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# Effectiveness of Advanced versus Conventional Wound Dressings on Healing of Chronic Wounds: Systematic Review and Meta-Analysis

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**Key Words**

Chronic wounds · Leg ulcers · Pressure ulcers · Diabetic foot ulcers · Wound dressings · Effectiveness · Wound healing · Meta-analysis · Systematic review

**Abstract**

***Background:*** Wound dressings are essential in the treatment of chronic wounds and should be selected on valid and recent evidence. ***Objective:*** Effectiveness of advanced compared to conventional dressings for chronic wound healing. ***Methods:*** Comprehensive literature search, systematic review and meta-analyses of the results of advanced dressing studies on chronic wound treatment. Comprehensiveness and coverage of all relevant studies is the most striking difference in relation to other meta-analyses and systematic reviews. ***Results:*** The mean odds ratio of complete healing was 1.52 favouring advanced over conventional dressings in 65 controlled trials. In 287 study conditions including uncontrolled studies, mean odds were 0.97 (advanced dressings/controlled studies), 0.77 (conventional/controlled) and 0.47 (advanced/uncontrolled). The overall healing rate was 33%. When causal treatment was applied, a reduced effect was observed. The consideration of all types of chronic wounds, advanced wound dressings and studies resulted in more study effects, more reliable estimates of mean effects and more statistical power. These differences in the design are likely to explain the differences in the meta-analytic results. ***Conclusion:*** A general superiority of advanced dressings on complete healing was shown. The generalizability of the results is limited by the methodological and report quality within studies identified, unexplained heterogeneity in study effects and possibly by publication bias.



## Background

The treatment of chronic wounds is of high clinical and socio-economic importance since chronic wounds are frequent [1] (up to 2 million Germans suffer from a chronic wound [2], show long courses of disease [3], pose a substantial burden of disease [4, 5], and raise high costs of illness [6, 7]). From the patient's perspective a chronic wound is often accompanied by physical pain and a restraint in quality of life. Further reported problems are wound odour, leakage of exudate, reduced mobility and activity as well as a reduction of choices regarding clothes and shoes [8]. Advanced and conventional wound dressings are a basic part of the treatment of chronic wounds. Whereas conventional (traditional, dry) dressings are only drug carriers, therapeutic substances are an integral part in advanced (wet) dressings. The indications for specific dressings vary with requirements of specific wound

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treatments. An efficient decision of dressing choice has to be based on valid and recent evidence.

However, clinical trials, reviews, and meta-analyses [9–14] of the effectiveness of dressings in the treatment of chronic wounds show heterogeneous results and, thus, present varying conclusions and recommendations. The differences in the results of reviews are likely to be explained by varying methods and restrictive in- and exclusion criteria for studies considered. To date, only a small proportion of all published clinical trials of wound dressings in the treatment of chronic wounds have been the subject to meta-analysis. Moreover, meta-analyses were conducted selectively for different indications or for specific classes of dressings. Therefore, it was decided to conduct a comprehensive meta-analysis on the effectiveness of advanced versus conventional wound dressings for chronic wounds, including all relevant diagnoses, types of dressings and types of studies.

The study was conducted to determine the effectiveness of advanced compared to conventional dressings in the treatment of chronic wounds.

## Methods

*General Study Approach*

The research question was addressed by a systematic literature review followed by meta-analyses. All methods were defined a priori and documented in a research protocol. The distinction between advanced and conventional wound dressings was unambiguously defined and fixed in the protocol. The classification of dressings was based on a recent consensus paper [8, 15].

To conduct a comprehensive review, the most general objective was selected and translated into search algorithms for multiple literature sources (see online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000348331). The pool of studies identified was screened by a minimal set of inclusion and exclusion criteria in order to sort out inappropriate publications, followed by a critical appraisal. All publications selected as relevant were coded and prepared for statistical analysis according to a standard scheme.

*Literature Search*

The systematic and protocol-driven literature search for published empirical evidence was conducted in the following online databases: PubMed/Medline, Embase, CINAHL, Cochrane Collaboration, Google/Google Scholar. Secondly, international guidelines and international networks were screened for publications. Finally, publications of the following organizations and professional associations were screened: Agency for Health Care Policy and Research, Association of the Scientific Medical Societies in Germany, Center for Structural and Cell Biology in Medicine, German Diabetes Association, German Society of Phlebology, European Tissue Repair Society, European Wound Management Association (EWMA), European Pressure Ulcer Advisory Panel, Ministry of Health Singapore, Institute for Quality and Efficiency in Health Care, National Guideline Clearinghouse, National Institute for Health and Clinical Excellence, National Pressure Ulcer Advisory Panel, Royal College of Nursing, Robert Koch Institute, Registered Nurses' Association of Ontario, Scottish Intercollegiate Guidelines Network, World Union of Wound Healing Societies.

The search was performed between August 15 and September 30, 2010. No date restrictions were applied. The search was complemented by a manual search in published meta-analyses. The search terms were defined according to the objective and published search algorithms from the appropriate literature. Also several Health Technology Assessment reports and Medline MeSH terms were considered. Consensus was reached on the final terms, the algorithms, and the sources to search between two review specialists, two dermatologists, two wound nurses, and the authors.

*Selection of Studies*

Two reviewers independently screened the titles and abstracts of identified studies for appropriateness by a priori specified inclusion and exclusion criteria. Discrepancies were resolved by consensus, a third reviewer was consulted when necessary. For inclusion, the following criteria had to be met:

- empirical study;
- treatment of chronic wounds;
- advanced topical dressings for the treatment of chronic wounds (specific local procedures such as negative-pressure therapy, biosurgical treatments and transplantation were not considered as dressings);
- design: randomized controlled trial, controlled trial, observational study with/without control condition;
- publication language: English, German, Danish, French, Italian, Spanish, Portuguese, Chinese and Korean.

*Data Extraction*

Relevant information was extracted from the full text publications by one reviewer and independently checked for accuracy and plausibility by a second reviewer. Extraction and coding were supported by a specifically developed coding handbook including examples. Coding was trained by one of the authors. Disagreements in coding were resolved by consensus or consultation of a third reviewer. Multiple publications of the same study were considered as a single study. The following information was extracted:

- study details (author, year, country, type of publication, dropouts, associated publications/reports, study design, number randomized and treated, setting, duration of follow-up, sample size calculation, types of analyses);
- participant details (age, gender);
- clinical characteristics (duration of wound, wound size and diagnoses, comorbidities);
- treatment characteristics (type of advanced dressing, type of control dressing, causal treatment);
- outcomes (healing, healing time, wound reduction, smell, exudate, satisfaction, pain, quality of life, infection rate).

In the category 'causal' were included therapies like pressure relief, e.g. professional fitted shoe provision or orthotics for diabetic foot ulcers, also pressure relief, like promotion of movement and positioning, considered for pressure ulcers, or compression, e.g. stockings or compression bandages, for venous leg ulcers.

*Statistical Analysis*

Complete healing of wounds was the primary outcome for analyses, since it is the internationally agreed 'gold standard' for effectiveness in the area of wound treatment research. Analyses of secondary outcomes, e.g. wound size reduction, health-related quality of life or pain reduction, were dismissed for reasons of further conceptual and modelling complexities in the presence of missing data. For these data, no further data inspection or analysis was done to prevent reporting bias due to knowledge of results on these outcomes (selective outcome reporting).

*General Strategy of Analyses.* Two sets of analyses were planned a priori. In the first set of analyses the effects of advanced versus conventional dressings in controlled studies were estimated. These analyses comprised the usual computation of within-study effects, i.e. the effects of advanced versus conventional dressings within each controlled study. The study effects were computed as odds ratios and aggregated to mean effects in a 2-factorial fixed effect model and a 2-factorial mixed effect model for sensitivity analysis. In the second set of analyses the effects of advanced versus conventional dressings in controlled and uncontrolled studies were estimated by computation of effects within each study arm. The effect measure computed was the odds. This odds of complete healing was computed for each wound treatment (study arm) involving: (a) advanced dressings, (b) conventional dressings in controlled studies and (c) advanced dressings in uncontrolled studies. Mean odds were computed in a 3-factorial fixed effect model and a 3-factorial mixed effect model for sensitivity analysis.

*Effect Measures.* The odds ratio and odds were chosen as effect measures for comparability between the sets of analyses. Mean rates of complete healing were computed and aggregated additionally. For all types of effect measures (odds ratio, odds and rate), the usual Yates [16] (1934) continuity correction was applied in the case of zero cell frequencies, i.e. 0.5 was added to each cell. All effects were computed as intention-to-treat effects, i.e. drop-outs and patients lost to follow-up were treated as having achieved no complete healing and, thus, the sample sizes considered are those at randomization/start of the studies.

*Predictors of Effects.* Diagnostic subgroups and the application of causal treatment were specified as independent but possibly interacting predictors of the study effects in a 2-factorial model. The factor levels for the diagnostic subgroups were: (1) ulcus cruris (venous, arterial or mixed aetiology), (2) pressure ulcers, (3) diabetic foot ulcers or (4) mixed diagnoses (any mixes of diagnoses). Factor levels for causal treatment were (1) application of causal treatment and (2) no application/no report of causal treatment (since 'no causal treatment' was reported in 3 studies, only both levels had to be combined). For the second set of analyses, a third factor contrasting (1) modern dressings in controlled, (2) modern dressings in uncontrolled and (3) conventional dressings in controlled study conditions was modelled.

*Fixed Effect Models.* To derive the mean effects, fixed effects were modelled by the inverse variance method. In these analyses, the reciprocals of the effect variances (precisions) served as the weights of the study effects [17, 18]. All study effects (odds ratio, odds, rates) were transformed by natural logarithm to normalize the distribution before computing effect variances, standard errors, confidence intervals (CI), study weights and weighted mean effects along with weighted homogeneity (Q and $I^2$ statistics) by meta-analysis [19, 20]. Study effects as well as mean effects within groups and the grand mean including CI were graphically displayed by forest plots. Funnel plots served as a graphical assessment of a probable presence of publication bias. For descriptive interpretation, results were transformed back to the original metric (odds ratio, odds, rate) by appropriate exponentiation. Fixed effect analyses were conducted with validated SPSS routines of the senior author [17] using SPSS version 20. Forest plots were prepared in Microsoft Excel 2003.

*Mixed Effect Models.* Since a generalization of results to studies other than those included in the analysis requires homogeneity of the study effects involved, sensitivity analyses were planned a priori to assess and quantify the consequences of a violation of this assumption. To quantify the consequences for interpretation and discussion, the study effects were allowed to vary randomly on a normal distribution around a study population effect (random effect). The variance component of the random effect was estimated by restricted maximum likelihood. Mixed effect analyses were conducted by meta-regression with the recently published R package metafor [21, 22]. The analysis of variance was designed by appropriate dummy coding of the factors. Interaction terms were derived by appropriate pairwise multiplication of dummy variables involved; dummy variables representing a factor/interaction were added as sets of predictors.

*Descriptive Analyses.* For a description of the studies included in the first and second set of analyses, fixed effect meta-analyses were performed for percentage of male study participants, mean age in the sample, mean duration of wounds and treatments. As standard deviations for these variables were often missing, the studies were simply weighted by sample size.

## Results

*Literature Search*

2,071 potentially relevant publications (k) were identified by title and abstract (fig. 1). Selection and critical appraisal resulted in 231 publications for complete data extraction. The set of analysis included all 170 studies reporting complete wound healing as an outcome (see online suppl. table 2). Out of these, 105 studies were non-comparative trials and 65 studies were trials with at least one comparison.

The first set of publications analysed (advanced vs. conventional dressings in controlled trials) consisted of 65 controlled trials with a total of 5,690 wounds. These included 37 publications on 3,342 leg ulcers, 10 publications on 1,297 diabetic foot ulcers, 14 publications on 768 pressure ulcers, and 4 publications on 283 mixed diagnoses.

The second set of publications analysed consisted of the 65 controlled and additional 105 non-comparative trials (complete wound healing in controlled and uncontrolled studies). These included a total of 22,492 wounds (170 publications), 6,205 leg ulcers (77 publications),

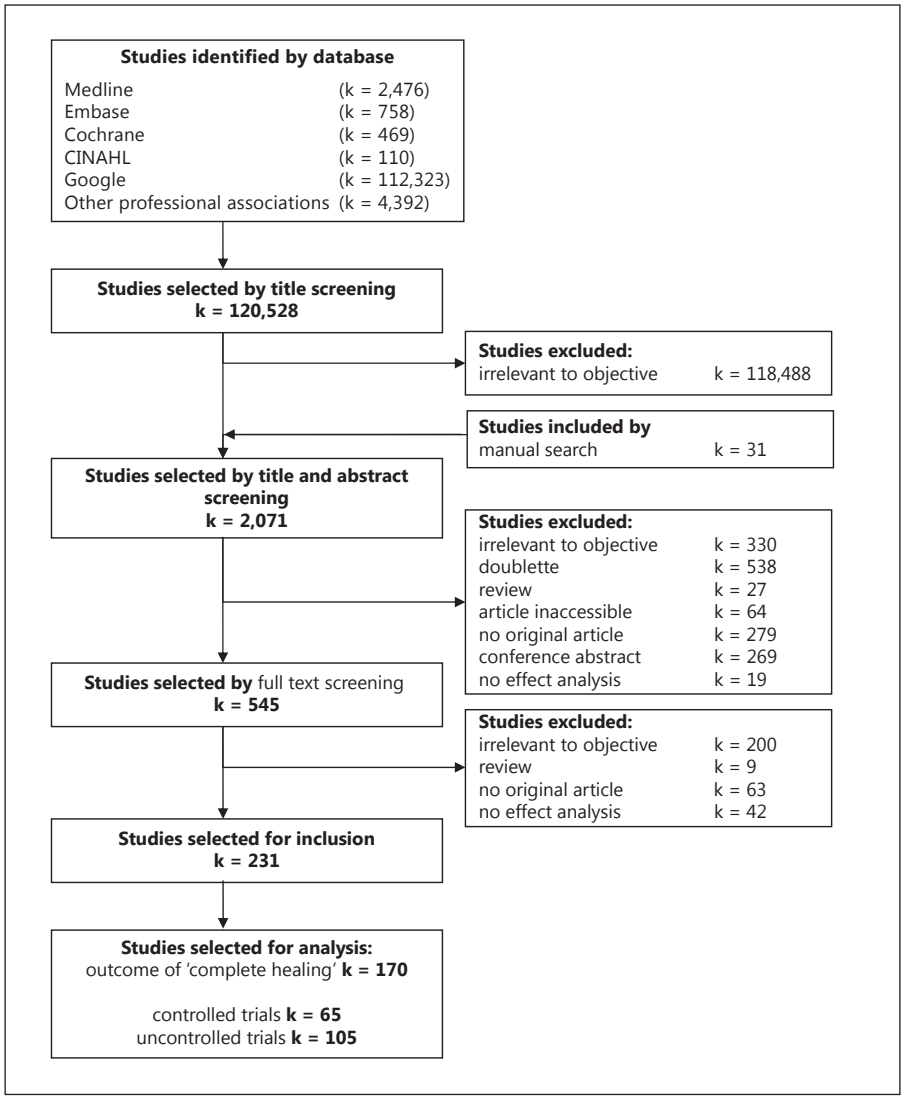


**Fig. 1.** Results of multiple database literature search.

1,772 diabetic foot ulcers (20 publications), 2,677 pressure ulcers (46 publications), and 11,838 mixed diagnoses (27 publications).

*First Set of Analyses: Advanced versus Conventional Dressings in Controlled Studies*

*Description of Controlled Studies*

In the controlled studies, an average of 33% of patients were male in the advanced wound dressing group and 32% in the comparison group (table 1).

The mean duration of illness in the studies of advanced dressings was 10.4 versus 12.4 months in the conventional dressing studies. The mean duration of illness was higher (14.5 months) for patients with diabetic foot ulcers and markedly lower than the average for mixed diagnoses (2.2 months). The mean duration of treatment in studies of advanced dressings was 109 and 113 days in the studies of conventional dressings (113 days).

The most frequent dressings in the advanced dressing study conditions were hydrocolloid dressings with or without silver (35.4% of studies) and 'active dressings' (18.5%) (table 2). Moist saline compresses with/without zinc oxide were the most frequently applied dressings in the conventional dressing study conditions (table 3).

*Effect on Wound Healing in Controlled Studies*

The mean total odds ratio for complete healing of 1.52 was significant. This corresponds to a 52% higher chance

**Table 1.** Gender and age (in years) in the controlled clinical trials by advanced and conventional wound dressings (k = 65; n = 5,690)

| | Gender | | | | Age | | | |
|---|---|---|---|---|---|---|---|---|
| | n | k | mean proportion male | CI | n | k | mean | CI |
| Advanced dressings | | | | | | | | |
| Ulcus cruris | 920 | 17 | 0.30 | 0.28–0.33 | 1,309 | 26 | 66.96 | 66.91–67.02 |
| Pressure ulcers | 220 | 9 | 0.30 | 0.23–0.38 | 336 | 11 | 66.25 | 66.14–66.36 |
| Diabetic foot ulcers | 469 | 6 | 0.42 | 0.37–0.47 | 484 | 7 | 58.86 | 58.77–58.95 |
| Mixed diagnoses | 22 | 1 | 0.08 | 0.02–0.28 | 12 | 1 | 58.80 | 58.23–59.37 |
| Total | 1,631 | 33 | 0.33 | 0.31–0.36 | 2,141 | 45 | 64.97 | 64.93–65.02 |
| Conventional dressings | | | | | | | | |
| Ulcus cruris | 884 | 17 | 0.29 | 0.26–0.32 | 1,277 | 26 | 67.13 | 67.46–67.18 |
| Pressure ulcers | 164 | 8 | 0.31 | 0.24–0.39 | 253 | 10 | 67.58 | 60.48–67.70 |
| Diabetic foot ulcers | 420 | 6 | 0.43 | 0.38–0.49 | 435 | 7 | 60.57 | 62.73–60.67 |
| Mixed diagnoses | 10 | 1 | 0.17 | 0.04–0.49 | 12 | 1 | 63.30 | 67.07–63.87 |
| Total | 1,478 | 32 | 0.32 | 0.30–0.35 | 1,977 | 44 | 65.72 | 65.68–65.76 |

**Table 2.** Advanced wound dressings observed (k = 65 studies; n = 5,690 patients)

| | k | Percent |
|---|---|---|
| Hydrocolloid dressings with/without silver | 23 | 35.4 |
| Active dressings | 12 | 18.5 |
| Mixed dressings | 7 | 10.8 |
| Hydrogel with/without polyhexanide or octenidine | 5 | 7.7 |
| Fine-pored polyurethane foam dressings, hydropolymer dressings with/without silver, polyhexanide or ibuprofen | 5 | 7.7 |
| Antiseptic dressings with/without silver, with/without polyhexanide | 4 | 6.2 |
| Film dressing or semipermeable transparent dressings or permeable film dressings | 3 | 4.6 |
| Alginates with/without silver | 2 | 3.1 |
| Hydroactive impregnated dressings | 2 | 3.1 |
| Coal dressings with/without silver | 1 | 1.5 |
| Hydrophobic dressings | 1 | 1.5 |
| Total | 65 | 100.0 |

of wound healing with advanced in comparison to conservative wound dressings (table 4; fig. 2).

Subgroup effects were estimated as odds ratios for complete healing in a 2-factorial fixed effect meta-analytic model involving the factors of causal therapy, and diagnosis and study design. The model failed to reach significance ($Q = 12.41$; d.f. = 7; $p \leq 0.088$) and a substantial degree of variability was unexplained ($Q = 133.61$; d.f. = 57; $p \leq 0.0001$). Table 4 shows the results for the interaction effect between the causal therapy and diagnosis factor. Descriptively, the highest mean odds ratio of com-

**Table 3.** Conventional dressings observed (k = 65 studies; n = 5,690 patients)

| | k | Percent |
|---|---|---|
| Moist saline compresses with/without zinc oxide | 28 | 43.1 |
| Standard therapy | 24 | 36.9 |
| Impregnated gauze dressings | 8 | 12.3 |
| Placebo e.g. without substance | 5 | 7.7 |
| Total | 65 | 100.0 |

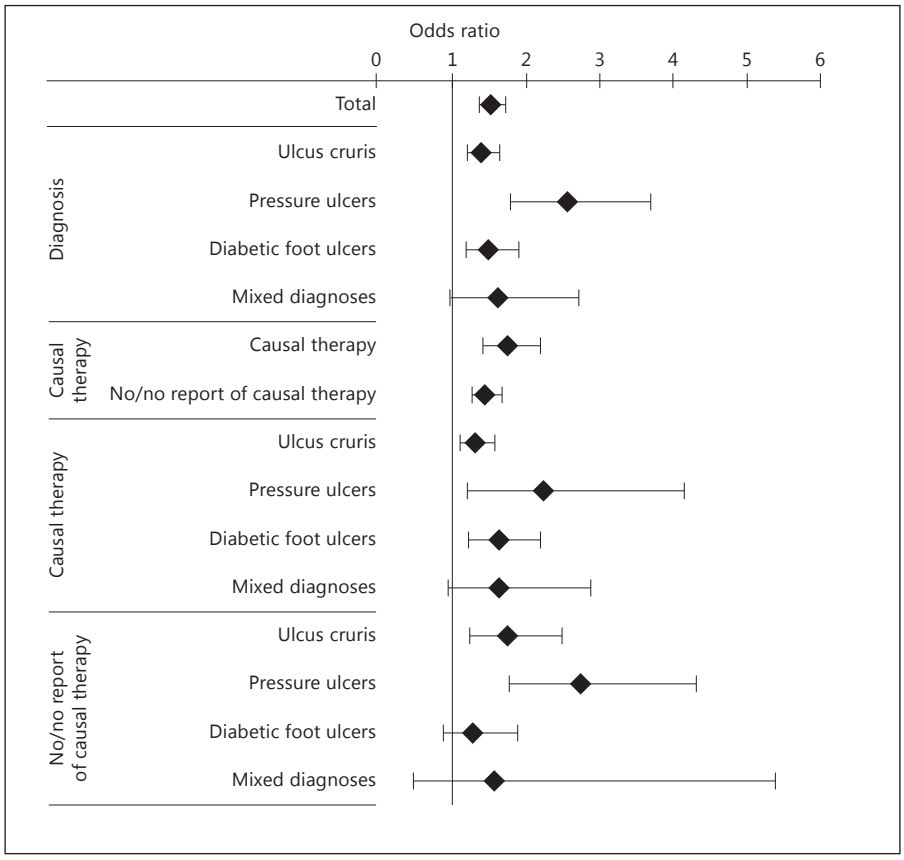


**Fig. 2.** Forest plot of mean odds ratios (fixed effects ANOVA) of advanced wound dressings versus conventional dressings, by causal therapy and diagnosis (k = 65; n = 5,698). Note: funnel plots of individual study effects can be obtained on request from the authors.

**Table 4.** Mean odds ratios (OR; fixed effects ANOVA) of advanced wound dressings versus conventional dressings, by causal therapy and diagnosis (k = 65; n = 5,698)

| | n | k | OR | Lower 95% CI limit | Upper 95% CI limit | Q | d.f. | p | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| Causal therapy | | | | | | | | | |
| Ulcus cruris | 2,565 | 27 | 1.31 | 1.10 | 1.57 | 42.76 | 26 | ≤0.021 | 39.20 |
| Pressure ulcers | 334 | 5 | 2.23 | 1.19 | 4.15 | 5.97 | 4 | ≤0.201 | 32.99 |
| Diabetic foot ulcers | 874 | 8 | 1.63 | 1.21 | 2.19 | 7.15 | 7 | ≤0.413 | 2.13 |
| Mixed diagnoses | 226 | 2 | 1.63 | 0.93 | 2.86 | 0.06 | 1 | ≤0.809 | 0.00 |
| No/no report of causal therapy | | | | | | | | | |
| Ulcus cruris | 781 | 10 | 1.74 | 1.22 | 2.48 | 63.68 | 9 | ≤0.001 | 85.87 |
| Pressure ulcers | 436 | 9 | 2.75 | 1.75 | 4.30 | 13.02 | 8 | ≤0.111 | 38.54 |
| Diabetic foot ulcers | 423 | 2 | 1.27 | 0.86 | 1.88 | 0.00 | 1 | ≤0.982 | 0.00 |
| Mixed diagnoses | 59 | 2 | 1.56 | 0.45 | 5.37 | 0.98 | 1 | ≤0.323 | 0.00 |
| Total | 5,698 | 65 | 1.52 | 1.35 | 1.72 | 146.02 | 64 | ≤0.001 | 56.17 |

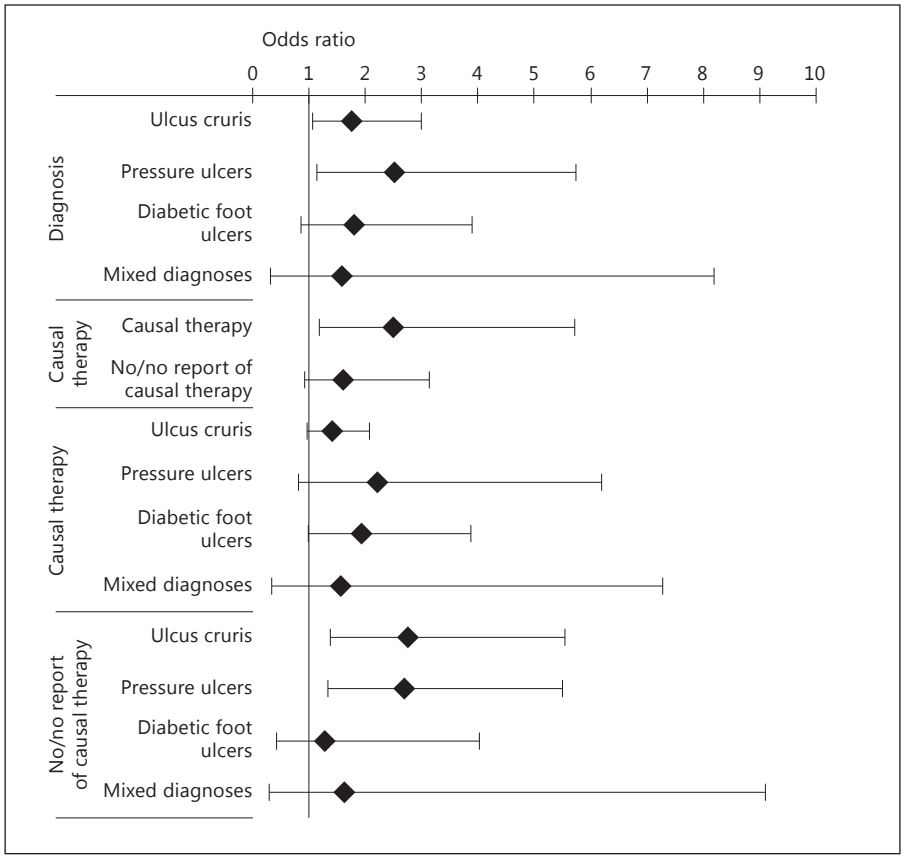


**Fig. 3.** Forest plot of mean odds ratios (mixed effects ANOVA) of advanced wound dressings versus conventional dressings. Causal therapy by diagnosis (k = 65; n = 5,698). Note: funnel plots of individual study effects can be obtained on request from the authors.

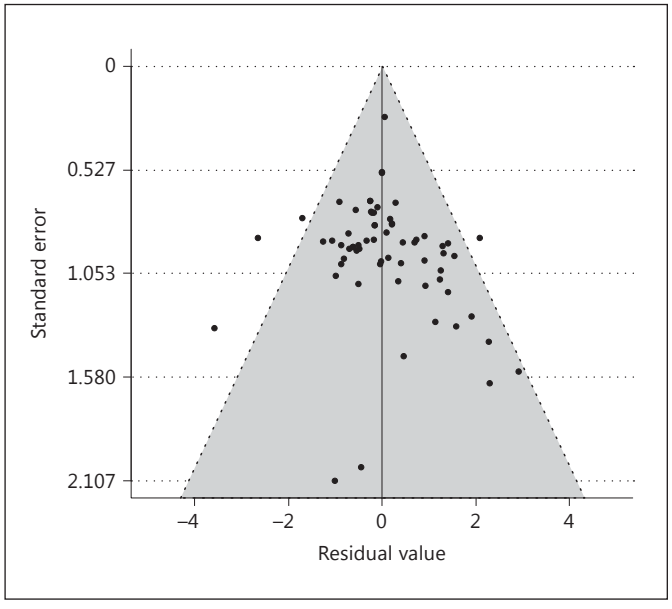


**Fig. 4.** Funnel plot of the log odds ratios (k = 65; n = 5,698).

plete healing was observed for patients with pressure ulcers and causal therapy (odd ratio = 2.23). With the exception of ulcus cruris, the effects within the study groups are homogeneous (see last columns in table 4).

Figure 2 depicts the mean odds ratios for the full 2-factorial model along with the 95% CI in a forest plot. As can be seen from the graph, the mean odds ratios are significantly different from 1, the most obvious exception being mixed diagnosis. The highest mean odds ratio was observed for pressure ulcers and the mean odds ratio was higher for studies including causal therapy.

*Sensitivity Analysis*

To assess the generalizability of the results, the data were re-analysed under the assumption of a random effect for the studies (mixed effects model). The model was not significant ($Q = 0.73$; d.f. = 7; $p \leq 0.647$) and the variance component of the random effect was estimated as $\tau^2 = 0.51$ (95% CI = 0.30–1.28). Again, significant residual heterogeneity was left unexplained ($Q = 133.61$; d.f. = 57; $p \leq 0.001$). The mean odds ratios are given only in a forest plot (fig. 3).

**Table 5.** Gender and age in the controlled and uncontrolled trials (k = 170; n = 22,492)

| | Gender | | | | Age | | | |
|---|---|---|---|---|---|---|---|---|
| | n | k | mean proportion male | CI | n | k | mean | CI |
| Ulcus cruris | 4,399 | 52 | 0.29 | 0.27–0.30 | 5,554 | 66 | 69.59 | 69.56–69.62 |
| Pressure ulcers | 1,799 | 33 | 0.28 | 0.26–0.31 | 2,486 | 41 | 71.09 | 71.05–71.13 |
| Diabetic foot ulcers | 1,146 | 13 | 0.42 | 0.39–0.45 | 1,700 | 18 | 60.46 | 60.42–60.51 |
| Mixed diagnoses | 10,355 | 18 | 0.29 | 0.28–0.30 | 10,587 | 21 | 66.75 | 66.73–66.77 |
| Total | 17,699 | 116 | 0.29 | 0.29–0.30 | 20,327 | 146 | 67.53 | 67.52–67.55 |

**Table 6.** Products of advanced dressings in the study conditions

| | k | Percent |
|---|---|---|
| Hydrocolloid dressings with/without silver | 40 | 23.5 |
| Fine-pored polyurethane foam dressings, hydropolymer dressings with/without silver, polyhexanide or ibuprofen | 39 | 22.9 |
| Active dressings | 26 | 15.3 |
| Hydrogel with/without polyhexanide or octenidine | 13 | 7.6 |
| Mixed dressings | 12 | 7.1 |
| Alginates with/without silver | 10 | 5.9 |
| Antiseptic dressings with/without silver, with/without polyhexanide | 10 | 5.9 |
| Film dressing or semipermeable transparent dressings or permeable film dressings | 8 | 4.7 |
| Hydrofibre dressings with/without silver | 3 | 1.8 |
| Hydroactive impregnated dressings | 3 | 1.8 |
| Hydrophobic dressings | 3 | 1.8 |
| Fleece pad | 1 | 0.6 |
| Moist wound dressings | 1 | 0.6 |
| Coal dressings with/without silver | 1 | 0.6 |
| Total | 170 | 100.0 |

In summary, the consideration of a random effect for the studies leads to minor changes in the mean odds ratios, but to considerable wider CI. As a consequence, only the mean odds ratio of ulcus cruris and pressure ulcers – at least on the factor level 'no or no reported causal therapy' – remained significant.

To judge the probability of the existence of a publication bias, the log odds ratios were plotted against their standard errors in a funnel plot (fig. 4). As studies in the lower left quadrant are underrepresented and studies of mean sample size and positive effects are overrepresented, a slight publication bias cannot be ruled out.

*Second Set of Analyses: Advanced versus Conventional Dressings in Controlled and Uncontrolled Studies*

*Description of Controlled and Uncontrolled Studies*

The 170 studies of controlled and uncontrolled trials included 22,492 patients. The statistical analyses of these 170 studies included 117 controlled study conditions.

On average, 30% of the study patients were male (table 5), with a higher percentage in the studies on diabetic foot ulcers (42%). The mean age was approximately 68 years. Studies on pressure ulcers showed the highest and studies on diabetic foot ulcers the lowest mean ages.

The mean duration of wounds was longest in studies on diabetic foot ulcers (13.8 years) and shortest in studies on pressure ulcers (4.3 years).

**Table 7.** Mean odds (fixed effects ANOVA) of advanced wound dressings and conventional dressings, by study design and causal therapy (k = 287; n = 22,504)

| | n | k | Odds | Lower 95% CI limit | Upper 95% CI limit | Q | d.f. | p | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| *Advanced, uncontrolled* | | | | | | | | | |
| Causal therapy | | | | | | | | | |
| Ulcus cruris | 1,987 | 44 | 0.68 | 0.61 | 0.75 | 300.64 | 43 | ≤0.001 | 85.70 |
| Pressure ulcers | 467 | 11 | 0.78 | 0.64 | 0.96 | 73.80 | 10 | ≤0.001 | 86.45 |
| Diabetic foot ulcers | 323 | 9 | 1.08 | 0.84 | 1.39 | 49.89 | 8 | ≤0.001 | 83.97 |
| Mixed diagnoses | 2,709 | 11 | 0.76 | 0.71 | 0.82 | 67.75 | 10 | ≤0.001 | 85.24 |
| No/no report of causal therapy | | | | | | | | | |
| Ulcus cruris | 700 | 19 | 0.56 | 0.47 | 0.67 | 105.64 | 18 | ≤0.001 | 82.96 |
| Pressure ulcers | 1,628 | 38 | 0.81 | 0.72 | 0.90 | 222.45 | 37 | ≤0.001 | 83.37 |
| Diabetic foot ulcers | 259 | 6 | 0.60 | 0.46 | 0.79 | 31.88 | 5 | ≤0.001 | 84.32 |
| Mixed diagnoses | 8,846 | 19 | 0.28 | 0.27 | 0.30 | 181.54 | 18 | ≤0.001 | 90.08 |
| *Advanced, controlled* | | | | | | | | | |
| Causal therapy | | | | | | | | | |
| Ulcus cruris | 1,304 | 27 | 0.84 | 0.75 | 0.95 | 151.39 | 26 | ≤0.001 | 82.83 |
| Pressure ulcers | 186 | 5 | 2.57 | 1.77 | 3.72 | 34.20 | 4 | ≤0.001 | 88.30 |
| Diabetic foot ulcers | 468 | 8 | 0.77 | 0.63 | 0.93 | 42.47 | 7 | ≤0.001 | 83.52 |
| Mixed diagnoses | 113 | 2 | 1.72 | 1.14 | 2.58 | 6.93 | 1 | ≤0.008 | 85.58 |
| No/no report of causal therapy | | | | | | | | | |
| Ulcus cruris | 388 | 10 | 1.11 | 0.89 | 1.39 | 35.94 | 9 | ≤0.001 | 74.96 |
| Pressure ulcers | 234 | 9 | 1.42 | 1.07 | 1.89 | 29.37 | 8 | ≤0.001 | 72.76 |
| Diabetic foot ulcers | 211 | 2 | 0.80 | 0.61 | 1.05 | 0.00 | 1 | ≤0.975 | 0.00 |
| Mixed diagnoses | 34 | 2 | 1.27 | 0.62 | 2.61 | 3.62 | 1 | ≤0.057 | 72.40 |
| *Conventional controlled* | | | | | | | | | |
| Causal therapy | | | | | | | | | |
| Ulcus cruris | 1,211 | 26 | 0.81 | 0.71 | 0.92 | 195.61 | 25 | ≤0.001 | 87.22 |
| Pressure ulcers | 147 | 5 | 2.57 | 1.67 | 3.97 | 16.30 | 4 | ≤0.003 | 75.46 |
| Diabetic foot ulcers | 423 | 9 | 0.52 | 0.43 | 0.65 | 28.61 | 8 | ≤0.001 | 72.03 |
| Mixed diagnoses | 113 | 2 | 1.06 | 0.72 | 1.56 | 5.26 | 1 | ≤0.022 | 80.98 |
| No/no report of causal therapy | | | | | | | | | |
| Ulcus cruris | 392 | 10 | 0.77 | 0.60 | 1.01 | 79.09 | 9 | ≤0.001 | 88.62 |
| Pressure ulcers | 230 | 10 | 0.65 | 0.48 | 0.89 | 41.43 | 9 | ≤0.001 | 78.28 |
| Diabetic foot ulcers | 106 | 1 | 0.63 | 0.43 | 0.93 | 0.00 | 0 | n.a. | 100.00 |
| Mixed diagnoses | 25 | 2 | 0.68 | 0.25 | 1.86 | 7.02 | 1 | ≤0.008 | 85.76 |
| Total | 22,504 | 287 | 0.55 | 0.54 | 0.57 | 2,896.00 | 286 | ≤0.001 | 90.12 |

n.a. = Not assessed.

The mean duration of treatment ranged from approximate 77 days (mixed diagnoses) to 102 days (ulcus cruris) with an overall mean of 88 days.

The highest number of studies (22.9%) examined polyurethane foam dressings, hydropolymer dressings with/without silver or hydropolymer foam dressings (table 6). The distribution of conventional wound dressings is the same as presented above.

*Effects on Wound Healing in Controlled and Uncontrolled Studies*

The meta-analysis resulted in a mean odds of 0.55 (table 7), i.e. 0.55 wounds closed per treatment failure (not healed). This corresponds to a mean healing rate of 33%.

Subgroup effects of advanced and conventional dressings were estimated as odds of complete healing in a 3-factorial fixed effect meta-analytic model involving the factors of causal therapy, diagnosis and study de-

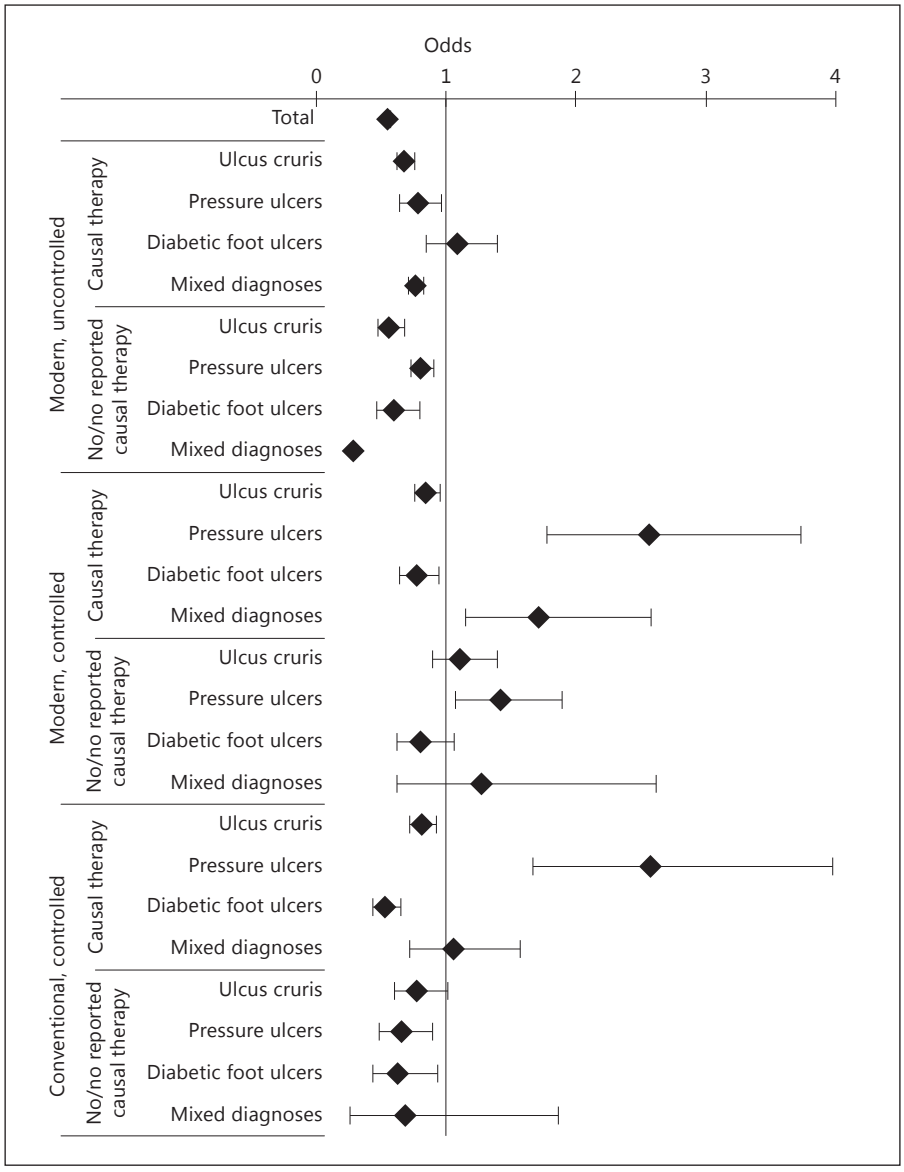


**Fig. 5.** Forest plot of mean odds (fixed effects ANOVA) of advanced wound dressings and conventional dressings, by study design and causal therapy (k = 287; n = 22,504). Note: funnel plots of individual study effects can be obtained on request from the authors.

sign. The model was highly significant (Q = 1,185.17; d.f. = 23; $p \leq 0.001$) and significance was also observed for each factor and all interaction effects (results not shown). Again, a substantial degree of variability was unexplained (Q = 1,710.83; d.f. = 263; $p \leq 0.001$), and within-group study effects remained heterogeneous. Results are given for the 3-way interaction effect only (table 7).

To summarize further results not shown in table 7, the mean odds of complete healing were higher for each diagnosis (odds = 0.71–0.91) with the exception of mixed diagnoses, and a lower mean odds (0.47) was observed for advanced dressings in uncontrolled studies than in both advanced and conventional controlled studies (odds = 0.97–0.77). Apparently, the mean healing rates are lower than 50% and thus, fewer than half of all wounds closed.

Figure 5 shows the mean odds for the full 3-factorial model along with the 95% CI in a forest plot. As can be seen, the relatively high mean odds of complete healing in studies of advanced dressings is mainly due to controlled studies, especially for the diagnoses of pressure ulcers and mixed diagnoses. In conventional studies, the mean odds of complete healing were below 50%, except pressure ulcers with causal therapy. The differences in the odds between advanced and conventional dressings were

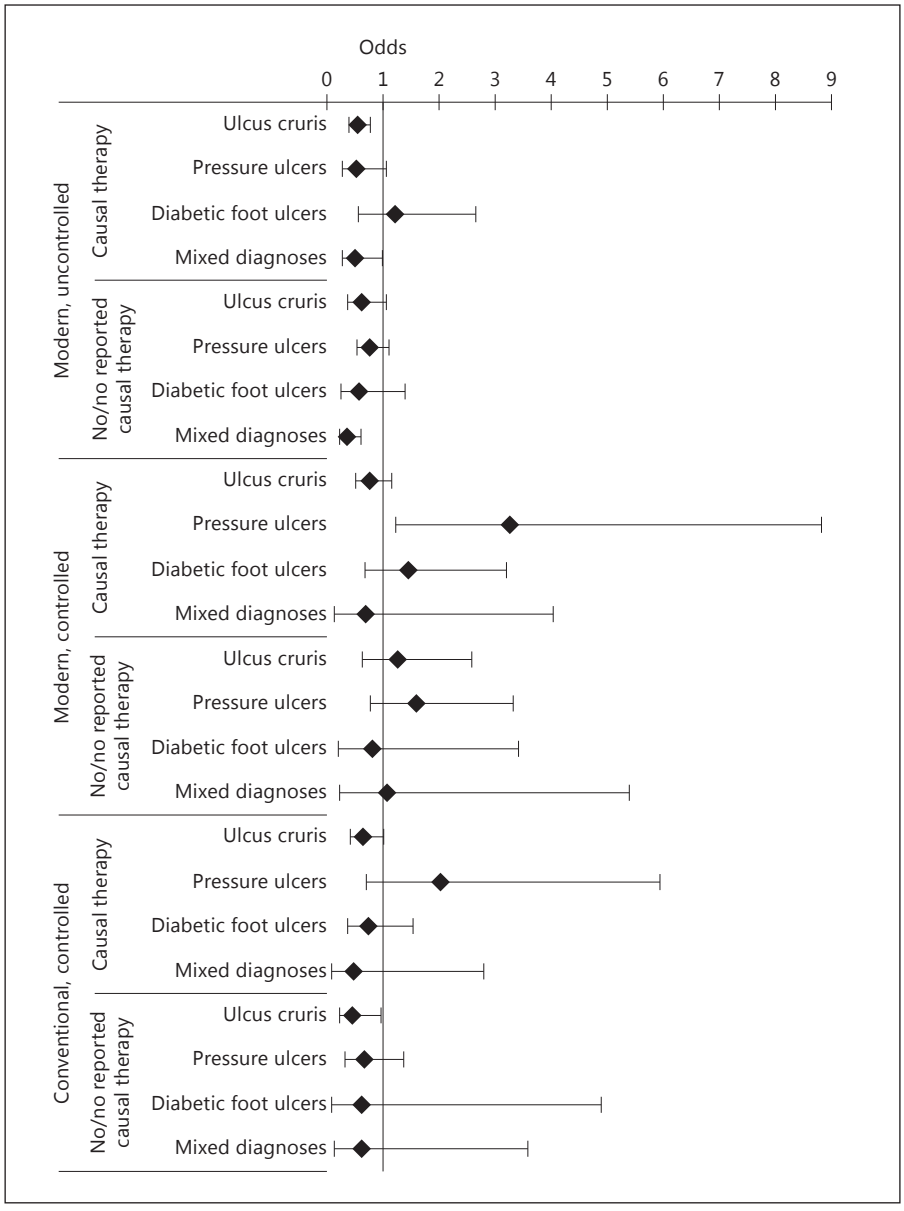


**Fig. 6.** Mean odds ratios, controlled studies, interaction effect in a 2-factor analysis (fixed effects; k = 287; n = 22,504). Note: funnel plots of individual study effects can be obtained on request from the authors.

lower in the studies involving causal therapy. With the exception of advanced and uncontrolled studies on diabetic foot ulcer, the mean healing rates were significantly below 50%.

*Sensitivity Analysis*

Since heterogeneity statistics were highly significant, a sensitivity analysis to explore the generalizability of the results was indispensable. The results are given as a funnel plot only (fig. 6). The most striking differences are the broadened CI and more conservative significance results.

Figure 7 shows the funnel plot for the log odds of this analysis. Since a high degree of symmetry is apparent and at least positive results are missing, the probability of a publication bias seems very low.

## Discussion

In contrast to published reviews and meta-analyses on the effectiveness of advanced dressings in the treatment of chronic wounds, this comprehensive meta-analysis includes all diagnoses of chronic wounds, all types of ad-

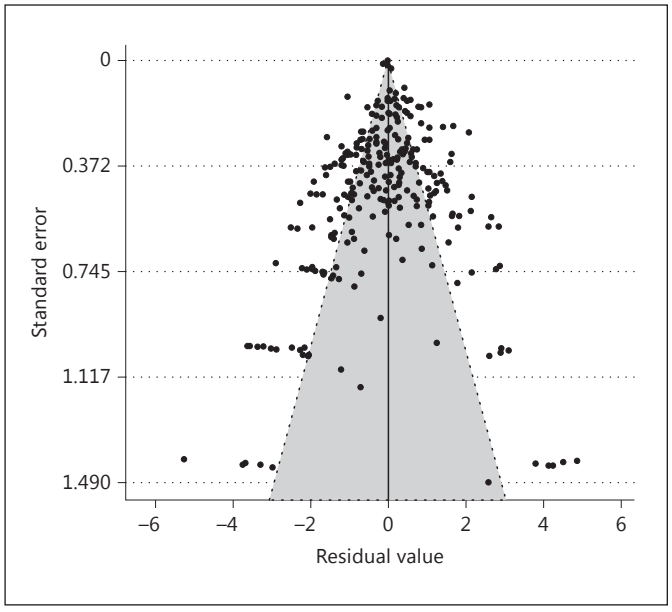


**Fig. 7.** Funnel plot of the log odds (k = 287; n = 22,504).

vanced wound dressings, and all types of empirical studies in this area of clinical research and care. Furthermore, this meta-analysis incorporates causal treatment as a potential relevant effect modifier.

In summary, the meta-analyses of controlled studies on chronic wounds showed a significant superiority of advanced compared to conventional dressings in complete wound healing. In total, the chance for complete healing was 52% higher with advanced dressings. This effect was not shown to statistically depend on diagnosis or on additional causal treatment. But descriptively, the superiority varies between diagnoses and the effect was reduced when causal treatment was applied – at least for ulcus cruris and pressure ulcer. The interpretation regarding causal treatment is also limited, since the factor levels of no causal treatment and no report of causal therapy had to be collapsed for the analysis.

Considering the low base rate of complete healing in the natural history of chronic wounds, the observed increase of approximately 50% in the chance of healing is clinically relevant. The relevance is limited by the residual heterogeneity of study effects, which was not explained by the models applied. A deduction of individual treatment decisions or recommendations is hard to justify, since neither product, patient nor clinical characteristics have been modelled. In mixed effect models, the superiority of advanced dressings remained significant for ulcus cruris and pressure ulcers without or with no reported causal treatment. However, a generalization of the results to other studies is limited, since CI are wide. As most of the mean effects increase when sensitivity to generalization is considered, the results of the fixed effect model can be accepted as conservative estimates of effectiveness in controlled studies.

When generalization to routine clinical care is considered, the evidence from uncontrolled studies should be incorporated. The results of these analyses generally confirm the interpretation provided above, but some very relevant results give additional insights: The overall mean healing rates are lower (33%) and especially low in uncontrolled studies of advanced dressings. These low healing rates might be due to the often found short duration of treatment in empirical studies and the effects might rise with prolongation. For uncontrolled studies, probable factors might be a difference in the patient populations (more hard-to-heal wounds) or less methodological rigor, e.g. in standardization of study procedures. The ratio of the mean odds of advanced versus conventional dressings in controlled studies is 0.97/0.77 = 1.26, thus lower than the mean odds ratio of 1.52 observed for controlled studies. This implies varying overall healing rates and points to more general differences between studies, e.g. different patient populations, different treatment regimen. However, the superiority of advanced dressings in controlled trials was replicated on a slightly lower level.

The conclusion does not change when considering publication bias. Whereas there is some evidence for a slight overestimation of the mean odds ratios, no evidence of publication bias was found in the analyses of the controlled and uncontrolled studies.

The decision for sparse inclusion and exclusion criteria resulted in a huge pool of studies representing the whole unfiltered published evidence. The only selection criterion for analysis was the report of information on complete healing, which was chosen a priori as the primary outcome. Other outcomes were coded, but were not further considered. A bias due to selective outcome reporting is therefore implausible.

The comprehensiveness of this review and the coverage of all relevant studies on the treatment of chronic wounds is the most striking difference in the design of this meta-analysis in relation to other meta-analyses and systematic reviews [9, 10–14]. The consideration of all types of chronic wounds, all types of advanced wound dressings and all types of studies resulted in more study effects, more reliable estimates of mean effects and more statistical power. These differences in the meta-analytic design are likely to explain the differences in the meta-analytic results.

As expected, this comprehensive approach resulted in a high degree of variability in study effects, which in turn was reflected in the heterogeneity statistics. Diagnoses, causal treatment and study design were a priori defined as potentially variance generating factors but did not explain the variance in the effects observed. One explanation for the persistent heterogeneity might be the quality of report or the quality of information reported in the studies. Another explanation might be the grading of coding, e.g. the level of differentiation between aetiological subtypes of ulcers or product types of dressings. Finer gradings might have resulted in more homogeneous results. Finally, the variability of study effects suggests that other variables than those considered in these analyses might be more relevant predictors of the effectiveness of advanced dressings in the treatment of chronic wounds. In the analyses presented, clinically relevant predictors had to be discarded because of reporting inconsistencies, missing data and model complexity. Future analyses should incorporate a finer differentiation between classes of wound dressing, e.g. types of modern and conventional dressings.

The most obvious limitation of this study was the omission of uncontrolled studies on conservative dressings and controlled studies comparing conservative dressings. As a consequence, a quasi-nested factor had to be incorporated in the design of the analysis and the results had to be interpreted in the absence of very relevant adjuvant information. Another major limitation of the meta-analysis is the low reporting quality in the publications included. Deficiencies in reporting constrain the reader from comprehension, preclude the conduct of valid meta-analyses and impede the evolution of science and knowledge. With respect to this limitation, it is urgently suggested to improve the reporting quality in clinical wound trials as has been proposed by a EWMA group recently [23].


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## Disclosure Statement

The authors declare no conflicts of interest.

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