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ARTICLE

Prospective randomised placebo-controlled trial assessing the efficacy of silver dressings to enhance healing of acute diabetes-related foot ulcers

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Abstract

Aims/hypothesis Silver dressings are used for their antimicrobial properties but there is limited evidence of clinical benefit when managing diabetes-related foot ulcers (DFUs). We aimed to assess whether silver dressings in acute DFUs increased the proportion of ulcers healed compared with non-silver dressings.

Methods In this open-labelled, randomised controlled trial, consecutive individuals who presented to a tertiary multidisciplinary diabetic foot service with a DFU without osteomyelitis or tendon on view of <6 weeks' duration were randomised 1:1 via a computer-generated randomisation process to receive Acticoat (Smith & Nephew, England) dressing (silver group) or dressing without silver (control group) in addition to standard care. Stratified randomisation was performed to ensure that the presence of peripheral arterial disease and infection were equally managed within the two groups. The primary outcome was the proportion of ulcers healed at 12 weeks. Secondary outcomes included time to heal and to 50% ulcer reduction, rates of osteomyelitis and amputation, and need for and duration of antibiotics.

Results Seventy-six ulcers (55 participants) in the control group and 91 ulcers (63 participants) in the silver group were included. There was no difference in the proportion of ulcers healed by 12 weeks in the control vs silver group (75% vs 69%, p=0.49). After adjustment for presence of peripheral arterial disease, infection and initial ulcer size, silver dressing was not associated with odds of healing (OR 0.92; CI 0.26, 3.22; p=0.53). There was no difference in time to healing, progression to osteomyelitis, need for amputation, or duration of or need for antibiotic treatment.

Conclusions/interpretation In individuals with acute DFUs without osteomyelitis or tendon on view, Acticoat silver dressings did not improve wound healing or reduce need for antibiotics compared with non-silver dressings.

Trial registration Australian New Zealand Clinical Trials Registry ACTRN12614001234606

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Keywords Diabetic foot · Foot infection · Foot ulcer · Silver dressing · Ulcer care · Ulcer healing · Wound dressing

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Abbreviations

DFU Diabetes-related foot ulcer
PAD Peripheral arterial disease

Research in context

What is already known about this subject?

- Diabetes-related foot ulcers are a major cause of morbidity and mortality
- Silver has antimicrobial properties, and silver dressings have been widely used to treat diabetes-related foot ulcers despite the increased cost and limited evidence of improved healing

What is the key question?

- Does the use of silver dressings in the management of diabetes-related foot ulcers, in addition to standard of care, improve the proportion of ulcers healed?

What are the new findings?

- The use of silver dressings did not improve the proportion of ulcers healed at 12 weeks compared with non-silver dressings, nor the time to heal
- The use of silver dressings did not reduce the risk of progression to osteomyelitis or amputation, nor the need for or duration of antibiotics compared with non-silver dressings

How might this impact on clinical practice in the foreseeable future?

- Silver dressings are not required for the management of acute diabetes-related foot ulcers. The extra costs associated with using these dressings can be re-directed to other aspects of patient care

Introduction

Diabetes continues to be a global issue. More than 537 million people worldwide have diabetes, and this number is expected to increase to 643 million by 2030 [1]. Diabetes can lead to the development of micro- and macro-vascular complications which affect long-term morbidity, productivity, health expenditure and mortality [2, 3]. Diabetes-related foot ulcers (DFUs) are the major cause of non-traumatic amputations in Australia and other developed countries [4]. It is therefore crucial to optimise healing of DFUs in order to reduce the risk of amputation.

DFUs develop and fail to heal as a result of varying degrees of peripheral neuropathy, deformity, trauma, peripheral arterial disease (PAD) and infection. It is therefore not surprising that clinical outcomes are better when managed by a dedicated interdisciplinary unit [5]. Aspects of care include ulcer debridement, ulcer dressing, pressure offloading, optimising vascular supply, identifying and managing infection and optimising glycaemic control [6, 7]. All pathogenic factors, including infection and PAD, delay ulcer healing and increase amputation rates [8, 9].

Silver has been used in wound management dating back to 69 BCE [10]. Silver ions have antimicrobial effects, including direct inhibition of bacterial cell respiration, inactivation of intracellular enzymes and alteration to cell membranes [11]. This leads to very broad-spectrum antimicrobial coverage of yeast, fungi, mould and bacteria, including some antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci if treated with high enough doses [10]. Silver is also known to have low toxicity and rare systemic toxicity.

As a result of its antimicrobial properties and low toxicity, dressings with nanocrystalline silver have been developed with sustained release of silver ions at therapeutic concentrations for days, allowing for reduced frequency of dressing changes [8]. Acticoat (Smith & Nephew, England) is a barrier dressing coated with nanocrystalline silver particles with the highest silver concentration of this type of dressing (70–100 ppm), but which has been shown to be less toxic to fibroblasts derived from chronic DFUs than other dressings with lower silver concentrations [12–14].

DFUs are predisposed to polymicrobial infections. The use of silver can reduce bacterial burden and theoretically should promote healing [15]. This has led to its widespread use, despite limited evidence of clinical benefit in this population. After a review of the literature and multiple systematic reviews, there is insufficient evidence to recommend the use of silver dressings in the management of DFUs [15–21]. The aim of our study was to assess whether silver dressings combined with standard of care in acute DFUs improve the proportion of ulcers that completely heal compared with non-silver dressings.

Methods

Study design This was an investigator-initiated, prospective, open-label, randomised placebo-controlled study at the Royal Melbourne Hospital, Australia, a tertiary referral centre with

an interdisciplinary diabetic foot unit. This study was approved by the Human Research Ethics Committee at Melbourne Health and all participants provided written informed consent prior to study entry. This trial was registered with the Australian New Zealand Clinical Trials Registry (registration no. ACTRN12614001234606).

Participants Consecutive individuals managed by the Diabetic Foot Unit at the Royal Melbourne Hospital were invited to participate by the treating team. Participants had to have a confirmed diagnosis of diabetes and an ulcer distal to the level of the ankle, and the ulcer had to be of less than 6 weeks' duration at the time of recruitment. Exclusion criteria included age less than 18 years and individuals who were pregnant; who had a life expectancy of less than 12 weeks; who had an allergy to silver, Mepilex (Mölnlycke, Sweden) or Zetuvit (Hartmann, Germany); and who had ulcers with tendon on view or underlying osteomyelitis. If more than one ulcer was present in an individual, all ulcers were enrolled in the study and their outcomes were analysed.

Randomisation Upon providing written consent, individuals with ulcers that met the inclusion criteria were randomised to a treatment group. Individuals were randomised 1:1 via a computer-generated randomisation process to receive either a silver-impregnated dressing in combination with a foam dressing (Acticoat and Mepilex or Zetuvit) (silver group) or similar silver-free control dressing (DuoDERM (ConvaTec, England), AQUACEL (ConvaTec, England) or IntraSite (Smith & Nephew, England) conformable with Mepilex or Zetuvit) (control group). Stratified randomisation was performed for the presence of PAD and infection. PAD was defined as a toe pressure of less than 60 mmHg [22]. Infection was defined as presence of purulent discharge or two or more of redness, pain/tenderness, swelling and warmth [23]. As randomisation occurred at the individual level (rather than ulcer level), if a participant had more than one ulcer enrolled, the randomised dressing group allocation would be the same for all ulcers.

Intervention Ulcers either received their designated dressing plan for 12 weeks, until the ulcer healed, or the ulcer characteristics were such that these dressings could no longer be safely applied, whichever occurred first. Ulcer healing was defined as 100% epithelialisation.

All participants received standard care, including sharp ulcer debridement, antibiotics in the setting of infection, revascularisation in the setting of PAD, tailored offloading to the ulcer (custom shoe, offloading shoe including LEIPZIG Rehabilitation (Fior & Gentz, Germany) or Darco All Purpose shoe (DARCO International, USA), Controlled Ankle Motion walker (OAPL, Australia) or total contact cast) and optimisation of glucose control. All dressings were provided free of charge to participants, as is the usual practice of the unit, to promote compliance. Dressings between visits were changed by the patient, carer, general practitioner or district nurses, depending on the patient's ability, as is standard of care. The only variation to care was the randomisation of the ulcers to have dressings that contained silver or a similar silver-free dressing.

Data collection Ulcers were assessed at recruitment then during each review. Review appointments were scheduled as per usual clinical practice, usually every 1–2 weeks. During assessment, ulcer area (mm^2), presence of infection, and antibiotic requirement and duration were recorded. Ulcer area was determined by measuring the longest ulcer length, then the width of a line that ran perpendicular to the longest length.

Study endpoints The primary endpoint of the study was the proportion of ulcers healed at 12 weeks and the odds of healing based on treatment group. Secondary endpoints included progression to osteomyelitis, progression to amputation, need for and duration of antibiotics, and time to heal and to 50% reduction in ulcer size.

Statistical analysis Baseline characteristics and outcomes were compared between treatment groups using Fisher's exact test for categorical variables. Continuous variables were presented as mean (SD) and compared with *t* test for normally distributed variables or presented as median (Q1 and Q3) and compared with Kruskal–Wallis tests for non-normally distributed variables. The primary endpoint, proportion of ulcers healed at 12 weeks, was assessed using Fisher's exact test. In addition, to account for the study design of randomisation at individual level stratified by PAD and infection (stratified cluster randomisation), with analysis of outcomes at the ulcer level, a mixed-level multivariable logistic regression was performed. The regression model assessed the odds of healing based on treatment group, and adjusted for PAD and infection (as both were factors used for stratified randomisation) and initial ulcer size (as it was strongly associated with healing) as fixed variables, and participant as a random variable (to account for cluster randomisation). Kaplan–Meier curves were constructed to analyse time to heal, and time to 50% reduction in ulcer size, based on treatment group and adjusted for PAD, infection and ulcer size as fixed variables and participant as a random variable. Intention-to-treat analysis was performed and included all participants who had at least one follow-up assessment. Exploratory subgroup analyses were performed according to presence or absence of PAD and/or infection.

We planned to recruit 200 ulcers, with 50 ulcers with infection and PAD, 50 with infection and no PAD, 50 with PAD and no infection and 50 without PAD or infection. However, we had difficulty recruiting participants with infection and PAD as most required surgical intervention, and hence an interim analysis was conducted. A post hoc power calculation for a mixed-model multivariable logistic regression was performed based on 55 participants and 75 ulcers in each group (mean 1.4 ulcers per person). For the primary outcome of ulcers healed at 12 weeks, and healing rate of 75% in the control group, using two-sided α 0.05 and interclass correlation 0.1, the study had 80% power to detect a 30% difference in relative rate of healing with the silver group. Recruitment was therefore ceased. Statistical analyses were performed using Stata 15 statistical software (StataCorp, College Station, TX, USA).

Results

Participant numbers Recruitment occurred between January 2015 and January 2017. A total of 176 ulcers, in 125 participants, were recruited with 81 ulcers randomised to the control group and 95 to the silver group. Five ulcers randomised to the control group were excluded as one participant (two ulcers) was found subsequently not to have diabetes and three participants (one ulcer each) failed to return for follow-up. In the silver group, two participants (three ulcers in total) were excluded as they failed to attend follow-up and one participant (one ulcer) was excluded due to a silver allergy. A total of 76 ulcers (55 participants) in the control group and 91 ulcers (63 participants) in the silver group were included in the analysis (Fig. 1).

Participant characteristics The control group and the silver group were well matched (Table 1). The mean age was 62 ± 14 years in the control group and 61± 12 years in the silver group, with median diabetes duration of 20 years in both groups. As would be expected, most participants were male (78% and 84% in control and silver groups, respectively) and had type 2 diabetes, and most required insulin therapy. Most participants in both groups (69% in control and 89% in silver group, p=0.019) had a history of previous ulcers. Rates of previous amputations were similar in both groups (38% in control and 44% in silver group, p=0.58).

Ulcer characteristics Ulcer characteristics were comparable between the two groups. There was no significant difference in median ulcer size between groups and over 90% of all individuals had evidence of neuropathy. In the control group, 25% had clinical evidence of PAD and 32% had ulcer infection at randomisation compared with 31% with PAD and 46% infection in the silver group (p value 0.49 and 0.059, respectively). Other ulcer types included burns, physical trauma and gout.

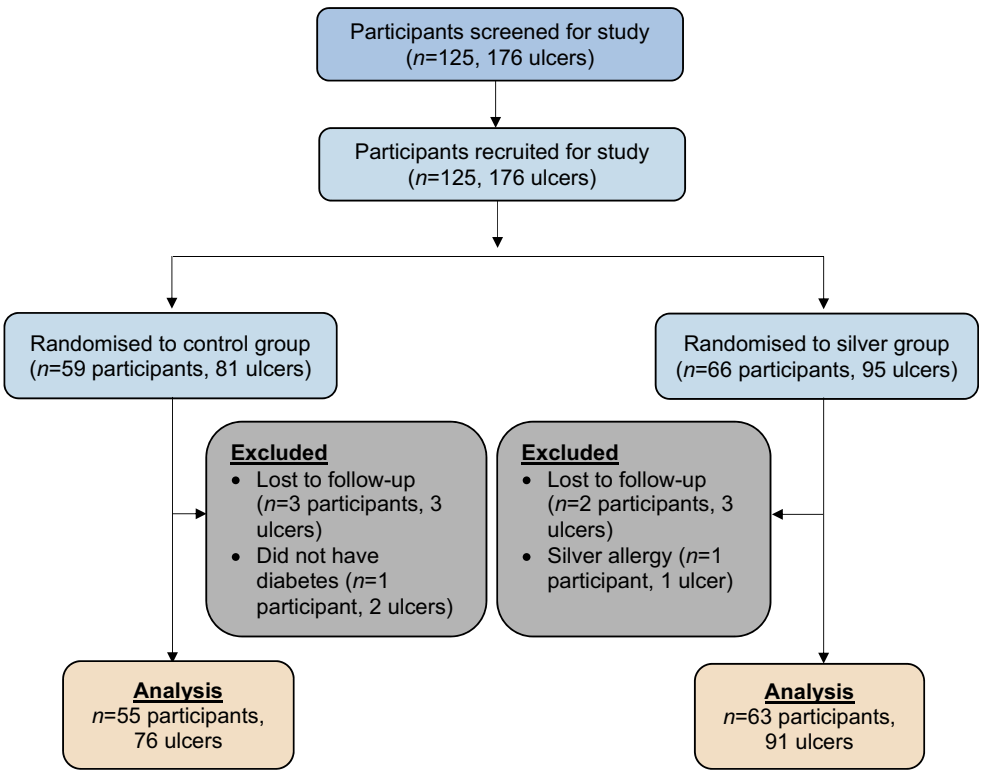

Fig. 1 CONSORT diagram of study flow

Table 1 Baseline characteristics

Characteristic	Control group	Silver group	*p* value
Participant characteristics (*n*)	55	63	
Age, years, mean (SD)	62 (14)	61 (12)	0.75
Sex, female, *n* (%)	12 (22)	10 (16)	0.48
Type of diabetes, *n* (%)			0.44
Type 2 diabetes, diet	2 (3)	2 (3)	
Type 2 diabetes, non-insulin medications	10 (18)	16 (25)	
Type 2 diabetes, insulin	35 (64)	31 (49)	
Type 1 diabetes	8 (15)	14 (22)	
Diabetes duration, years, median (Q1, Q3)	20 (15, 30)	20 (12, 33)	0.61
HbA_{1c}, mmol/mol, median (Q1, Q3)	68 (55, 89)	64 (55, 73)	0.08
HbA_{1c}, %, median (Q1, Q3)	8.4 (7.2, 10.3)	8.0 (7.2, 8.8)	
Comorbidities, *n* (%)			
Neuropathy	52 (95)	57 (90)	0.5
Retinopathy	28 (51)	27 (43)	0.46
Nephropathy	27 (49)	33 (52)	0.85
Dyslipidaemia	36 (65)	37 (59)	0.57
Hypertension	43 (78)	50 (79)	0.90
Ischaemic heart disease	21 (38)	24 (38)	0.90
Stroke	5 (9)	10 (16)	0.41
History of PAD	16 (29)	22 (35)	0.56
Smoking status, *n* (%)[a]			0.81
Never smoked	22 (42)	28 (47)	
Ex-smoker	22 (42)	24 (41)	
Current smoker	8 (16)	7 (12)	
Previous ulcer, *n* (%)	38 (69)	56 (89)	0.019*
Previous amputation, *n* (%)	21 (38)	28 (44)	0.58
Ulcer characteristics (*n*)	76	91	
Infected ulcers at randomisation, *n* (%)	24 (32)	42 (46)	0.059
PAD, *n* (%)	19 (25)	28 (31)	0.49
Toe pressures[a]			0.98
≥60 mmHg, *n* (%)	47 (87)	53 (87)	
<60 mmHg, *n* (%)	7 (13)	8 (13)	
Toe pressures, mmHg, mean (SD)	94 (32)	90 (33)	0.57
Ulcer size, mm^2, median (Q1, Q3)	66 (20, 225)	95 (40, 280)	0.067
Ulcer type, *n* (%)			0.08
Neuropathic	53 (70)	51 (56)	
Ischaemic	1 (1)	2 (2)	
Mixed	21 (28)	26 (29)	
Other	1 (1)	10 (11)	

[a] Data not available for all participants

*$p<0.05$

Most ulcers were offloaded using either LEIPZIG Rehabilitation or Darco All Purpose offloading shoes (54% control and 48% silver group), followed by Controlled Ankle Motion walker (22% and 25%, respectively), custom shoes (18% and 23%, respectively) and total contact cast (6% and 3%, respectively), with no difference between the two groups (p=0.78).

Primary outcome Seventy-five per cent of ulcers in the control group healed by 12 weeks compared with 69% in the silver group (p=0.49) (Table 2) and 69% of participants in the control group compared with 60% in the silver group had all ulcers healed (p=0.32). Mixed-level logistic regression analyses, adjusting for PAD, infection and ulcer size at randomisation, showed that the silver

Table 2 Outcome of ulcers

Outcome	Control	Silver	*p* value
Ulcers (*n*)	76	91	
Primary outcome			
Ulcers healed at 12 weeks, *n* (%)	57 (75)	63 (69)	0.49
Secondary outcomes, *n* (%)			
Progressed to osteomyelitis	9 (12)	8 (9)	0.61
Progressed to amputation	6 (8)	5 (5)	0.55
New infection developing after recruitment	13 (17)	12 (13)	0.52
Received antibiotic treatment	47 (62)	63 (69)	0.33
Duration of antibiotics, days, median (Q1, Q3)	14 (0, 35)	14 (0, 30)	0.86
Time to heal (weeks), median (Q1, Q3)	4 (2, 6)	4 (2, 8)	0.50
Time to 50% reduction in ulcer size (weeks), median (Q1, Q3)	2 (1, 4)	2 (2, 4)	0.32

group was not associated with healing at 12 weeks (OR 0.92; CI 0.26, 3.22; p=0.53) (Table 3).

Secondary outcomes There was no difference between the control group and the silver group in terms of progression to osteomyelitis (12% vs 9%, respectively, p=0.61), progression to amputation (8% vs 5%, respectively, p=0.55) or new infection following randomisation (17% vs 13%, respectively, p=0.52) (Table 2). All amputations were minor amputations including nine toe amputations and two transmetatarsal amputations. There were no major amputations. Duration of antibiotics was similar in both groups (median 14 days) and 61% of ulcers in the control group compared with 69% in the silver group (p=0.33) received systemic antibiotics. There was no difference in time to heal or time to 50% reduction in ulcer size (Fig. 2).

Exploratory analysis Subgroup analysis demonstrated no interaction between silver dressing and PAD or silver dressing and infection (Table 4). There was no difference in healing at 12 weeks for: (1) ulcers with no evidence of PAD or infection at randomisation (78% healed at 12 weeks in both groups, p=0.90); (2) ulcers with infection and no PAD at randomisation (85% healed in control group vs 68% in silver group, p=0.20); (3) ulcers with PAD and no infection at randomisation (60% and 76%, respectively, p=0.45); or (4)

Table 3 Odds of healing based on treatment group (silver vs control)

Variable	OR (95% CI)	β-coefficient (95% CI)	*p* value
Silver	0.92 (0.26, 3.22)	−0.08 (−1.34, 1.17)	0.53
PAD	0.19 (0.04, 0.86)	−1.68 (−3.21, −0.14)	0.032*
Infection	1.03 (0.27, 3.92)	0.03 (−1.29, 1.37)	0.96
log (ulcer size)	0.36 (0.18, 0.75)	−1.02 (−1.73, −0.29)	0.006**

Mixed-level logistic regression model where PAD, infection and log-transformed initial ulcer size were included as fixed variables and participant was included as a random variable

*p<0.05, **p<0.01

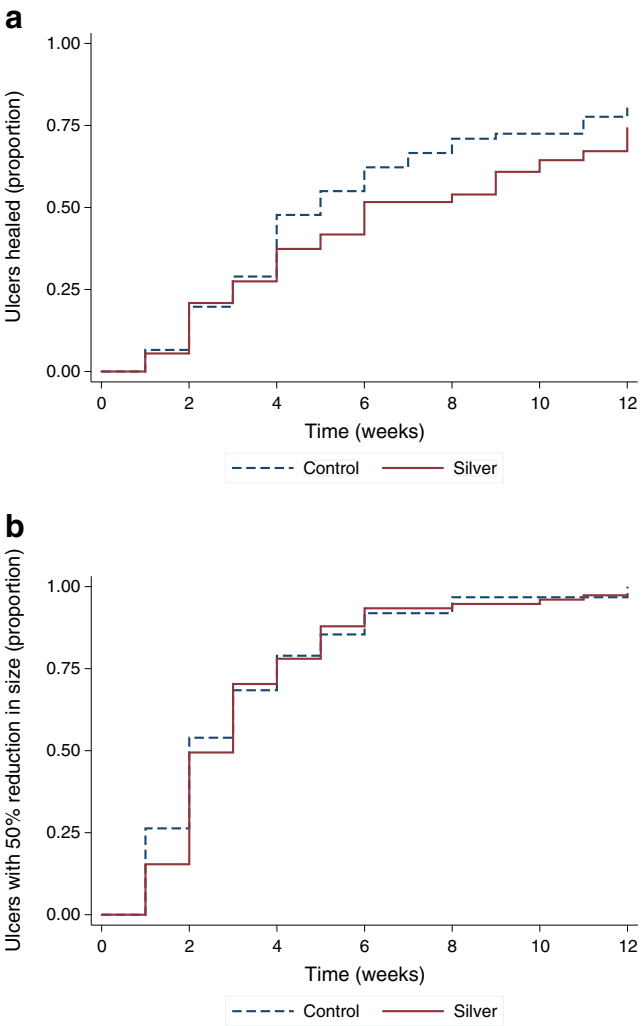

Fig. 2 Proportion of ulcers healed (**a**) and achieving 50% reduction in size (**b**) by each treatment group, adjusted for presence of infection, PAD and initial ulcer size

Table 4 Healing at 12 weeks by subgroups

Subgroup	Control *n* (%)	Silver *n* (%)	OR (95% CI) silver vs control[a]	*p* value	*p* value for interaction
No PAD	46/57 (81)	46/63 (73)	0.79 (0.31, 2.05)	0.63	0.31
PAD	11/19 (58)	17/28 (61)	1.68 (0.46, 6.18)	0.44	
No infection	38/52 (73)	38/49 (78)	1.32 (0.51, 3.40)	0.57	0.22
Infection	19/24 (79)	25/42 (60)	0.51 (0.15, 1.76)	0.28	

[a] Logistic regression for healing with silver vs control adjusted for log-transformed initial ulcer size

ulcers with PAD and infection at randomisation (50% and 36%, respectively, p=0.90) (Table 5).

Discussion

DFUs have a negative impact on individuals and the healthcare system due to their high requirement for staff and financial allocation, the reduction in an individual's physical and psychological health and by increasing financial burden due to reduced work productivity [2, 24]. Management strategies that reduce time to complete healing are crucial if we are to improve outcomes, prevent amputations and reduce health expenditure. Given the multiple factors that need to be addressed to optimise healing of DFUs and the burden imposed on the health budget, it is important to ensure that funding is directed at treatments that are demonstrated to improve outcomes or to reduce overall costs.

Silver dressings have been demonstrated to reduce pathogenic bacterial load in DFUs with mild infection without systemic antibiotics [15] but data demonstrating clinical benefit are less clear [18, 21]. Systematic reviews have identified small studies, with risk of bias, that provide low-certainty evidence for antimicrobial dressings, including silver dressings, increasing wound healing [21]. A prospective study comparing AQUACEL Hydrofibre dressings (silver containing) with Algosteril calcium alginate dressings (Les Laboratoires Brothier, France) in the management of non-ischaemic DFUs demonstrated no difference in the primary endpoint of healing rate between the two dressing types. However, it did report a greater depth reduction at 8 weeks in the AQUACEL group [16]. Another study demonstrated an increased number of wounds with 50% reduction in wound area at 4 weeks in people with non-infected, non-ischaemic DFUs of more than 30 days' duration receiving collagen/oxidised regenerated cellulose/silver treatment compared with placebo. However, the dressing in the silver group also contained collagen/oxidised regenerated cellulose which is known to increase healing [17, 25]. Most recently, a prospective, randomised, double-blinded controlled study of non-ischaemic DFUs of greater than 6 weeks' duration demonstrated increased healing rates in the SilvrSTAT Gel dressing group compared with control; however, the control group had wet-to-moist dressings with or without povidone-iodine, with daily dressing changes compared with every 72 h in the silver group [26]. Both the frequency of dressing changes and povidone-iodine could have contributed to differences in healing rates.

Given the concern for confounding in these previous studies, we performed this study where we compared silver dressings with similar non-silver dressings in addition to standard of care in people with DFUs. Our results demonstrate that in people with acute DFUs, there was no difference in the proportion of ulcers healed at any point during the 12 weeks when silver-impregnated Acticoat was used compared with similar non-silver dressings. Our reported ulcer healing rates were similar to previously published studies using only foam dressings [27, 28]. Both dressings performed similarly with regard to subsequent infection, progression to osteomyelitis, amputation and duration of antibiotics.

In subgroup analysis, we identified no benefit in the use of silver dressings in ulcers with infection, where one would have expected the most benefit. Participants underwent regular sharp debridement at review appointments and received antibiotics if they were deemed to have clinical signs of infection. It is possible that the antimicrobial benefit of silver is not additive to antibiotics. However, silver dressings also did not reduce the need for antibiotic treatment or antibiotic duration, again providing no clinical or financial benefit. These were exploratory analyses and additional research is required to elucidate this relationship further.

Despite the lack of evidence for improved healing, silver dressings are commonly used. During this study, four times the budget was allocated for the dressings in the silver group as compared with the control group, consistent with the

Table 5 Subgroup analysis: healing rates at 12 weeks in four subgroups categorised based on PAD and infection at randomisation

Subgroup	Control *n* (%)	Silver *n* (%)	*p* value
Ulcers with no PAD and no infection	29/37 (78)	25/32 (78)	0.90
Ulcers with infection without PAD	17/20 (85)	21/31 (68)	0.20
Ulcers with PAD without infection	9/15 (60)	13/17 (76)	0.45
Ulcers with PAD and infection	2/4 (50)	4/11 (36)	0.90

increased cost these dressings pose to patients and healthcare systems alike. The findings of this study demonstrate no benefit in clinical outcomes or reduced health expenditure from using the more expensive silver dressings. There were high healing rates in both groups, illustrating that standard interdisciplinary care for DFUs (including sharp ulcer debridement, antibiotic use in the setting of infection, revascularisation in the setting of PAD, tailored offloading and optimisation of glycaemic control) can lead to significant rates of ulcer healing with or without silver dressings.

This is the largest randomised controlled trial to date to assess silver dressings in the management of DFUs. It was investigator led and was powered to detect a clinically significant difference in the proportion of ulcers healed. Other strengths of this study include the prospective randomised controlled design and continuation of all other aspects of standard care, which allowed us to minimise confounding. We included a wide variety of ulcer characteristics, which improves the generalisability of our study, and all dressings were provided to participants, improving compliance rates. We randomised ulcers according to the presence or absence of PAD and infection, two factors known to affect healing rates. Both groups were well matched for other factors.

Limitations of our study include an open-label design causing potential for detection bias. The exclusion criteria of this study included ulcers with tendon on view or osteomyelitis, which would limit the generalisability of our study. The silver group had a higher proportion of participants with a history of prior ulceration; however, this is a risk factor for further ulceration rather than for healing rates. Recruitment for participants with ulcers that were infected and who had PAD was difficult, as they often had osteomyelitis or needed amputation at recruitment.

Conclusion This study has demonstrated that there was no difference in the proportion of DFUs healed at 12 weeks with use of the silver dressing Acticoat as compared with a non-silver dressing in participants with DFUs of less than 6 weeks' duration, without osteomyelitis or tendon on view, in addition to standard of care. This is the largest randomised controlled trial to date and the results should be used to demonstrate that there is a lack of clinical evidence for using silver-impregnated dressings in managing DFUs.

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Data availability The data are not publicly available but may be accessed through the corresponding author on reasonable request.

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Author's relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement NL was involved in data collection and interpretation of data, and wrote the first and subsequent manuscripts. JJ was involved in the coordination of the study and data collection and commented on the drafts of the manuscript. MK was involved in the analysis and interpretation of the data and in the writing of the manuscript. PW conceived this study, supervised its conduct and data analysis, and was involved in writing the manuscript. All authors were involved in data collection, provided comments to the drafts of the manuscript and approved the final version. PW is the guarantor of this study.

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