 7.4 C2: 7.0 ($p > 0.05$; non-parametric test)	Three patients were not evaluable and their data are not presented in the baseline characteristics. I: Three patients were omitted from the final analysis. No reasons were given for these withdrawals. C1: No withdrawals. C2: No withdrawals.	One patient in the C1 treatment group (hydrocolloid) had mild irritation, and another had minor sensitivity to the C1 dressing. One case of inflammation occurred in the I (hydrogel) group, and another patient had excoriation which was possibly related to I. There were no adverse reactions to C2 (saline).

TABLE 8 *Enzyme preparations versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Ågren and Strömberg, 1985[9] Sweden Wound type: Pressure sores. Method of randomisation: Patients consecutively matched in pairs (for what not stated). Each member of the pair was randomly allocated to one of the two treatments. Objective outcome: Wound area was traced and the size measured by planimetry. A photograph was taken at each assessment. Setting and length of treatment: Single-blind trial for 8 weeks. One of the authors was responsible for measuring all the wounds at weekly intervals. An independent surgeon from another hospital assessed the photographs.	Inclusion criteria: Elderly in-patients and out-patients with one or more necrotic pressure sores. Exclusion criteria: Not stated.	Treatment: I: Streptokinase/streptodornase enzyme preparation (Varidase Topical) applied to a sterile gauze compress. Dressings changed twice daily, *n* = 14. C: Zinc oxide (400 mg ZnO/cm^2) applied to a sterile gauze compress. Dressings changed once daily, *n* = 14. All dressings were secured with porous acrylic-based tapes. Where multiple wounds existed they were all treated uniformly, but only the largest was monitored. Prior to treatment loosely attached necrotic material was removed, but no surgical debridement was performed thereafter. No patients received antibiotics. Nursing care followed its usual procedure.	Median wound area (cm^2): I: 4.2 (range, 1.2–18.2) C: 5.8 (range, 1.2–26.0) Other characteristics: I C Median age (years): 86 81 M:F ratio: 1:3.7 1:1.8 Diabetes mellitus (*n*): 4 5	% median change in wound area at final assessment: I: +18.7% C: –2.4%	I: Three patients were withdrawn because of unsuccessful treatment. In one of these patients a skin reaction occurred on the heel after 3 weeks of treatment. In another patient necrosis developed to 8x its original size. In the third patient *Pseudomonas aeruginosa* infection developed after 6 weeks. C: No withdrawals All withdrawals were included in the analysis.	I (enzyme) was associated with an increase in wound size. This may be due to excessive wound debridement, or inhibition of tissue growth by the enzyme.

continued

TABLE 8 contd *Enzyme preparations versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Gordon, 1975[51] UK Wound type: Leg ulcers. Method of randomisation: Not stated. Objective outcome: Wound area was estimated by measuring the two largest diameters and multiplying together. Each wound was photographed. Setting and length of treatment: Patients attending a clinic for leg ulcer treatment. Assessments were made at weekly intervals for 6 weeks.	Inclusion criteria: Patients with leg ulcers considered to be post-thrombotic. Exclusion criteria: Not stated.	Treatment: C: Formulation A – hydrocortisone acetate and neomycin palitate, $n = 9$. I: Formulation B (Chymacort). This treatment was the same as formulation A but with the addition of the pancreatic enzymes chymotrypsin and trypsin in the proportion of 1:6, $n = 10$. All wounds were covered with a non-adherent dressing; a tube gauze; an absorbent gauze dressing pad over the wound area; and finally a 4-inch crêpe bandage applied from the toes to the knee Dressings were changed at the clinic. Patients were instructed not to interfere with dressings and to remain fully ambulant.	Approximate mean wound area (cm^2): C: 14.50 (22.13 SD) I: 15.82 (19.67 SD) Other characteristics: All groups Mean age (years): 61 M:F ratio: 1:9.5 There was no statistical difference between the two groups with respect to the given baseline characteristics.	Approximate mean wound area at 6 weeks: C: 8.40 (9.79 SD) I: 5.37 (7.82 SD) (C vs. baseline, $p < 0.05$; I vs. baseline, $p < 0.01$; statistical test method not stated) Number of wounds healed after 6 weeks: C: 0/9 (0%) I: 2/10 (20%)	C: One patient defaulted after the first week of treatment and was excluded from the analysis. I: No withdrawals.	Pain caused by treatment was insufficient to cause withdrawal in either group.
Lee & Ambrus, 1975[50] USA Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Two diameters of the wound measured and a colour photograph taken. In addition a volume mould was made with Jeltrate or Kerr No.1, and the volume determined by water displacement. Setting and length of treatment: Setting not stated. Patients were treated for 4 weeks or until complications developed or the patient died. Measurements where taken weekly and on completion of the study.	Inclusion criteria: Patients with advanced pressure sores. Exclusion criteria: Not stated.	Treatment: I: Collagenase enzyme preparation (Santyl) applied at 250 units per gram of white petrolatum, $n = 17$. C: Placebo (heat-inactivated Santyl) applied in the same proportions as for I, $n = 11$. Before application of either treatment the wound was washed with sterile saline (pH 7.5). Each application was applied once daily to each wound unless more frequent cleansing was required because of contamination from incontinence of urine, faeces or both. All wounds were covered with a sterile gauze pad.	Mean wound area (cm^2): Not stated. Mean wound volume (cm^3): I: 15.44 (19.92 SD) C: 1.25 (1.62 SD) Other characteristics: All groups Mean age (years): 67.6 (13.7 SD) M:F ratio: 1:2.7 Baseline wound volume is significantly different between groups ($p < 0.01$). 11 patients with 28 advanced pressure sores were included in the study. All had chronic disease and were in poor physical condition. Four had neoplastic disease; four had atherosclerotic heart disease or had a cerebrovascular accident, or both; two had Parkinson's disease; and one had a femoral neck fracture.	Mean % change in wound volume at completion of the trial: I: +13.14 (59.8 SD) C: +78.79 (94.6 SD) (Pressure sores in both groups increased in size.)	I: Patients were removed from day 6 to day 30 (termination of the trial). C: Patients were withdrawn from day 3 to day 10. No patient in this group continued to be treated after 10 days.	One wound treated with I (enzyme) experienced mild bleeding and a burning sensation.

continued

TABLE 8 contd *Enzyme preparations versus traditional or control treatments*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Parish and Collins, 1979[37] USA Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Number of ulcers healed. Setting and length of treatment: Community (nursing home) 4-week trial.	Inclusion criteria: Patients with pressure sores residing in a nursing home. Exclusion criteria: Not stated.	I: Collagenase enzyme preparation (Santyl) applied daily after a saline wash and covered with a dry dressing, *n* = 11 wounds from five patients. C: Sugar and egg white applied after a saline wash. Changed four times a day. Allowed to dry and not covered, *n* = 9 wounds from five patients.	Mean wound size = √ of surface area (cm): I: 3.2 C: 2.4 No statistical difference between the groups for ulcer size. Other characteristics: I C Age range (years): 28–59 32–70 M:F ratio: Not stated Mean duration (months): Not stated	Number of wounds healed at 4 weeks: I: 1/11 (9%) C: 0/9 (0%) Number of patients with healed ulcers at 4 weeks: I: 1/5 (20%) C: 0/5 (0%)	No withdrawals.	No side-effects reported by patients with any of the treatments.
Westerhof *et al*, 1987[52] The Netherlands Wound type: Chronic leg ulcers. Method of randomisation: Patients allotted a code number, one per leg. Treatments were also randomised and codes concealed from the investigators. Objective outcome: Number of wounds healed and the number where skin grafting was a success. A colour photograph was taken by standardised photography at each assessment period. Setting and length of treatment: Assessments were made twice weekly. Both the patient and assessor were blind to the treatment given. Final assessment was made by two independent investigators. Treatment was continued until the assessor was confident to initiate grafting.	Inclusion criteria: Patients with chronic leg ulcers referred for skin grafting. Exclusion criteria: Pregnancy; hypersensitivity to Elase; in ability to be treated by the usual pregrafting method.	Treatment: I: Enzyme preparation (Elase; a freeze-dried powder containing 25 U fibrinolysin and 15,000 U desoxyribonuclease), *n* = 16. C: Placebo powder (freeze-dried powder without active ingredients), *n* = 17. Wounds were first cleaned with saline. The treatment and placebo powders were dissolved in 30 ml of saline and used to soak gauze pads. The soaked pad was applied to the ulcer and covered with a paraffin dressing and bandaged. Dressings were changed three times a day by nurses familiar with the procedures. 34 patients were enrolled for the trial with 37 leg ulcers. Patient allocation details are only available for those patients completing the study.	Mean wound area (cm^2): I: 25.7 (2, 273 range) C: 20.2 (2, 48 range) Other characteristics: I C Mean age (years): 75.9 73.5 M:F ratio: 1:2.2 1:1.3 Mean duration (months): 19.8 13.8 Venous stasis ulcers: 10 9 Complex ulcers: 6 8 Baseline characteristics are only available for 30 of the 34 patients.	% of wounds successfully grafted or needing no grafting: I: 69 (95% CI: 44, 86) C: 35 (95% CI: 17, 59) % of complex ulcers successfully grafted or needing no grafting: I: 50 (95% CI: 19, 81) C: 38 (95% CI: 14, 69) % of venous stasis ulcers successfully grafted or needing no grafting: I: 80 (95% CI: 49, 94) C: 33 (95% CI: 12, 65)	Four patients were excluded from the analysis for reasons unrelated to the therapy. These withdrawals were not included in the baseline data.	The authors state that debridement with I (enzyme) helped to make the wound receptive to skin grafting. The presence of complex leg ulcers may have extended the length of treatment needed prior to grafting.

continued

TABLE 9 *Zinc oxide tape versus traditional treatment*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Apelqvist *et al*, 1990[53] Sweden Wound type: Diabetic foot ulcers. Method of randomisation: Not stated. Objective outcomes: Area of necrotic tissue measured and a colour photograph taken. A successful outcome was when the necrotic area had reduced by 50% or more. Evaluations were blinded. Setting and length of treatment: Outpatient clinic. Assessments were made weekly for 5 weeks.	Inclusion criteria: Patients with necrotic diabetic foot ulcers (superficial full thickness skin ulcer below ankle and with systolic toe pressure above 45 mmHg or absence of cutaneous erythema; ulcers between 1–25 cm^2 in area with > 50% of area covered with dry/wet necrotic tissue). Where there was more than one ulcer the largest was chosen. Exclusion criteria: Positive patch test; clinical signs of cellulitis; ulcers where the application of these dressings was inappropriate.	Treatment: I: Adhesive zinc oxide tape (MeZinc®), *n* = 22. C: Hydrocolloid dressing (DuoDerm), *n* = 22. All patients were offered the same additional treatment: the foot wear was corrected and external pressure on the ulcer relieved. Ulcers were cleaned with sterile saline and dressed according to the manufacturers guidelines. Dressings were changed daily for the first week and every 3 days afterwards. No surgical debridement was allowed.	Mean wound area (cm^2): I: 2.2 (1, 10.5 SD) C: 2.2 (0.9, 20.4 SD) Mean necrotic area of wound (cm^2): I: 1.5 (0.5, 10.5 SD) C: 1.6 (0.9, 19.2 SD) Other characteristics: I / C Mean age (years): 63 / 62 M:F ratio: 1:1.2 / 1:0.5 Mean duration (years) of diabetes: 22 / 19 Insulin: 17 / 18 Systolic toe pressure (mmHg): 66 / 68 Systolic ankle pressure (mmHg): 104 / 114	Number of wounds reduced by 50% or more at 5 weeks: I: 14/21 (67%) C: 6/21 (29%) Mean % change in wound area at 5 weeks: I: 60% reduction (*n* = 18) C: 5% increase (*n* = 17)	I: Four patients because of > 50% increase in area of necrotic tissue, associated pain and oedema or signs of cellulitis. C: Five patients because of > 50% increase in area of necrotic tissue, associated pain and oedema or signs of cellulitis.	Common adverse effects were seen in both groups which were usually maceration of the skin edges. The compliance of patients was reported as excellent.

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TABLE 10 *Cadexomer iodine polysaccharide versus other debriding agents*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Moss *et al*, 1987[13] UK Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcomes: The wound perimeter was drawn onto polythene squares and the area calculated by computer planimetry. The number of wounds healed was also recorded. Setting and length of treatment: 6-week trial. Measurements taken at 0, 2, 4 and 6 weeks. After 6 weeks patients were allowed to cross-over.	Inclusion criteria: Out-patients with unresponsive venous leg ulcers for > 3 months. Patients with ischaemic venous insufficiency were included. Exclusion criteria: Not stated 56 patients were recruited and observed on a variety of standard treatments. Those not improving after 6 weeks were admitted to the trial (n = 43).	I: Cadexomer iodine polysaccharide powder (Iodosorb), n = 21. C: Dextranomer polysaccharide beads (Debrisan), n = 21. Both agents were covered with a non-adhesive pad, cotton-wool wadding, stockinette and a firm elastic bandage. If bacterial infection occurred a 2-week course of oral antibiotics was allowed.	Median wound area (cm^2): I: 19.7 (19.8 SD) C: 25.5 (29.5 SD) Other characteristics: I / C Median age (years): 70 / 68 M:F ratio: 1:3.5 / 1:4.2 Median duration (months): 75 / 61 Ischaemia: 6 / 5 No statistical differences between the two groups. Data are only available for 42 of the 43 patients.	% reduction in mean wound area at 6 weeks: I: 4 (95% CI: 5, –14) C: 3 (95% CI: 4, –9) (p > 0.05; two sample t-test) No significant change in wound size from baseline over 6 weeks (paired t-test). Number of wounds healed at 6 weeks: I: 0/21 (0%) C: 0/21 (0%)	One patient was withdrawn from the trial at week 4 because of poor compliance. Data are only available for the 42 patients remaining for the 6-week treatment period.	The antibacterial properties of I (cadexomer polysaccharide) were of little advantage in the treatment of resistant chronic leg ulcers.
Stewart and Leaper, 1987[55] UK Wound type: Leg ulcers. Method of randomisation: Computer allocation. Objective outcome: Number of wounds healed. Setting and length of treatment: 10-week trial. Measurements taken weekly for 6 weeks and then once at 8 and 10 weeks thereafter.	Inclusion criteria: Out-patients with leg ulcers of various aetiologies. Exclusion criteria: receiving steroids, cytotoxics, or antibiotics; poor nutritional status; abnormal thyroid function; unable to give informed consent.	I: Cadexomer iodine polysaccharide powder (Iodosorb) applied to a depth of 3 mm, n = 46. C: Hydrogel dressing (Scherisorb/Intrasite) applied to a depth of 5 mm, n = 49. Both treatments were covered with gauze, a non-adherent dressing and padding. A crêpe bandage, or for those with a venous ulcer a Tubigrip stocking were supplied if the patient agreed to wear them.	Median wound area (cm^2): I: 2.8 (range, 0.2–50.5) C: 2.6 (range, 0.4–74.4) (p > 0.05; Mann-Whitney U test). Other characteristics: I / C Mean age (years): 70 / 77 M:F ratio: 1:1.4 / 1:2.8 Mean duration (months): 12.0 / 24.0 No statistical differences between the groups with the exception of age (p < 0.01; Mann-Whitney U test).	Number of wounds healed at 10 weeks: I: 14/46 (30%) C: 14/49 (29%) (p > 0.05; chi-squared analysis).	I: 13 patients. C: 11 patients. Three patients died; 18 were withdrawn by request; two had allergies; one was lost to follow-up.	Both agents were similar for dressing time and pain experienced by the patient. Cost for one week of treatment per person: I: £4.68 C: £3.33

continued

TABLE 10 contd *Cadexomer iodine polysaccharide versus other debriding agents*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Tarvainen, 1988[54] Finland Wound type: Chronic leg ulcers. Method of randomisation: Sealed envelopes. Objective outcome: Number of ulcers healed. Length of treatment: Outpatient clinic. 8-week trial. Measurements taken at 0, 2, 5 and 8 weeks.	Inclusion criteria: Out-patients > 18 years with chronic exuding leg ulcers presenting at one of three clinics. Exclusion criteria: Insulin-dependent diabetes mellitus; rheumatoid arthritis and other connective tissue diseases; goitre or known allergy to iodine.	Treatment: I: Cadexomer iodine polysaccharide powder (Iodosorb), *n* = 14. C: Dextranomer polysaccharide powder (Debrisan), *n* = 13. Both agents applied to a depth of 3 mm and covered with a clean compress. A compression bandage was applied around the leg. Dressings changed once daily by soaking. Wounds were cleansed mechanically before applying a new dressing.	Mean wound area: Not stated. Other characteristics: I C Mean age (years): 67.7 68.8 M:F ratio: 1:2.5 1:3.3 Mean duration (months): 54.8 12.2	Number of wounds healed at 8 weeks: I: 7/14 (50%) C: 2/13 (15%)	I: Three patients had bacterial infection; one patient experienced pain; and in one patient the wound increased in size. C: Two patients had bacterial infection; and one patient experienced pain.	Three patients in the I group (cadexomer polysaccharide) and one in the C group (dextranomer polysaccharide) complained of pain during the treatment period. This pain was severe in two of the patients, one in each treatment group, and resulted in withdrawal from the study.

TABLE 11 *Dextranomer polysaccharide versus other debriding agents*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Colin *et al*, 1996[56] France Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Percentage reduction in area of non-viable tissue (wound area x (% yellow + % black tissue) x 1/100). Photographs were taken at the initial and final assessment. Setting and length of treatment: Open, multicentre, multi-national, parallel group trial. Six different centres were involved with approximately equal numbers of patients in each trial. Assessments were made every 7 days until the wound was cleansed or on the completion of 21 days.	Inclusion criteria: Male and female patients ≥ 16 years with pressure sores present in any area that needed cleansing. Exclusion criteria: Pregnancy, immunodeficiency, clinical infection of the wound, hard black eschar covering more than 20% of the wound, diabetes, inability to follow the demands of the protocol in for any reason, non-consenting patients.	Treatment: I: Dextranomer polysaccharide paste (Debrisan), *n* = 68. C: Hydrogel dressing (Intrasite Gel), *n* = 67. The two interventions were applied in accordance with the manufacturers' instructions. An absorbent plastic film dressing (Melolin) was used as a standardised secondary dressing for both treatments. Where a patient had more than one wound only the largest was evaluated in the trial. Other wounds were treated with the same randomised dressing if this was considered appropriate by the clinical investigator.	Wound area: I / C < 4 cm^2: 18 / 15 4–13 cm^2: 25 / 25 > 13 cm^2: 25 / 27 Non-viable tissue area: I / C < 3 cm^2: 18 / 15 3–9 cm^2: 27 / 24 > 9 cm^2: 23 / 28 Other characteristics: I / C Median age (years): 81 / 79 M:F ratio: 1:1 / 1:1.4 Sore duration: < 1 month: 22 / 24 1–3 months: 35 / 28 > 3 months: 11 / 15 Sore grade: 1: 1 / 0 2: 10 / 16 3: 45 / 38 4: 12 / 13 Authors state groups were well matched. All patients gave written consent and were capable of participating in the trial.	Median % reduction in wound area at 21 days: I: 7 (–340, 98% range) C: 35 (–185, 91% range) (p = 0.03; Wilcoxon Rank Sum test). Number of wounds by degree of cleansing at 21 days: I / C 100%: 14 / 13 75–99%: 15 / 20 50–74%: 13 / 12 25–49%: 6 / 9 0–25%: 7 / 5 Deteriorated: 13 / 8 Overall median % reduction in non-viable tissue at 21 days: I: 62 (–340, 100 range) C: 74 (–103, 100 range) (p = 0.20; Wilcoxon Rank Sum test)	I: 19 lost to follow-up, two died, four adverse reactions (one related to pain on application of the agent, no details on the other three). C: 11 lost to follow-up, two died, and one adverse reaction.	Five adverse events were reported, one in the C group (hydrogel) and four in the I group (dextranomer polysaccharide). The only one considered to be dressing related was pain reported by one patient in the I group. C was found to be easier to apply and remove than the I. C was also found to be associated with less pain.

continued

TABLE 11 contd *Dextranomer polysaccharide versus other debriding agents*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Hulkko *et al*, 1981[58] Finland Wound type: Venous leg ulcers. Method of randomisation: Not stated. Objective outcome: Longest and shortest diameters of each wound were measured, the product of which was used as a measure of wound size. Wounds were also photographed at each assessment. Setting and length of treatment: Hospital-based trial. Assessments were made at 7 and 14 days.	Inclusion criteria: In-patients with venous leg ulcers. Exclusion criteria: Not stated.	Treatment: I: Dextranomer polysaccharide beads (Debrisan) in a glycerin paste (ratio 4:1) applied to the wound in a layer at least 3 mm thick. The wound was covered with a dry sterile compress. Dressings were removed by rinsing with water or saline irrigation Dressings were changed twice a day and dextranomer was applied to only moist wounds, *n* = 18. C: Streptokinase/streptodornase enzyme preparation (Varidase Topical). One ampule was diluted with 20 ml of physiological saline. The solution was either placed directly onto the wound or a sterile compress was soaked in the solution prior to application. A waterproof sheet was placed on top of the compress. Applications were changed twice daily, *n* = 13. All hard necrosis was excised from wounds in both groups before commencement of the trial.	Mean wound size: Not stated. Other characteristics: I C Median age (years): 68.8 65.1 M:F ratio Not stated Ulcer duration: < 1 month 1 1 1–12 months 8 6 > 12 months 9 6 All wounds were exuding and many of them were also necrotic.	Mean reduction in wound size at 14 days (mm): I: 9.3 C: 9.8 Mean % reduction in wound size at 14 days: I: 14.5 C: 11.9 (NS)	I: Three patients were withdrawn, no reasons given. C: Treatment was interrupted between the day 7 and day 14 in one patient because of pain.	No adverse effects were reported in patients treated with I (dextranomer polysaccharide). Two patients in the C group (enzyme) experienced pain, and in one it was severe. One wound treated with I increased in size. There was no size increase reported in the C group.
Parish and Collins, 1979[37] USA Wound type: Pressure sores. Method of randomisation: Not stated. Objective outcome: Number of wounds healed. Setting and length of treatment: Community (nursing home) 4-week trial.	Inclusion criteria: Patients with pressure sores, residing in a nursing home. Exclusion criteria: Not stated	Treatment: I: Dextranomer polysaccharide beads (Debrisan) applied to a depth of at least 3 mm covered with a dry dressing. Changed 1–3 times daily depending on exudate, *n* = 14 wounds from seven patients. C: Collagenase enzyme preparation (Santyl) applied daily after a saline wash and covered with a dry dressing, *n* = 11 wounds from five patients.	Mean wound size = √ of surface area (cm): I: 4.5 C: 3.2 No statistical difference between the groups for wound size. Other characteristics: I C Age range (years) 29–57 28–59 M:F ratio: Not stated Mean duration (months): Not stated	Number of wounds healed at 4 weeks: I: 6/14 (43%) C: 1/11 (9%) Number of patients with healed wounds at 4 weeks: I: 4/7 (57%) C: 1/5 (20%)	No withdrawals	No side-effects reported by patients with any of the treatments.

continued

TABLE 11 contd *Dextranomer polysaccharide versus other debriding agents*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Thomas and Fear, 1993[57] UK Wound type: Pressure sores. Method of randomisation: Computer-generated randomisation code. Objective outcome: The number of wounds fully cleansed. Cleansing was determined by measuring the % of total wound area covered in slough. Setting and length of treatment: 2-week trial. After 14 days those wounds showing no improvement were withdrawn while the remaining wounds were followed for a further 14 days.	Inclusion criteria: Hospitalised patients with grade 3 or 4 pressure sores. The wounds had to be covered or partially covered with yellow/brown slough. Exclusion criteria: Age < 16 years, insulin-dependent diabetes, immuno-suppression, pregnancy, cellulitis and redness of the surrounding tissue (indicative of infection).	Treatment: I: Dextranomer polysaccharide beads (Debrisan) made into a paste with polyethylene glycol 600 and water. The paste was applied to a depth of 10 mm over a layer of polyamide net, *n* = 20. C: Hydrogel dressing (Intrasite Gel) applied to a depth of 5 mm. Covered with a perforated plastic film absorbent dressing held in place with tape or a bandage, *n* = 20. Dressings were changed as required, and the wound cleansed with saline before reapplication.	Mean wound area (cm^2): I: 15.6 (16.2 SD; range 1.5–68.9) C: 22.2 (23.4 SD; range, 2.6–91.4) % wound area covered in slough: I: 75.3 (22.4 SD; range, 20–100) C: 73.5 (29.7 SD; range, 20–100) Other characteristics: 		I	C
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Mean age (years):	81.0	83.5
M:F ratio:	1:5.7	1:3.8
Ratio of grade 3:4 ulcers	5.7:1	3.8:1	 Values are only given for 39 of the 40 patients entering the trial.	Number of wounds cleansed at 14 days: I: 1/20 (5%) C: 8/20 (40%) (p = 0.008; Fischer's exact test) After 14 days all ulcers were reassessed. Wounds showing no evidence of debridement were classed as failures and withdrawn. The remaining wounds were followed for another 14 days. Additional wounds cleansed after follow-up at 28 days: I: 4/20 (overall – 5/20; 25%) C: 0/20 (overall – 8/20; 40%)	Up to 14 days: I: three because of difficulty in applying the dressing. Classed as failures in the results. C: one patient because the case report forms were mislaid. Up to 28 days: Withdrawals occurred over the follow-up period leaving four patients in the C group and two patients in the I group.	C (hydrogel) had to be changed more frequently than I (dextranomer polysaccharide). However, even with frequent dressing the cost of the C per patient was less than for the I. Mean cost per patient: I: £44.70 C: £22.60 (NB. Only successes costed not failures)

TABLE 12 *Hydrogel dressings versus hydrogel dressings*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Gibson, 1995[59] UK Wound type: Leg ulcers. Method of randomisation: Not stated. Objective outcomes: Wound area, and the area of wound covered in slough. Setting and length of treatment: A multicentre parallel trial conducted for 21 days or until the wound was considered to be cleansed. Measurements were taken at 0, 10 and 21 days or when the wound was clean.	Inclusion criteria: Patients with sloughy leg ulcers (> 10% surface area of wound covered in slough). Exclusion criteria: Not stated.	Treatment: I: Hydrogel dressing (Granugel), *n* = 30. C: Hydrogel dressing (Intrasite Gel), *n* = 32. Both hydrogels were covered with either an absorbent plastic film dressing (Melolin) or a knitted viscose dressing (Tricotex). Dressings were changed daily.	Mean wound area (cm^2): I: 24.9 C: 18.7 Other characteristics: I C Mean age (years): 77 76 M:F ratio: 1:2.3 1:3.5 Years since first ulcer: 8 4 88% of patients were treated in the community.	Median reduction in wound area over a 7-day period (cm^2): I: 0.744 C: 0.540 (p = 0.62; Wilcoxon Rank Sum test) Median reduction in slough over a 7-day period (cm^2): I: 1.511 C: 1.118 (p = 0.25; Wilcoxon Rank Sum test) % reduction in mean area of wound after 21 days: I: 14 C: 10 (p = 0.358; Wilcoxon Rank Sum test) % reduction in mean area of ulcer covered in slough after 21 days: I: 37 C: 32	Not stated.	Total costs for treatment per person from baseline to final assessment are: £43.25 for I and £40.25 for C. Both products were reported to be safe and convenient to use.

TABLE 13 *Enzyme preparations versus enzyme preparations*

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Hellgren, 1983[60] UK Wound type: Leg ulcers. Method of randomisation: Not stated. Objective outcomes: Wound area drawn onto a transparency and weighed to give an indirect measurement of wound size. At each evaluation a photograph was taken. Cleansing was also determined from the % wound area covered with granulating tissue. Setting and length of treatment: A randomised double-blind trial. Assessments were made at 7, 14 and 21 days. Both the patient and assessor were blind to the treatment given. Treatment was only terminated before 21 days if the ulcer was totally clean, or if serious side-effects occurred.	Inclusion criteria: Patients with leg ulcers covered with pus and debris. Exclusion criteria: Wounds < 3 cm^2, > 400 cm^2 or more than 6 cm deep.	Treatment: I: Trypsin enzyme preparation (Trypure). One ampule (50 mg) was mixed with 15 ml of saline, *n* = 19. C: Streptokinase/streptodornase enzyme preparation (Varidase Topical). One ampule (streptokinase-streptodornase 100,000 U and 25,000 U respectively) was mixed with 20 ml of saline, *n* = 21. Before application of the test treatment, each ulcer was washed with distilled water. Thereafter, wet compresses impregnated with enzymes were applied twice daily.	Mean wound area: Not stated. % granulated area of total ulcer area: I: 25% C: 22% Other characteristics: I / C Mean age (years): 68.9 / 69.7 M:F ratio: 1:1.4 / 1:4.3 Mean duration (months): Not stated Venous leg ulcers: 14 / 15 Arterial/venous and arterial leg ulcers: 3 / 3 Other leg ulcers, vasulitis, decubitus: 2 / 3 Concomitant diabetes mellitus (patients): 7 / 6 Concomitant treatment was left unchanged throughout the trial period.	Mean wound area at 21 days: There was no decrease in ulcer area. % granulated area of total wound area at 14 days: I: 56% C: 60% ($p < 0.01$ for both treatments compared with baseline. Student's *t*-test) Number of wounds fully cleansed at 21 days: I: 5/19 (26%) C: 13/21 (62%) A comparison of granulated area at 21 days was not made due to the high withdrawal rates.	I: Three patients because of pain associated with the dressing. Another five patients were withdrawn due to the wound being cleansed. C: 13 patients were withdrawn due to wound cleansing.	13/19 patients in the I group (Trypure), and 4/21 patients in the C group (Varidase) reported pain associated with the dressing. Pain was reported a severe in four of the I patients, while pain was recorded as mild in the C group. In nine patients treated with I and in three treated with C, chronic pain increased in intensity.

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This report was identified as a priority by the Pharmaceutical Panel.

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ISSN 1366-5278