

AVURT: aspirin versus placebo for the treatment of venous leg ulcers – a Phase II pilot randomised controlled trial

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Declared competing interests of authors: Catriona McDaid is a member of the National Institute for Health Research Health Technology Assessment and Efficacy and Mechanism Evaluation Editorial Board. Christine Moffatt has received grant funding from 3M UK PLC and Smith and Nephew, two health science-based technology companies, outside the submitted work.

Published October 2018

DOI: 10.3310/hta22550

Scientific summary

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Health Technology Assessment 2018; Vol. 22: No. 55

DOI: 10.3310/hta22550

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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Background

Venous leg ulcers (VLUs) are wounds of the lower limb caused by disease of the venous system that result in chronically swollen legs and damage to the tissues, usually around the ankles. Chronic ulcers are those present for ≥ 6 weeks or those that are recurrent. VLUs may take many months to heal and 25% fail to heal. Estimated prevalence of VLUs is between 1% and 3% of the elderly population. At present, compression is the mainstay of treatment for VLU and few additional therapies exist to improve healing. This has been shown to be effective in many clinical trials. However, despite this treatment, patients take many months to heal (with median healing times of approximately 12 weeks in previous trials) and, for some patients, compression therapy does not result in resolution of their leg ulcers.

Objectives

The objectives were to assess the efficacy of aspirin for time to healing of chronic VLUs, to examine the safety of this aspirin intervention in this cohort of patients and to inform the feasibility of study procedures, such as recruitment, in order to proceed from a Phase II trial to a Phase III randomised controlled trial of clinical effectiveness and cost-effectiveness.

Primary objective

To compare the effects of 300 mg of aspirin plus standard care with placebo plus standard care on time to healing of the reference chronic VLU (largest eligible venous ulcer).

Secondary objectives

To assess the safety of aspirin in patients with VLUs and feasibility of leading directly from the pilot Phase II trial into a larger pragmatic study (Phase III) of effectiveness and efficiency, and check, in accordance with the Acceptance Checklist for Clinical Effectiveness Pilot Trials (ACCEPT) criteria, whether or not the pilot study fulfilled four criteria:

1. confirming that the effect sizes in the British and Spanish RCTs were too large, but
2. confirming that smaller effect sizes were still plausible, while
3. confirming that the intervention does not lead to unacceptably high rates of serious adverse events (SAEs), and
4. confirming that we can recruit at the planned rate.

Design

The Aspirin for Venous leg Ulcers Randomised Trial (AVURT) was a multicentred, pilot, Phase II randomised double blind, parallel-group, placebo-controlled efficacy trial. Participants were randomised to receive 300 mg of aspirin or placebo in a 1 : 1 ratio.

Setting

Participants were recruited from 10 centres in England, Wales and Scotland that were treating leg ulcers. Centres were recruited throughout the trial.

Participants

Inclusion criteria

To be eligible for the study, it was necessary for participants to meet all of the following criteria.

- Having at least one chronic VLU, that is, the VLU has (1) been present for > 6 weeks or (2) occurred in a person with a history of venous leg ulceration. Ulcers were considered purely venous if clinically no other aetiology was suspected. The ulcer was required to be venous in appearance (i.e. moist, shallow, of an irregular shape) and lie wholly or partially within the gaiter region of the leg. If the patient had more than one ulcer, then we chose the largest ulcer as the reference ulcer for purposes of the analysis.
- Having an ulcer with an area of > 1 cm².
- Having had an ankle–brachial pressure index (ABPI) of ≥ 0.8 taken within the previous 3 months or, when the ABPI is incompressible, other accepted forms of assessment included peripheral pulse examination/toe pressure/Duplex ultrasonography in combination with clinical judgement to be used to exclude peripheral arterial disease.
- Being aged ≥ 18 years (there was no upper age limit).
- Being able to provide informed consent.

Exclusion criteria

Potential participants were excluded if they fulfilled any of the following criteria.

- Being unable or unwilling to provide consent.
- Having a foot (below the ankle) ulcer.
- Having a leg ulcer of non-venous aetiology (i.e. arterial).
- Having an ABPI of < 0.8.
- Using (self-administered or prescribed) regular concomitant aspirin.
- Having a previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement).
- Taking contraindicated medication: probenecid, oral anticoagulants including coumarins [warfarin and acenocoumarol (Sinthrome®, Merus Labs Luxco S.a.R.L., Amsterdam, the Netherlands)] and phenindione (Dindevan®, Concordia International Corp., Oakville, ON, Canada), dabigatran (Pradaxa®, Boehringer Ingelheim Limited, Bracknell, UK), rivaroxaban (Xarelto®, Bayer AG, Leverkusen, Germany), apixiban (Eliquis®, Bristol-Myers Squibb, New York, NY, USA), heparin, clopidogrel, dipyridamole, sulfapyrazone and iloprost.
- Having known lactose intolerance.
- Being a pregnant or lactating/breastfeeding woman.
- Being male or a pre-menopausal female of child-bearing potential unwilling to use an effective method of birth control.
- Currently participating in another study evaluating leg ulcer therapies.
- Having another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgement).
- Having previously been recruited to this trial.

Patients were pre-screened on the basis of three criteria (concomitant aspirin, wound size and ulcer duration or history of venous ulceration) by study research nurses to determine which patients might be eligible for the study.

Interventions

A 300-mg dose of daily oral aspirin for 24 weeks (four \times 75-mg tablets were encapsulated in size 00 capsules with added lactose and magnesium stearate blend as filler) and placebo (size 00 capsules with lactose and magnesium stearate blend as filler, which were identical in weight, colour and size to the aspirin capsules).

All participants were offered an evidence-based standardised approach to the management of their leg ulcers in accordance with Scottish Intercollegiate Guidelines Network (SIGN) guidance. This consisted of multicomponent compression therapy aiming to deliver 40 mmHg of pressure at the ankle, when possible. The type of dressing used was at the discretion of the health-care professionals managing the participants.

Randomisation

Recruiting sites contacted the Research Pharmacy (St George's University Hospitals NHS Foundation Trust, London, UK), which conducted the random allocation. Patients were randomly allocated in a 1 : 1 ratio to either aspirin or placebo using a randomisation schedule generated by the investigational medicinal product (IMP) manufacturer in advance. Randomisation was stratified according to ulcer size ($\leq 5 \text{ cm}^2$ or $> 5 \text{ cm}^2$), as ulcer size is the strongest predictor of outcome. The randomisation identifier on the schedule corresponded to IMP bottle number.

Participants, investigators, research and treating nurses and other attending clinicians were blind to treatment throughout the trial. There was a 24-hour emergency code break facility at the Research Pharmacy.

Outcome measures

Outcome measures included time to healing of the reference ulcer (primary outcome), ulcer size, adverse events (AEs), ulcer recurrence (following healing), ulcer-related pain measured using a visual analogue scale (VAS), treatment compliance and resource use.

Methods

Outcome assessments were made by research nurses or treating nurses weekly or fortnightly for a minimum of 25 weeks post randomisation.

Following the confirmation of a participant's eligibility, and before randomisation, a baseline assessment was conducted by the study or research nurse, including participant details and ulcer history assessment. Digital photographs and tracings were taken, as was information on baseline ulcer-related pain.

Measurement of primary outcome

Healing was defined as complete epithelial cover in the absence of a scab (eschar) with no dressing required. This was determined by the treating nurse or research nurse and a digital photograph was taken of the wound area. After the ulcer was initially judged to be healed, participants were followed for a further 2 weeks to confirm healing.

Measurement of secondary outcomes

The reference ulcer was measured using wound grid tracings at screening, baseline and at final follow-up and at other follow-up visits when a photograph could not be taken.

Ulcer-related pain was collected at baseline and at weeks 4, 5 and 6 after randomisation using a 21-point box scale.

Participant concordance with treatment (IMP and compression) was recorded in the weekly case report forms (CRFs) and at the end of the study with return of the empty container to the Research Pharmacy, which undertook a pill count.

Resource use was recorded on CRFs, with change to type of changes of dressing/compression recorded as well as the number of wound consultations.

At each follow-up appointment, treating nurses asked participants if they had experienced any SAEs, AEs or adverse reactions and indicated the participant's response ('yes' or 'no') in the CRFs.

Participants were deemed to have exited the trial when they withdrew consent, were lost to follow-up, died or had completed follow-up.

Results

The original participant recruitment window was extended from 6 to 8 months owing to poor patient recruitment.

The main reasons for participant ineligibility were:

- already taking aspirin or other prohibited medication
- having a small or otherwise ineligible ulcer.

Modifying the eligibility criteria to improve recruitment was not possible except for adopting a smaller wound size. However, this was rejected as ulcers with a wound area of < 1 cm² usually heal very rapidly.

There were external factors outside the control of the research team that meant that sites were slow to open. A range of options were considered and explored to improve recruitment, including recruitment from primary care. Preliminary searches of records in primary care also indicated very few potentially eligible participants. In addition, the trial's short recruitment window and budget constraints meant that many of the options considered were not viable without a funded extension.

Analyses were conducted following the principles of intention to treat with all events analysed according to the participant's original treatment allocation. Pre-screening was under-reported as the first pre-screening log was not completed by some sites. The number of patients for whom we had pre-screening data was 457 and the number of participants who consented was 29. Two patients were excluded after consent was given and before randomisation.

The average age of the 27 randomised participants was 62 years [standard deviation (SD) 13 years], and two-thirds were male ($n = 18$). Participants had had their reference ulcer for a median of 15 months and the median size of ulcer was 17.1 cm².

There was one withdrawal during the course of the study (placebo), for whom data on primary outcome were not possible to obtain. This was reported at week 2 and so no follow-up data are available for this patient beyond week 1. The other four patients (placebo, $n = 2$; aspirin, $n = 2$) either agreed to withdraw from treatment but provided full follow-up until week 25 or healed at a point before withdrawal and, thus, all four provided primary outcome data.

Overall, 13 out of the 26 participants (50.0%) who were followed up were recorded as healing during the course of the study. All the reference ulcers reported to be healed on a CRF were confirmed healed approximately 2 weeks later. Seven out of 12 participants (58.3%) followed up in the placebo group and 6 out of 14 (42.9%) in the aspirin group were observed to have a healed reference ulcer. It was not possible

to estimate median time to healing and/or corresponding 95% confidence intervals (CIs) because less than, or close to, half of the patients were observed to have healed during the follow-up period of the study.

The primary analysis investigated the difference in time to healing by trial arm. Hazard ratios (HRs) and corresponding 95% CIs were obtained from a Cox regression model adjusted for ulcer area and ulcer duration at baseline (both logarithmically transformed): the HR of aspirin versus placebo (allocation) was 0.58 (95% CI 0.18 to 1.85; $p = 0.36$). Overall, these data do not provide evidence of a difference in time to healing with the addition of aspirin to usual care. The numbers within this feasibility study are small and results are inconclusive in terms of the primary outcome.

Secondary outcomes

Adverse events

Six out of the 26 (23.1%) participants who were followed up had no reported AEs (placebo, $n = 3$; aspirin, $n = 3$) and the remaining 20 had AEs (placebo, $n = 9$; aspirin, $n = 11$). The total number of events experienced by participants was compared by trial arm, adjusting for the prognostic factors (log of baseline reference ulcer area and log of baseline reference ulcer duration) using negative binomial regression as per the statistical analysis plan. There was no evidence that participants receiving aspirin were more likely to suffer an AE than those receiving placebo (incidence rate ratio 1.31, 95% CI 0.51 to 3.41; $p = 0.58$).

One participant suffered one SAE during the course of the study, requiring a blood transfusion for gastrointestinal bleeding. There were 88 non-serious AEs (placebo, $n = 36$; aspirin, $n = 52$) recorded in total among 20 participants (placebo, $n = 9$; aspirin, $n = 11$). The majority of these were not related to the IMP.

The mean baseline VAS score for ulcer-related pain was 37.7 (95% CI 22.0 to 53.4) in the placebo group and 45.4 (95% CI 24.6 to 66.2) in the aspirin group; the mean VAS score at week 5 was 13.3 (95% CI 0.3 to 26.3) in the placebo group and 28.5 (95% CI 10.6 to 46.3) in the aspirin group.

Of the 13 participants who healed, 12 were assessed for ulcer recurrence using the recurrence assessment form. Recurrence was reported for two patients (placebo, $n = 1$; aspirin, $n = 1$).

Participants took their first dose of study drug a median of 4 days after randomisation (range 1–12 days) and the majority took their first dose in the morning (70.8%; placebo, $n = 9$; aspirin, $n = 8$).

Compliance

The mean number of visits attended up until healing or study exit was 13.3 (SD 7.3) and 17.4 (SD 6.8) in the placebo and aspirin groups, respectively. Ten out of the 12 participants (83.3%) in the placebo group and 10 out of the 14 participants (71.4%) in the aspirin group were fully compliant with their compression therapy. Two participants in the placebo group (16.7%) and four participants in the aspirin group (23.1%) were partially compliant.

Eight out of the 12 participants (66.7%) in the placebo group were deemed fully compliant with taking the study medication while four (33.3%) were partially compliant. In the aspirin group, 11 out of the 14 participants (78.6%) were deemed fully compliant and three (21.4%) were partially compliant.

All participants in the placebo group were prescribed high-level compression therapy (≥ 40 mmHg) at baseline and, of those in the aspirin group, 12 were prescribed high-level compression therapy and two medium-level compression therapy (20–39 mmHg).

The total number of changes to the compression therapy prescribed at baseline during the study was 16, with five changes (31.3%) to a medium-compression level, nine changes (56.3%) to a high-compression level, one change (6.2%) to a low-compression level and one change (6.2%) to no compression at all.

The mean number of wound consultations per week was 2.1 (SD 1.4) in the placebo group, 1.9 (SD 0.7) in the aspirin group and 2.0 (SD 1.0) overall.

One participant was unblinded after the trial had completed and analysis was being undertaken, in accordance with the emergency unblinding procedure. There were no protocol violations.

Conclusions

AVURT was a Phase II randomised pilot trial of aspirin versus placebo for the treatment of patients with chronic venous leg ulceration. It was not possible to recruit the planned number of patients despite an unfunded extension to the trial and, therefore, it can be concluded that a larger Phase III (effectiveness) trial would not be feasible.

Trial registration

This trial is registered as Clinical Trials.gov NCT02333123 and European Clinical Trials Database (EudraCT) 2014-003979-39.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/87/08. The contractual start date was in January 2015. The draft report began editorial review in December 2016 and was accepted for publication in June 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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