

# Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT

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## Scientific summary

### The EVRA RCT

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# Scientific summary

## Background

Venous ulceration is a common and costly health problem worldwide, with poor healing rates affecting patient quality of life and health service costs. Compression bandaging has been shown to improve healing rates and reduce recurrence but does not address the underlying causes of venous hypertension (e.g. superficial venous reflux). In addition, patient concordance with compression is often poor. Traditionally, varicose vein surgery has been used to treat superficial venous reflux, and this has been shown to reduce ulcer recurrence; however, no effect on ulcer healing has been demonstrated. Surgery also has low patient acceptance, but novel, minimally invasive, endovenous methods have increased in popularity in recent years. Cohort studies have suggested that early endovenous ablation of superficial venous reflux can reduce time to healing, yet no robust evidence currently exists to demonstrate the clinical effectiveness or cost-effectiveness of this approach.

## Objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of compression therapy with early endovenous ablation of superficial venous reflux compared with compression therapy with deferred endovenous ablation in patients with venous ulceration. The secondary objectives were to investigate the ulcer-free time to 1 year, assess patient quality of life and evaluate the technical success of the endovenous ablation in the group that received early ablation.

## Methods

### Design

This was a pragmatic, two-arm, multicentre, parallel, open randomised controlled trial with a health economic evaluation.

### Setting

The setting was 20 secondary care vascular centres across England with ability to provide early endovenous ablation and established referral pathways for patients who have venous ulceration.

### Participants

Written informed consent was obtained from all participants, who then underwent clinical assessment and duplex Doppler ultrasound examination to assess eligibility for entry to the trial. For patients with bilateral venous ulcers, the worse leg according to the patient was included and designated the 'reference leg'.

### Inclusion criteria

- Active leg ulceration of duration > 6 weeks but < 6 months.
- Able to give informed consent to participate in the trial after reading the patient information documentation.
- Aged  $\geq 18$  years.
- Ankle-brachial pressure index of  $\geq 0.8$ .
- Primary or recurrent superficial venous reflux on colour duplex Doppler ultrasonography assessment (defined as retrograde flow of > 0.5 seconds in superficial veins and > 1 second in deep veins) deemed to warrant endovenous ablation by the treating clinician.

### Exclusion criteria

- Patients who are unable to tolerate compression therapy.
- Inability of the patient to receive early endovenous ablation by recruiting centre.
- Pregnancy (female participants of reproductive age were eligible for inclusion in the trial, subject to a negative pregnancy test prior to randomisation).
- Leg ulcer of non-venous aetiology (as assessed by the responsible clinician).
- Ulcer deemed to require skin grafting (as assessed by the responsible clinician).

### Randomisation

Randomisation lists were created using randomly permuted blocks and stored in a secure online location. Eligible patients were automatically assigned the next available entry in the appropriate list. Participants were randomised 1 : 1 to either early or deferred endovenous ablation.

### Interventions

Participants in the early-ablation group received compression therapy and endovenous ablation of superficial venous reflux within 2 weeks of randomisation. For participants randomised to deferred ablation, treatment consisted of compression therapy followed by endovenous ablation once the ulcer had healed. Multilayer elastic compression (two, three or four layer), short-stretch compression and compression hosiery were all permitted. Ablation was allowed in the deferred ablation group if the ulcer had not healed within 6 months of randomisation. Endovenous laser ablation or radiofrequency laser ablation, ultrasonography-guided foam sclerotherapy, cyanoacrylate glue and mechanochemical endovenous ablation were all permitted; the individual ablation modality was decided by each clinician on a case-by-case basis. However, the endovenous ablation had to include ablation of truncal venous reflux (to the lowest point of incompetence) and ablation of any significant reflux identified on a further duplex Doppler ultrasonography scan performed 6 weeks after randomisation. Once the ulcer had healed, participants were provided with and advised to wear elastic stockings as per local guidelines.

### Follow-up

Participants in the early-ablation group underwent duplex Doppler ultrasonography at 6 weeks post randomisation to assess the technical success of the ablation procedure. Participants were contacted on a monthly basis to determine ulcer healing dates with disease-specific [Aberdeen Varicose Vein Questionnaire (AVVQ)] and generic [EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and Short Form questionnaire-36 items (SF-36)] quality of life questionnaires at baseline, 6 weeks and 6 and 12 months.

### Main outcome measures

The primary outcome measure was time to ulcer healing from randomisation, confirmed by blinded core laboratory assessment. Secondary outcomes included 24-week ulcer healing rates, ulcer-free time, Venous Clinical Severity Score (VCSS), technical success, costs and quality of life. Ulcer healing was defined as complete re-epithelialisation in the absence of a scab, with no dressing required. If the participant or clinical care teams suspected that the ulcer was healed, a series of digital photographs (once per week for up to 4 weeks) were taken and assessed by blinded clinical experts.

A within-trial cost-effectiveness analysis was undertaken at 1 year. In the base-case analysis, only complete cases were included. The price year was 2015–16 and the perspective was the UK NHS and Personal Social Services. No discounting was applied in the 1-year analysis. Only resource items related to the venous leg ulcer or treatments were included in the total mean cost. Quality-adjusted life-years (QALYs) were estimated from EQ-5D-5L using the crosswalk tariff recommended by the National Institute for Health and Care Excellence in August 2017 [EuroQol.org. *NICE position statement on the EQ-5D-5L*. 2017. URL: <https://euroqol.org/nice-position-statement-on-the-eq-5d-5l/> (accessed 15 May 2019)]. Uncertainty was estimated using bootstrap methods. Sensitivity analyses were carried out using multiple imputation of missing data, using an alternative tariff for the EQ-5D-5L instrument and assuming a bivariate normal distribution for costs and QALYs. All analyses were performed on an intention-to-treat basis using Stata® v14.2 (StataCorp LP, College Station, TX, USA), with statistical significance set at the two-sided 5% level.

## Results

In total, 450 participants were randomised into the trial (224 into the early-ablation group and 226 into the deferred-ablation group). An unadjusted Cox regression model, with recruitment centre as a random effect, demonstrated that ulcer healing was quicker in the early-ablation group than in the deferred-ablation group [hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.13 to 1.68;  $p = 0.001$ ], with median time to ulcer healing being 56 (95% CI 49 to 66) days in the early-ablation group, compared with 82 (95% CI 69 to 92) days in deferred-ablation group. Adjusting for participant age, ulcer duration and size gave similar results (HR 1.42, 95% CI 1.16 to 1.73;  $p = 0.001$ ).

Kaplan–Meier estimates of 24-week ulcer healing rates, which are unadjusted, were higher in the early-ablation group than in the deferred-ablation group (85.6%, 95% CI 80.6% to 89.8% vs. 76.3%, 95% CI 70.5% to 81.7%, respectively). Similarly, a post hoc analysis showed a 12-week healing rate of 63.5% (95% CI 57.2% to 69.8%) in the early-ablation group, compared with 51.6% (95% CI 45.2% to 58.3%) in the deferred-ablation group. At 1 year, ulcer healing had occurred in 89.8% of randomised participants overall ( $n/N = 404/450$ ): 93.8% ( $n/N = 210/224$ ) in the early-ablation group and 85.8% ( $n/N = 194/226$ ) in the deferred-ablation group. There was a 7.9% (95% CI 2.3% to 13.5%) absolute difference in healing rates between the groups.

Recurrence rates at 1 year were calculated as a proportion of the participants in whom the ulcer had healed. By 1 year post randomisation, 24 of 210 (11.4%) participants in the early-ablation group and 32 of 194 (16.5%) participants in the deferred-ablation group had experienced ulcer recurrence.

Ulcer-free time was determined only in participants who completed 1 year of follow-up and the difference between the early-ablation and deferred-ablation groups was assessed using the Mann–Whitney *U*-test. Median ulcer-free time over 1 year was 306 [interquartile range (IQR) 240–328] days ( $n = 204$ ) in the early-ablation group, compared with 278 (IQR 175–324) days ( $n = 203$ ) in the deferred-ablation group ( $p = 0.002$ ). The results were not affected when adjustments were made for participant age, ulcer size, ulcer duration and recruitment centre. Participants in the early-ablation group were more likely to have a longer ulcer-free time of being in a higher quartile of ulcer-free time (odds ratio 1.54, 95% CI 1.07 to 2.21;  $p = 0.02$ ).

Mean VCSS was similar in the two trial groups at baseline {15.8 [standard deviation (SD) 3.3] in the early-ablation group and 15.7 [SD 3.1] in the deferred-ablation group}. At 6 weeks, mean VCSS was 10.5 (SD 4.7) in early-ablation group and 12.6 (SD 4.4) in the deferred-ablation group.

At baseline, AVVQ, EQ-5D-5L and SF-36 scores were similar in the early- and deferred-ablation groups. When compared over the whole follow-up period, there were significant differences in repeated measures of AVVQ score between the two groups ( $p < 0.001$ ), with lower scores (indicating better disease-specific quality of life) seen in the early-ablation group. Significant differences over time were also observed between the groups in EuroQol-5 Dimensions index value ( $p = 0.03$ ) and SF-36 body pain ( $p = 0.05$ ), again with more favourable scores in those randomised to early ablation; however, differences between the groups for the other generic quality-of-life measures were not significant. The most common complications of endovenous ablation were pain and asymptomatic deep-vein thrombosis.

The base-case economic analysis (complete cases only) included 173 participants in the early-ablation group and 171 in the deferred-ablation group. This analysis showed insignificant differences in total mean cost per patient over 1 year between early and deferred ablation {mean difference £163 [standard error (SE) £318];  $p = 0.607$ }. The greater initial mean cost of the early-ablation strategy was partly offset by the reduced cost of treating unhealed leg ulcers in this group. There was, however, a substantial and statistically significant gain in QALY over 1 year, with the mean difference being 0.041 (SE 0.017;  $p = 0.017$ ). The incremental cost-effectiveness ratio of early ablation at 1 year was, therefore, £3976 per QALY, compared

with deferred ablation, with a high probability (89%) of early ablation being more cost-effective at conventional UK decision-making thresholds (currently £20,000 per QALY). Sensitivity analyses using alternative tariffs for EQ-5D-5L, a bivariate normal distribution for costs and QALYs, and multiple imputation of missing data found similar results.

## Conclusions

Early endovenous ablation of superficial venous reflux in addition to compression therapy reduces the time to healing of venous leg ulcers, increases ulcer-free time and is highly likely to be cost-effective.

### *Implications for health care*

Findings from this trial suggest that early diagnosis and endovenous ablation of superficial venous reflux in addition to compression therapy can accelerate healing of venous leg ulcers and produce health economic benefits. Implementation of early diagnosis and endovenous ablation of superficial venous reflux will require further development of care pathways between primary and secondary care.

### *Recommendations for research (numbered in order of priority)*

1. Carry out a longer-term follow-up to determine if early endovenous ablation influences ulcer recurrence rates in the medium and long term.
2. Evaluate the benefit of early ablation for superficial venous reflux in patients with venous leg ulceration of > 6 months duration.
3. Determine the implications of deep-venous incompetence and occlusive disease and the potential role of deep-venous stenting to improve venous outflow of the limb.
4. Evaluate the optimal technique and the extent of eradication of superficial venous incompetence in patients with venous ulceration.

## Trial registration

This trial is registered as ISRCTN02335796.

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