Low dose aspirin as adjuvant treatment for venous leg ulceration: pragmatic, randomised, double blind, placebo controlled trial (Aspirin4VLU)

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ABSTRACT

OBJECTIVE
To determine the effect of low dose aspirin on ulcer healing in patients with venous leg ulcers.

DESIGN
Pragmatic, community based, parallel group, double blind, randomised controlled trial.

SETTING
Five community nursing centres in New Zealand.

PARTICIPANTS
251 adults with venous leg ulcers who could safely be treated with aspirin or placebo: 125 were randomised to aspirin and 126 to placebo.

INTERVENTIONS
150 mg oral aspirin daily or matching placebo for up to 24 weeks treatment, with compression therapy as standard background treatment.

MAIN OUTCOME MEASURES
The primary outcome was time to complete healing of the reference ulcer (largest ulcer if more than one ulcer was present). Secondary outcomes included proportion of participants healed, change in ulcer area, change in health related quality of life, and adverse events. Analysis was by intention to treat.

RESULTS
The median number of days to healing of the reference ulcer was 77 in the aspirin group and 69 in the placebo group (hazard ratio 0.85, 95% confidence interval 0.64 to 1.13, P=0.25). The number of participants healed at the endpoint was 88 (70%) in the aspirin group and 101 (80%) in the placebo group (risk difference −9.8%, 95% confidence interval −20.4% to 0.9%, P=0.07). Estimated change in ulcer area was 4.1 cm^2 in the aspirin group and 4.8 cm^2 in the placebo group (mean difference −0.7 cm^2, 95% confidence interval −1.9 to 0.5 cm^2, P=0.25). 40 adverse events occurred among 29 participants in the aspirin group and 37 adverse events among 27 participants in the placebo group (incidence rate ratio 1.1, 95% confidence interval 0.7 to 1.7, P=0.71).

CONCLUSION
Our findings do not support the use of low dose aspirin as adjuvant treatment for venous leg ulcers.

TRIAL REGISTRATION
ClinicalTrials.gov NCT02158806.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Two small trials of patients with venous leg ulcers (total of 71 participants) found increased rates of healing in those treated with 300 mg oral aspirin daily in addition to compression

There was no trial evidence for the effect of low dose aspirin (≤150 mg) as an adjuvant treatment for venous leg ulcers

WHAT THIS STUDY ADDS

Low dose aspirin does not increase time to healing of venous leg ulcers, percentage healed, estimated change in venous leg ulcer area, or change in health related quality of life

Introduction

About 1% of the adult population will develop a venous leg ulcer during any one year.[1] Compression therapy, either in the form of bandage systems or hosiery, is the mainstay of treatment, but in trials of venous leg ulcers about half the participants remain unhealed after three months of treatment.[2 3] Pentoxifylline and micronised purified flavonoid fraction are recommended adjuvants to compression,[4] but there are barriers to use, including frequency of dosing regimen,[5] off-label use,[5] cost, and the quality of evidence.[6]

Aspirin has been advocated as an adjuvant treatment for venous leg ulcers,[7] based on suggestive evidence from two trials using 300 mg doses,[8 9] although a Cochrane review concluded the evidence was insufficient to be definitive.[10] The use of aspirin for treating venous leg ulcers has biological plausibility. The haemodynamic forces associated with venous hypertension in venous leg ulcers activate leucocytes and cause platelet aggregation and activation. Patients with chronic venous insufficiency have statistically significantly higher platelet counts compared with normal controls or people with non-venous leg ulcers,[11 12] increased platelet reactivity compared with normal controls,[13] and increased levels of platelet microparticles (shed by activated platelets).[12]

Aspirin could interrupt platelet aggregation and activation through inhibition of platelet cyclooxygenase or vessel wall cyclooxygenase. Platelet inhibition by aspirin is achieved by doses as low as 81 mg,[14] although variability in response has been described with formulation, obesity, and rate of platelet turnover.[15] Bleeding risks are associated with aspirin use and the risks increase with dose, particularly in elderly people.[16] The prevalence of leg ulceration also increases with age,[17] such that a 300 mg dose of aspirin could be an unnecessary barrier to treatment choice in older adults if the US Preventive Services Taskforce guidance is followed.[16] Reanalysis of a previous trial suggested 150 mg aspirin was strongly associated with healing (hazard ratio 1.77, 95% confidence interval 1.13 to 2.75).[3] This dose, although lower than in the previous trials, would achieve platelet inhibition while allowing for individual variability in response (aspirin

resistance), as well as managing the increased risk of side effects in older people. Thus we evaluated the effect of 150 mg aspirin daily compared with placebo as an adjuvant to compression for treating venous leg ulcers.

Methods

Study design

The study design has been described in detail elsewhere.[18] Briefly, Aspirin4VLU was a pragmatic, community based, parallel group, double blind, placebo controlled randomised trial. We recruited participants from patients receiving care from community nursing services at five study centres throughout New Zealand (Auckland, South Auckland, Waikato, Christchurch, and Dunedin).

Participants

Patients were eligible if they were aged 18 years or older, they could tolerate compression therapy, they could give written informed consent, their general practitioner had confirmed that it was safe for them to take aspirin or placebo, and they had a venous leg ulcer. Patients met the case definition for venous leg ulcers if they had an incident or prevalent ulcer, defined as a skin break on the lower leg that had remained unhealed for four or more weeks, where the ulcer clinically presented as venous (moist, shallow, irregularly shaped and with associated haemosiderin pigmentation, venous eczema, ankle oedema, ankle flare, or lipodermatosclerosis), the ankle brachial index was greater than 0.8, and other causes had been ruled out.

We excluded patients if they were pregnant or breast feeding; had a history of myocardial infarction, stroke, transient ischaemic attack, angina, or major peripheral arterial disease; had a history of adverse effects related to aspirin use (hypersensitivity, allergy, aspirin induced or non-steroidal anti-inflammatory drug induced asthma); were already using aspirin or other anticoagulant treatment; had a coexisting condition or treatment that was an indication or contraindication to aspirin use; or were judged as being unable to safely participate in the trial.

Recruitment began on 1 March 2015 and was due to conclude on 30 September 2016 but was extended to 23 December 2016. As the contract period ended on 31 March 2017, 22 participants were followed up earlier than the full 24 weeks.

Randomisation and masking

Randomisation was stratified by study centre and prognostic index for risk of venous leg ulcers healing at 24 weeks when treated with compression. The prognostic index was based on whether the area of the venous leg ulcer was greater than 5 cm^2 or had been present for more than six months, or both.[19] The study statistician created a computer generated random sequence (using randomly varying block sizes of 2 and 4) in separate lists (one for each study centre and prognostic stratums) and provided this to the independent compounding pharmacy, which prepared and packaged the trial treatments in matching bottles of capsules, identical except for a unique identifier on the bottle.

A trained research nurse at each of the five study sites screened and registered the participants. Eligible participants gave informed consent at registration. Participants were randomised by the research nurses using a computer tablet that provided the unique identifier for the bottle of trial treatment that was to be given to the participant after random assignment. The participants, research nurses, investigators, coder, and statistician were blinded to allocation. The trial results were interpreted blind by the trial steering committee before the code was broken.

Procedures

The 150 mg dose of aspirin was not available as a registered medicine in New Zealand. Consequently, the drug was compounded and encapsulated from raw materials by Optimus Healthcare, a pharmacy certified for Good Manufacturing Practice by the New Zealand Ministry of Health and a member of the Professional Compounding Centers of America. The intervention consisted of 168 capsules of 150 mg aspirin (acetylsalicylic acid) with calcium lactate as a bulking agent in a gelatin shell. The placebo consisted of 168 capsules containing the bulking agent alone. The intervention and placebo were manufactured on separate days for each batch, with the two batches approximately nine months apart. The drug was packaged in opaque high density polyethylene security sealed bottles.

Participants saw the research nurses at least one week before randomisation for registration, further screening eligibility, and informed consent. When the participant was a new patient to the district nursing service, the research nurse initiated compression therapy for at least one week. Eligibility was reassessed and confirmed at baseline and measures obtained before randomisation. When participants had more than one ulcer, the largest ulcer was selected and recorded as the reference ulcer. Each randomised participant received a bottle with sufficient capsules for 24 weeks of treatment. Participants were instructed to take one capsule daily with a glass of water until the ulcer healed or the treatment course was completed, whichever was sooner.

The participants received district nursing care for their leg ulcer between the randomisation visit and the endpoint visit by the research nurses at or about 24 weeks. Because of the extended recruitment period some participants received the endpoint visit and measures earlier. Compression systems and dressings were drawn from the standard formulary in use at each study centre, with choice determined by patient or clinician preference, or both. The compression systems included Coban (3M, USA), Coban Self-adherent (3M, USA), Coban Lite (3M, USA), Profore (Smith & Nephew, UK), Profore Lite (Smith & Nephew, UK), Roselastic (KOB, Germany), Comprilan (Jobst, Germany),

Setopress (Molnlycke, USA), Lastodur (Hartmann, Germany), and compression hosiery.

Outcomes

The primary outcome was time to complete healing of the reference ulcer (the largest ulcer at baseline if more than one ulcer was present), with healing defined as complete epithelialisation with absence of scab. Secondary outcomes were proportion of participants healed at the endpoint visit, change in estimated ulcer area at the endpoint visit, change in health related quality of life at the endpoint visit (measured by RAND-36, EuroQoL-5D, and the Charing Cross venous ulcer questionnaire), treatment adherence (measured by pill count <80%), efficacy of blinding, and incidence of adverse events, categorised using ICD10-AM (international classification of diseases and procedures, Australian modification) codes and some study specific codes. An adverse event was defined as any untoward clinical event, whether or not it was considered related to treatment.

The trial was monitored by an internal data safety monitoring board. This board consisted of members with roles at the University of Auckland but outside of the National Institute for Health Innovation. Members of the data safety monitoring board wrote their own charter, reviewed all the safety data at meetings held every six months, and had access to unblinded data.

Statistical analysis

Analyses were conducted using SAS (version 9.4). Data were tested for normality within groups, and when the data were not normally distributed in both we reported the mean and median values with standard deviations and interquartile ranges. All main analyses followed the intention-to-treat principle where participants were analysed in the groups to which they were randomised. For missing outcome data, treatment failure was presumed and thus participants were presumed to have remained unhealed (if healing state was unknown) or the baseline value was carried forward (for estimated change in ulcer area). No data were imputed for change in quality of life measures and thus only participants for whom paired data were available were included in the analysis. Time to complete healing was analysed using Kaplan-Meier plots, log rank test, and Cox regression to adjust for study centre, prognostic index, and imbalance on covariates (age and first ulcer). We tested the proportional hazards assumption using scaled Schoenfeld residuals. Proportion healed and treatment adherence were tested for sensitivity to removal of the 22 participants with early endpoint visits, and per protocol analyses were conducted in which we excluded participants with major protocol violations, treatment adherence less than 80%, and early follow up (<20 weeks). We used χ^2 tests and calculated absolute risk differences with 95% confidence intervals for proportion healed and adherence at endpoint. Continuous outcomes were analysed using multiple linear regression with adjustment for baseline value and other covariates. We reported adverse events as incidence rate ratios. To evaluate levels of agreement for the efficacy of blinding we calculated κ values.

We estimated that 318 participants would be sufficient to show a four week difference in time to healing at 90% power with an α of 5%, assuming the median time to event over 24 weeks was 92 days and there was no loss to follow-up on the primary outcome.[2] This four week difference was suggested by a survey of older people, and the difference equated to a hazard ratio of 1.45 for healing of venous leg ulcers and was lower than the observed effect from previous trials and reanalysis of data from one of our previous trials.[3] The same assumptions suggested 238 participants would be necessary for 80% power.

A senior biostatistician in the coordinating centre who was not involved in the trial, peer reviewed the analysis for the primary outcome and obtained congruent results from an independent analysis. An independent laboratory conducted a blind test at the completion of the trial for the presence of aspirin in bottles from each batch using the procedures outlined in US Pharmacopeia monograph for aspirin (USP 29).[20] Data management staff matched the results from each bottle to the unique identifiers on the bottle and the trial treatment codes. Independent testing confirmed the product, and identifiers on the bottles matched the trial treatment codes.

Patient involvement

We commissioned a small survey of lay older people to assist in calculating the required sample size. A minimal important difference in time to healing to persuade most people to use aspirin was four weeks. We did not otherwise involve patients in the design of or recruitment to the study, or assess the burden of the trial treatment on participants. Our dissemination plan includes providing a lay summary of our findings to participants by email or post on publication of the results.

Results

We screened 1563 potential participants with venous leg ulcers (fig 1); 1069 did not meet the inclusion or exclusion criteria, 151 declined, 10 could not be contacted, and 31 could not be enrolled for other reasons. Overall, 302 participants meeting the initial eligibility screen were enrolled, but 51 were excluded after enrolment, mainly because their general practitioners considered it unsafe for them to receive aspirin or placebo. In total we randomised 251 participants, 125 (50%) to the aspirin group and 126 (50%) to the placebo group. We obtained information on the healing status and date of healing for the primary endpoint on all participants. However, nine participants were lost to follow-up for some secondary endpoints (estimated change in ulcer area, treatment adherence, efficacy of blinding, health related quality of life): four (3%) in the aspirin group and five (4%) in the placebo group.

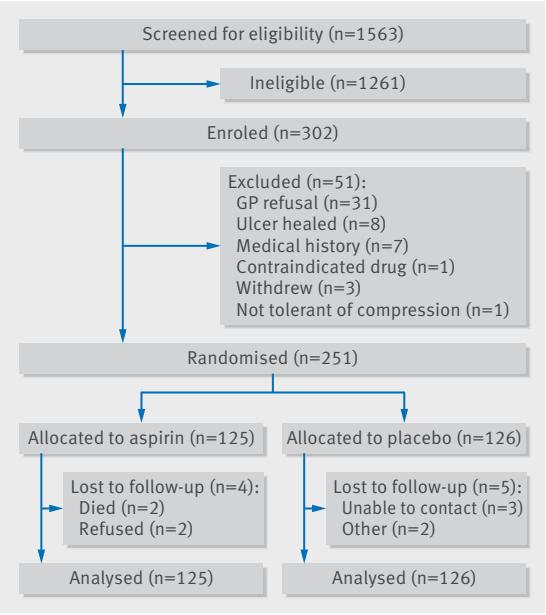

Fig 1 | Participant flow diagram. All people screened were patients with venous leg ulcers. Information on healing status (and date of healing if appropriate) for the primary outcome analysis on all participants lost to follow-up were obtained from the participants' clinical records at the last point of contact

The groups were balanced across all measures at baseline, except for a difference of four years in the mean ages and a 7% difference in whether the reference ulcer was the first episode of venous leg ulcer (table 1). Overall, the mean age was 58.2 years (SD 16.7) and 118 participants (47%) were women. Most participants self identified ethnicity as New Zealand or other European (151, 60%), followed by Pasifika (53, 21%) and Māori (37, 15%). The mean age at which participants first developed a leg ulcer was 46.8 years (SD 16.3), and the median number of previous episodes was 3 (interquartile range 2-5) including the current episode. Most participants used high compression systems, and most were Coban systems (197, 78%), including Coban (111, 44%), Coban Self-adherent (67, 27%), and Coban Lite (19, 8%) evenly balanced between the groups.

Differences between the aspirin and placebo groups on primary or secondary healing outcomes were not significant. Median time to complete healing was 77 days in the aspirin group and 69 days in the placebo group (fig 2). Evidence was insufficient to reject the assumption of proportionality (ρ=0.089, χ^2=1.53, P=0.22), and the hazard ratio for time to complete healing was 0.85 (95% confidence interval 0.64 to 1.13, P=0.25) in favour of placebo. These results were robust to adjustment for study centre,

Table 1 | Baseline characteristics for trial participants. Values are numbers (percentages) unless stated otherwise

Characteristics	Aspirin group (n=125)	Placebo group (n=126)
Mean (SD) age (years)	60.1 (17.1)	56.2 (16.1)
Women	60 (48)	58 (46)
Men	65 (52)	68 (54)
Ethnicity:		
Māori	21 (17)	16 (13)
Pasifika	23 (18)	30 (24)
NZ European	77 (62)	74 (59)
Asian	4 (3)	5 (4)
Other	-	1 (0.8)
Smoking status:		
Never	62 (50)	63 (50)
Former smoker	47 (38)	44 (35)
Current smoker	16 (13)	19 (15)
Medical history:		
Diabetes	13 (10)	13 (10)
Joint replacement	16 (13)	19 (15)
Deep vein thrombosis	11 (9)	7 (6)
Ulcer history:		
Median (interquartile range) ulcer area (cm^2)	2.6 (0.9-6.8)	2.3 (0.9-6.1)
Mean (SD)* ulcer area (cm^2)	5.4 (7.4)	6.9 (16.1)
Median (interquartile range) duration (weeks)	16 (10-30)	16 (10-28)
Mean (SD)* duration (weeks)	26.6 (33.1)	38.7 (97.8)
First ulcer	54 (43)	46 (36)
Median (interquartile range) No of episodes	3 (2-6)	3 (2-4)
Prognostic index (ulcer area and duration):		
0 (≤5cm^2 and ≤6 months)	66 (53)	71 (56)
1 (>5cm^2 or >6 months)	39 (31)	37 (29)
2 (>5cm^2 and >6 months)	20 (16)	18 (14)
Compression system:		
High compression	105 (84)	102 (81)
Light compression	11 (9)	11 (9)
Hosiery	8 (6)	13 (10)
Other	1 (0.8)	-

*Non-parametric distributions.

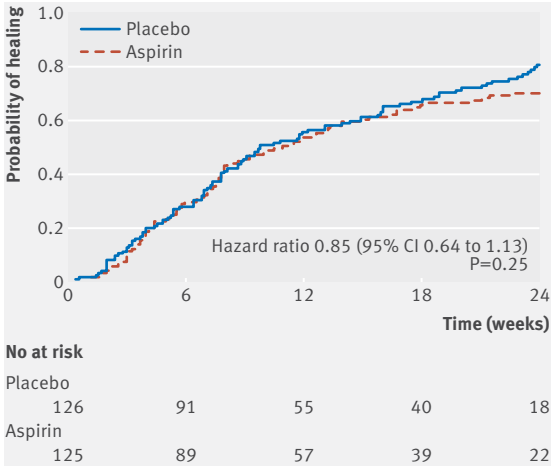

Fig 2 | Kaplan-Meier plot for time to complete healing of venous leg ulcer by trial treatment group

prognostic index, and the covariate imbalances—namely, age and first ulcer (0.88, 0.65 to 1.19, P=0.39). The adjusted analysis was also robust to substituting ulcer size and ulcer duration for the prognostic index in the model (0.83, 0.61 to 1.12, P=0.23). A per protocol analysis did not change the effect (0.98, 0.69 to 1.38, P=0.90).

The percentage of participants completely healed at endpoint was lower in the aspirin group (70.4% *v* 80.2%, table 2), as was estimated change in ulcer area from baseline (4.1 cm^2 in the aspirin group and 4.8 cm^2 in the placebo group, mean difference −0.7 cm^2, 95% confidence interval −1.9 to 0.5 cm^2, P=0.25), but neither were statistically significant. Rates of adherence to the trial treatment were similar across both groups (table 2), and tests for the efficacy of blinding showed no more than chance agreement as to whether the participants (level of agreement 51.5%) or research nurses (level of agreement 51.0%) believed the participant was taking aspirin or placebo (table 2).

Forty adverse events occurred among 29 participants in the aspirin group and 37 adverse events among 27 participants in the placebo group (incidence rate ratio 1.1, 95% confidence interval 0.7 to 1.7, P=0.71, table 2); 19 serious adverse events were reported in

Table 2 | Secondary outcomes and safety information. Values are numbers (percentages) unless stated otherwise

Outcomes	Aspirin group (n=125)	Placebo group (n=126)	Risk difference (%) (95% CI)	P or κ values
Healed at endpoint:	88 (70.4)	101 (80.2)	−9.8 (−20.4 to 0.9)	0.07
Sensitivity analysis*	81 (71.7)	94 (81.0)	−9.4 (−20.3 to 1.6)	0.10
Per protocol	62 (77.5)	67 (81.7)	−4.2 (−16.6 to 8.2)	0.52
Treatment adherence	92 (73.6)	92 (73.0)	0.6 (−10.4 to 11.5)	0.92
Capsule count only*	77 (74.8)	74 (70.5)	4.3 (−7.8 to 16.4)	0.49
Efficacy of blinding				
Participant belief:	(n=121)	(n=120)		
Aspirin	68 (56.7)	65 (53.7)	51.5†	*k*=0.03 (95% CI −0.10 to 0.16)
Placebo	52 (43.3)	56 (46.3)		
Research nurse's belief:	(n=125)	(n=125)		
Aspirin	73 (58.4)	71 (56.8)	51.0	*k*=0.02 (−0.11 to 0.14)
Placebo	52 (41.6)	54 (43.2)		
All adverse events‡:	40	37	1.1§ (0.7 to 1.7)	0.71
Cancer	6	1		
Cardiovascular	-	4		
Gastrointestinal	8	4		
Respiratory	3	-		
Genitourinary	2	-		
Skin and subcutaneous	1	5		
Accident	4	4		
Signs and symptoms	7	5		
Psychiatric	1	-		
Other	2	3		
Leg ulcer bleeding	2	2		
Leg ulcer infection	2	4		
Extension of ulcer	1	2		
New leg ulcer	1	3		
Serious adverse events:	19	12	1.6 (0.8 to 3.3)	0.21
Death	2	-		
Hospital admission	15	10		
Other event	2	2		
Bleeding events:	9	6	1.5 (0.5 to 4.3)	0.43
Major¶	2	2		
Minor	7	4		

*Sensitivity analysis excluded 22 participants (12 in aspirin and 10 in placebo groups) with endpoint visits done at early (<20 weeks). Per protocol analysis excluded 89 participants (45 in aspirin and 44 in placebo groups) for protocol violation, <80% treatment adherent, or early endpoint visit.
†Level of agreement.
‡Included multiple events in same participants.
§Incidence rate ratio.
¶Required transfusion or hospital admission.

Table 3 | Changes in health related quality of life scores from baseline to endpoint, adjusted for differences in baseline value

Domain	Aspirin group (n=116)		Placebo group (n=115)			
	Mean (SD) at baseline	Mean (SE) change	Mean (SD) at baseline	Mean (SE) change	Mean difference (95% CI)	P value
RAND-36:						
Physical functioning	60.9 (29.9)	5.0 (2.2)	60.3 (28.7)	3.8 (2.2)	1.1* (−5.0 to −7.2)	0.714
Role physical	51.7 (44.3)†	11.7 (3.4)	53.9 (43.1)	10.3 (3.4)	1.4 (−8.0 to 10.8)	0.768
Bodily pain	57.9 (23.8)†	11.4 (2.2)	56.7 (23.4)	9.0 (2.2)	2.3* (−3.7 to 8.4)	0.449
General health	69.3 (18.0)	−1.1 (1.4)	65.2 (19.1)	−0.8 (1.4)	−0.3 (−4.3 to 3.6)	0.873
Vitality	60.1 (17.9)	3.9 (1.6)	60.7 (19.1)	−0.3 (1.6)	4.2 (−0.1 to 8.5)	0.057
Social functioning	72.1 (27.4)	5.8 (2.2)	70.1 (24.8)	4.9 (2.2)	1.0* (−5.1 to −7.0)	0.756
Role emotional	72.4 (40.9)	10.5 (3.1)	70.1 (40.3)	6.8 (3.1)	3.7 (−4.9 to 12.3)	0.400
Mental health	78.3 (14.6)	−1.2 (1.4)	75.4 (16.7)	1.2 (1.4)	−2.3* (−6.2 to 1.5)	0.236
EQ-5D:						
Health state	69.5 (24.4)	7.4 (1.6)	66.6 (18.8)	4.0 (1.7)	3.4 (−1.3 to 8.0)	0.156
Utility value	0.7 (0.2)†	0.1 (0.0)	0.7 (0.3)	0.1 (0.0)	0.0 (0.0 to 0.1)	0.459
CXVUQ:	(n=115)					
Social function	35.5 (16.7)	−5.6 (1.2)	36.0 (15.1)	−6.2 (1.3)	−1.5* (−5.2 to 2.2)	0.438
Domestic activities	31.5 (15.2)	−6.2 (1.1)	31.1 (16.4)	−6.6 (1.2)	−1.4 (−4.5 to 1.9)	0.408
Cosmesis	45.0 (18.1)	−5.4 (1.5)	49.1 (18.7)	−6.1 (1.6)	−1.3 (−5.6 to 3.1)	0.568
Emotional status	51.9 (21.8)	−6.5 (1.8)	54.4 (19.9)	−9.4 (1.8)	−3.0* (−8.1 to 2.2)	0.257
Overall	41.1 (13.8)	−5.5 (1.2)	42.7 (13.3)	−7.4 (1.2)	−1.9 (−5.2 to 1.5)	0.273

CXVUQ=Charing Cross venous ulcer questionnaire.
All scores are 0-100; higher scores in RAND-36 and EQ-5D show improved health related quality life, whereas lower scores in CXVUQ show reduced impact of ulcer on health related quality of life. Thus a negative sign shows deterioration for RAND-36 and EQ-5D but improvement for CXVUQ.
*Mean differences subject to rounding error.
†n=117.

the aspirin group, including two deaths, compared with 12 serious adverse events and no deaths in the placebo group. Neither death was related to aspirin. Nine bleeding events occurred in the aspirin group and six in the placebo group. The major events requiring hospital admission or transfusion, or both included epistaxis and haematemesis in the aspirin group and intermittent haematochezia and blood stained diarrhoea in the placebo group. The minor bleeding events in the aspirin group included bleeding venous leg ulcers (n=2), contusions (n=2), prolonged bleeding from cuts (n=2), and gastric ulceration (n=1). Minor events in the placebo group included bleeding from the venous leg ulcers (n=2), contusions (n=1), and epistaxis (n=1).

Two hundred and thirty two (92.4%) participants answered the quality of life questionnaires at baseline and endpoint. No statistically significant changes took place from baseline in any domain in any of the three instruments (table 3).

Discussion

In people with venous leg ulcers, treatment with low dose aspirin for up to 24 weeks does not speed time to complete healing, increase percentage of participants with healed ulcers, or improve change in ulcer area or health related quality of life when used as an adjuvant to compression.

Strengths and limitations of this study

Our trial has several strengths. It is the largest trial to have evaluated the use of aspirin for venous leg ulcers and is the only study to have investigated the use of low dose aspirin. We used a pragmatic design to maximise external validity, as well as a robust and transparent design to ensure internal validity. Furthermore, we tested the efficacy of blinding on both participants and outcome assessors (research nurses), neither of whom could predict the trial treatment, and we had 100% follow-up on the primary outcome.

Our trial was subject to two limitations. Firstly, recruitment was lower than anticipated for 90% power. Initial estimations suggested about 40% of patients with venous leg ulcers might be ineligible in the recruiting centres, but our screening found a much smaller pool of aspirin naive participants was available. That required extension of the recruitment period and earlier than planned endpoint assessment on a small number of participants. However, we were able to achieve sufficient recruitment for 82% power if our initial assumed treatment effect had been correct. Secondly, we only collected information on the reference ulcer and assumed that healing of the largest ulcer was a marker for healing of all ulcers, an approach similar to that of other leading venous leg ulcers trials.[2 21]

A further challenge could be levelled against our trial—namely, that of its external validity; we had to screen a large number of patients with venous leg ulcers to obtain an aspirin naïve population who could safely participate in the trial. We did not have ethical approval to collect the specific reason for patients being screened out, only for whether they met the inclusion or exclusion criteria. Our impression is, however, that the rate of aspirin or other anticoagulant use was more common than we anticipated (40%) and that it was indicated use of aspirin or other anticoagulants that screened out many patients. We consider that the trial findings are generalisable to all patients with venous leg ulcers for whom aspirin is not contraindicated—that is, those who could receive or are already taking low dose aspirin. Therefore, at best, patients currently using low dose aspirin should expect no acceleration of healing and at worst they should expect some delay

to healing (but about 7 out of every 10 will still heal within 24 weeks if treated with compression).

Comparison with previous studies

Methodological differences may explain the disparity between our findings and those of previous research. Past research was limited to two trials, both small, which reported statistically significant effects in favour of aspirin. The first trial, conducted in England, recruited 20 participants and did not report random sequence generation or allocation concealment but was described as double blinded.[8] The second trial, conducted in Spain, recruited 51 participants and reported random sequence generation but did not report allocation concealment or methods for blinding[9]; this trial described blinding ambiguously as having a double blind control, the control group as receiving no drug treatment, and the follow-up as being blinded. Lack of information on sequence generation and allocation concealment has been associated with exaggerated treatment effects,[22] as has the lack of assessor blinding.[23]

The second possible explanation for the difference in findings between previous trials and Aspirin4VLU may lie with clinical differences. Both previous trials excluded patients with venous leg ulcers smaller than 2 cm^2. By comparison, Aspirin4VLU had open inclusion criteria, and the exclusion criteria were safety criteria only. Approximately 50% of our participants had an ulcer area less than 2 cm^2. Ulcer area is only one of the prognostic factors to delay healing and we stratified by prognostic index to ensure balance between the groups. Our analyses, adjusted for small imbalances in prognostic groups and age, did not reverse the direction of effect. Both previous trials also treated the participants with a standard compression system whereas we allowed clinician and participant preference to guide choice of compression system. A range of systems was used, but there was balance between groups on the type of system (high or light compression, and hosiery) and thus is unlikely to account for difference in findings.

The principal clinical difference between previous trials and Aspirin4VLU was the dose of aspirin. Both previous trials used a 300 mg daily dose compared with the 150 mg daily dose in our trial. If the target pathway is other than platelet inhibition, a 300 mg dose of aspirin may be more effective. Altered haemodynamics associated with venous hypertension cause dilation of the capillaries, with resulting leakage and oedema.[24] Vessel wall prostanoids linked to dilatation may not be inhibited by low dose aspirin, but seem to be inhibited by higher anti-inflammatory doses of aspirin.[25] Two new trials evaluating 300 mg doses are yet to report, but will help address the effect of higher doses.[10]

Conclusion

Low dose aspirin does not increase healing of venous leg ulcers when used in addition to effective compression. Indeed, the direction of effect seems to be the opposite of that in previous trials. Explanations may lie with bias in previous trials or with the dose of aspirin. Until the evidence base has been expanded by anticipated reports from new trials evaluating 300 mg doses, aspirin should not be used as an adjuvant for the treatment of venous leg ulcers.

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Ethical approval: This study was approved by the Northern A Health and Disability Ethics Committee (14/NTA/136), and institutional approvals were obtained from each participating study centre.

Data sharing: Requests for deidentified individual participant data or study documents will be considered where the proposed use aligns with public good purposes, does not conflict with other requests, or planned use by the trial steering committee, and the requestor is willing to sign a data access agreement. Contact is though the corresponding author.

Transparency: The guarantor (AJ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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