ORIGINAL ARTICLE

A Randomized Trial of Early Endovenous Ablation in Venous Ulceration

Manjit S. Gohel, M.D., Francine Heatley, B.Sc., Xinxue Liu, Ph.D.,
Andrew Bradbury, M.D., Richard Bulbulia, M.D., Nicky Cullum, Ph.D.,
David M. Epstein, Ph.D., Isaac Nyamekye, M.D., Keith R. Poskitt, M.D.,
Sophie Renton, M.S., Jane Warwick, Ph.D., and Alun H. Davies, D.Sc.,
for the EVRA Trial Investigators*

ABSTRACT

BACKGROUND

Venous disease is the most common cause of leg ulceration. Although compression therapy improves venous ulcer healing, it does not treat the underlying causes of venous hypertension. Treatment of superficial venous reflux has been shown to reduce the rate of ulcer recurrence, but the effect of early endovenous ablation of superficial venous reflux on ulcer healing remains unclear.

METHODS

In a trial conducted at 20 centers in the United Kingdom, we randomly assigned 450 patients with venous leg ulcers to receive compression therapy and undergo early endovenous ablation of superficial venous reflux within 2 weeks after randomization (early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred until after the ulcer was healed or until 6 months after randomization if the ulcer was unhealed (deferred-intervention group). The primary outcome was the time to ulcer healing. Secondary outcomes were the rate of ulcer healing at 24 weeks, the rate of ulcer recurrence, the length of time free from ulcers (ulcer-free time) during the first year after randomization, and patient-reported health-related quality of life.

RESULTS

Patient and clinical characteristics at baseline were similar in the two treatment groups. The time to ulcer healing was shorter in the early-intervention group than in the deferred-intervention group; more patients had healed ulcers with early intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI], 1.13 to 1.68; P=0.001). The median time to ulcer healing was 56 days (95% CI, 49 to 66) in the early-intervention group and 82 days (95% CI, 69 to 92) in the deferred-intervention group. The rate of ulcer healing at 24 weeks was 85.6% in the early-intervention group and 76.3% in the deferred-intervention group. The median ulcer-free time during the first year after trial enrollment was 306 days (interquartile range, 240 to 328) in the early-intervention group and 278 days (interquartile range, 175 to 324) in the deferred-intervention group (P=0.002). The most common procedural complications of endovenous ablation were pain and deep-vein thrombosis.

CONCLUSIONS

Early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. (Funded by the National Institute for Health Research Health Technology Assessment Program; EVRA Current Controlled Trials number, ISRCTN02335796.)

From Cambridge University Hospitals NHS Foundation Trust, Cambridge (M.S.G.), the Department of Surgery and Cancer (M.S.G., F.H., A.H.D.) and Imperial Clinical Trials Unit (X.L., J.W.), Imperial College London, London, University of Birmingham, Birmingham (A.B.), Gloucestershire Hospitals NHS Foundation Trust, Gloucester (R.B., K.R.P.), the Medical Research Council Population Health Research Unit and the Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford (R.B.), University of Manchester, Manchester (N.C.), Worcestershire Acute Hospitals NHS Trust, Worcester (I.N.), North West London Hospitals NHS Trust, Harrow (S.R.), and University of Warwick, Coventry (J.W.) — all in the United Kingdom; and the University of Granada, Granada, Spain (D.M.E.). Address reprint requests to Dr. Davies at the Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, London W6 8RF, United Kingdom, or at a.h.davies@imperial.ac.uk.

*A complete list of the Early Venous Reflux Ablation (EVRA) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

2105

Venous disease is the most common cause of leg ulceration, and compression therapy improves venous ulcer healing.[1,2] Superficial venous reflux (varicose veins) is usually present in patients with venous leg ulcers.[3] Endovenous interventions (ultrasound-guided foam sclerotherapy and thermal and nonthermal ablation) are effective, minimally invasive procedures that are used for the treatment of varicose veins and have largely replaced traditional surgery at many centers.[4-6] In the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study, superficial venous surgery in combination with compression therapy resulted in lower rates of recurrence of venous leg ulcers than compression therapy alone[7,8] but was not associated with higher rates of ulcer healing. Observational studies have suggested that endovenous treatment of varicose veins — a treatment that may be particularly appropriate for the elderly population with venous leg ulcers — may improve ulcer healing.[9-12] However, a lack of reliable evidence has resulted in weak support for endovenous ablation in current management guidelines.[13,14] We performed the Early Venous Reflux Ablation (EVRA) trial to evaluate the role of early endovenous treatment of superficial venous reflux as an adjunct to compression therapy in patients with venous leg ulcers.

METHODS

TRIAL DESIGN AND OVERSIGHT

The EVRA trial was a multicenter, parallel-group, randomized, controlled trial that was funded by the National Institute for Health Research Health Technology Assessment Program. Details of the trial design and implementation are provided in the protocol, which is available with the full text of this article at NEJM.org.[15] The trial was approved by the South West–Central Bristol Research Ethics Committee, and trial oversight was provided by an independent trial steering committee and an independent data and safety monitoring committee (the members of these committees are listed in the Supplementary Appendix, available at NEJM.org). Data were collected by trial staff at each recruitment center and were uploaded to the Web-based electronic data-capture system (InForm, Oracle Health Sciences). The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

TRIAL SETTING AND PATIENTS

From October 2013 through September 2016, patients with open venous leg ulcers were screened by personnel in the vascular surgery departments at 20 participating centers across the United Kingdom (Table S1 in the Supplementary Appendix). All the centers had established referral pathways for patients with venous leg ulcers and could provide early endovenous interventions. Patients were screened for eligibility by clinical assessment and duplex ultrasonography.

ELIGIBILITY CRITERIA

Patients older than 18 years of age were eligible for inclusion if they had an open venous leg ulcer that had been present for a period of between 6 weeks and 6 months, an ankle–brachial index of 0.8 or higher, and primary or recurrent superficial venous reflux that was deemed by the treating clinician to be clinically significant. Venous reflux was defined as a duration of retrograde flow of greater than 0.5 seconds in superficial veins and greater than 1 second in deep veins.[16] The presence of deep venous reflux was recorded but was not an exclusion criterion. Patients were excluded if they were pregnant, were unable to adhere to compression therapy, had deep venous occlusive disease or any other condition precluding superficial venous ablation, had leg ulcers for which the cause was deemed to be nonvenous, or were thought to require skin grafting. In patients with venous leg ulcers in both legs, the leg with more severe disease (as determined by the patient) was designated as the "reference leg" and was included in the outcome analyses. Written informed consent was obtained from all participants.

RANDOMIZATION

Randomization sequences for each recruitment center were created with the use of randomly permuted blocks with two block sizes; the sequences had been prepared in advance by a trial statistician and uploaded to the data-capture system before recruitment. Treatment assignment was concealed as follows: each potential participant was enrolled in the data-capture system by staff at the local recruitment centers and, if eligibility was confirmed, was automatically assigned the next available entry in the appropriate randomization list. Participants were randomly assigned, in a 1:1 ratio, to receive compression therapy and undergo early endovenous ablation

(early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred (deferred-intervention group).

TRIAL INTERVENTIONS

Compression therapy was administered by trained community and hospital-based nursing teams according to the local standard of care. Multi-layer elastic compression (two to four layers), short-stretch compression, and compression hosiery were all deemed to be acceptable.[17]

Among the patients assigned to the early-intervention group, the aim was for superficial venous reflux to be ablated within 2 weeks after randomization. Among the patients in the deferred-intervention group, an ablation procedure was considered after the ulcer had healed or at least 6 months after randomization if the ulcer had not healed. After the ulcer was healed, patients were offered elastic compression stockings according to local institutional policy. In both treatment groups, delivery of wound care and frequency of clinical follow-up were guided by local models of care.

Endovenous laser or radiofrequency ablation, ultrasound-guided foam sclerotherapy, or non-thermal, nontumescent methods of treatment (such as cyanoacrylate glue or mechanochemical ablation) were performed either alone or in combination. The treating clinical team determined the method and strategy of endovenous treatment. For all interventions, treating clinicians were asked to ablate the main refluxing truncal vein, treat to the lowest point of reflux where possible, and continue compression therapy immediately after endovenous treatment. Among the patients in the early-intervention group, duplex ultrasonography was to be performed 6 weeks after the intervention. Superficial venous reflux observed during follow-up was treated at the discretion of the treating clinician.

OUTCOME ASSESSMENTS

The primary outcome measure was the time to ulcer healing from the date of randomization through 12 months. The definition of ulcer healing used in the trial is provided in the Supplementary Appendix. Data from patients in whom no ulcer healing had been verified by 12 months after randomization were censored at the date of their last follow-up examination.
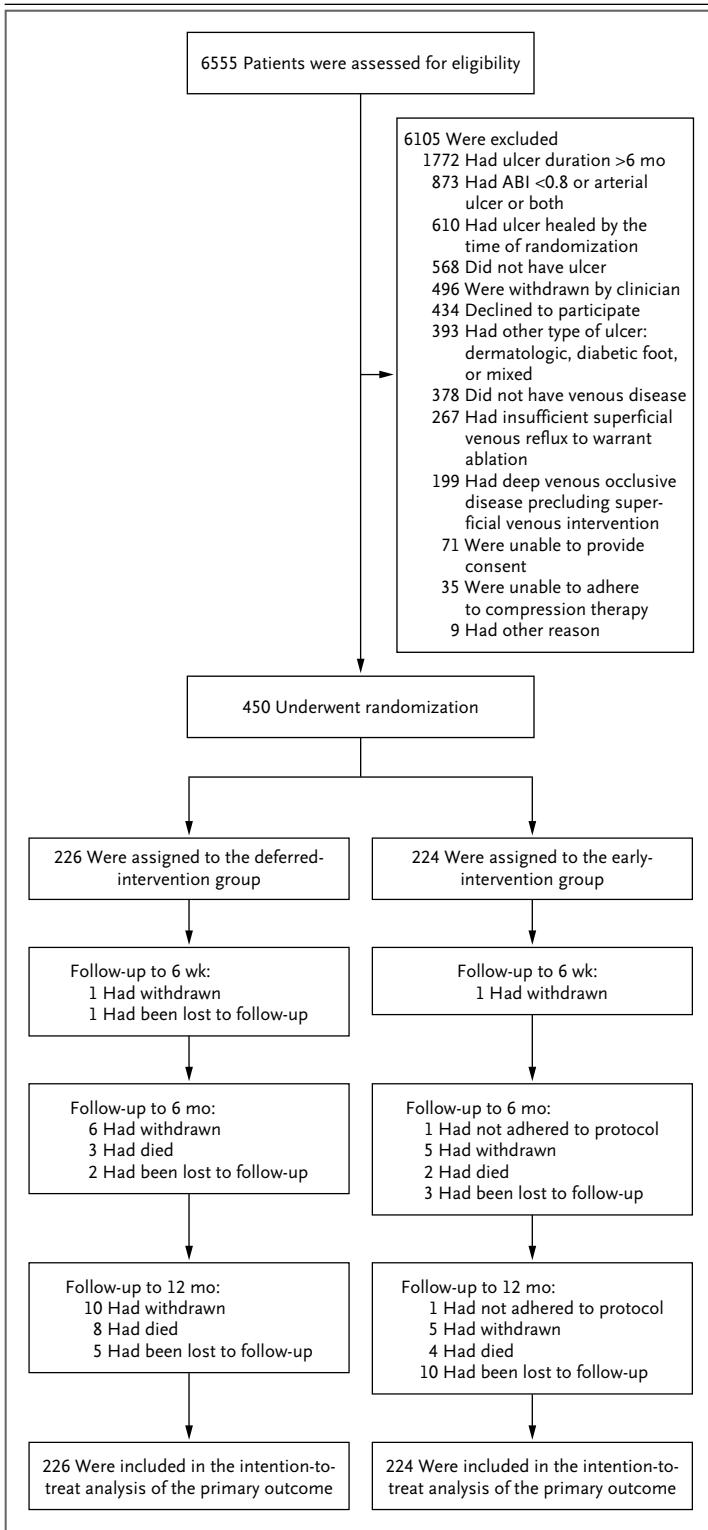
The secondary outcome measures were the rate of ulcer healing at 24 weeks, the rate of ulcer recurrence, the length of time free from ulcers (ulcer-free time) during the first year after randomization, and patient-reported health-related quality of life. Ulcer-free time was assessed only in patients who completed 1 year of follow-up. Clinical disease severity was assessed with the Venous Clinical Severity Score assessment tool (scores range from 0 to 30, with higher scores indicating more severe venous disease)[18] at randomization and 6 weeks after randomization. A disease-specific quality-of-life assessment (the Aberdeen Varicose Vein Questionnaire; scores range from 0 to 100, with higher scores indicating worse health related to varicose veins)[19] and two generic quality-of-life assessments (the EuroQol Group 5-Dimension 5-Level questionnaire [EQ-5D-5L; scores on the visual-analogue health scale range from 0 to 100 and scores on the descriptive health index range from 0 to 1, with higher scores indicating better quality of life] and the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36; scores range from 1 to 100, with higher scores indicating better quality of life]) were performed at randomization and at 6 weeks, 6 months, and 12 months after randomization (Tables S2 through S5 in the Supplementary Appendix). A health economic analysis was prespecified in the trial protocol, but the results are not reported in the current article.

STATISTICAL ANALYSIS

Assuming a 60% rate of ulcer healing at 24 weeks among the patients who received compression therapy alone and anticipating a 10% rate of loss to follow-up, we estimated that with 254 events (healed leg ulcers) among a total of 416 patients, the trial would have 90% power to detect a 15 percentage-point difference between the treatment groups in the healing rate at 24 weeks at a two-sided alpha level of 5% (log-rank test). To further allow for protocol violations and unexpected dropouts, the target sample size was 450 patients.

We tested the hypothesis that there would be no difference in the time to healing between the early-intervention group and the deferred-intervention group, first using an unadjusted Cox regression model with recruitment center as a random effect (prespecified primary analysis) and subsequently adjusting for the age of the patients, the length of time that the ulcer had been present (ulcer duration, also known as ulcer

6555 Patients were assessed for eligibility

6105 Were excluded
- 1772 Had ulcer duration >6 mo
- 873 Had ABI <0.8 or arterial ulcer or both
- 610 Had ulcer healed by the time of randomization
- 568 Did not have ulcer
- 496 Were withdrawn by clinician
- 434 Declined to participate
- 393 Had other type of ulcer: dermatologic, diabetic foot, or mixed
- 378 Did not have venous disease
- 267 Had insufficient superficial venous reflux to warrant ablation
- 199 Had deep venous occlusive disease precluding superficial venous intervention
- 71 Were unable to provide consent
- 35 Were unable to adhere to compression therapy
- 9 Had other reason

450 Underwent randomization

226 Were assigned to the deferred-intervention group

224 Were assigned to the early-intervention group

Follow-up to 6 wk:
1 Had withdrawn
1 Had been lost to follow-up

Follow-up to 6 wk:
1 Had withdrawn

Follow-up to 6 mo:
6 Had withdrawn
3 Had died
2 Had been lost to follow-up

Follow-up to 6 mo:
1 Had not adhered to protocol
5 Had withdrawn
2 Had died
3 Had been lost to follow-up

Follow-up to 12 mo:
10 Had withdrawn
8 Had died
5 Had been lost to follow-up

Follow-up to 12 mo:
1 Had not adhered to protocol
5 Had withdrawn
4 Had died
10 Had been lost to follow-up

226 Were included in the intention-to-treat analysis of the primary outcome

224 Were included in the intention-to-treat analysis of the primary outcome

percentage of patients in whom the ulcer had healed within 1 year after randomization but recurred before the end of the 1-year postrandomization follow-up period. Ulcer-free time was calculated as the number of days during the 1-year follow-up period on which the reference leg was fully healed. Ordered logistic regression (with ulcer-free time categorized in quartiles) was used to assess the effect of early versus deferred intervention on ulcer-free time. The difference between the two treatment groups in each measure of quality of life was assessed at each follow-up time point with the use of mixed models that were adjusted separately for participant age, ulcer size, and ulcer duration and included recruitment center as a random effect. All analyses were performed on an intention-to-treat basis with STATA software, version 14.2 (StataCorp), with statistical significance set at a two-sided alpha level of 5%.

RESULTS

PATIENTS

From October 2013 through September 2016, a total of 6555 patients were screened, 6105 were excluded, and 450 consented to participate in the EVRA trial and underwent randomization (Fig. 1). The most common reasons for ineligibility were an ulcer that had been present for more than 6 months (1772 patients), arterial disease (defined as an ankle–brachial index <0.8 or the presence of an arterial ulcer or both; 873 patients), or an ulcer that had already healed by the time of randomization (610 patients). The most common reason for potentially eligible patients not undergoing randomization was a treatment preference expressed by either the patient or the treating clinician.

chronicity), and the size of the ulcers. Unadjusted rates of ulcer healing at 12 weeks and 24 weeks were calculated with the Kaplan–Meier method.[20] Recurrence rates at 1 year were calculated as the

Table 1. Baseline Characteristics of the Trial Participants.*

Characteristic	Early Intervention (N = 224)	Deferred Intervention (N = 226)
Age — yr	67.0±15.5	68.9±14.0
Body-mass index†	30.1±7.8	30.4±7.4
Sex — no. (%)		
Female	97 (43.3)	106 (46.9)
Male	127 (56.7)	120 (53.1)
Smoking status — no. (%)		
Current	23 (10.3)	19 (8.4)
Former	86 (38.4)	101 (44.7)
Never	115 (51.3)	106 (46.9)
Race — no. (%)‡		
White	206 (92.0)	208 (92.0)
Asian	11 (4.9)	12 (5.3)
Black	3 (1.3)	5 (2.2)
Other	4 (1.8)	1 (0.4)
History of deep-vein thrombosis in the reference leg — no. (%)§	15 (6.7)	15 (6.6)
Diabetes — no. (%)	34 (15.2)	28 (12.4)
Previous leg ulceration in the reference leg — no. (%)§	118 (52.7)	117 (52.0)¶
Ulcer duration — mo‖	3.2 (2.3–4.2)	3.0 (1.7–4.2)
Reference leg — no. (%)§		
Right	107 (47.8)	115 (50.9)
Left	117 (52.2)	111 (49.1)
Ulcer location		
Medial	116 (51.8)	118 (52.2)
Lateral	92 (41.1)	93 (41.2)
Circumferential	9 (4.0)	7 (3.1)
Not recorded	7 (3.1)	8 (3.5)
Median ulcer size (interquartile range) — cm²**	2.4 (1.0–7.1)	2.9 (1.1–8.2)
Median score on Venous Clinical Severity Score assessment tool at baseline (interquartile range)††	15 (14–18)	16 (14–18)
Presence of deep venous reflux‡‡	74 (33.0)	69 (30.5%)

* Plus–minus values are means ±SD. Patients assigned to the early-intervention group received compression therapy and underwent early endovenous ablation of superficial venous reflux within 2 weeks after randomization, and the patients assigned to the deferred-intervention group received compression therapy, with consideration of endovenous treatment deferred until after the ulcer had healed or until 6 months after randomization if the ulcer was unhealed. No significant differences were identified between the treatment groups in any baseline variable. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 43 patients in the early-intervention group and 7 patients in the deferred-intervention group.
‡ Race was determined by a member of the local research team.
§ In patients with venous leg ulcers in both legs, the leg with more severe disease (as determined by the patient) was designated as the "reference leg" and was included in the outcome analyses.
¶ Information on previous leg ulceration was missing for 1 patient in the deferred-intervention group.
‖ The length of time that the ulcer had been present (ulcer duration, also known as ulcer chronicity) was reported by the patient.
** Ulcer size was evaluated in a blinded manner by an assessor with the use of digital planimetry on standardized digital photographs.
†† Scores on the Venous Clinical Severity Score assessment tool range from 0 to 30, with higher scores indicating more severe venous disease. The Venous Clinical Severity Score assessment at baseline was missing for 1 patient in the early-intervention group.
‡‡ Deep venous reflux was defined as a duration of retrograde flow of more than 1 second in common femoral, femoral, or popliteal veins after augmentation.

Baseline characteristics were similar in the early-intervention group and the deferred-intervention group (Table 1, and Table S6 in the Sup- plementary Appendix). Factors that are thought to affect the healing of venous leg ulcers, includ- ing ulcer duration, ulcer size, patient age, and

Table 2. Timing and Type of Endovenous Intervention.

Variable	Early Intervention (N=224)	Deferred Intervention* (N=226)
	no. (%)	
Timing of endovenous treatment after randomization†		
Within 2 wk	203 (90.6)	1 (0.4)
Before ulcer healing	200 (89.3)	1 (0.4)
After ulcer healing	3 (1.3)	0
Between 2 and 4 wk	9 (4.0)	1 (0.4)
Before ulcer healing	9 (4.0)	1 (0.4)
After ulcer healing	0	0
Between 4 wk and 6 mo	6 (2.7)	103 (45.6)
Before ulcer healing	4 (1.8)	4 (1.8)
After ulcer healing	2 (0.9)	99 (43.8)
After 6 mo	0	66 (29.2)
Before ulcer healing	0	19 (8.4)
After ulcer healing	0	47 (20.8)
No treatment	6 (2.7)	55 (24.3)‡
Type of endovenous intervention		
Endothermal ablation only§	71 (31.7)	54 (23.9)
Foam sclerotherapy only¶	111 (49.6)	100 (44.2)
Mechanochemical ablation only	5 (2.2)	1 (0.4)
Endothermal ablation and foam sclerotherapy§¶	27 (12.1)	16 (7.1)
Mechanochemical ablation and foam sclerotherapy¶	3 (1.3)	0
Abandoned treatment‖	1 (0.4)	0
No treatment	6 (2.7)	55 (24.3)

* Up to 6 months after randomization, the intervention was performed before ulcer healing in 6 patients in the deferred-intervention group: 3 patients had clinical deterioration of the ulcer, 2 patients were unwilling to continue the deferred-intervention strategy and requested intervention, and 1 patient was treated early in error. After 6 months, the intervention was performed before ulcer healing in 19 patients, as decided by the treating clinical team.

† The timing is reported for the first endovenous intervention only. The timing of any additional intervention was left to the discretion of the treating clinician.

‡ Among the 55 patients (24.3%) in the deferred-intervention group who did not receive treatment by 1 year after randomization, the ulcer had healed in 27 and had not healed in 9 (the reasons for not undergoing endovenous treatment were not recorded for these 9 patients); among the remaining 19 patients, 7 had died, 7 had withdrawn from the trial, and 5 were lost to follow-up. Among the 27 patients with healed ulcers, 16 declined intervention, 3 were no longer deemed to be suitable for intervention (as determined by the treating clinician), and 6 were on the waiting list for intervention and may have been treated after 12 months; the reason for not receiving treatment was unclear in 2 patients.

§ Endovenous thermal ablation procedures included laser and radiofrequency ablation.

¶ Ultrasound-guided foam sclerotherapy to treat tributary veins or subulcer venous plexus was performed according to the standard technique of the treating clinician.

‖ "Abandoned" indicates that the procedure could not be completed because of the inability to cannulate the vein to be treated.

history of deep-vein thrombosis, were similar in the two treatment groups. The last 1-year patient follow-up examination was completed on September 28, 2017.

ENDOVENOUS INTERVENTIONS

Among the 224 patients in the early-intervention group, 203 (90.6%) underwent an endovenous procedure within 2 weeks after randomization (Table 2). One patient (0.4%) who was assigned to the deferred-intervention group but was mistakenly thought to be in the early-intervention group underwent an endovenous procedure within 2 weeks after randomization. Among the 105 patients in the deferred-intervention group who underwent an endovenous procedure within 6 months after randomization, 6 (5.7%) were treated before the ulcer had healed, including the 1 patient who underwent an endovenous procedure within 2 weeks after randomization in error, 3 patients who had clinical deterioration of the ulcer, and 2 patients who were unwilling to continue the deferred-intervention strategy and requested intervention. A total of 218 of 224 patients (97.3%) in the early-intervention group and 171 of 226 patients (75.7%) in the deferred-intervention group underwent an endovenous intervention within 1 year after randomization.

Among the 389 patients who underwent an endovenous intervention in the trial, 472 procedures were performed within 1 year after randomization (Table S7 in the Supplementary Appendix). A total of 215 patients underwent duplex ultrasonography at 6 weeks after the intervention; in 179 of these patients (83.3%), the treated segments were observed to be completely ablated (as assessed by the local principal investigator). Among the 36 patients with incomplete ablation, 20 underwent a repeat intervention.

PRIMARY OUTCOME

The time to ulcer healing was shorter in the early-intervention group than in the deferred-intervention group; more patients had healed ulcers with early intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI], 1.13 to 1.68; P=0.001) (Fig. 2). The median time to ulcer healing was 56 days (95% CI, 49 to 66) in the early-intervention group and 82 days (95% CI, 69 to 92) in the deferred-intervention group.

After adjustment for patient age, ulcer size, ulcer duration, and recruitment center, the results were consistent, with quicker ulcer healing in the early-intervention group than in the deferred-intervention group (hazard ratio, 1.42; 95% CI, 1.16 to 1.73; P=0.001).

SECONDARY OUTCOMES

The unadjusted Kaplan–Meier time-to-event rate of ulcer healing was higher in the early-intervention group than in the deferred-intervention group at 24 weeks (85.6% [95% CI, 80.6 to 89.8] vs. 76.3% [95% CI, 70.5 to 81.7]). In a post hoc analysis, the rates of ulcer healing at 12 weeks were 63.5% (95% CI, 57.2 to 69.8) in the early-intervention group and 51.6% (95% CI, 45.2 to 58.3) in the deferred-intervention group. Among the 450 patients who underwent randomization, 404 (89.7%) had healed ulcers within 1 year after randomization (210 of 224 [93.8%] in the early-intervention group and 194 of 226 [85.8%] in the deferred-intervention group). The between-group difference in healing rates at 1 year was 8.0 percentage points (95% CI, 2.3 to 13.5).

Among the 404 patients whose ulcers had healed within 1 year after randomization, the rate of ulcer recurrence before the end of the 1-year postrandomization follow-up period was 11.4% (24 of 210 patients) in the early-intervention group and 16.5% (32 of 194 patients) in the deferred-intervention group. The total length of follow-up after ulcer healing was 156.5 person-years in the early-intervention group and 139.7 person-years in the deferred-intervention group; the rate of ulcer recurrence was lower in the early-intervention group than in the deferred-intervention group by 0.08 events per person-year (95% CI, −0.02 to 0.18). The median ulcer-free time during the 1-year follow-up was 306 days (interquartile range, 240 to 328) among 204 patients in the early-intervention group and 278 days (interquartile range, 175 to 324) among 203 patients in the deferred-intervention group (P=0.002 by the Mann–Whitney test). Adjustment for patient age, ulcer size, ulcer duration, and recruitment center did not significantly affect the results. However, patients in the early-intervention group were more likely to have longer ulcer-free time than those in the deferred-intervention group (odds ratio of being in a higher quartile of ulcer-free time, 1.54; 95% CI, 1.07 to 2.21;

Figure 2. Kaplan–Meier Curves for Time to Ulcer Healing in the Two Treatment Groups.
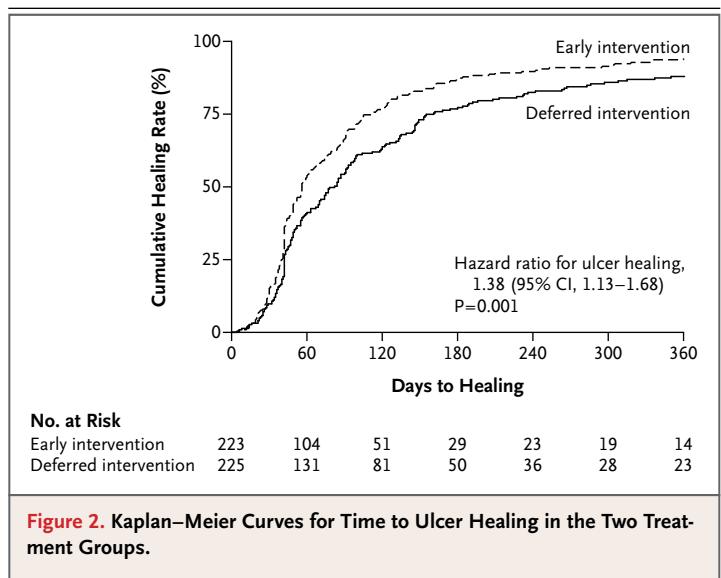
P=0.02). Mean (±SD) scores on the Venous Clinical Severity Score assessment tool did not differ significantly between the two treatment groups at randomization (15.8±3.3 in the early-intervention group and 15.7±3.1 in the deferred-intervention group). At 6 weeks, scores on the Venous Clinical Severity Score assessment tool were 10.5±4.7 in the early-intervention group and 12.6±4.4 in the deferred-intervention group.

Quality-of-life outcomes are summarized in Table 3, and in Tables S8 (SF-36 domain scores) and S9 (includes multiple imputation of missing values) in the Supplementary Appendix. At baseline, scores on the Aberdeen Varicose Vein Questionnaire, EQ-5D-5L, and SF-36 were similar in the early-intervention group and the deferred-intervention group. There was no clear difference in Aberdeen Varicose Vein Questionnaire scores between the treatment groups over the follow-up period, although scores were generally lower (indicating better disease-specific quality of life) in the early-intervention group than in the deferred-intervention group. Similarly, there was no clear difference between the treatment groups in the EQ-5D-5L index value during the follow-up period. Observed differences were not deemed to be significant when adjustment was made for multiple testing.

A total of 163 protocol deviations were recorded in the treatment groups, the majority of which were due to late or missed follow-up ap-

2111

Table 3. Summary of Disease-Specific and Generic Patient-Reported Quality-of-Life Outcomes.*

Outcome	Early Intervention		Deferred Intervention		Between-Group Difference in Score (95% CI)†
	No. of Patients	Score	No. of Patients	Score	
Aberdeen Varicose Vein Questionnaire‡					
Baseline	200	44.1±9.0	192	44.3±8.7	−0.2 (−2.0 to 1.6)
6 wk	176	39.4±10.2	170	41.2±9.3	−2.1 (−4.0 to −0.2)
6 mo	139	34.6±9.4	140	39.5±10.3	−4.8 (−6.9 to −2.7)
12 mo	127	32.4±8.3	130	34.3±10.4	−1.8 (−4.0 to 0.3)
EQ-5D-5L health scale§					
Baseline	222	70.2±17.7	225	70.1±17.1	0.1 (−3.1 to 3.4)
6 wk	212	72.7±18.6	205	71.1±18.7	1.7 (−1.6 to 5.1)
6 mo	185	74.1±15.8	193	71.4±19.6	1.8 (−1.7 to 5.2)
12 mo	183	74.8±16.9	184	73.7±17.4	1.3 (−2.1 to 4.8)
EQ-5D-5L health index¶					
Baseline	222	0.73±0.2	226	0.73±0.2	−0.01 (−0.04 to 0.03)
6 wk	211	0.79±0.2	208	0.75±0.2	0.04 (0.00 to 0.08)
6 mo	186	0.81±0.2	192	0.76±0.2	0.04 (0.00 to 0.08)
12 mo	184	0.83±0.2	182	0.80±0.2	0.03 (−0.01 to 0.07)
SF-36 Physical Component Summary‖					
Baseline	222	38.5±9.9	223	38.8±10.8	−0.8 (−2.8 to 1.1)
6 wk	212	40.4±10.2	207	39.6±11.6	0.3 (−1.7 to 2.2)
6 mo	187	41.5±11.5	193	40.4±12.1	0.3 (−1.7 to 2.3)
12 mo	181	42.1±11.6	178	41.8±12.0	0.3 (−1.7 to 2.3)
SF-36 Mental Component Summary‖					
Baseline	222	49.2±10.9	223	49.4±11.6	−0.3 (−2.2 to 1.7)
6 wk	212	51.1±10.4	207	50.2±11.0	0.9 (−1.1 to 2.9)
6 mo	187	52.2±9.8	193	50.2±10.4	1.5 (−0.5 to 3.6)
12 mo	181	51.6±9.5	178	52.0±10.0	−0.7 (−2.7 to 1.4)

* Plus–minus values are means ±SD.
† The between-group differences were estimated by a mixed model that adjusted for time, age, ulcer size, and ulcer duration as fixed effects and recruitment center as a random effect; the deferred-intervention group was the reference group. The widths of the confidence intervals were not adjusted for multiple comparisons and should not be used for formal inference.
‡ Scores on the Aberdeen Varicose Vein Questionnaire range from 0 to 100, with higher scores indicating worse health related to varicose veins.
§ Scores on the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) health scale (a visual-analogue scale) range from 0 to 100, with higher scores indicating better health.
¶ Score on the EQ-5D-5L health index range from 0 to 1, with higher scores indicating better health. The EQ-5D-5L health index was calculated with the value set for England.[21]
‖ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical Component Summary and Mental Component Summary range from 1 to 100, with higher scores indicating better quality of life.

pointments. The most common procedural complications of endovenous ablation were pain and deep-vein thrombosis. Summaries of protocol deviations and procedural complications of endovenous ablation and the results of prespecified subgroup analyses based on baseline character-

istics and type of endovenous treatment (presented in forest plots) are provided in Tables S10 and S11 and Figures S1 and S2 in the Supplementary Appendix.

DISCUSSION

This multicenter, pragmatic, randomized trial showed that early endovenous ablation of superficial venous reflux as an adjunct to compression therapy was associated with a significantly shorter time to healing of venous leg ulcers than compression therapy alone. Patients assigned to the early-intervention group also had longer ulcer-free time during the first year after randomization.

Previous studies have also shown a benefit of superficial venous intervention in patients with venous leg ulcers. The ESCHAR study showed that the rate of ulcer recurrence was lower with superficial venous surgery as an adjunct to compression therapy than with compression therapy alone,[7,8] and for this reason, the treatment of superficial venous reflux is recommended in international guidelines for the management of venous ulcers.[13] However, worldwide, many patients with venous leg ulcers are not assessed or treated for superficial venous reflux, possibly because of the perception that treatment for varicose veins does not improve ulcer healing.[13,22]

In the current trial, we found that faster ulcer healing can be attained if an endovenous intervention is performed promptly. This benefit was observed despite the provision of high-quality compression therapy, which might explain the good healing rates observed in both treatment groups. Such effective compression therapy is probably not commonplace outside randomized trials, which may help explain the much slower healing times seen in the "real world."[23,24] Accordingly, the improvement in ulcer healing with early endovenous intervention is likely to be greater in clinical practice than was observed in this trial. Because endovenous intervention is usually performed as a single procedure, the clinical benefits are likely to be less dependent on ongoing patient adherence than they would be with compression therapy.

Pathways of care for leg ulcers, in general, do not include a provision for early assessment and treatment of superficial venous reflux.[22] The lack of standardized models of care for leg ulcers and the involvement of a range of specialists may contribute to the inconsistent care delivered.

Although a benefit of endovenous intervention was observed in the current trial, the best method of ablation among those currently available remains unclear. In this pragmatic trial, treating clinicians were permitted to use the method of treatment for superficial venous reflux that they deemed to be most appropriate for the patients in their center. Ultrasound-guided foam sclerotherapy was the most common method of treatment used, which probably reflects the versatility and acceptability of this minimally invasive procedure. Results of large randomized studies have suggested that the rate of technical success (i.e., complete venous occlusion) may be lower with foam sclerotherapy than with endovenous thermal ablation.[5,6] Whether this difference in the rate of complete venous occlusion will result in differing rates of ulcer recurrence in the medium or long term remains to be seen.

Our trial has several limitations. First, although all the recruitment centers had an established pathway of care for leg ulcers, considerable variations existed among centers, the most notable of which was the choice of endovenous treatment method. All treating clinicians were asked to abide by standardized intervention principles, and by stratifying the findings according to center, we attempted to ensure that any variations were equally distributed across the two treatment groups. Second, we screened more than 6500 patients to reach our target sample size of 450. Patients were often not eligible for inclusion in the trial because the ulcer had been present for longer than 6 months or had already healed by the time of randomization. This probably reflects failures in the referral pathways from primary care teams or wound-care centers to the vascular center. Third, variations were noted in the superficial veins that were refluxing and the presence and extent of deep venous reflux. However, findings from the current trial support other data showing that the clinical benefits of treating superficial venous reflux can be attained even in the presence of concomitant deep venous reflux.[25-27] Finally, follow-up duplex ultrasonography at 6 weeks after the intervention was required only in the early-intervention group; this could have led to more repeat procedures and a higher rate of

procedural success in that group than in the deferred-intervention group.

In conclusion, this multicenter, randomized trial showed that early endovenous ablation of superficial venous reflux as an adjunct to compression therapy was associated with a shorter time to healing of venous leg ulcers than compression therapy alone.

REFERENCES

1. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012; 11:CD000265.
2. Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and management of lower-extremity ulcers. N Engl J Med 2017;377: 1559-67.
3. Adam DJ, Naik J, Hartshorne T, Bello M, London NJ. The diagnosis and management of 689 chronic leg ulcers in a single-visit assessment clinic. Eur J Vasc Endovasc Surg 2003;25:462-8.
4. Varicose veins in the legs CG168: the diagnosis and management of varicose veins. London: National Institute for Health and Care Excellence, 2013 (https://www.nice.org.uk/guidance/cg168).
5. Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med 2014;371: 1218-27.
6. Rasmussen L, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. J Vasc Surg Venous Lymphat Disord 2013;1:349-56.
7. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854-9.
8. Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335:83.
9. Mauck KF, Asi N, Undavalli C, et al. Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers. J Vasc Surg 2014;60(2):Suppl:60S-70S.e1.
10. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. J Vasc Surg 2006; 44:563-71.
11. Marston WA, Crowner J, Kouri A, Kalbaugh CA. Incidence of venous leg ulcer healing and recurrence after treatment with endovenous laser ablation. J Vasc Surg Venous Lymphat Disord 2017;5:525-32.
12. Sinabulya H, Östmyren R, Blomgren L. Mid-term outcomes of endovenous laser ablation in patients with active and healed venous ulcers: a follow-up study. Eur J Vasc Endovasc Surg 2017;53:710-6.
13. O'Donnell TF Jr, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2014;60: Suppl:3S-59S.
14. Samuel N, Carradice D, Wallace T, Smith GE, Chetter IC. Endovenous thermal ablation for healing venous ulcers and preventing recurrence. Cochrane Database Syst Rev 2013;10:CD009494.
15. National Institute for Health Research. EVRA study protocol (https://www.journalslibrary.nihr.ac.uk/programmes/hta/11129197).
16. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53: Suppl:2S-48S.
17. Ashby RL, Gabe R, Ali S, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet 2014;383:871-9.
18. Passman MA, McLafferty RB, Lentz MF, et al. Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National Venous Screening Program. J Vasc Surg 2011;54: Suppl:2S-9S.
19. Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH. Towards measurement of outcome for patients with varicose veins. Qual Health Care 1993;2:5-10.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
21. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ 2018;27:7-22.
22. Grothier L. Leg ulcer management guidelines. Essex, England: Provide Community Interest Company, 2017 (http://www.legulcerforum.org/downloads/LUF_Leg_Ulcer_Clinical_Guidelines_15.pdf).
23. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018;15:29-37.
24. Heyer K, Protz K, Glaeske G, Augustin M. Epidemiology and use of compression treatment in venous leg ulcers: nationwide claims data analysis in Germany. Int Wound J 2017;14:338-43.
25. Padberg FT Jr, Pappas PJ, Araki CT, Back TL, Hobson RW II. Hemodynamic and clinical improvement after superficial vein ablation in primary combined venous insufficiency with ulceration. J Vasc Surg 1996;24:711-8.
26. Gohel MS, Barwell JR, Earnshaw JJ, et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study) — haemodynamic and anatomical changes. Br J Surg 2005;92: 291-7.
27. Adam DJ, Bello M, Hartshorne T, London NJ. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. Eur J Vasc Endovasc Surg 2003;25:469-72.

Copyright © 2018 Massachusetts Medical Society.