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Effectiveness of an enhanced silver-containing dressing in hard-to-heal venous leg ulcers: a randomised controlled trial

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Effectiveness of an enhanced silver-containing dressing in hard-to-heal venous leg ulcers: a randomised controlled trial

Objective: To assess the efficacy and safety of a carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride (CISEB) versus a dialkylcarbamoyl chloride-coated dressing (DACC) in hard-to-heal venous leg ulcers (VLUs).
Method: In a multinational, multicentre, randomised controlled trial, patients with hard-to-heal VLUs were randomised 1:1 to receive CISEB (n=100) or DACC (n=103) for up to four weeks. VLUs that were not healed by week 4 were managed with standard of care for up to 12 weeks or until healed (whichever was sooner). The primary endpoint was complete wound closure at week 12. Additional endpoints included time to complete wound closure and incidence of adverse events (AEs).
Results: The trial cohort included 203 patients. CISEB achieved a higher rate of complete wound closure by week 12 compared to DACC (74.8% versus 55.6%, respectively; p<0.0031), and was associated with a 35% increased likelihood of healing (risk ratio, 1.35; 95% confidence interval: 1.10–1.65). Median time to complete wound closure was shorter in the CISEB arm (56 days) compared to the DACC arm (70 days; p<0.0272). A smaller proportion of patients experienced an AE with CISEB compared to DACC (5.0% versus 17.6%, respectively).
Conclusion: Management of hard-to-heal VLUs with CISEB was associated with improved healing outcomes compared to DACC, without additional safety concerns. CISEB is a gelling fibre dressing with antimicrobial, metal-chelating and surfactant components that may promote an optimal healing environment to address the challenge of hard-to-heal wounds.
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chronic • CISEB • DACC • hard-to-heal • randomised controlled trial • silver-containing gelling fibre dressing • ulcer • venous leg ulcer • wound • wound care • wound dressing • wound healing

Hard-to-heal wounds, such as venous leg ulcers (VLUs), pose a significant challenge to patients and global healthcare systems.[1] The estimated global incidence is 1.51–2.21 per 1000 people, and predicted to rise with the ageing population.[2,3] The risk of wounds transitioning to a hard-to-heal state depends on various factors including: patient age, underlying pathology, comorbidities and wound-related factors, such as the presence of ischaemia or infection/inflammation.[4] VLUs are often hard-to-heal and are typically associated with chronic venous disease, post-thrombotic syndrome, varicose veins and venous hypertension.[5] In the UK, approximately one-third of VLUs are infected at time of presentation, which contributes to delayed healing.[6] Management of unhealed VLUs is associated with a 4.5-times increased cost compared to healed VLUs.[6] The national cost of treating VLUs was estimated to be £102 million in 2015/2016 (per person annual cost of £4787.70), with higher cost being attributed to antimicrobial dressing use or where wound care was delivered in the home.[7] Similarly, the estimated cost of VLU-related care in the US was $15,000 USD per patient per year, with a significant increase for patients with delayed healing (up to $34,000 USD per patient per year).[8,9] Most costs are attributed to outpatient visits, nursing care and admissions to hospitals for related complications, usually infection.[8,9]

The standard of care (SoC) treatment for VLUs is compression therapy in combination with wound dressings.[8] There is a wide range of wound dressings available with differing mechanisms (e.g., foam dressings, hydrocolloids, alginates and gelling fibre dressings, with or without antimicrobial components), but all ultimately aim to provide an optimal wound healing environment.[10] Choice of dressing may depend upon wound location, its area and depth, level of exudate, presence of infection and periwound skin condition. The knowledge and skills of health professionals are also increasingly important factors in successful treatment, given the complexity of such wounds. Despite the plethora of dressings and advanced therapies available for VLUs, treatment decisions remain a significant challenge due to the

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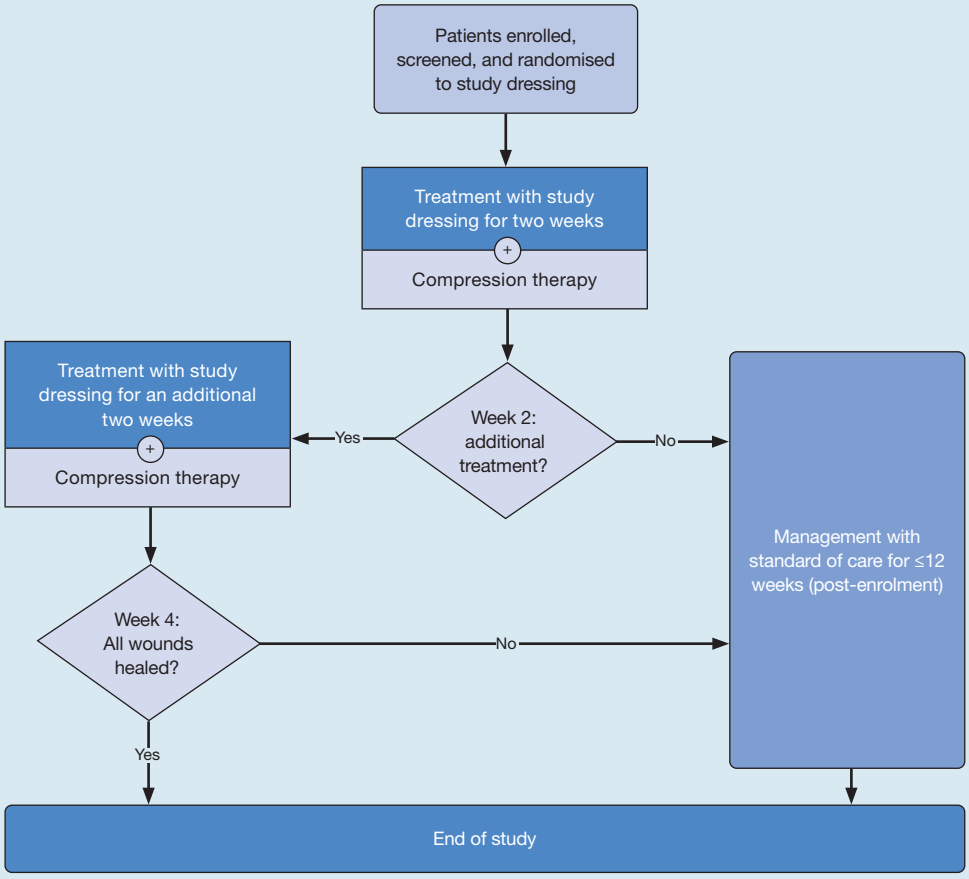
Fig 1. Treatment flow chart



limited clinical evidence on comparative effectiveness of different dressings.[11]

Patients with VLUs represent a population at risk of infection.[12,13] Risk factors for wound infection and delayed healing include: ulcer area ≥10cm^2; slough in the wound bed tissue; duration of wound; and the presence of surface-associated or aggregated microorganisms.[12–15] Hard-to-heal VLUs may therefore benefit from management with antimicrobial dressings to facilitate healing. A carboxymethylcellulose (CMC) fibre dressing containing ionic silver, ethylenediaminetetraacetic acid (EDTA), and benzethonium chloride (BEC) (CISEB) was developed to provide an enhanced solution for hard-to-heal wounds. While the performance of CISEB in hard-to-heal wounds, including VLUs, pressure ulcers (PUs) or diabetic foot ulcers (DFUs), has previously been demonstrated in several studies (63–90% of wounds healed or improved after approximately four weeks of treatment),[16–20] there are a limited number of studies comparing CISEB with other dressings.[21,22] A dialkylcarbamoyl chloride-coated dressing (DACC) is also indicated for the treatment of hard-to-heal wounds, including VLUs.[23–25] Single-arm studies have reported healing or improvement in 71–95% of hard-to-heal wounds (including VLUs, PUs or DFUs) after management with DACC for 4–12 weeks.[26–29] Due to the lack of comparative studies in hard-to-heal wounds, we conducted a randomised controlled trial (RCT) to compare the effectiveness and safety of CISEB versus DACC in hard-to-heal VLUs.

Methods

Study design

This was an RCT (ClinicalTrials.gov NCT05892341) to evaluate the efficacy and safety of CISEB (Aquacel Ag+ Extra/Aquacel Ag Advantage; Convatec Ltd., UK) versus DACC (Cutimed Sorbact, Essity, Germany) in hard-to-heal VLUs. The study was performed across 20 investigational sites in Colombia (ConvaCare Clinics Colombia: Bogotá, Medellín, Cali, Cartagena, Barranquilla, Bucaramanga), Germany (Vivantes Hospital in Friedrichshain Berlin, DRK Hospital Mölln-Ratzeburg, WZ-WundZentren [Recucare] with WZ-WundZentrum Augsburg, WZ-WundZentrum Holzkirchen, WZ-WundZentrum Ingolstadt, WZ-WundZentrum Munich, WZ-WundZentrum

Nuremberg, WZ-WundZentrum Rosenheim) and the UK (VCTC clinics with Cornwall Partnership NHS Foundation Trust, Kent NHS Foundation Trust, Central London NHS Trust, Norfolk NHS Trust, Nottinghamshire NHS Foundation Trust, Preston Hill Surgery).

Patients were enrolled by the principal investigator or designee (e.g., clinical research coordinator). Eligible patients were randomised 1:1 to receive either CISEB or DACC in accordance with the manufacturers' instructions for use. Randomisation occurred at a patient level so that all wounds for a patient were treated with the same dressing. The randomisation sequence was generated by the study statistician and was stratified by study centre, using permuted block sizes of 2 and 4, and administered using sequenced, opaque envelopes.

Patients were treated with the study dressing and therapeutic compression (secondary dressing) at 40mmHg for up to four weeks (Fig 1). At week 2, patients could continue to receive the study dressing (for an additional two weeks) or transition to long-term management with the SoC (non-antimicrobial, silver-free dressing as per each site's normal practice) for up to 12 weeks post-enrolment at the discretion of the investigator. VLUs that were treated with the study dressing for four weeks and did not heal were managed with the SoC for up to 12 weeks post-enrolment, or until the wound had healed or the dressing was no longer clinically indicated. The choice of compression bandages as the secondary dressing was at the discretion of the investigator and patient adherence was monitored at each study or interim visit by checking the positioning of the compression devices.

Study participants

Patients included in the study had a clinical history of chronic venous disease documented by Doppler ultrasound or supported by clinical findings compatible with venous insufficiency, such as telangiectasias, reticular veins, varicose veins associated with oedema, secondary skin changes (pigmentation, eczema), lipodermatosclerosis, white atrophy, or traces of healed ulcers associated with active ulcers. The full inclusion criteria were as follows:

- Patient ≥18 years of age
- Venous insufficiency as per CEAP (Clinical, Etiology, Anatomy, Pathophysiology) classification C6[30]
- ≥1 hard-to-heal VLU suitable for treatment with the study dressings
- VLU present for ≥2 months and ≤18 months
- Patient able and willing to give informed consent
- Tolerance to compression therapy for VLUs (40mmHg)
- Wound size of 1–100cm^2
- Ankle–brachial pressure index of 0.8–1.3.

Exclusion criteria were:

- Patients with known hypersensitivities or allergies to the dressing materials
- Recent or active cancer treatment
- Severe malnutrition
- Malignant wounds
- Systemic infection treated with antibiotics
- Uncontrolled diabetes with a glycated haemoglobin (Hb)A1c ≥10
- Certain chronic diseases that impair wound healing (e.g., autoimmune disorder in an acute flare phase).

Ethical considerations and patient consent

This study was conducted in compliance with the Declaration of Helsinki, ISO 14155 (2020), and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the institutional review board (IRB) or independent ethics committee (IEC) of each participating centre: Colombia: El Comité de Ética de Investigación Clínica (330333099; 18 October 2022); Germany: Ethik-Kommission der Medizinischen Fakultät der Ruhr-Universität Bochum (22-7742-BR; 29 March 2023) and Ethikkommission bei der Ärztekammer Schleswig-Holstein (034/23 m; 11 May 2023); UK: Health Research Authority and Health and Care Research Wales (23/WM/0081; 31 May 2023).

All patients provided written informed consent.

Study endpoints and data collection

The primary study endpoint was complete wound closure (100% re-epithelialisation of the wound surface[31]) by week 12. Secondary endpoints were percentage reduction in wound area at weeks 4 and 12, and satisfactory clinical progress (≥40% reduction in study wound area at week 4). A percentage area reduction of ≥40% is associated with a significantly increased likelihood of complete wound healing in VLUs.[32] An exploratory endpoint was time to complete wound closure. Safety endpoints were the incidence of adverse events (AEs) and serious AEs, including those that were dressing-related.

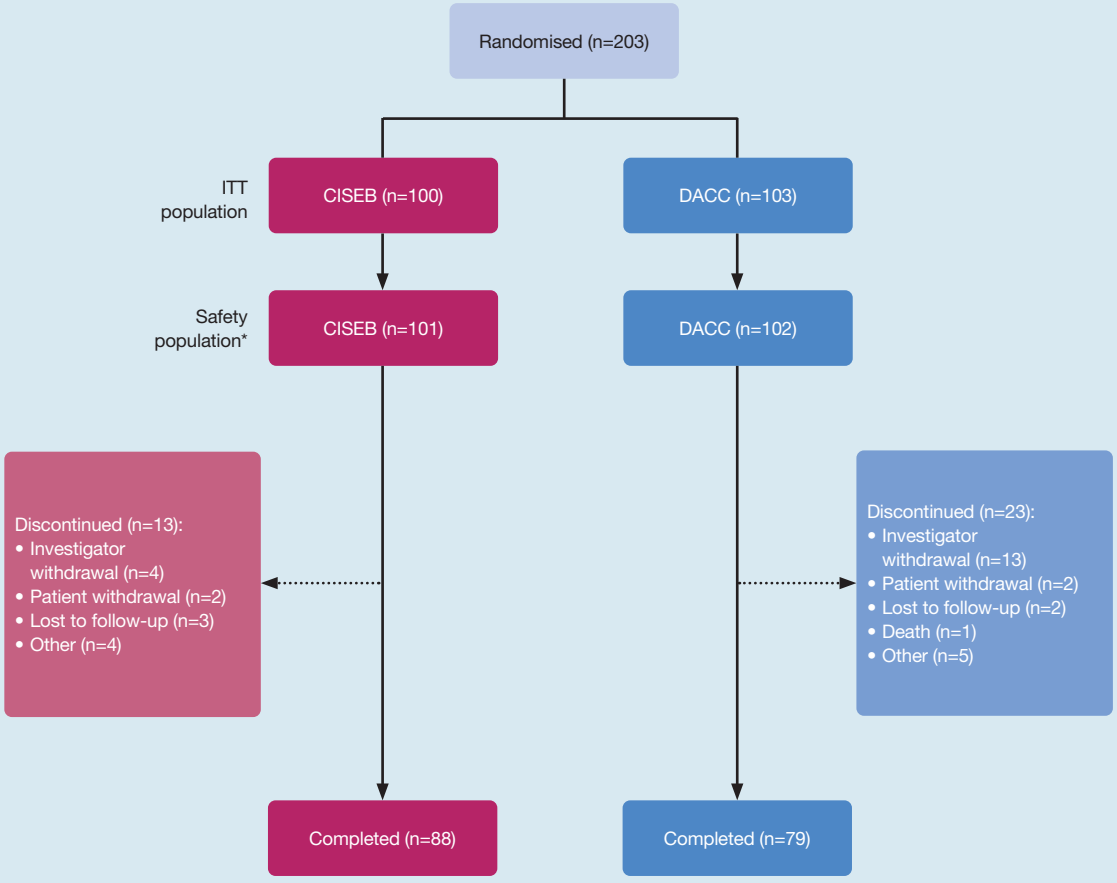
Patient demographics, medical history and wound characteristics (tissue type, exudate volume and type, odour level, wound edge and periwound skin condition, skin surface temperature, erythema, and infection status) were recorded at baseline and follow-up visits were scheduled every two weeks until week 12 (end of study).

All AEs (regardless of relationship to the study procedures or severity) which occurred from enrolment up to and including the final study visit were recorded by the investigator. AEs were either spontaneously reported or elicited during questioning and examination. Relatedness of AEs was determined by the investigator (in accordance with ISO 14155) and categorised as: 'definitely related' (directly and clearly related to the dressing); 'possibly related' (reasonable likelihood that the AE is related to the dressing); or 'unrelated' (unlikely to have had any reasonable association with the dressing).

Trial oversight and review

The trial was designed by the sponsor and trial investigators. The protocol was approved by the IRB or

Fig 2. Patient disposition. *One patient randomised to DACC arm received CISEB. CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing; ITT—intention-to-treat



IEC of each participating centre. The study adheres to the consolidated standards of reporting trials (CONSORT) statement.

Statistical analysis

Sample size

Under the assumption that the proportion of completely healed VLUs by week 12 would be 80%, a sample size of 206 patients and a minimum 206 wounds randomised 1:1 to experimental (CISEB) and control (DACC) arms was determined to have 85% power to reject the non-inferiority null hypothesis with a non-inferiority margin of –0.15 (–15%).

Analysis populations

Baseline characteristics (demographics and wound characteristics) were reported for the intention-to-treat (ITT) population, which included all randomised patients regardless of whether treatment was received. Efficacy endpoints were reported for the full analysis population which included all randomised patients who received treatment and had at least one follow-up visit after baseline. Safety endpoints were reported for all randomised patients who received treatment.

Endpoint analysis

For complete wound closure (primary endpoint) and satisfactory clinical progress (secondary endpoint), a z-test with non-inferiority margin of –0.15 (–15%) and one-sided alpha of 0.05 was used to test for significant difference between the two treatment arms. The Kaplan–Meier method was used to estimate time to complete wound closure. For wound area reduction (secondary endpoint), estimates for least square mean percentage change were calculated using an analysis of covariance model with treatment arm, country, treatment×country (2×3 interaction) and baseline wound area as covariates. All primary and secondary endpoints were tested for non-inferiority, followed by superiority testing if non-inferiority was met. Differences in baseline characteristics between the two treatment groups (baseline wound area, country and sex) were adjusted for with sensitivity analyses. A post hoc tipping point analysis was conducted to assess the impact of study

discontinuations on the study results.

All descriptive statistical analyses were performed using SAS statistical software (version 9.4 or higher; SAS Institute Inc., US).

Results

Between December 2022 and February 2024, 203 patients with VLUs were randomised to receive CISEB (n=100) or DACC (n=103) (ITT population; Fig 2). A single patient randomised to the DACC arm received CISEB (safety population: CISEB, n=101/DACC, n=102). Overall, 82% of the patients completed the study (study wounds healed or attended week 12 visit). A total of 776 dressings were applied in the CISEB arm and 753 dressings were applied in the DACC arm, with a mean±standard deviation (SD) wear time of 7.2±4.6 days and 7.7±4.7 days, respectively (median dressing wear time was five days for both arms).

Baseline characteristics

Patient demographics and baseline wound characteristics are presented in Table 1. The median (range) age of patients was 68 (38–91) years in the CISEB arm and 66 (36–95) years in the DACC arm. The mean±SD wound area was 10.2±12.6cm^2 in the CISEB arm compared with 17.3±22.3cm^2 in the DACC arm. In the CISEB arm, six patients had wound infection at baseline (no patients in the DACC arm had infection). Additional baseline wound characteristics were comparable between the CISEB and DACC populations (e.g., exudate type, odour level, wound edge condition, periwound skin condition, skin surface temperature and erythema).

Complete wound closure (primary endpoint)

CISEB-treated VLUs were significantly more likely to close by week 12 compared to DACC-treated VLUs (74.8% versus 55.6%, respectively; 19.2% difference, 95% confidence interval (CI): 6.7, 31.7; superiority: p=0.0031) (Fig 3a), corresponding to a risk ratio of 1.35 (95% CI: 1.10, 1.65). The results were robust when adjusted for differences in baseline wound area, country and sex via sensitivity analysis (p<0.0001). Overall, a greater proportion of patients in the CISEB arm achieved complete wound closure by week 12 compared to patients in the DACC arm (73.7% versus 56.4%, respectively; 17.3% difference, 95% CI: 4.3, 30.3; superiority: p=0.0103) (Fig 3b). Median time to wound closure was 56 days (quarter(Q)1–Q3, 32–82) for the CISEB arm and 70 days in the DACC arm (Q1–Q3, 42–non-estimable; 14-day difference; p<0.0272).

The tipping point analysis identified no critical threshold where study discontinuations would reverse the statistical significance of the findings. Even under the worst-case scenario, in which all patients who discontinued in the DACC arm were classified as 'healed' and all patients who discontinued in the CISEB arm were classified as 'not healed', CISEB was still non-inferior to DACC (p=0.0135).

Table 1. Demographics and baseline wound characteristics (intention-to-treat population*)

Characteristics	CISEB (n=100)	DACC (n=103)
Country, n (%)		
Colombia	59 (59.0)	59 (57.3)
Germany	21 (21.0)	22 (21.4)
UK	20 (20.0)	22 (21.4)
Age, years		
Mean±SD	67.2±13.3	66.8±13.1
Median	68	66
Q1, Q3	58, 77	59, 75
Min, max	38, 91	36, 95
Female, n (%)	71 (71.0)	56 (54.4)
BMI, kg/m^2	n=99	n=99
Mean±SD	31.8±8.3	30.1±6.1
Median	30.1	28.7
Min, max	16.4, 65.6	15.0, 48.4
Baseline wound area, cm^2	n=107	n=110
Mean±SD	10.2±12.6	17.3±22.3
Median	5.8	8.1
Min, max	0.2, 80.0	0.3, 100.0
Tissue type evaluation, n (%)	n=92	n=94
Eschar	6 (6.5)	9 (9.6)
Slough/fibrin	68 (73.9)	75 (79.8)
Healthy granulation	77 (83.7)	83 (88.3)
Unhealthy granulation	5 (5.4)	4 (4.3)
Epithelial	14 (15.2)	11 (11.7)
Other tissue	0 (0.0)	4 (4.3)
Exudate volume, n (%)	n=92	n=94
High	3 (3.3)	7 (7.5)
Medium	31 (33.7)	27 (28.7)
Low	56 (60.9)	56 (59.6)
None	2 (2.2)	4 (4.3)
Wound infection, n (%)	n=92	n=94
No	86 (93.5)	94 (100.0)
Yes	6 (6.5)	0 (0.0)

*The intention-to-treat population included all randomised patients, regardless of whether treatment was received. BMI—body mass index; CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing; max—maximum; min—minimum; Q—quarter; SD—standard deviation

Fig 3. Complete wound closure in venous leg ulcers (VLUs) **(a)** and overall patients **(b)** (full analysis population). The full analysis population included all randomised patients who received treatment and had at least one follow-up visit after baseline (Visit 1). Bars represent the percentage of VLUs or patients with complete wound closure and error bars show 95% confidence intervals. CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing

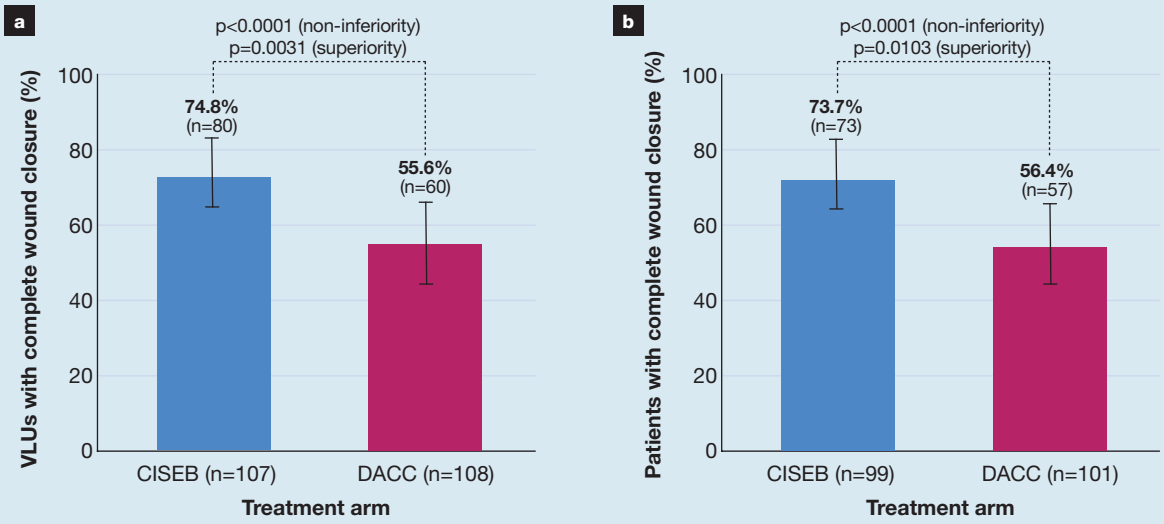
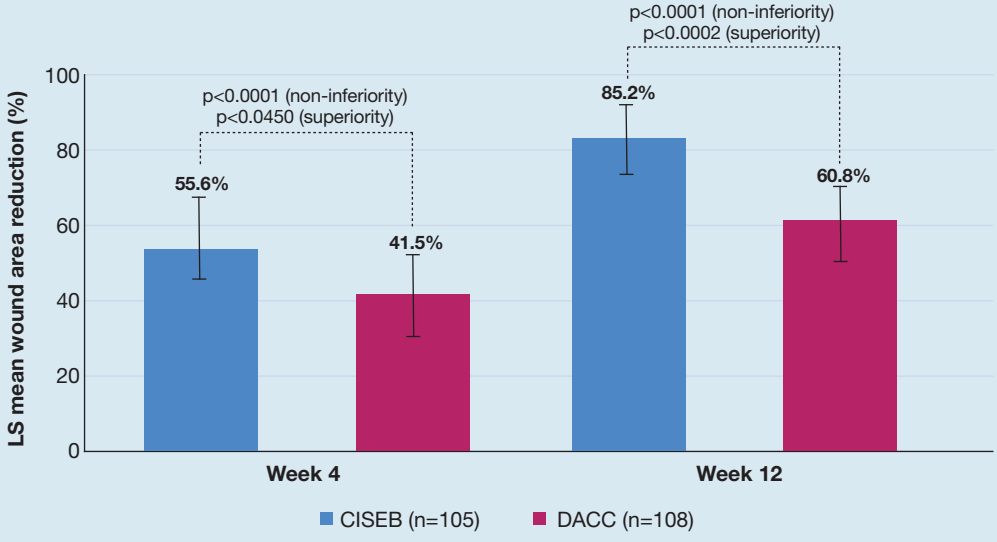


Fig 4. Least square (LS) mean percentage reduction in wound area (full analysis population). The full analysis population included all randomised patients who received treatment and had at least one follow-up visit after baseline (Visit 1). Error bars show 95% confidence intervals. CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing

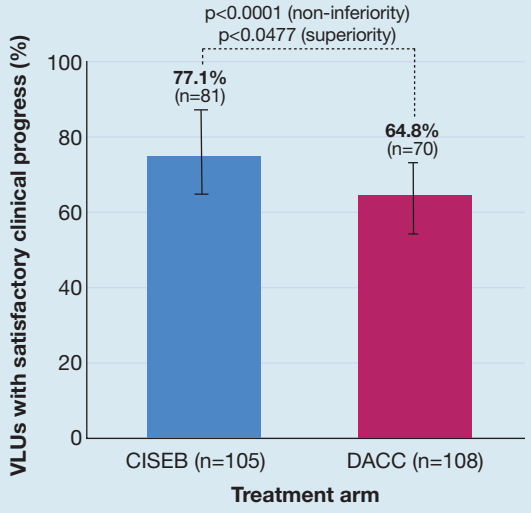


Wound area reduction

At week 4, mean percentage reduction in wound area was greater in the CISEB arm compared to the DACC arm (62.7% versus 48.3%, respectively). The least square mean percentage reduction in wound area at week 4 was 55.6% in the CISEB arm (standard error (SE): 5.0; 95% CI: 45.6, 65.5) and 41.5% in the DACC arm (SE: 4.8; 95% CI: 32.1, 50.9), representing a 14.1% difference between the two arms (SE: 7.0; 95% CI: 0.3, 27.8; superiority: p<0.0450) (Fig 4).

At week 12, mean percentage reduction in wound area was greater in the CISEB arm compared to the DACC arm (90.3% versus 67.2%, respectively). The least square mean percentage reduction in wound area at week 12 was 85.2% in the CISEB arm (SE: 4.7; 95% CI: 75.9, 94.5) and 60.8% in the DACC arm (SE: 4.5; 95% CI: 52.0, 69.6), representing a 24.5% difference (SE: 6.5; 95% CI: 11.6, 37.3; superiority: p<0.0002) (Fig 4).

Fig 5. Satisfactory clinical progress (≥40% reduction in study wound area) (full analysis population). The full analysis population included all randomised patients who received treatment and had at least one follow-up visit after baseline (Visit 1). Bars represent the percentage of venous leg ulcers (VLUs) with satisfactory clinical progress and error bars show 95% confidence intervals. CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing



Satisfactory clinical progress

A greater proportion of wounds in the CISEB arm achieved a ≥40% reduction in wound area at week 4 (satisfactory clinical progress) compared to the DACC arm (77.1% versus 64.8%, respectively; 12.3% difference; 95% CI: 0.3, 24.4; superiority: p<0.0477) (Fig 5). VLUs treated with CISEB were associated with a 19% increased likelihood of achieving satisfactory clinical progress compared to those treated with DACC (risk ratio: 1.19; 95% CI: 1.0, 1.4). The non-inferiority results were robust when adjusted for baseline wound size and country via sensitivity analysis (superiority results were not significant after adjustment; p>0.05).

Adverse events

In all, five (5.0%) patients experienced a total of 11 AEs in the CISEB arm, and 18 (17.6%) patients experienced a total of 27 AEs in the DACC arm (Table 2). In the CISEB arm, one AE was considered to be related to the dressing (ulcer bleeding). In the DACC arm, four AEs (infection) were considered to be related to the dressing, one of which required hospitalisation. In the DACC arm, one patient died due to bronchopneumonia which was considered unrelated to the dressing.

Discussion

In this RCT, management of VLUs with CISEB was associated with a statistically significant increased rate of complete wound closure at week 12 (primary endpoint) compared to DACC, as well as a faster time to complete wound closure. A significant increase in percentage of VLUs with satisfactory clinical progress and a significant decrease in least square mean wound area with CISEB were also observed. Moreover, CISEB had a favourable safety profile compared with DACC during the study period. SoC compression therapy was applied throughout the study, suggesting dressing choice plays a key role in healing outcomes of hard-to-heal VLUs. While cross-study results should be interpreted with caution due to differences in study design and populations, our findings are consistent with several non-comparative studies in VLUs which demonstrated high healing rates or wound size reduction after treatment with CISEB.[17,19,20,33] To our knowledge, the results from this study represent the first published data of CISEB from an RCT.

CISEB contains ionic silver for its antimicrobial activity, and the advantages of silver-containing dressings in the management of hard-to-heal wounds (including VLUs) have previously been reported in the literature.[34] CMC is a fibre that forms a cohesive gel in contact with wound exudate, intimately contacting the wound bed and reducing dead space where microorganisms can grow, while also retaining the harmful components found within exudate, such as proteases, devitalised tissue, metabolic waste and microorganisms.[35,36] Furthermore, in vitro studies have shown that EDTA weakens structures of surface-associated or aggregated microorganisms (i.e., biofilm) through binding and removal of structural ions such as calcium, iron and magnesium; and also that BEC reduces surface tension within the gelled dressing to lift and loosen the weakened surface-associated or aggregated microorganism.[35,37,38] In contrast, DACC is a fatty acid that attracts and immobilises microorganisms (bacteriostatic) via hydrophobic interactions; however, it lacks viable mechanisms to both disrupt and kill surface-associated or aggregated microorganisms.[23,24] There is some evidence of the ability of DACC to adhere to these communities in vitro;[24] however, another study reported lack of activity against mature surface-associated or aggregated microorganisms[39] and in vivo observations of activity against this phenotype from DFUs were not associated with reductions in overall wound bioburden.[40] While the superior healing outcomes observed with CISEB may possibly be attributed to its mechanism of action, it is important to note that a major limitation of this present study is the absence of direct biofilm-related data. However, despite some detection methods being described in the literature, there is no standardised protocol or routine test for diagnosis in clinical practice.[41]

VLUs are a wound type at risk of infection and both locally infected and non-infected wounds were sought for inclusion in this study.[12,13] However, only six VLUs in the CISEB arm had baseline infection. Despite the limited number of baseline infections included in the study, better healing outcomes were still observed with

CISEB compared with DACC. These findings highlight the importance of proactively managing wounds at risk of infection as preventing progression to clinical infection will reduce patient burden and minimise costs associated with treatment and delayed healing. Moreover, focusing the appropriate use of enhanced antimicrobial dressings as part of good wound hygiene practices reduces the need for systemic antibiotics, thereby contributing to antimicrobial stewardship in wound care (one of the largest healthcare sectors for antibiotic prescriptions).[42]

A strength of this study was the randomised and controlled design which minimised the effect of confounding factors and allowed for the performance of two dressings with distinct mechanisms to be directly compared. Additionally, our study was conducted across multiple sites in three countries with differing SoC that may increase the generalisability of the findings.

Limitations

A notable study limitation was that enrolment was restricted to patients with VLUs, and other common hard-to-heal wound types were not included. However, biofilm colonisation is non-specific and present in >80% of hard-to-heal wounds,[15] and as the study dressings act locally and not on the pathophysiology of the underlying disease, the study findings may be considered relevant to other hard-to-heal wound types. Furthermore, while the majority of wounds enrolled in this study were not infected at baseline, patients with VLUs still largely represent a population at risk of infection and therefore our findings may be generalised to an at-risk population.[12,13]

Other limitations include the absence of participant blinding due to the distinct appearance of the dressings. Future potential directions of research include investigations in larger populations and in diverse wound types, cost-effectiveness comparisons, evaluating antibiotic use and microbiology studies.

Conclusion

The results from this study demonstrated that management of hard-to-heal VLUs with CISEB was associated with superior healing outcomes compared to DACC, including a 35% increased likelihood of complete wound closure and a faster time to healing, combined with a favourable safety profile. The data suggest that CISEB is more effective than DACC in the treatment of VLUs and may be considered as a SoC. JWC

Table 2. Summary of adverse events (safety population*)

	CISEB (n=101)†	DACC (n=102)
Patients with an AE, n (%)	5 (5.0)	18 (17.6)
Total AEs, n	11	27
Local AE, n		
Wound infection	3	8
Other ulcer (non-VLU)	1	6
Bleeding ulcer	1	0
Overgranulation	1	0
Cellulitis of abdominal wall	0	1
Cellulitis of leg	0	1
Other	1	2
Systemic AE, n		
Urinary tract infection	2	1
Wound pain	0	2
Ischaemic heart disease	1	0
Chest infection	1	0
Gastrointestinal bleeding	0	1
Unilateral leg swelling	0	1
Allergic reaction to drug	0	1
Hypercholesterolaemia	0	1
Itching all over	0	1
Death	0	1

*The safety population included all randomised patients who received one of the study dressings.
†One patient randomised to the DACC arm received CISEB. AE—adverse event; CISEB—carboxymethylcellulose dressing containing ionic silver, ethylenediaminetetraacetic acid and benzethonium chloride; DACC—dialkylcarbamoyl chloride-coated dressing; VLU—venous leg ulcer

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Availability of data and materials
Data are available upon reasonable request through submission of a proposal and subject to agreement of a contract. Requests for data should be submitted to the corresponding author. Access to patient-level data and supporting clinical documents is subject to certain criteria, conditions and exceptions.

References

1 Olsson M, Jarbrink K, Divakar U et al. The humanistic and economic burden of chronic wounds: a systematic review. Wound Repair Regen 2019; 27(1):114–125. https://doi.org/10.1111/wrr.12683
2 Sen CK. Human wound and its burden: updated 2020 compendium of estimates. Adv Wound Care (New Rochelle) 2021; 10(5):281–292. https://doi.org/10.1089/wound.2021.0026
3 Martinengo L, Olsson M, Bajpai R et al. Prevalence of chronic wounds in the general population: systematic review and meta-analysis of observational studies. Ann Epidemiol 2019; 29:8–15. https://doi.org/10.1016/j.annepidem.2018.10.005
4 European Wound Management Association. Position document: Hard-to-heal wounds: a holistic approach. MEP Ltd, 2008. https://tinyurl.com/ytjrws74 (accessed 10 February 2025)
5 Raffetto JD, Ligi D, Maniscalco R et al. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. J Clin Med 2021; 10(1):29. https://doi.org/10.3390/jcm10010029
6 Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018; 15(1):29–37. https://doi.org/10.1111/iwj.12814
7 Urwin S, Dumville JC, Sutton M, Cullum N. Health service costs of

Reflective questions

- Which factors contribute to delayed healing in venous leg ulcers?
- Why is biofilm management important in hard-to-heal wounds?
- What are the potential reasons for the observed differences in treatment outcomes between the two study dressings?

treating venous leg ulcers in the UK: evidence from a cross-sectional survey based in the north west of England. BMJ Open 2022; 12(1): e056790. https://doi.org/10.1136/bmjopen-2021-056790
8 O'Donnell TF Jr., Passman MA, Marston WA et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2014; 60(2 Suppl):3S–59S. https://doi.org/10.1016/j.jvs.2014.04.049
9 Ma H, O'Donnell TF, Jr., Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord 2014; 2(4):355–361. https://doi.org/10.1016/j.jvsv.2014.04.006
10 Obagi Z, Damiani G, Grada A, Falanga V. Principles of wound dressings: a review. Surg Technol Int 2019; 35:50–57
11 Shi C, Wang C, Liu H et al. Selection of appropriate wound dressing for various wounds. Front Bioeng Biotechnol 2020; 8:182. https://doi.org/10.3389/fbioe.2020.00182
12 Parker CN, Finlayson KJ, Shuter P, Edwards HE. Risk factors for delayed healing in venous leg ulcers: a review of the literature. Int J Clin Pract 2015; 69(9):967–977. https://doi.org/10.1111/ijcp.12635
13 Bui UT, Edwards H, Finlayson K. Identifying risk factors associated with infection in patients with chronic leg ulcers. Int Wound J 2018; 15(2):283–290. https://doi.org/10.1111/iwj.12867
14 Bowler PG. Wound pathophysiology, infection and therapeutic options. Ann Med 2002; 34(6):419–427. https://doi.org/10.1080/078538902321012360
15 Malone M, Bjarnsholt T, McBain AJ et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. J Wound Care 2017; 26(1):20–25. https://doi.org/10.12968/jowc.2017.26.1.20
16 Metcalf DG, Bowler PG. Clinical impact of an anti-biofilm Hydrofiber dressing in hard-to-heal wounds previously managed with traditional antimicrobial products and systemic antibiotics. Burns Trauma 2020; 8:tkaa004. https://doi.org/10.1093/burnst/tkaa004
17 Metcalf DG, Parsons D, Bowler PG. Clinical safety and effectiveness evaluation of a new antimicrobial wound dressing designed to manage exudate, infection and biofilm. Int Wound J 2017; 14(1):203-213. https://doi.org/10.1111/iwj.12590
18 Metcalf D, Parsons D, Bowler P. A next-generation antimicrobial wound dressing: a real-life clinical evaluation in the UK and Ireland. J Wound Care 2016; 25(3):132–138. https://doi.org/10.12968/jowc.2016.25.3.132
19 Walker M, Metcalf D, Parsons D, Bowler P. A real-life clinical evaluation of a next-generation antimicrobial dressing on acute and chronic wounds. J Wound Care 2015; 24(1):11–22. https://doi.org/10.12968/jowc.2015.24.1.11
20 Harding KG, Szczepkowski M, Mikosinski J et al. Safety and performance evaluation of a next-generation antimicrobial dressing in patients with chronic venous leg ulcers. Int Wound J 2016; 13(4):442–448. https://doi.org/10.1111/iwj.12450
21 Dissemond J, Aare K, Ozer K et al. Aquacel Ag Advantage/Ag+ Extra and Cutimed Sorbact in the management of hard-to-heal wounds: a cohort study. J Wound Care 2023; 32(10):624-633. https://doi.org/10.12968/jowc.2023.32.10.624
22 Morilla-Herrera JC, Morales-Asencio JM, Gomez-Gonzalez AJ et al. Effectiveness of a hydrophobic dressing for microorganisms' colonization of vascular ulcers: protocol for a randomized controlled trial (CUCO-UV Study). J Adv Nurs 2020; 76(8):2191–2197. https://doi.org/10.1111/jan.14412
23 Ljungh A, Yanagisawa N, Wadstrom T. Using the principle of hydrophobic interaction to bind and remove wound bacteria. J Wound Care 2006; 15(4):175–180. https://doi.org/10.12968/jowc.2006.15.4.26901
24 Cooper R, Jenkins L. Binding of two bacterial biofilms to dialkyl carbamoyl chloride (DACC)-coated dressings in vitro. J Wound Care 2016; 25(2):76–82. https://doi.org/10.12968/jowc.2016.25.2.76
25 Totty JP, Bua N, Smith GE et al. Dialkylcarbamoyl chloride (DACC)-coated dressings in the management and prevention of wound infection: a systematic review. J Wound Care 2017; 26(3):107–114. https://doi.org/10.12968/jowc.2017.26.3.107
26 Kammerlander G, Locher E, Suess-Burghart A et al. An investigation of Cutimed Sorbact as an antimicrobial alternative in wound management. Wounds UK 2008; 4(2):10–18
27 Brambilla R, Aloisi D, Weingard I et al. VERUM – A European approach for successful venous leg ulcer healing: implementation of a comprehensive therapy concept (VERUM) in daily practice. EWMA J 2013; 13(2):19–23. https://tinyurl.com/4y9amb4a (accessed 14 February 2025)
28 Hampton S. An evaluation of the efficacy of Cutimed Sorbact in different types of non-healing wounds. Wounds UK 2007; 3(4):113–119
29 Sibbald G, Woo KY, Coutts P. The effectiveness of a new antimicrobial dressing with microbinding action for the management of chronic wounds. Wound Care Canada 2012; 10(3):20–22
30 Zegarra TI, Tadi P. CEAP classification of venous disorders. StatPearls Publishing, 2024. https://www.ncbi.nlm.nih.gov/books/NBK557410/
31 Gould L, Li WW. Defining complete wound closure: Closing the gap in clinical trials and practice. Wound Repair Regen 2019; 27(3):201–224. https://doi.org/10.1111/wrr.12707
32 Lammert A, Kiehlmeier S, Dissemond J et al. Percentage area reduction as surrogate for complete healing of hard-to-heal wounds: a review of clinical trials. J Wound Care 2024; 33(10):737–755. https://doi.org/10.12968/jowc.2023.0117
33 Kammerlander G, Lantin A, Geyrhofer C et al. [Critically colonised and locally infected wounds: effectiveness of a new hydrofibre with silver, EDTA and BeCl in stabilisation] [in German]. Procare 2015. https://tinyurl.com/5n6sycy7 (accessed 10 February 2025)
34 Zhao M, Zhang D, Tan L, Huang H. Silver dressings for the healing of venous leg ulcer: a meta-analysis and systematic review. Medicine (Baltimore) 2020; 99(37):e22164. https://doi.org/10.1097/md.0000000000022164
35 Bowler PG, Parsons D. Combatting wound biofilm and recalcitrance with a novel anti-biofilm Hydrofiber wound dressing. Wound Medicine 2016; 14:6–11. https://doi.org/10.1016/j.wndm.2016.05.005
36 Walker M, Hobot JA, Newman GR, Bowler PG. Scanning electron microscopic examination of bacterial immobilisation in a carboxymethyl cellulose (AQUACEL) and alginate dressings. Biomaterials 2003; 24(5):883–890. https://doi.org/10.1016/s0142-9612(02)00414-3
37 Parsons D, Meredith K, Rowlands VJ et al. Enhanced performance and mode of action of a novel antibiofilm Hydrofiber wound dressing. Biomed Res Int 2016; 2016:7616471. https://doi.org/10.1155/2016/7616471
38 World Union of Wound Healing Societies. Wound exudate and the role of dressings: a consensus document. Int Wound J 2008; 5(Suppl 1):iii-12. https://doi.org/10.1111/j.1742-481X.2008.00439.x
39 Brackman G, De Meyer L, Nelis HJ, Coenye T. Biofilm inhibitory and eradicating activity of wound care products against Staphylococcus aureus and Staphylococcus epidermidis biofilms in an in vitro chronic wound model. J Appl Microbiol 2013; 114(6):1833–1842. https://doi.org/10.1111/jam.12191
40 Malone M, Radzieta M, Schwarzer S et al. In vivo observations of biofilm adhering to a dialkylcarbamoyl chloride-coated mesh dressing when applied to diabetes-related foot ulcers: a proof of concept study. Int Wound J 2023; 20(6):1943–1953. https://doi.org/10.1111/iwj.14054
41 Silva NBS, Marques LA, Röder DDB. Diagnosis of biofilm infections: current methods used, challenges and perspectives for the future. J Appl Microbiol 2021; 131(5):2148–2160. https://doi.org/10.1111/jam.15049
42 Torkington-Stokes R, Moran K, Martinez DS et al. Improving outcomes for patients with hard-to-heal wounds following adoption of the Wound Hygiene Protocol: real-world evidence. J Wound Care 2024; 33(5):304–310. https://doi.org/10.12968/jowc.2024.33.5.304

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