A randomized trial of early Endovenous Ablation in Venous Ulceration

EVRA Trial Investigators

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gohel MS, Heatley F, Liu X, et al. A randomized trial of early endovenous ablation in venous ulceration. N Engl J Med. DOI: 10.1056/NEJMoa1801214

A randomized trial of early endovenous ablation in venous ulceration

Supplementary Appendix

This supplement consists of 28 pages.

Table of contents

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The EVRA team would like to thank the NHS trusts and participating principal investigators and their colleagues for recruiting and monitoring trial participants. These include (in alphabetical order of participating hospitals followed by the local principal investigators and their colleagues): Addenbrooke's Hospital, Cambridge – M.S. Gohel, D. Read, S. Hargreaves, K. Dhillon, M. Anwar, A. Liddle, H. Brown; Bradford Royal Infirmary, Bradford – K. Mercer, F. Gill, A. Liu, W. Jepson, A. Wormwell, H. Rafferty; Charing Cross & St Mary's Hospitals, London – A.H. Davies, K. Dhillon, R. Kaur, E. Solomon, K. Sritharan, R. Velineni, C. S. Lim, A. Busuttil, R. Bootun, C. Bicknell, M. Jenkins, T. Lane, E. Serjeant; Cheltenham General Hospital – K. Poskitt, R. Bulbulia, J. Waldron, G. Wolfrey, F. Slim, C. Davies, L. Emerson, M. Grasty, M. Whyman, C. Wakeley, A. Cooper, J. Clapp, N. Hogg, J. Howard, J. Dyer, S. Lyes, D. Teemul, K. Harvey, M. Pride, A. Kindon, H. Price, L. Flemming, G. Birch, H. Holmes, J. Weston; Cumberland Infirmary – T. Joseph, R. Eiffel, T. Ojimba, T. Wilson, A. Hodgson, L. Robinson, J. Todhunter, D. Heagarty, A. Mckeane, R. McCarthy; Derriford Hospital, Plymouth – J. Barwell, C. Northcott, A. Elstone, C. West; Frimley Park Hospital – P. Chong, D. Gerrard, A. Croucher, S. Levy, C. Martin, T. Craig; Hull Royal Infirmary – D. Carradice, A. Firth, E. Clarke, A. Oswald, J. Sinclair, I. Chetter, J. El-Sheikha, S. Nandhra, C. Leung; Leeds General Infirmary – J. Scott, N. Dewhirst, J. Woods, D. Russell, R. Darwood, M. Troxler, J. Thackeray, D. Bell, D. Watson, L. Williamson; Musgrove Park Hospital, Taunton – J. Coulston, P. Eyers, K. Darvall, I. Hunter, A. Stewart, A. Moss, J. Rewbury, C. Adams, L. Vickery, L. Foote, H. Durman, F. Venn, P. Hill, K. James, F. Luxton, D. Greenwell, K. Roberts, S. Mitchell, M. Tate, H. Mills; New Cross Hospital, Wolverhampton – A. Garnham, D. McIntosh, M. Green, K. Collins, J. Rankin, P. Poulton, V. Isgar; Northwick Park Hospital, Harrow – S. Renton, K. Dhillon, M. Trivedi, M. Kafeza, S. Parsapour, H. Moore, M. Najem, S. Connarty, H. Albon, C. Lloyd, J. Trant; Queen Elizabeth Hospital, Birmingham – R. Vohra, J. McCormack, J. Marshall, V. Hardy, R. Rogoveanu, W. Goff; Russell's Hall Hospital, Dudley – A. Garnham, R. Gidda, S. Merotra, S. Shiralkar, A.

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Trial Committees

We would also like to thank members of our two oversight committees; Trial Steering Committee: Professor Julie Brittenden (Chair); Miss Rebecca Jane Winterborn (Consultant Vascular Surgeon); Professor Andrea Nelson (Head of School and Professor of Wound Healing); Dr Richard Haynes (Research Fellow and Honorary Consultant Nephrologist) and Mr Bruce Ley-Greaves (lay member) who provided invaluable input and advice as the independent lay member over the course of the study; Data Monitoring Committee (Professor Gerard Stansby (Chair, Professor of Vascular Surgery); Professor Frank Smith (Professor of Vascular Surgery & Surgical Education); Professor Marcus Flather (Professor of Medicine - Clinical Trials); Dr Ian Nunney (Medical Statistician) for their support and guidance.

Trial definition of ulcer healing

Ulcer healing was defined as complete re-epithelialization with no scab and no requirement for dressing. If the patient, community or hospital wound care teams suspected that the ulcer was healed, a verification process was triggered in which photographs were taken (within 1 week) and repeated up to 3 times for confirmation and assessed by blinded clinical experts.[1] If healing was confirmed after review of the first verification photograph, the date of notification was accepted as the date of healing. If healing was confirmed after review of subsequent verification photographs, the date of the photograph was accepted as the date of healing. If healing was not confirmed, follow-up continued as described above until healing was verified or the end of the 12-month follow-up period had been reached.

Figure S1. Forest plot of subgroup analysis for primary outcome. The healing advantage in pre-specified subgroups was not significantly different to the overall healing benefit. Broken line indicates overall hazard ratio for ulcer healing in entire study population.

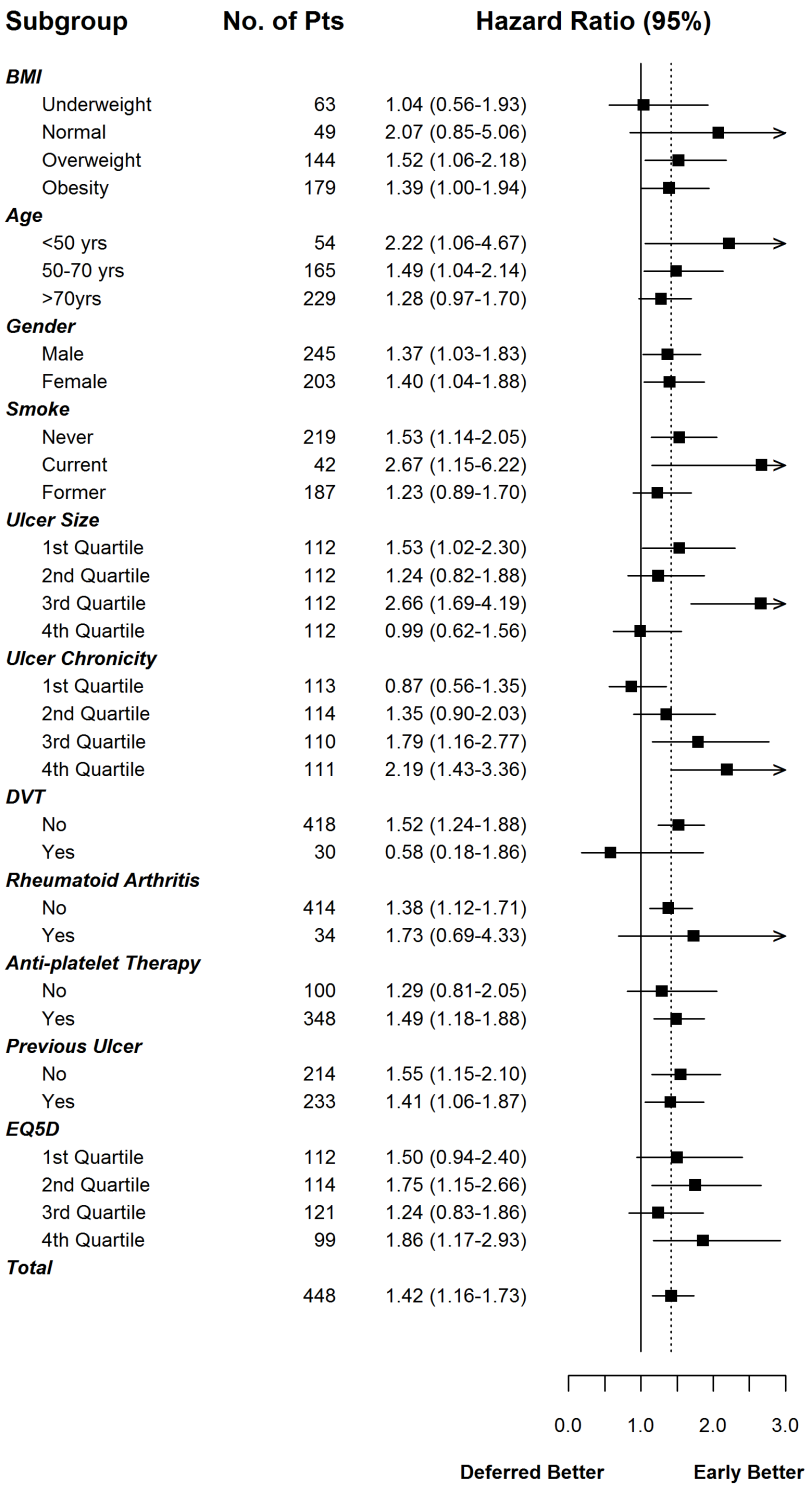


Figure S2. Forest plot of different endovenous treatments for primary outcome. The healing advantage in pre-specified subgroups treated with different ablation modalities was not significantly different to the overall healing benefit. Broken line indicates overall hazard ratio for ulcer healing in entire study population.

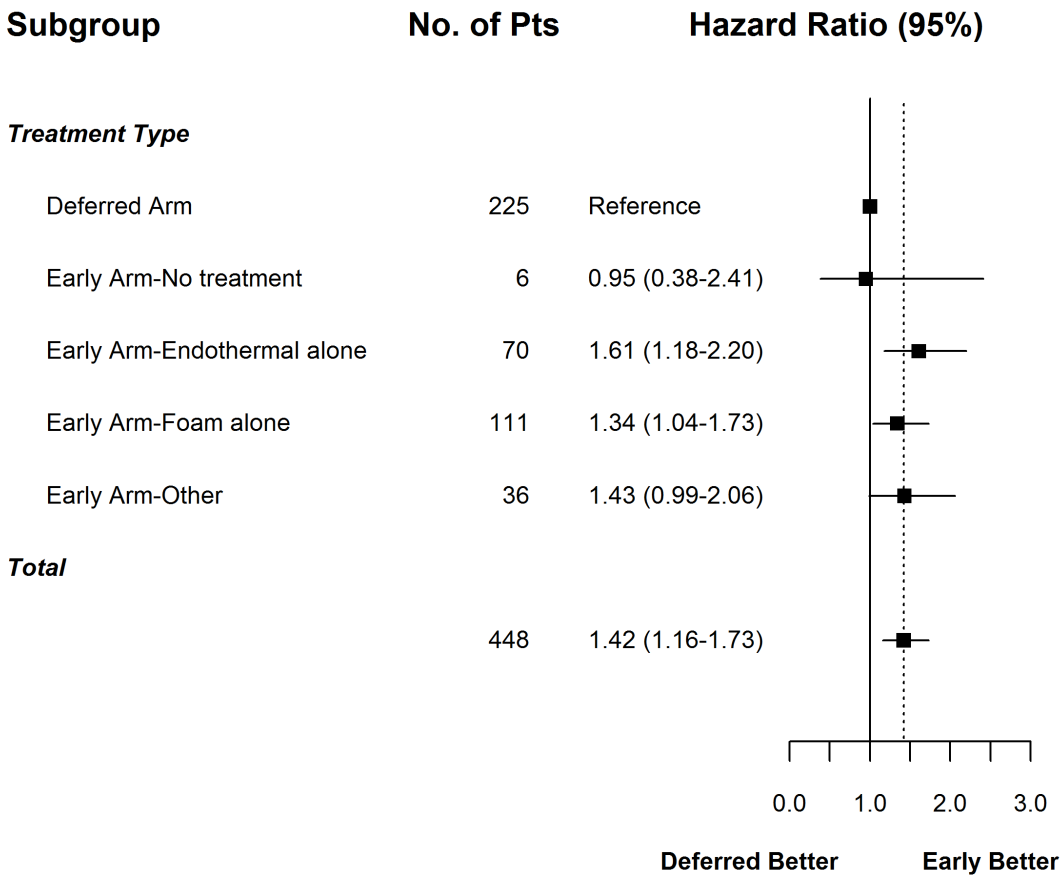


Table S1. EVRA study: recruiting centers

EVRA Site	Participants recruited
Imperial College Healthcare NHS Trust	45
Cambridge University Hospitals NHS Foundation Trust	27
Worcestershire Acute Hospitals NHS Trust	20
North West London Hospitals NHS Trust	29
Gloucestershire Hospitals NHS Trust	124
Heart of England NHS Trust	51
University Hospitals Birmingham NHS Foundation Trust	9
North Cumbria University Hospitals NHS Trust	32
The Dudley Group NHS Foundation Trust	8
The Royal Wolverhampton Hospitals NHS Trust	3
York Hospitals NHS Foundation Trust	2
Hull and East Yorkshire Hospitals NHS Trust	7
Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust	22
Frimley Park Hospital NHS Foundation Trust	6
Plymouth Hospitals NHS Trust	23
Bradford Teaching Hospitals NHS Foundation Trust	6
Salisbury NHS Foundation Trust	5
Leeds Teaching Hospitals NHS Trust	4
Sheffield Teaching Hospitals NHS Foundation Trust	6
Taunton and Somerset NHS Foundation Trust	21

Table S2. Summary of secondary outcome measures and quality of life tools used in EVRA study

Details of outcome measure	Type of assessment	Range of scores	Comments
Venous Clinical Severity Score (VCSS)[2]	Physician assessed clinical severity evaluation	0 – 30	Higher scores indicate worse severity of venous disease
Aberdeen Varicose Vein Questionnaire [3]	Patient reported disease specific quality of life	0 – 100 *	Higher scores indicate worse health related to varicose veins
EuroQol – 5 Dimension (EQ-5D-5L) [4]	Patient reported generic quality of life	0 – 100 (health scale)	Consists of a health scale and health index (with higher scores indicating better health)
Short-Form 36 (SF-36) [5]	Patient reported generic quality of life	0 – 100 (for each domain)	Eight scores covering different domains of health, with higher scores indicating better health

* previous studies have used 0.25SD as a clinically important difference [6]

Table S3. Venous Clinical Severity Score (revised)[2]

Score	None (0)	Mild (1)	Moderate (2)	Severe (3)
Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning) Presumes venous origin	None	Occasional pain or other discomfort (i.e., not restricting regular daily activity)	Daily pain or other discomfort (i.e., interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e., limits most regular daily activities)
Varicose Veins "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position	None	Few: scattered (i.e., isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous Edema Presumes venous origin	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin Pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e., vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis) Includes white atrophy and lipodermatosclerosis	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active Ulcer Number	None	1	2	≥3
Active Ulcer Duration (longest active)	N/A	<3 months	>3 months but <1 y	Not healed for >1 y
Active Ulcer Size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of Compression Therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

Table S4. Aberdeen Varicose Vein Questionnaire (AVVQ)

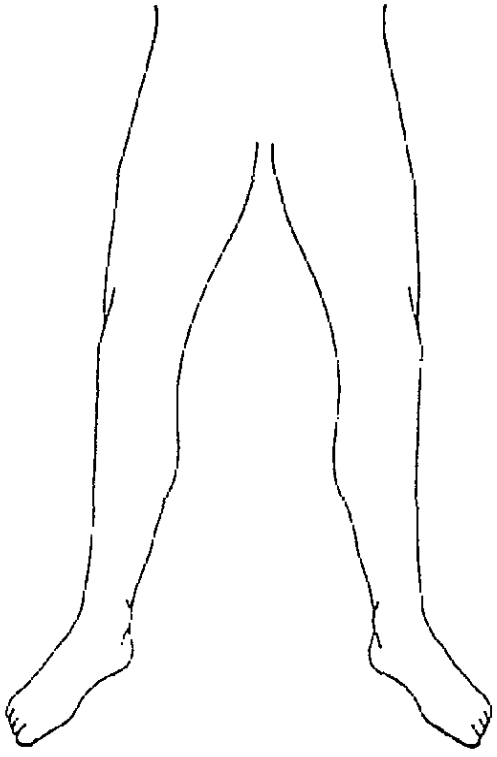
Aberdeen Varicose Veins Questionnaire (AVVQ)

Please answer all 13 questions

YOUR VARICOSE VEINS

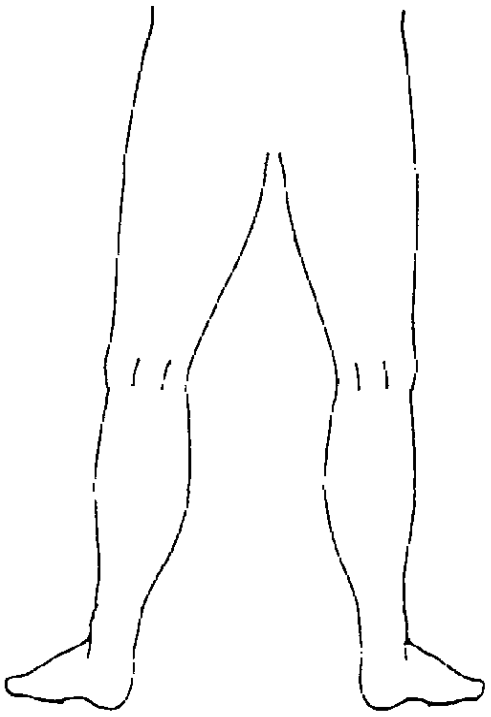
1. Please draw in your varicose veins in the diagram(s) below:-

Legs viewed



from front

Legs viewed



from back

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2. In the last two weeks, for how many days did your varicose veins cause you pain or ache?

(Please tick one box for each leg)

	R Leg	L Leg
None at all	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins?

(Please tick one box)

None at all	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

4. In the last two weeks, how much ankle swelling have you had?

(Please tick one box)

None at all	☐
Slight ankle swelling	☐
Moderate ankle swelling (eg. causing you to sit with your feet up whenever possible)	☐
Severe ankle swelling (eg. causing you difficulty putting on your shoes)	☐

5. In the last two weeks, have you worn support stockings or tights?

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes, those I bought myself without a doctor's prescription	☐	☐
Yes, those my doctor prescribed for me which I wear occasionally	☐	☐

Yes, those my doctor prescribed for me which I wear every day	☐	☐

6. In the last two weeks, have you had any itching in association with your varicose veins?

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

7. Do you have purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins?

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes	☐	☐

8. Do you have a rash or eczema in the area of your ankle?

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

9. Do you have a skin ulcer associated with your varicose veins?

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes	☐	☐

10. Does the appearance of your varicose veins cause you concern?

(Please tick one box)

- No ☐
- Yes, their appearance causes me slight concern ☐
- Yes, their appearance causes me moderate concern ☐
- Yes, their appearance causes me a great deal of concern ☐

11. Does the appearance of your varicose veins influence your choice of clothing including tights?

(Please tick one box)

- No ☐
- Occasionally ☐
- Often ☐
- Always ☐

12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities?

(Please tick one box)

- No ☐
- I have been able to work but my work has suffered to a slight extent ☐
- I have been able to work but my work has suffered to a moderate extent ☐

My veins have prevented me from working one day or more ☐

13. During the last two weeks, have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)?

(Please tick one box)

No ☐

Yes, my enjoyment has suffered to a slight extent ☐

Yes, my enjoyment has suffered to a moderate extent ☐

Yes, my veins have prevented me taking part in any leisure activities ☐

Table S5. EuroQol-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

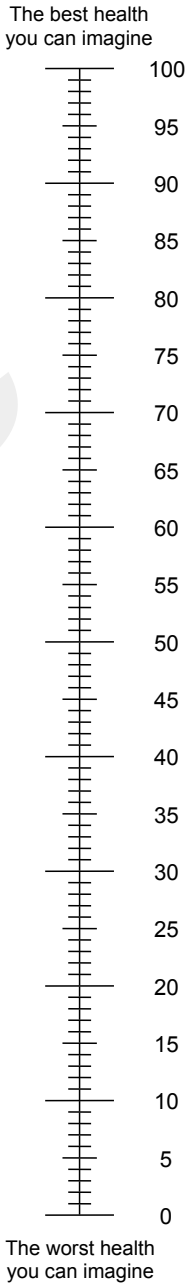

Table S6. Baseline compression types and patterns of superficial reflux at initial assessment

	Early intervention (n=224)	Deferred intervention (n=226)
Compression at baseline		
4-layer bandaging	59 (26.3%)	59 (26.1%)
3-layer modified compression	42 (18.8%)	41 (18.1%)
2-layer compression system	32 (14.3%)	29 (12.8%)
European short stretch	43 (19.2%)	36 (15.9%)
Compression stocking	42 (18.8%)	53 (23.5%)
Other compression	2 (0.9%)	1 (0.4%)
Not recorded	1 (0.4%)	0 (0%)
No compression *	3 (1.3%)	7 (3.1%)
Pattern of superficial reflux at baseline		
GSV reflux alone	123 (54.9%)	125 (55.4%)
SSV reflux alone	25 (11.2%)	30 (13.3%)
GSV and SSV reflux	65 (29.0%)	56 (24.8%)
Other pattern of reflux †	11 (4.9%)	15 (6.6%)

Data presented as frequency (percentage)

No significant differences were identified between early and deferred intervention groups for any baseline variable

* for patients not treated with compression at baseline, compression therapy was commenced at randomization

† accessory saphenous, perforator vein or tributary vein reflux

Table S7. Numbers of endovenous procedures performed categorized by study group

	Early intervention (n=224)	Deferred intervention (n=226)
Patients receiving intervention	218 (97.3%)	171 (75.7%)
Total number of procedures	269	203
Number of procedures per patient		
1	173	147
2	39	17
3	6	6
4	0	1

Data presented as frequency (percentage)

Table S8. Summary of quality of life outcomes – sub-domains of SF-36

	Baseline	6 weeks	6 months	12 months
SF-36 Physical Function				
Early intervention	37.3 (12.0) [n=223]	39.1 (12.7) [n=212]	39.1 (12.8) [n=187]	39.4 (12.9) [n=182]
Deferred intervention	37.5 (12.5) [n=225]	37.4 (13.0) [n=207]	37.4 (13.7) [n=193]	38.7 (13.4) [n=180]
Difference†	-1.0 (-3.1, 1.1)	1.0 (-1.2, 3.1)	0.7 (-1.5, 2.8)	0.3 (-1.9, 2.6)
SF-36 Role-Physical				
Early intervention	39.0 (12.2) [n=223]	40.3 (12.5) [n=211]	43.6 (12.6) [n=187]	43.0 (12.7) [n=181]
Deferred intervention	39.7 (12.1) [n=224]	41.4 (12.7) [n=207]	42.4 (12.7) [n=192]	44.3 (12.9) [n=180]
Difference†	-1.3 (-3.5, 0.9)	-1.7 (-4.0, 0.6)	0.4 (-2.0, 2.7)	-1.7 (-4.1, 0.7)
SF-36 Body Pain				
Early intervention	41.3 (11.1) [n=223]	46.6 (10.6) [n=212]	48.2 (11.0) [n=187]	49.3 (11.0) [n=182]
Deferred intervention	41.6 (11.9) [n=224]	44.3 (12.3) [n=207]	45.9 (12.2) [n=193]	47.8 (11.2) [n=180]
Difference†	-0.5 (-2.6, 1.6)	2.2 (0.1, 4.4)	2.1 (-0.2, 4.3)	1.1 (-1.1, 3.3)
SF-36 General Health				
Early intervention	45.8 (9.2) [n=223]	45.7 (9.1) [n=212]	44.9 (9.8) [n=187]	45.3 (10) [n=183]
Deferred intervention	46.0 (9.8) [n=225]	45.6 (9.2) [n=207]	44.5 (10.1) [n=193]	45.1 (10) [n=181]
Difference†	-0.3 (-2.1, 1.5)	0 (-1.8, 1.8)	0 (-1.9, 1.8)	0.4 (-1.5, 2.3)

SF-36 Vitality				
Early intervention	48.2 (10.2) [n=222]	49.1 (10.0) [n=212]	49.4 (9.5) [n=187]	50.5 (9.4) [n=182]
Deferred intervention	47.8 (10.6) [n=224]	47.5 (11.3) [n=207]	48.8 (10.8) [n=193]	49.6 (9.8) [n=179]
Difference†	0.1 (-1.7, 2.0)	1.4 (-0.5, 3.3)	0 (-1.9, 2.0)	0.9 (-1.0, 2.9)
SF-36 Social Functioning				
Early intervention	42.6 (12.4) [n=223]	44.9 (11.6) [n=212]	47.0 (10.5) [n=186]	47.4 (10.7) [n=182]
Deferred intervention	42.4 (13.5) [n=224]	44.0 (12.1) [n=207]	44.7 (12.5) [n=193]	47.3 (11.4) [n=181]
Difference†	-0.1 (-2.3, 2.0)	0.6 (-1.6, 2.8)	1.5 (-0.8, 3.7)	-0.4 (-2.7, 2.0)
SF-36 Role-Emotional				
Early intervention	42.7 (13.8) [n=222]	46.1 (12.8) [n=212]	47.2 (12.2) [n=187]	45.9 (13.0) [n=182]
Deferred intervention	43.7 (13.6) [n=224]	45.9 (13.3) [n=207]	45.1 (13.2) [n=193]	47.5 (12.2) [n=179]
Difference†	-1.4 (-3.8, 1.0)	0 (-2.5, 2.5)	1.7 (-0.9, 4.2)	-1.7 (-4.3, 0.9)
SF-36 Mental Health				
Early intervention	49.2 (10.3) [n=222]	50.6 (10.4) [n=212]	51.7 (9.7) [n=187]	51.0 (9.3) [n=182]
Deferred intervention	49.3 (10.7) [n=224]	49.2 (10.8) [n=207]	49.5 (10.4) [n=193]	50.7 (10.1) [n=179]
Difference†	-0.2 (-2.1, 1.7)	1.3 (-0.7, 3.2)	1.7 (-0.3, 3.7)	-0.2 (-2.2, 1.8)

Data presented as mean (SD). Widths of the confidence intervals have not been adjusted for multiplicity and should not be used for formal inference

† Difference between two arms estimated by mixed model adjusting for time, age, ulcer size and chronicity as fixed-effect, and study center and patient as random-effect; deferred intervention arm as reference; the 95% confidence intervals have not been adjusted for multiplicity

Table S9. Summary of quality of life outcomes with multiple imputation of missing values*

	Baseline	6 weeks	6 months	12 months
AVVQ				
Early intervention	44.0 (9.0)	39.1 (10.2)	34.9 (10.1)	33.0 (9.7)
Deferred intervention	44.2 (8.9)	41.2 (9.7)	39.4 (10.3)	34.8 (10.8)
Difference†	-0.2 (-2.1,1.7)	-2.2 (-4.7,0.3)	-4.5 (-6.5, -2.5)	-1.8 (-4.1, 0.5)
EQ-5D Health Score (Visual Analogue Scale)				
Early intervention	70.2 (17.7)	72.6 (18.7)	73.6 (16.3)	74.8 (17.5)
Deferred intervention	70.0 (17.1)	70.7 (19.1)	71.5 (19.4)	73.0 (17.8)
Difference†	0 (-3.3, 3.3)	1.8 (-1.8, 5.4)	1.8 (-2.0, 5.7)	1.8 (-1.6, 5.1)
EQ-5D Index Value‡				
Early intervention	0.73 (0.2)	0.79 (0.2)	0.81 (0.2)	0.83 (0.2)
Deferred intervention	0.73 (0.2)	0.74 (0.2)	0.77 (0.2)	0.80 (0.2)
Difference†	-0.01 (-0.05, 0.03)	0.04 (0, 0.09)	0.04 (0, 0.08)	0.03 (-0.01, 0.07)
SF-36 Physical Function				
Early intervention	37.4 (12.0)	39.1 (12.9)	39.4 (12.9)	39.7 (13.3)
Deferred intervention	37.5 (12.5)	37.4 (13.0)	37.9 (13.6)	38.3 (13.7)
Difference†	-1.0 (-3.2, 1.1)	0.8 (-1.4, 3.1)	0.6 (-1.7, 3.0)	0.7 (-1.6, 3.0)

SF-36 Role-Physical				
Early intervention	39.1 (12.2)	40.3 (12.6)	43.6 (12.6)	43.3 (12.9)
Deferred intervention	39.7 (12.1)	41.5 (12.6)	42.6 (12.8)	43.8 (13.1)
Difference†	-1.2 (-3.5, 1.0)	-1.9 (-4.1, 0.4)	0.4 (-2.6, 3.3)	-0.9 (-3.4, 1.5)
SF-36 Body Pain				
Early intervention	41.3 (11.1)	46.6 (10.6)	48.3 (11)	49.4 (11.1)
Deferred intervention	41.6 (11.9)	44.0 (12.2)	46.1 (12)	47.5 (11.5)
Difference†	-0.5 (-2.6, 1.6)	2.4 (0, 4.7)	2.1 (-0.2, 4.4)	1.9 (-0.3, 4.0)
SF-36 General Health				
Early intervention	45.8 (9.2)	45.5 (9.1)	44.8 (9.8)	45.1 (10.0)
Deferred intervention	46.0 (9.8)	45.5 (9.3)	44.7 (10.2)	44.6 (10.2)
Difference†	-0.3 (-2.1, 1.5)	-0.1 (-1.9, 1.8)	-0.1 (-2.1, 2.0)	0.4 (-1.4, 2.2)
SF-36 Vitality				
Early intervention	48.2 (10.2)	49.0 (10.2)	49.1 (9.6)	50.2 (9.7)
Deferred intervention	47.9 (10.5)	47.4 (11.2)	48.7 (10.7)	49.0 (10.0)
Difference†	0.1 (-1.7, 2.0)	1.3 (-0.6, 3.2)	0.2 (-2.0, 2.4)	1.0 (-0.9, 3.0)
SF-36 Social Functioning				
Early intervention	42.6 (12.4)	44.8 (11.6)	46.9 (10.7)	47.1 (11.0)
Deferred intervention	42.4 (13.5)	43.8 (12.1)	44.9 (12.4)	46.7 (11.7)
Difference†	-0.1 (-2.2, 2.1)	0.6 (-1.7, 2.9)	1.6 (-0.9, 4.1)	0.1 (-2.1, 2.4)

SF-36 Role-Emotional				
Early intervention	42.7 (13.7)	46.1 (12.8)	47.0 (12.5)	45.6 (13.4)
Deferred intervention	43.7 (13.6)	45.8 (13.3)	45.1 (13.1)	47.1 (12.7)
Difference†	-1.4 (-3.8, 1.0)	0 (-2.7, 2.7)	1.4 (-1.3, 4.1)	-1.9 (-4.5, 0.8)
SF-36 Mental Health				
Early intervention	49.2 (10.3)	50.4 (10.5)	51.2 (10.1)	50.5 (10.2)
Deferred intervention	49.3 (10.7)	49.0 (10.8)	49.4 (10.5)	50.2 (10.6)
Difference†	-0.2 (-2.1, 1.8)	1.4 (-0.7, 3.4)	1.6 (-0.7, 4.0)	0.1 (-1.9, 2.2)
SF-36 Physical Component Summary				
Early intervention	38.5 (10.0)	40.4 (10.4)	41.8 (11.4)	42.6 (11.8)
Deferred intervention	38.8 (10.7)	39.6 (11.5)	40.8 (12.1)	41.2 (12.2)
Difference†	-0.8 (-2.7, 1.2)	0.2 (-1.8, 2.2)	0.4 (-1.9, 2.7)	1.0 (-1.1, 3.1)
SF-36 Mental Component Summary				
Early intervention	49.2 (10.8)	51 (10.4)	51.7 (10.2)	50.9 (10.2)
Deferred intervention	49.4 (11.5)	50 (11.1)	50.1 (10.4)	51.5 (10.4)
Difference†	-0.2 (-2.2, 1.7)	0.9 (-1.2, 3.1)	1.5 (-0.8, 3.8)	-0.7 (-2.8, 1.4)

Data presented as mean (SD). Widths of the confidence intervals have not been adjusted for multiplicity and should not be used for formal inference

* Missing scores were imputed using chained equation

† Difference between two arms estimated by mixed model adjusting for time, age, ulcer size and chronicity as fixed-effect, and study center and patient as random-effect; deferred intervention arm as reference; the 95% confidence intervals have not been adjusted for multiplicity

‡ EQ-5D index calculated using the value set for England

Table S10. Summary of protocol deviations. Some participants may have had more than one protocol deviation

	Early intervention n=89*	**Deferred intervention** n=74†
Delayed treatment in early intervention group	17 (19.1%)	0 (0%)
Non-compliance with bandaging	9 (10.1%)	12 (16.0%)
Early treatment in deferred intervention group	0 (0%)	16 (21.3%)
Other	63 (70.8%)	46 (62.2%)
Late or missing follow-up visit	40 (63.5%)	34 (73.9%)
Photo / tracing not taken	4 (6.4%)	4 (8.7%)
Incorrect consent initially completed	3 (4.8%)	4 (8.7%)
Ineligible	2 (3.2%)	4 (8.7%)
Other	14 (22.2%)	0 (0%)

Data presented as frequency (percentage) for categorical variables

* Includes 38 that were treatment related (Delayed treatment in early intervention group (n=17), Non-compliance with bandaging (n=9), Ineligible (n=2), Intervention not completed for technical reasons (n=1), Intervention outside 2 weeks (n=4), no intervention (n= 5))

† Includes 32 that were treatment related (Non-compliance to bandaging (n=12), Early treatment in deferred arm (n=16), Ineligible (n=4))

Table S11. Summary of procedural complications after endovenous intervention

	Early intervention n=28	Deferred intervention n=24
Allergic reaction requiring local or no treatment	5	3
Bleeding requiring intervention	2	1
Cough / chest tightness	0	1
Deep vein thrombosis (DVT)	9*	3†
Infection ‡	3	5
Edema	1	0
Pain	6¶	6
Patient reported paresthesia	1	1
Superficial thrombophlebitis	1	4

* Post-intervention DVT in early intervention group: calf vein thrombosis (n=6). In 4 of these patients, the thrombosis was identified on routine post-UGFS duplex ultrasound scanning performed 7-days post ultrasound guided foam sclerotherapy (as this was the local scanning regimen in one of the recruiting centers); endothermal heat induced thrombosis (non-occlusive) (n=3)

† Post-intervention DVT: calf vein thrombosis (n=3)

‡ Occurred in the peri-operative period

¶ Deemed severe in one patient

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