Leg ulcer outcomes

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Dedication

In memory of my beautiful daughter Beth.

Statement of originality

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Copyright Declaration

Acknowledgements

Abstract

Background

Venous disease is the most common cause of leg ulceration. 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. It is generally accepted that there is considerable global variation in the management of leg ulcers.

Objectives

To determine: the clinical and cost-effectiveness of early endovenous treatment of superficial venous reflux in addition to standard care compared to standard care alone in patients with venous ulceration; the current standards of global management of venous leg management and the impact on these following the results of the randomised controlled trial.

Methods

i. The Early Venous Reflux Ablation Trial (EVRA) multi-centre randomised clinical trial of 450 participants compared early versus deferred intervention at 12 months and at 3.5 years.

ii. Health professionals treating patients with leg ulcers globally were surveyed before and after the publication of the RCT results to gain insight on the management of venous leg ulceration, and subsequent impact on practice.

Results

i. EVRA: time to ulcer healing was shorter in the early group at 12 months; no clear difference in time to first ulcer recurrence at 3.5 years; early intervention at 3 years is 91% likely to be cost-effective at £20,000/QALY.

ii. Surveys: - Pre/post-EVRA UK primary care: 90/643 responses received; Pre/post-EVRA global clinicians: 799/644 responses were received.

Conclusions

The EVRA RCT showed that early intervention reduces the time to healing of venous leg ulcers, does not affect the time to recurrent ulceration but is highly likely to be cost-effective and therefore is beneficial for both patients and healthcare providers. The surveys demonstrated that the management of venous ulceration is disparate globally. It is likely that the EVRA RCT results influenced the timing of intervention worldwide.

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Abbreviations

4LB: Four-layer bandage
ACP: Australasian College of Phlebology
ACP: American College of Phlebology
AD: Anno Domini
AE: Adverse event
ABPI: Ankle–brachial pressure index
AVF: American venous forum
AVVQ: Aberdeen varicose vein Questionnaire

BC: Before Christ

BPC: British Pharmaceutical Codex
BD: Twice daily

BMI: Body mass index

CCG: Clinical commissioning group

CCVUQ: Charing Cross Venous Ulcer Questionnaire
CEAC: Cost-effectiveness acceptability curve
CEAP: Clinical, Etiological, Anatomical and Pathophysiological
CI: Confidence interval
CHIVA: Conservatrice et Haemodynamique de l'insuffisance Veinuse en Ambulatoire

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CKS: Clinical knowledge summary
CONSORT: Consolidated Standards of Reporting Trials
CQUIN: Commissioning for Quality and Innovation
CRF: Case report form
CRN: Clinical research network
CTV: Computed tomography venography
CUA: Cost utility analysis
CVD: Chronic venous disease
CVI: Chronic venous insufficiency
CVU: Chronic venous ulceration
DVI: Deep venous insufficiency

LMM: Linear mixed model
MMP: Matrix metalloproteinase
MOCA: Mechanochemical endovenous ablation
MRV: Magnetic resonance venography
NA: Non-adhesive
NHS: National Health Service
NICE: National Institute of Health and Care Excellence
NIHR: National Institute of Health Research
NRES: National Research Ethics Service
NWCSP: National Wound Care Strategy Programme
OC: Oral contraception
OD: Once daily
OOP: Out of pocket
OR: Odds ratio
PCT: Primary Care trusts

PIC: Patient identification centre

PIS: Participant information sheet

PISIC: Participant information sheet and informed consent form
POL: Polidocanol

PPI: Patient and Public Involvement

PSS: Personal social services

PSSRU: Personal Social Services: Expenditure and Unit Costs

(PY) per person years

QALY: Quality-adjusted life-year

RCN: Royal College of Nursing
RCT: Randomised controlled trial
REC: Research Ethics Committee
RFA: Radiofrequency laser ablation
RR: relative risk
SAE: Serious adverse event
SAN: Storage Area Network
SAP: Statistical Analysis Plan

DVT: Deep vein thrombosis
DN: District nurse
DMC: Data Monitoring Committee
DUS: Duplex ultrasonography
EQ-5D®: European Quality of Life-5 Dimensions
EVLA: Endovenous Laser Ablation
ESCHAR: Effect of Surgery and Compression on Healing And Recurrence
ESVS: European Society for Vascular Surgery
EVF: European Venous Forum
EVRA: (Early Venous Reflux Ablation)
FDA: Food and Drug Administration
FU: Follow up
GCP: Good Clinical practice
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
GPRD: General Practice Research Database
GSV: Great saphenous vein
GP: General Practitioner
HES: Hospital Episode Statistic
HH: Two-layer compression hosiery
HR: Hazard ratio
HRA: Health research authority
HRG: Healthcare Resource Group
HRT: Hormone replacement therapy
HRQoL: Health-related quality of life
HTA: Health technology assessment
ICER: Incremental cost-effectiveness ratio
ICH: International conference of harmonisation
ICTU: Imperial Clinical Trials Unit
IDP: Individual patient data
IRR: Incidence Rate Ratio
ITT: Intention to treat
IQR: Interquartile range
KM: Kaplan Meier
LLLT: Low-level light therapy

SEPS: Subfascial endoscopic perforator surgery
SD: Standard deviation
SE: Standard error
SF-36: Short Form questionnaire-36
SFJ: Saphenofemoral junction
SIGN: Scottish Intercollegiate Guidelines Network
SPJ: Saphenopopliteal junction
SSB: Short stretch bandage
SSV: Short saphenous vein
STS: Sodium tetradecyl sulfate
SVI: Superficial venous insufficiency
SVS: Society of Vascular Surgery
SVT: Superficial thrombophlebitis
SVT: Society of Vascular Technology
SVU: Society for Vascular Ultrasound
THIN: The Health Improvement Network
TIA: Transient ischaemic attack
TMG: Trial Management Group
TSC: Trial Steering Committee
TVN: Tissue Viability Network
UGFS: Ultrasound guided foam sclerotherapy
UIP: Union Internationale de Phlébologie (UIP)
UK: United Kingdom
USA: United States of America
USABLE: Ulcer surgery as adjuvant to compression bandaging for leg ulcers
VAI: Venous Association of India
VCSS: Venous Clinical Severity Score
VSGBI: Vascular Society of Great Britain & Ireland
VV: Varicose veins
VenUS IV: Venous leg Ulcer Study IV
VLU: Venous leg ulceration
WHO: World health organisation
WREN: Wounds Research Network
WTP: Willingness to pay

Chapter 1: Introduction

The word 'ulcer' was first used in 14th century English and is derived in the Latin word 'ulcus' meaning "*a source or element of corruption or evil"* but references to wounds have been noted for thousands of years. In fact, one of the oldest medical texts (2200 BC) written on a clay tablets describes "*three healing gestures*" to treat wounds; washing, using plasters and using bandages - with the ancient Egyptians also documenting the use of honey as a wound treatment. Both the Edwin Smith Papyrus (1650 BC) and the Ebers Papyrus (1550 B.C) reference leg wounds, whilst the later also describes treatments of honey, lint and grease (1).

The first known mention of leg ulcers however, was made by Hippocrates (460–377 BC), in *De Ulceribus,* where he described an association between ulcers and varicose veins, and suggested washing the wound with wine, followed by "*puncturing and bandaging"* and bed rest to aid healing (2, 3). He later introduced the humoral theory into medicine which persisted until the eighteenth century. This theory advocated not healing ulcers fully in order to let humors escape the body, as it was thought that otherwise they would accumulate, causing madness, cancer or even death (4).

Not all physicians agreed that ulcers should be left as open wounds, for example, during Roman times, the physicians Aurelius Cornelius Celsus (25 BC–50AD), Claudius Galen (130–200 AD), and Aetios of Amida (502–574 AD) advocated the use of plasters and linen bandages and treating varicose veins by avulsion '*with a blunt hook'* and cauterization. Galen also described washing ulcers in vinegar and believed that pus was necessary for ulcer healing (5).

During the sixteenth century, Ambroise Paré (1510–1590), a progressive French barber surgeon believed the underlying cause of ulceration was the accumulation of black bile, or menstrual blood collecting in the legs. He advocated the control of local venous hypertension via compression bandaging to aid healing and, like Hippocrates, he also supported bed rest and elevation (5, 6).

The term 'varicose ulcer' was created by Richard Wiseman in the seventeenth century when he noticed that ulcers were caused by stagnation of the blood and venous dilation as a result

of incompetence valves and, in 1676, he created a laced stocking made from leather to provide compression to aid healing. The varicose ulcer theory however, was largely ignored during the eighteenth century, with treatments utilised such as plasters, bandages and tightfitting, overlapping paste bandages, as recommended by Thomas Baynton in 1797 in his '*Descriptive account of a new method of treating old ulcers of the legs'* (4, 5).

In 1868, John Gay noted that ulcers could occur in the absence of varicose veins and that deep vein thrombosis (DVT) could play a role, introducing the term 'venous ulcer'; while others including Brodie, Home and Hodgson stressed the importance of varicose veins in the aetiology of leg ulceration. The twentieth century saw John Homans establish the term 'post-phlebitic syndrome' to describe complications following a previous DVT. He divided ulcers into two types; those associated with varicose veins of the leg (varicose ulcers) which could be cured by vein removal, and those caused by a previous DVT (venous ulcers) which are not amenable to vein removal (5).

A historical survey was published by Franklin in 1927, which encouraged a wider interest in venous pathology and physiology (7), prompting Cockett in 1955 to suggest that the skin changes associated with venous chronic venous insufficiency (CVI) were due to the transmission of high pressure to the skin through incompetent perforating veins (8).

Even in modern day there remains a lack of consensus surrounding the exact definition of chronic venous leg ulceration (CVU), mainly due to a lack of clarity of how 'chronic' should be defined, which commonly ranges from four to six weeks. The Scottish Intercollegiate Guidelines Network (SIGN) defines CVU as '*an open lesion between the knee and the ankle joint that remains unhealed for at least four weeks and occurs in the presence of venous disease*' (9) whereas most clinicians and recent literature refer to a chronic ulcer remaining unhealed for over six weeks. The UK 2013 National Institute of Health and Care Excellence (NICE) guideline for varicose veins recommend that ulcers unhealed for two weeks should be referred for investigation but do not make reference to these as chronic ulcers (10), whereas the US guidelines simply define a venous leg ulcer as "*an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension*" (11).

1.1.   Venous system

1.1.1.   Anatomy

Leonardo da Vinci provided the first drawings of the vascular and the venous system in 1452. A century later in 1543, Vesalius, a Flemish anatomist described the venous system in detail in his book '*De Humani Corporis Fabrica'*. Salomon Alberti later illustrated venous valves and described them in detail in '*Tres Orationes'* in 1585 (12) and subsequently William Harvey built on this knowledge in 1628 by describing the role of valves in providing a unidirectional flow of blood to the heart (12).

The venous system carries blood against gravity towards the heart from the organs. The lower limbs house two venous systems, the deep and superficial; the deep system lies below the fascia within the muscle whilst the superficial system is found in the subcutaneous tissues and drains a smaller volume of blood from the skin and surrounding tissue.

There are many anatomical variations within the lower limb superficial veins, but there are usually two main truncal veins of the superficial system; the great saphenous vein (GSV) and the small saphenous vein (SSV), which drain into the deep systems via the saphenofemoral (SFJ) and saphenopopliteal (SPJ) junctions respectively, as well as a number of smaller perforator veins which connect the two systems (13).

The deep veins, namely the femoral and popliteal carry the majority of blood away from the lower limbs upon contraction of the leg muscles; in particular the calf muscle, which acts as a pump to force blood out of the veins towards the heart via an increase of pressure. During standing, venous pressure in the ankle may reach 80 to 90mmHg, whilst during ambulation the pressure drops to less than 30mmHg as the blood is forced out (14).

One-way bicuspid valves are present throughout the deep and superficial veins, including the junctions, which open when blood is forced out of the veins through the contraction of the leg muscles, and close to prevent both retrograde flow of blood from the deep to the superficial veins and blood returning to the feet (15). The normal valve mechanism allows a small interval of retrograde flow following the antegrade flow which closes the valve completely (16).

1.1.2. Venous hypertension

Damage to the venous valves makes it difficult for the blood to return to the heart against gravity, allowing blood to flow in a retrograde direction, raising the pressure in the smaller veins and resulting in venous hypertension. Venous reflux is generally defined as a duration of retrograde flow of >0.5 seconds in superficial veins and >1 second in deep veins (17) (16). This venous hypertension can lead to the signs and symptoms of venous disease in the lower limb defined as chronic venous disease (CVD) which will be discussed below (15).

1.1.3. Chronic venous disease and chronic venous insufficiency

Dilated cutaneous veins and varicose veins are a common presentation in patients with CVD, who may also present with signs and symptoms ranging from pain and oedema to venous eczema, hyperpigmentation, *atrophie blanche* and ulceration. In the present day, the term CVD describes the broad clinical spectrum caused by morphological and functional abnormalities of venous disease, whereas the term CVI is often used to describe the disease once it progresses to skin changes (14).

1.2. Classification / Scoring systems

Due to advances in the understanding of venous disease, the last few decades of the 20th century saw changes in the classifications of both CVD and CVI, and the development of various classification and scoring systems to provide clinicians with comprehensive standards for classifying venous disease. These will be discussed in the following section.

1.2.1. Widmer Classification (1978)

The Widmer Classification was the first classification of CVI, published in 1978 and based on epidemiological studies performed in Switzerland describing objective clinical signs alone (18).

The classification consists of 3 stages:

- Grade I: Abnormally dilated veins at the ankle, or oedema
- Grade II Hyperpigmentation
- Grade III Active or healed ulcer

Despite the simplistic nature of the classification it was used in both the German Tübinger Epidemiological Study in the 1970s (19) and the Edinburgh Vein study to provide a detailed population survey of the prevalence of all grades of venous disease in a random sample of the adult population (20).

1.2.2. Porters Classification (1988)

The Widmer classification was superseded in 1988 during the International Society for Cardiovascular Surgery, when an ad hoc subcommittee composed a report detailing reporting standards for chronic venous disease known as the Porter Classification. This was later refined in 1995 to update numeric grading schemes for disease severity, risk factors, and outcome criteria present (5, 21).

1.2.3. Clinical ulcer assessment – CEAP (1994)

It was widely recognised that there was a need to devise a classification system that encompassed aetiology (E), venous anatomy (A) and pathophysiology (P) in addition to clinical signs (C). Hence, the CEAP (Clinical, Etiological, Anatomical and Pathophysiological) descriptive classification was developed by an American Venous Forum ad hoc committee in 1994 to further standardise the worldwide classification of chronic venous disease (21).

The simplified version involves stating only the highest Clinical (C) class from C0 to C6 which covers the entire spectrum of CVD signs and symptoms, whilst CVI is usually restricted to the skin changes of C4 to C6. The 'advanced' CEAP utilises the basic CEAP criteria with the addition of 18 named venous segments to map the refluxing veins. The classification was updated in 2004 to refine some of the definitions and introduce the simpler basic CEAP as seen in *Table 1* (22) and then further revised in 2020 to include Corona phlebectatica into the C4c clinical subclass, using "r" to depict recurrent varicose veins and venous ulcers, and utilising common abbreviations of the venous segments in place of their numeric descriptions (23). Although CEAP is the most commonly utilized CVD grading system, it does not enable differentiation between mild forms of CVD and cannot predict who will benefit from interventions.

Clinical Classification
C_0 No visible or palpable signs of venous disease.
C_1 Telangiectasia or reticular veins.
C_2 Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more.
C_3 Oedema.
C_4 Changes in skin and subcutaneous tissue secondary to CVD, now divided into 2 subclasses to better define the differing severity of venous disease:
    C_{4a} Pigmentation or eczema.
    C_{4b} Lipodermatosclerosis or atrophie blanche.
C_5 Healed venous ulcer.
C_6 Active venous ulcer.
S Smptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A Asymptomatic

Etiological Classification
Ec Congenital
Ep Primary
Es Secondary (post-thrombotic)
En No venous cause identified

Anatomic classification
As Superficial veins
Ap Perforator veins
Ad Deep veins
An No venous location identified

Pathophysiologic classification
Basic CEAP
Pr Reflux
Po Obstruction
Pr,o Reflux and obstruction
Pn No venous pathophysiology identifiable

Advanced CEAP (addition that any of 18 named venous segments can be used as locators for venous pathology)
Superficial veins
Telangiectasia or reticular veins
Great saphenous vein above knee
Great saphenous vein below knee
Small saphenous vein
Nonsaphenous veins
Deep veins
Inferior vena cava
Common iliac vein
Internal iliac vein
External iliac vein
Pelvic: gonadal, broad ligament veins, other
Common femoral vein
Deep femoral vein
Femoral vein
Popliteal vein
Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
Muscular: gastrocnemial, soleal veins, other
Perforating veins: thigh, calf

1.2.4. Clinical ulcer assessment – VCSS (2010)

The venous clinical severity score (VCSS) is a component of the Venous Severity Scoring System designed in 2010 by an ad hoc American Venous Forum committee consensus, in order to compliment the CEAP classification and quantify the severity of disease and subsequent improvement or decline (24).

Table 2 details the 10 components of the VCSS (pain, varicose veins, venous oedema, skin pigmentation, inflammation, induration, compression used, and active ulcer duration, number and size). Each component has four associated categories assigned values of 0 to 3. Total VCSSs range from 0 (lowest severity) to 30 (highest severity).

Table 2 – Revised Venous Clinical Severity Score. Adapted from Multicenter assessment of the repeatability and reproducibility of the revised Venous Clinical Severity Score (rVCSS) (25)

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 Oedema 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 oedema 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

1.3.   Pathogenesis of venous leg ulceration

Leg ulceration has several underlying causes, namely venous insufficiency, arterial insufficiency, diabetes, neuropathy, either alone or in combination. The majority of leg ulcers are venous in origin and account for approximately 70% of all ulcers with arterial disease accounting for only 5% to 10% (26, 27). An Irish study by O'Brien et al., 2000 reported that 81% ulcers were venous in origin, but this is likely to be an overestimation as they did not fully diagnose the underlying cause, only measuring ankle pressure to determine arterial disease.

It is generally accepted that CVD and CVI are attributed to venous hypertension secondary to calf pump failure or caused by venous reflux or obstruction (or both) and may involve superficial venous insufficiency (SVI), deep venous insufficiency (DVI) or a combination of the two (15, 28). Venous obstruction is usually attributed to post-thrombotic syndrome or May Thurner syndrome and accounts for only a small number of cases (29). Despite this consensus, there is still a lack of agreement surrounding the exact mechanism of how reflux commences and subsequently progresses into CVI.

Engelhorn et al studied patterns of saphenous reflux in women with C2 disease and found that 80% showed reflux in both the GSV or SSV, with the prevalence of reflux significantly higher in the GSV (77%) than in the SSV (20%), whilst 17% had combined reflux. Only 2% of the total limbs contained deep venous reflux, with non-saphenous reflux noted in 20% (30). Similar patterns were also demonstrated in the Bonn vein study (31) and a duplex ultrasonography study of 1653 lower limbs in 1114 patients (29).

Later, Tassiopoulos et al reviewed 13 studies and included 1249 ulcerated legs with C5 or C6 disease and found that 88% had reflux in the superficial veins and 56% of the deep veins; 45% had isolated SVI, 12% had isolated DVI, and mixed SVI and DVI was identified in 43% limbs (32).

Other studies of duplex ultrasonograhy in patients with venous ulceration have corroborated these findings and therefore it is generally accepted that approximately 50% to 70% of patients with C6 disease have underlying SVI alone, with about 32-44% having a combination of superficial and deep venous disease. The deep disease can be segmental or total, depending on the extent of the reflux. Correction of superficial venous reflux has been shown to benefit both patients with SVI alone and those with both SVI and deep reflux by reducing the risk of ulcer recurrence (33) (34) (35) (36) (37). Isolated DVI is uncommon in

C6 disease and is only present in around 5-15% of patients with venous ulcers. Unfortunately this cannot be corrected surgically and, therefore, management is usually limited to compression bandaging alone in this patient group (38) (32).

1.3.1. Pathogenesis of chronic venous disease

The original theory of venous insufficiency, the 'descending theory', was first described by Trendelenburg in 1891. He theorised that mechanical failure of the SFJ or SPJ valves progresses distally leading to hypertension, vein dilation and subsequent incompetence of the valves below (39). This theory is supported by anatomical cadaver studies, which identified a significant reduction in the density and distribution of venous valves visible in the incompetent long saphenous vein, and explains the most commonly seen patterns of SVI (40).

The introduction of duplex ultrasonography allowed an alternative 'ascending theory' to emerge, which suggests a distal venous incompetence which progresses proximally caused by vein wall abnormalities, leading to weakness of the wall, dilation and secondary valve failure due to the lack of valve cusp apposition. Studies identified patients with saphenous reflux in the absence of SFJ or SPJ incompetence, or wall dilatation varicosities found below competent valves, furthermore varicose veins can occur with no evidence of truncal incompetence (39) (41). This evidence, coupled with findings that reflux can occur in any vein segment irrespective of the disease stage, further contradicted the descending theory and supported the ascending theory (42).

Qureshi et al 2010 performed a retrospective study evaluating colour duplex reports of 4020 limbs of patients with known venous disease. The reflux patterns identified were complex and varied, demonstrating that neither the ascending nor descending theories can fully explain the various patterns of reflux seen in the population. The authors therefore hypothesised that there is a multifactorial, possible systemic component to CVD yet to be identified (43).

Despite the conflicting theories, the end result is usually the same - i.e. an increase in hydrostatic pressure, leading to vein wall weakness and dilation.

1.3.2. Pathogenesis of chronic venous insufficiency

These are important in skin changes associated with venous disease. Oedema seems to be caused by plasma moving into the interstitium via net filtration pressure between the capillary

walls. Lipodermatosclerosis, characterised by pigmented, indurated warm skin usually proceeds ulcer formation. It is thought that extravasated red cells and hemosiderin deposition lead to skin pigmentation whilst hyperaemia and an inflammatory response contribute to the increased skin temperature (14).

The two main theories that currently exist for the development of venous leg ulceration (VLU) are the 'fibrin cuff hypothesis' and 'leukocyte trap hypothesis'.

Burnard et al proposed the fibrin cuff hypothesis in 1982 which suggests that venous hypertension results in dilation of the subcutaneous capillaries, leading to the extravasation of plasma proteins and fibrinogen into the soft tissue. This results in a fibrin cuff surrounding the capillaries, preventing oxygen perfusion into the tissue leading to hypoxia and necrosis (44). However, this theory does not fully explain the tissue damage in venous ulceration, as fibrin cuffs have also been found in ischaemic ulceration in the absence of venous hypertension, and it has not yet been shown that the fibrin cuff prevents oxygen diffusion so it likely other factors also play a role.

Coleridge-Smith hypothesised the Leukocyte Trap Hypothesis which suggests that venous hypertension leads to white cells becoming trapped in the capillaries with secondary escape of proteins, including fibrinogen, into the interstitial space which results in tissue hypoxia, and the fibrin cuff. Rat models have shown that leukocytes can become trapped in the capillaries during venous stasis leading to capillary occlusion and increased resistance. The trapped leukocytes cause endothelial damage by releasing enzymes and free radicals. Studies in patients with CVI showed that the number of functioning capillary loops visible in the skin on microscopy fell after the legs had been dependent for 30 minutes, and that 30% of leucocytes became trapped in the microcirculation (45, 46).

Animal models have shown that oedema, valve reflux and gross morphologic changes such as increased annulus diameter and valve height, were similar to those observed in human surgical specimens removed in treatment of venous insufficiency. Takase *et al* found that in rat animal models, venous reflux develops in response to a chronic hypertension via an inflammatory reaction in the valves leading to venous dilation and shortening of the valve leaflets resulting in incompetent valves and consequently elevated venous pressure (47).

A study of 236 limbs of patients with superficial venous reflux or deep venous reflux showed that ulceration did not occur in limbs with ambulatory venous pressure < 30 mmHg and the

risk of ulceration was greater as the ambulatory venous pressure increased. Pressures between 31 and 40 mmHg gave a 14% increased risk, whilst > 90 mmHg gave a risk of 100% (48). Payne et al subsequently demonstrated that increased ambulatory venous pressure correlated with more severe skin damage (49). It is likely that an inflammatory response is the driver in the development of CVI. Studies have shown that matrix metalloproteinases (MMPs), which induce degradation of the extracellular matrix and affect the structural integrity of the vein wall, are augmented by increased vein wall thickness Indeed elevation of inflammatory markers matrix metalloproteinase 2 (MMP-2) and MMP-9 is followed by value disappearance shortly thereafter. It has also been suggested that MMPs can cause changes to the endothelium and smooth muscle of the vein walls, changing constriction and relaxation properties, whilst endothelial damage can trigger leukocyte infiltration, activation and inflammation leading progressive venous insufficiency and varicose vein formation in a vicious cycle (50-52).

1.4. Burden of venous leg ulceration

1.4.1. Epidemiology

Prevalence can be divided into three main categories:

1) point prevalence - the proportion of people with the disease at a certain time point and can indicate the magnitude of the problem

2) overall prevalence - the proportion of people who will ever have the condition in a lifetime i.e. the number of people who have ever had a venous leg ulcer and therefore includes both open and healed wounds

3) period prevalence - the proportion of people with the disease over a specific period

In contrast, incidence captures the number of new cases per period of time (usually a year) and population (53).

Much of the epidemiological data surrounding leg ulceration is outdated with high variance in prevalence rates. The older studies pre-date the classification systems used today such as CEAP and the VCSS making it difficult to compare studies, furthermore, comparisons between studies are complicated by inconsistent study populations, sometimes drawing from the entire population, or occupation specific groups such as factory workers and may only include certain age groups, introducing many compounding factors. In addition, Nelzen at al noted that studies often confuse prevalence definitions leading to inaccuracies in reporting the true prevalence. It has also been noted that prevalence can be over or under estimated depending on the epidemiological methods used, for example studies may not include those who self-treat, or low response rates obtained from postal questionnaires may underestimate or not be generalisable to the population or lack of validation of the underlying aetiology may overestimate numbers (54). This, coupled with the chronic and recurrent nature of the disease, can often lead to the differences between point and overall prevalence figures reported in the literature. In fact, the incidence of venous leg ulcers is estimated to be only one tenth of the current point prevalence - i.e. one out of ten venous ulcers are a new case.

In the 1980s Callam et al. estimated the point prevalence of VLU at 1.48 per 1000 total population, based on the results of a postal survey across two health boards in Scotland, whereas another study reported an overall prevalence of 18 per 1000, rising to 38 in 1000 in those over 40 years of age (26, 55).

European prevalence of VLU in was first examined by Bobek et al in 1961 in Bohemia using a questionnaire to identify those with venous disease who were then examined clinically, identifying an overall prevalence of 1% open or healed ulcers. Subsequent studies of factory workers in Basle, Switzerland by Widmer et al and in Skövde, Sweden by Nelzén et al both reported similar overall prevalence of 1% of the adult population whereas the larger randomised German Bonn vein study reported 0.7% (54, 56, 57). The highest point prevalence of 0.29% was determined by two large random population samples from the Tübinger study in Germany and one in Sweden and included people who self-treat. The Tübinger and Edinburgh vein studies both showed significant increases in prevalence with age (54, 58)

The best available United Kingdom (UK) CVD overall prevalence data was obtained from the cross-sectional Edinburgh vein study, carried out between 1994 and 1996. The aim was to determine the prevalence of the different severities of venous disease in a randomly selected sample of 1566 adults aged 18 to 64 years (stratified by age). The study reported the overall prevalence of venous ulceration at less than 1% (59); 880 of these patients were followed up with a clinical examination at 13 years with only 3 cases (0.5%) developing an active ulceration which were not considered sufficient numbers to be reliable.

In 2002, Margolis et al studied the General Practice Research Database (GPRD) in thosed aged 65 to 95 and estimated that the overall incidence rate was 0.76 for men and 1.42 (per 100 person-years) for women (60). Two years later Moffat et al performed a questionnaire and non-invasive vascular based investigation to determine the point prevalence within Wandsworth, London. The study found a much lower rate of 0.45 per 1000, but this lower figure may have been due to the extensive questionnaire which may have led to a underestimation (61).

Interestingly Cullum et al recently conducted a systematic review of prevalence studies and the range of point prevalence reported for all leg ulcers was 0.039% to 0.48%. The group furthermore performed two point prevalence surveys, one across the whole health economy in Leeds and one across Greater Manchester which reported the point prevalence of venous ulceration of 0.029% and 0.03% respectively with mixed arterial / venous point prevalence of 0.011% and 0.008% which corresponds to an annual prevalence of 1.3 per 1000 (62) (63).

These rates are similar to readouts from the Health Improvement Network Database (THIN) and GPRD databases by a team from Leeds, who estimated the annual prevalence at 1.4 per 1000 people, which equates to 19000 open venous leg ulcers in the UK at any time (64). Guest et al (65) estimated from primary care data that there were 278000 leg ulcers in 2012 / 2013, at just over 0.5% of the UK adult population (equating to 5.6 per 1000) which is four times higher than previously reported (63, 64). The authors also estimated a further 420 000 leg ulcers with a unspecified diagnosis, suggesting the actual numbers could be higher, at just over 1% (65). It is worth noting however, that Dumville et al could not replicate these numbers and the authors did not respond to queries regarding the study methodology (66). The prevalence of VLUs in the adult population is therefore estimated at somewhere between 0.03-1%, with a marked increase of 1% to 4% in those over 65 years old (26, 53, 67). As episodes of ulcer recurrence are common, the number of patients with a high risk of ulceration may be five times higher than reported and with an increasing and ageing population, it is likely that the incidence and prevalence of venous ulceration will increase (68).

1.4.2. Clinical Morbidity

The usual symptoms of venous leg ulcerations are discomfort and pain, which can result in reduced mobility, for example in one study 81% of those with leg ulcers had their mobility affected. The study also found that leg ulcers were associated with greater time off work and subsequent loss of jobs, and a negative impact on finances, with 68% experiencing negative emotions (69). Other symptoms include wound leakage and malodour which most likely contribute to the low self-esteem, fear, anger and social isolation (70, 71). These symptoms can contribute to the reduced HRQoL experienced by leg ulcer patients.

1.4.3. Cost

The management of VLU is costly, accounting for approximately 1% to 2% of the total annual NHS budget (65, 72). In the 1990s the estimated cost of leg ulcer care in the United Kingdom was around £236m annually (73), although studies performed later that decade estimated these costs to be even higher, somewhere between £400m and £600m annually. These findings correlate with the 2004 National Audit of the Management of Venous Leg Ulcers performed by the Healthcare Commission which estimated this figure to be between £300–600m (74, 75).

Data from 2004 estimated the per patient cost to be around £1300 (76) which is similar (although inflation has not be taken into account) to £1200 per patient determined in 2011 (77). More recent data from Guest et al. in 2015 estimated that the total cost for treating 277 749 ulcers in 2012 / 2013 was between £596.55m and £921.94m, equivalent to £2147.8 and £3319.33 per venous leg ulcer. This study importantly highlighted that 12% of wounds did not have any diagnosis documented in the GP records, with a further 19% of leg ulcers not assessed for arterial or venous disease; therefore the real costs may be even higher than thought, potentially as high as £1.94 billion (65). As the costs were based on the Guest prevalence data as described above, they also could not be replicated by Dumville et al (66).

It is crucial to remember that these figures do not consider the social costs from loss of productivity, time off work and patient suffering, for example, it has been demonstrated that patients with venous leg ulcers miss more days off work resulting in a third higher costs (78, 79).

The Venous leg Ulcer Study (VenUS) IV study found, perhaps unsurprisingly, that the cost of leg ulcer treatment increases with ulcer area and duration (80), whilst Guest et al estimated that the management of a healed venous ulcer costed 4 to 5 times less than an open ulcer (£3000 versus £13500 respectively) (81).

Wound care is predominantly a nurse-led discipline, with up to 50% of district nursing activity spent on wound care (82). A recent NHS RightCare scenario report estimated that 8% of the entire district nursing workforce time is spent managing venous ulcers with 2.1 million visits annually (83). This was based on the assumption that 20% of ulcers were venous in origin and that 39% of wound care is district nursing workload (2016 NHS benchmarking report). Similarly, a wound care audit carried out in Hull in 2007 reported that 79% of patients were treated in community clinics, long-term care or home care and 21% in acute hospitals. Unsurprisingly Guest et al also found that currently 66% of the total annual NHS cost of wound care is incurred in the community with the remainder in secondary care. This nursing time, associated with multiple visits per patient, drives these high costs, with wound dressings only accounting for 14% of the total expenditure (65, 67).

1.5.   Risk Factors for developing VLU

There are several well-known risk factors which contribute to the development of VLU. Many of the risks and associations, however, are obtained from epidemiological studies which are dated and vary in both the quality and selection of patients, often failing to adjust for confounding factors.

1.5.1   Age

As the majority of VLU are caused by underlying venous insufficiency and hypertension, there is a strong correlation to age, due to increasing venous disease and immobility of the elderly. Both the prevalence and severity of CVI have been shown to have a strong link to increasing age, with both the Edinburgh and Bonn vein studies demonstrating this (26, 53, 55, 84, 85).

Scott et al performed a dual case-control study using multivariate analysis to compare questionnaires of 93 patients with venous ulcers and 129 patients with varicose veins, with 113 case-control subjects from the general population. The study found CVI to have several risk factors, with the majority found to be age related. The main limitation of this study was that the case controls did not appear to be generalisable to the general population (86).

As noted before, it is important to consider that some of these epidemiological studies may have been biased in patient selection, as postal surveys or directly contacting patients may have favoured the inclusion of the elderly. Nevertheless, it is clear that age is a definite risk factor for VLU.

1.5.2   Gender

Studies have found that venous ulceration can be two to three times more common in women (61, 87, 88), and with the exception of the Edinburgh vein study, varicose veins have been found repeatedly to be more common in women than men. The higher prevalence of varicose veins in women may be related to pregnancy, which has also been shown to be a risk factor for the developments of varicose veins (89) (31). Interestingly, trophic skin changes have been shown to be more common in men rather than women, but this can be perhaps accounted for women seeking medical treatment earlier than men. It is currently unexplained why women have a higher rate of venous ulceration overall, but may well be due to the different patterns of venous incompetence found between men and women, the latter having higher patterns of non-saphenous varicosities (86) (89).

1.5.3 Deep vein occlusive disease and deep vein thrombosis

DVT is a known risk factor for developing leg ulceration, and is thought to result from direct valve damage from the occlusion (90) (79). A team in New Zealand carried out a case control study of 465 patients and found that those with a previous DVT were approximately three times more likely to have a leg ulcer than those without. The study also found that those with a high risk of DVT, for example those with previous major limb surgery, were more likely to have a leg ulcer (OR 2.92; 95% CI, 1.47 - 6.08) (91).

1.5.4 Obesity

Obesity is also a risk factor for developing venous ulceration, presumably as a result of the greater strain placed on the venous system (87). Significant association between body mass index (BMI) and skin changes and ulceration have been shown, although some studies have only found a link in obese women (59) (92) (31).

1.5.5 Other risk factors

Other risk factors for the development of venous leg ulceration are; a family history (89), white race (79), previous leg injury or surgery (79, 93) and other lifestyle factors such as a sedentary lifestyle and prolonged standing (94, 95).

1.6 Risk factors for delayed healing and recurrence

In addition to risk factors for developing venous ulceration, there seem to be certain factors that indicate a poor prognosis or delayed ulcer healing or recurrence.

A 2003 study reviewed 1324 legs and found that patient age and duration of ulcer were independent risk factors for delayed healing; patient age (p<0.001, HR per year 0.989, 95% CI 0.984–0.995), ulcer chronicity (p=0.019, HR per month 0.996, 95% CI 0.993–0.999), whereas time to ulcer healing and untreated superficial reflux were risk factors for recurrence (68).

A 2015 systematic review of 27 studies of variable evidence levels concluded that larger ulcer size, longer ulcer duration, insufficient compression, and recurrent ulcers were all risk factors for delayed healing. Studies within the review seemed to suggest that DVT and deep venous insufficiency were also poor prognostic factors, but the evidence level for those studies was low (96). Finally, obesity was also linked to delayed healing, potentially due to the fat tissue being poorly vascularised (97).

1.7 Provision of Care

Patients with venous leg ulceration have traditionally been managed in the community or primary care setting, with poorly integrated services. A postal survey conducted in 1985 determined that 83% of patients were managed entirely in the community (26). The 1990s saw a redevelopment of the model of care, resulting from several studies which demonstrated that a systematic, multidisciplinary approach could optimise the effectiveness of services. The London Riverside project consolidated five home nursing districts, a tertiary setting and Charing Cross Hospital vascular service, which resulted in the 12-week healing rate improving from 22% to 69% (98, 99) and concluded that research-based interventions could lead to rapid improvements in healing rates. A subsequent randomised, controlled trial (RCT) showed improvements in healing rates, although the difference was of lesser magnitude (from 26% to 42% at 3 months) (73). Despite this, in the late 90s, an Effective Health Care Bulletin from the NHS Centre for Reviews and Dissemination reporting on compression therapies to treat ulceration concluded that "*there is widespread variation in practice, and evidence of unnecessary suffering and costs due to inadequate management of venous leg ulcers in the community*" (100).

It was hypothesised that a clinic-based model would improve outcomes through greater consistency of care and improved communication between services. The resulting model involved primary and secondary health professionals in a specialist setting, incorporating integrated, nurse-led community care. A Canadian RCT allocating mobile individuals to either home or nurse clinic leg ulcer management demonstrated no change in ulcer healing rates or quality of life at 3 months. In both arms, care was delivered by specially trained nurses who followed an evidence-based protocol. The researchers concluded that it was the organisation of care, not the setting which impacted healing rates (101).

Significant improvements in clinical outcomes were demonstrated across East and West Gloucestershire using this model (72). Unfortunately, this approach has not been adopted in most of the UK, and therefore a substantial proportion of patients are still treated in the community with widespread acceptance that the modern management of patients with can be suboptimal (102). Recently, a team conducted focus groups to gain insights into community nurses' experiences of treating leg ulceration and concluded that more leg ulcer management training was required, in addition to more time to deliver patient-centered, rather than task-oriented care (103). Another group, investigating the inequalities of leg ulcer care in the UK, found that although there were no differences in the provision of compression therapy, those

living in the most deprived areas were less likely to undergo Doppler assessment of their leg ulcer compared with those with higher socioeconomic status (88).

Disparate care is not restricted to the UK, an Australian observational study investigating care pathways of patients with leg ulcers found that only one-third of patients had an ankle-brachial pressure index (ABPI) or assessment by venous duplex and were seen by multiple health care providers, whereas once referred to a specialized wound clinic, the implementation of evidence-based care improved (p < 0.001). The USA faces similar issues with the management of venous disease, with a noted disconnect between different medical specialties with respect to investigation and treatment of the condition (104).

Worryingly, the 2016 King's fund report reported that the more specialised district nursing workforce had fallen by nearly one-third in the previous five years to just under 6000 district nurses working in the NHS in 2014, with a reduction of 8% of the general community nurses (105).

NHS England published the NHS Five Year Forward View in October 2014 to set a shared vision for the future of the NHS, with the intention of investing more in primary care to offer more out-of-hospital care, with the creation of 'Multispecialty Community Providers' – a combination of GPs, nurses, community health services and hospital specialists or 'Primary and Acute Care Systems', similar to the Accountable Care Organisations in other countries (106).

Subsequently, the two-year Commissioning for Quality and Innovation (CQUIN) scheme 2017-2019 was launched in November 2016 with the intention *"to deliver clinical quality improvements and drive transformational change"* by incentivising community services to improve the assessment of wounds, resulting in better patient and system outcomes (107).

The impact of these initiatives is yet to be determined.

1.7.1 Referral for assessment

At the time of writing, there is no standalone NICE guideline for leg ulcers in the UK and there is evidence of considerable variation as to who qualifies for referral or treatment of varicose veins and leg ulcers between the NHS Trusts and, hence, a substantial proportion of patients are still treated in the community (102, 108, 109).

Current American and European guidelines do not specific timelines or provisions for referral from primary to secondary care. However, in the British 2013 NICE guideline for the diagnosis and management varicose veins (10) recommends that patients with open ulceration are referred to a vascular service for assessment and treatment within two weeks. A team in Birmingham looked at the number of leg ulcer referrals before and after implementation of the guidelines and found that despite an increase in overall referrals since implementation, there was no impact on early referral (65, 110).

Clinical knowledge summaries (CKS) are designed to provide primary care practitioners with the latest evidence-based practice guidance for a range of clinical presentations to guide care. The NICE CKS for venous leg ulcers (111) was revised in July 2015 without a literature review and, therefore, based on evidence published before September 2012, excluding more recent high-quality research evidence in favour of both compression (80) and varicose vein surgery, and contradicting the NICE Guideline and CKS for varicose veins. Although this was subsequently updated in November 2015 to include the evidence relating to compression, and to ensure consistency with the varicose vein guidelines with respect to referrals to a specialise leg ulcer service, it was not updated to include evidence relating to surgical interventions (deemed out of scope for the guideline, personal communication Bruce Campbell). The Royal Society of Medicine Venous Forum communicated some further inconsistencies in early 2017, which were incorporated into the CKS in April 2017 but these frequent and sometimes misaligned revisions are likely to have caused confusion to professionals responsible for the management and referral of patients with venous leg ulcer during the periods of inconsistency. In an attempt to improve matters further, the Royal Society of Medicine's Venous Forum developed a guideline titled 'Management of Patients with Leg Ulcers' (112) and has suggested a patient pathway shown in

Figure 1.

Management of Patients with Leg Ulcers

Summary

- Leg ulcers cause great distress to patients and cost the NHS millions of pounds each year. The prevalence of leg ulcers is increasing.
- Most patients have an underlying vascular cause for their leg ulcers.
- All patients require specialist assessment and most would benefit from compression and treatment of their veins.
- Despite evidence-based guidelines for referral and treatment, current service provision remains poor.

Urgent action is needed to ensure that all patients with leg ulceration are offered the most appropriate care.

The Challenge

- Leg ulcers are non-healing wounds on the lower leg usually due to an underlying problem with veins (and sometimes the arteries).
- Most leg ulcers are caused by chronic venous hypertension.
- Leg ulcers usually take many months to heal.
- Without appropriate care, up to two-thirds of healed ulcers will recur within a year.
- Most patients with leg ulcers are managed in community healthcare settings.
- Data from GP records suggest that at least half these patients do not receive the care they need.
- Chronic wound care is estimated to cost between £4.5- £5.1 billion per year; a third of these wounds are leg ulcers.

Managements Recommendations

1. Every patient with a leg ulcer should have an ankle brachial pressure index (ABPI) assessment ('Doppler') on initial presentation to assess the arterial circulation.

   Rationale: Doppler assessment of ABPI is a valid and reliable way to detect arterial impairment in the lower limb.

2. All patients with an adequate arterial supply (ABPI>0.9) should be offered effective compression.

   Rationale: Good compression doubles the chance of healing venous leg ulcers.

3. All patients should be referred to a vascular service for assessment of their veins.

   Rationale: Duplex examination is the gold-standard method for identifying treatable venous problems.

4. All patients with treatable venous hypertension should be offered minimally invasive endovenous interventions (such as endothermal ablation or foam sclerotherapy).

   Rationale: Superficial venous treatment halves the risk of ulcer recurrence.

Suggested Patient Pathway

PATIENT PRESENTS WITH LEG ULCER
↓
EARLY ASSESSMENT (INCLUDING ABPI) & APPLY COMPRESSION
↓
REFER TO VASCULAR SERVICE (Assessment including Venous Duplex)
↓
TREATABLE VENOUS HYPERTENSION → YES → VENOUS TREATMENT
NO
↓
CONTINUE COMPRESSION & NURSING CARE
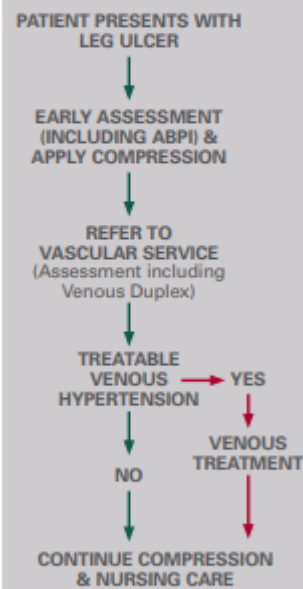
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Figure 1 – The Venous Forum Guidelines 'Management of Patients with Leg Ulcers suggested patient pathway' (112)

1.8 Assessment of venous ulceration

1.8.1 Identification

Most clinicians agree that the majority of ulcer types can be identifed based on the location and appearance of the wounds, along with the symptoms experienced and previous medical history. Approximately 95% of venous leg ulcers occur in the gaiter region of the leg, between the lower calf and medial malleolus and can be circumferential or stand alone. The ulcer bed is usually shallow, with flat irregular margins or gradually sloping edges and is covered by a fibrous layer mixed with a slough base, together with granulation tissue. Patients often include swollen, achey or painful legs, which can be relieved with elevation, and may have a medical history of DVT or previous surgery of the leg. (79, 113).

1.8.2 Diagnosis

The 'gold standard' technique for the diagnosis of venous incompetence is Duplex ultrasonography (DUS) as recommend by NICE in the UK (10), the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) practice guidelines in the USA (17), and the Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) (114).

This method is both non-invasive, non-ionizing, and has been proven to be reproducible evaluating chronic venous insufficiency. It is also dynamic, allowing both haemodynamic and anatomical information to be recorded concurrently. Colour duplex overlays colour coded velocity information onto B-mode, 2D greyscale images, which allows visualisation of each refluxing or obstructed vein (16, 115).

A number of national standards exist for the evaluation of venous disease by duplex ultrasound, such as the Society for Vascular Ultrasound (SVU) in the USA (116), the Society for Vascular Technology (SVT) in the UK (16) and the global 'Duplex Ultrasound Investigation of the Veins in Chronic Venous Disease of the Lower Limbs— Union Internationale de Phlébologie (UIP) Consensus Document. Part I. Basic Principles worldwide' (117).

The procedure is performed whilst the patient is in a standing position, with external rotation of the limb in a relaxed position and compression of the lower limb momentarily applied and released, where the time for venous reflux to occur is then measured in a particular vein (as mentioned previously a normal reflux time is defined as a retrograde flow of <0.5 seconds in superficial veins and <1 second in the deep veins). This procedure is repeated for each vein, which are all mapped onto a diagram creating a full visual representation to show the anatomy, valvular incompetence, and any venous obstruction. The assessment is complex and lengthy and must be performed by a highly skilled accredited individual. The major limitations of duplex Doppler ultrasonography are that it is more difficult to perform on obese patients, those with painful open wounds or oedema, or those unable to stand for long periods (118).

DUS can also be used for post-operative assessment of the technical success of intervention, and although currently this does not form part of standard care in the UK, it does form a recommendation in the USA for those who have symptoms or recurrence post venous procedure (17).

Other methods of investigations exist such as phlebography, plethysmography, venous pressure measurement, magnetic resonance venography (MRV) and computed tomography venography (CTV) but these will not be discussed.

1.9 Treatment options for venous ulceration

Once venous ulceration has been diagnosed, there are a range of surgical and endovenous treatments available for patients as well as pharmacological and physical adjuncts.

1.9.1 Conservative management

1.9.1.1 Compression therapy

Compression bandaging has been used for thousands of years to heal venous ulceration. In the 17th century bandages were made of inelastic material and therefore unable to offer sustained compression - as was the 'Unna-boot' described in 1885, consisting of a zinc-impregnated gauze that was wrapped tightly around the patient's leg. The 19th century saw the manufacture of elasticated stockings containing rubber and later, in the 20th century standards for bandages were introduced in a supplement to the 1911 British Pharmaceutical Codex (BPC).

Using compression bandages or stockings as a healing strategy is based on efforts to reduce superficial venous incompetence and venous hypertension by counteracting the gravitational force on the blood, in effect temporarily replacing the incompetent valves. The improvement in the microcirculation is demonstrated by a reduction in reflux and the ambulatory venous hypertension (119). Compression levels of 20 to 40 mm Hg are required to improve blood flow (120) whilst the top end of 40 mm Hg is generally accepted to be appropriate for managing venous leg ulceration. For optimal efficacy, compression should be graduated i.e. highest at the ankle and gradually decreasing towards the knee, and this should be individually fitted and regularly renewed (121). The four-layer bandaging (4LB) bandaging system was created by a team at Charing Cross Hospital (122) and was shown to achieve 12-week healing rates of 74%, compared with reported rates of 30% without compression and 45% with elasticated bandages (123). The 4LB system remains the gold standard of compression to treat venous ulceration in the UK today, but the healing rates found in the real-life community scenarios can often be lower due to trial selection bias, substandard application and lack of patient compliance.

Two studies carried out in the 1990s in the UK and USA identified risk factors of non-healing leg ulcers when using compression. The American study found that larger wound areas, longer wound duration, history of previous vein ligation, history of hip / knee replacement, ABPI less than 0.8, or 50% wound surface covered in fibrin, all significantly affected ulcer healing at 24 weeks in an outpatient setting. The UK study used a different model to assess

the risk factors in the alternate primary care setting, but also found that wound size and duration were risk factors to predict non-healing at 12 weeks. This study also found that male sex, poor limb joint mobility, poor general mobility, treatment at home and history of DVT were significantly inversely related to healing (124, 125).

O'Meara et al conducted a Cochrane review of compression effectiveness in 2012 which included 48 RCTs of varying quality, allowing 59 comparisons. The results showed that the use of compression improves healing rates compared with no compression use and also that multi-component systems are more effective than single-component systems, with two-component system healing rates equivalent to those using 4LB (*see Figure 2)* (126).
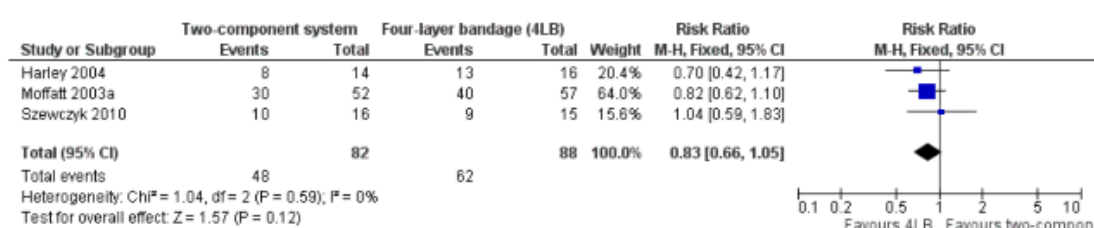
Figure 2 - Forest plot of two-component system vs four-layer bandage (4LB), with complete healing at 3 months.

The estimate suggested no statistically significant difference in healing between two-component systems and the 4LB: RR 0.83 (95% CI 0.66 to 1.05), P < 0.12 (126). Reprinted with permission (126)

An individual patient data (IPD) meta-analysis showed faster healing with 4LB use over short stretch bandage (SSB) use, and improved healing rates at two to four months using high-compression stockings over SSB, with 4LB being more cost effective than SSB (*see Figure 3)* (126).
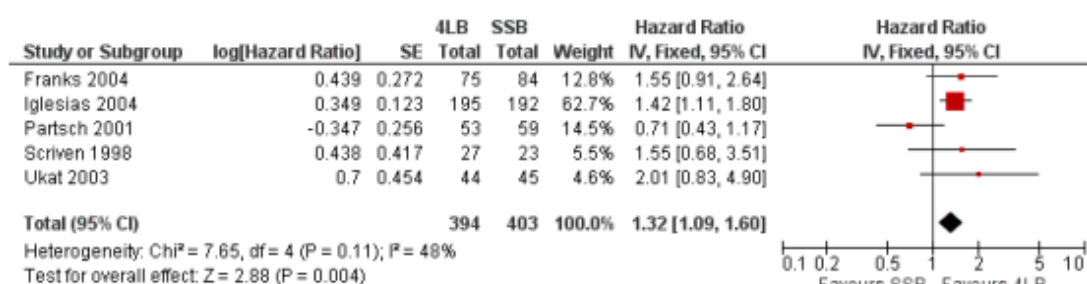
Figure 3 - Forest plot of 4LB vs multi-layer short-stretch bandage (SSB), Hazard ratio estimates for time to healing based on IPD (fixed-effect).

The Partsch 2001 study added significant heterogeneity which when removed showed an observed treated effect in favour of the 4LB in both fixed-effect and random models (126). Reprinted with permission (126).

The 2014 RCT VenUS IV, compared the clinical effectiveness and cost effectiveness of two-layer compression hosiery (HH) with the 4LB (which deliver the same amount of pressure) in the treatment of venous leg ulcers, and found no difference in time to healing rates between 4LB and two layer hosiery below the knee stockings *(see Figure 4),* the latter being easier to put on and wear, however; a high number of crossovers in the HH arm were seen, suggesting this method is not suitable for all patients. In a comparison of all available high-compression systems, HH had the highest probability of clinical and cost effectiveness but the authors noted that the evidence was weak and further research was required (80).
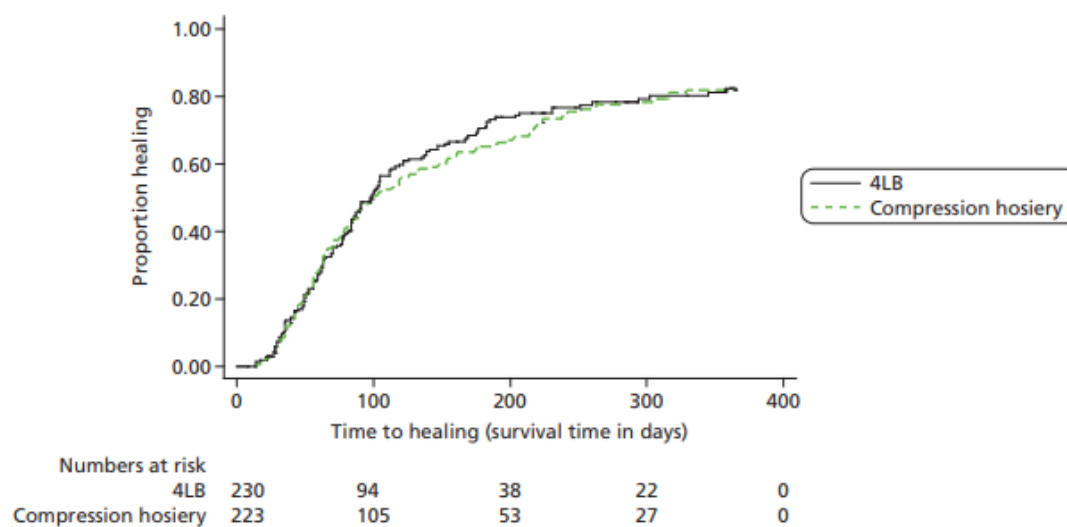
Figure 4 - Kaplan–Meier plot of blinded time to healing of 4LB vs. compression hosiery (80). Reprinted with permission.

1.9.1.2. Compression therapy for recurrence

Once healing is obtained, the clinical aim is to prevent ulcer recurrence which involves patients reverting to Class II compression hosiery. A small study conducted in 1991 study showed the 5-year recurrence rate for patients using a stocking was 29%, compared with 100% at 3 years for patients who did not use stockings (127), but there is little evidence from RCTs to assess the effects of compression on recurrence. A 2014 Cochrane review found one trial, by Vandongen et al 2000, that showed significantly reduced rates of recurrence at six months with the use of compression hosiery compared with no compression use (Risk ratio (RR) 0.46, 95% CI 0.27 to 0.76). Another study included in the review showed that the 3-year recurrence rates were lower in the high compression hosiery arm compared with medium compression, whereas another showed no difference in the 5-year rates. As mentioned earlier, the VenUS IV study concluded that HH may reduce ulcer recurrence rates compared with the 4LB (128).

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1.9.1.3. Disadvantages of compression

There are, however, two main drawbacks of compression bandaging; side effects and compliance issues.

Compression bandaging only offers a treatment benefit while in situ, with the heamodynamic effect returning to baseline almost immediately after its removal (129). Higher compression equates to improved healing rates, but the higher the compression the less tolerable it is for patients as demonstrated in the Cochrane review, which found high rates of patient intolerance of compression hosiery (130). Some studies have noted that cost and socioeconomic factors contribute to low compliance rates which is, perhaps, less relevant to the UK population serviced by the NHS, although variances in care around the UK do exist (131) (132). Overall it is recognised that in order to achieve good healing rates and reduce recurrence, compression should be tailored to the patient's tolerance levels to maximize compliance.

Compression bandaging can cause pressure damage, and is strongly contraindicated with the presence of arterial disease, as it can cause severe tissue damage or necrosis which in severe cases can lead to amputation (126). To avoid this, guidance in the UK and USA recommend that an ABPI is taken by Doppler to confirm the presence of arterial disease (9, 11, 111). The ABPI is a ratio calculated by dividing the highest ankle systolic pressure by the highest brachial systolic pressure. ABPIs of less than 0.8 are most usually taken as the cut off for clinically significant arterial disease, although other factors such as diabetes and peripheral neuropathy should be taken into account. Patients with mixed venous / arterial disease may have values of 0.5 to 0.7 and are usually candidates for reduced compression (126).

1.9.1.4. Limitations of compression

Despite compression therapy improving ulcer healing rates, it does little to address the underlying venous disease which may mean that the ulcer will recur. The best reported healing rates suggest that up to 30% of ulcers remain unhealed at 1 year, this coupled with low compliance rates and associated risks suggest that the conservative approach of compression alone is not sufficient for the treatment of VLU.

Interventional techniques can be used to correct the reflux, for example diseased superficial veins can be surgically removed or ablated using endovenous interventions without harming the overall venous function of the leg, theoretically removing a causative factor for

recurrence of the ulcer after the compression bandaging has ceased; however, the deep venous defects are generally less amenable to surgery (*see section 1.9.2*).

1.9.1.5. Dressings

Dressings are commonly used to absorb wound exudate and prevent compression bandages sticking to the wound whilst maintaining a moist environment for optimal wound healing (133). There are a huge number of types and varieties of dressing available and there is no evidence to suggest any differences in efficacy, if applied under effective compression bandaging, which has led SIGN and NICE to recommend simple non-adherent dressings in the treatment of leg ulcers (111, 134). A recent Cochrane review again did not find any significant differences between dressings, and despite a potential benefit for silver dressings over non-adherent dressings, the findings were inconclusive and the area requires further research (133).

1.9.1.6. Cleaning and debridement

Despite no trials comparing debridement versus non debridement in venous ulceration, cleansing the wound in tap water and debridement is recommended to reduce the chances of infection (111).

1.9.2 Open surgical techniques

Ambulatory hook phlebectomy, a procedure to remove varicose veins, can be traced back to the Romans in 45AD but was popularised by Trendeleburg in the 19th century, leading to saphenous ligation techniques based on ligation of the saphenous junction via a substantial groin incision coupled with resection of the affected veins and tributaries.

In 1906 Keller and Mayo developed venous 'stripping' by invagination, which remained the most popular method of treating superficial venous reflux for over a century. This technique involved surgical ligation of the SFJ, with or without stripping of the GSV and phlebotomy. This directly removes the source of reflux, but has major disadvantages as it requires general anaesthesia, with lengthy recovery times (and therefore less suitable for the older population) and is associated with post-operative complications such as infection, paresthesia and pain. A long-term study reported complications of nerve damage and recurrence rates of approximately 60% at 11 years after open surgery (135). In terms of patient acceptability, Ghauri et al showed that up to 25% patients declined open surgery when offered (136).

In 1954, a Swiss dermatologist Robert Muller refined the phlebectomy process, allowing stab avulsions of varicosed branch veins to be performed in an outpatient setting under local anaesthesia, which allowed patients to be mobilized early. This technique does not remove the source of reflux per se but does correct the signs of venous disease. It is thought to work by removing the branches where the blood can pool, allowing the blood to return back to the heart by the usual routes. Although initially skeptical, many surgeons have adopted this technique (137) (138).

1.9.2.1 Open surgical technique with preservation of the saphenous trunk

Some surgical procedures such as the *Conservatrice et Haemodynamique de l'insuffisance Veinuse en Ambulatoire* (CHIVA) technique preserve the saphenous trunk and work by creating a new, normalised heamodynamic flow. It relies on detailed mapping of the veins and blood flow by duplex ultrasound, followed by a strategy of interrupting or restricting the saphenous truncal reflux and closing the branches with reflux, yet preserving the interconnecting veins to allow blood to drain into the deep system, normalizing the venous pressure and allowing the veins to return to their original diameter within weeks. The technique is less traumatic than conventional open surgery but to date has only been extensively adopted by the French and Belgians to date, due to the complex technical nature of the procedure, coupled with the need for expert ultrasonography and therefore will not be discussed in any further detail.

1.9.2.2. Relevant research – surgical interventions

A small pilot RCT randomised 76 participants to compression bandaging alone versus superficial venous surgery and found no difference between the arms (139). A year later, the Ulcer Surgery as Adjuvant to compression Bandaging for LEg ulcers (USABLE) RCT randomised patients with venous leg ulcers to 4LB, or compression plus superficial venous surgery. Although the trial failed to recruit the 1000 patient sample size, it analyzed 75 randomised participants and also found that time to ulcer healing was similar between the groups (140). A larger Dutch trial then randomised 200 legs from 170 patients with venous leg ulcers to compression alone or compression with open surgical treatment of superficial reflux (141). The results did not reach statistical significance, but there was a clear trend towards improved ulcer healing rates and greater ulcer free time in the group randomised to surgery.

1.9.2.3. ESCHAR RCT – aims and results

The small size of these RCTs ultimately meant that the results were inconclusive; hence the ESCHAR trial was performed several years later, being the most prominent study of superficial venous intervention in patients with venous ulceration to date (Barwell et al., 2004, Gohel et al., 2007). Further to the suggested clinical benefit of surgical intervention, a systematic review by Tollow et al. on the patient quality of life benefit from compression bandaging and superficial venous surgery concluded that surgical methods may improve a patients quality of life compared with compression therapy alone (142).

The study aimed to evaluate the role of traditional superficial venous surgery in reducing ulcer recurrence in patients with open or recently healed venous ulcers. Following prospective observational studies to inform power calculations, a total of 500 patients were randomised to compression therapy alone or compression with open surgery for superficial venous reflux. At 4 years, the group randomised to the surgical arm had significantly lower venous ulcer recurrence rates compared with those randomised to compression alone; 56% in the compression alone arm compared with 31% in the surgical and compression arm *(Figure 5).*

Patients with isolated superficial venous reflux and those with superficial and segmental deep reflux both benefitted from the intervention with respect to recurrence rates, suggesting that the majority of patients with chronic venous ulceration could benefit from correction of superficial venous reflux, although the best clinical outcomes were demontrated in patients with isolated superficial venous reflux.

The ulcer healing rates, however, were comparable between both groups (*Figure 6*), leading many to conclude that treatment of venous reflux should not be utilized in patients with open ulceration.
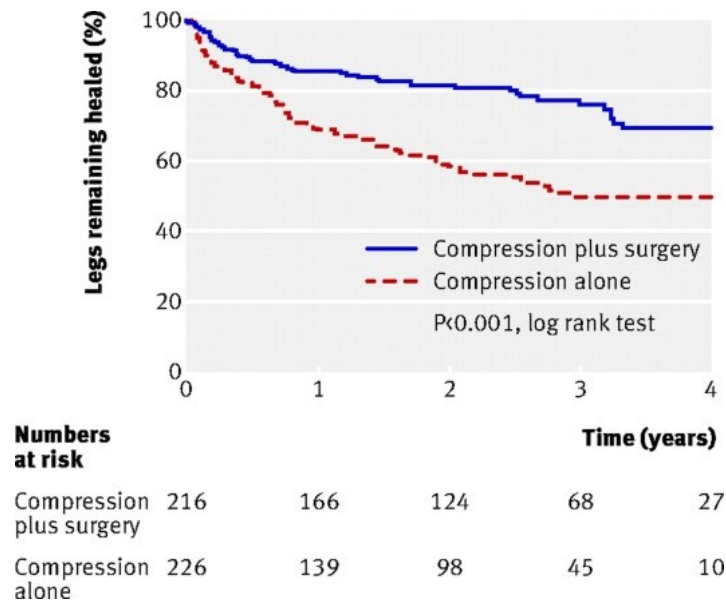
Figure 5. ESCHAR trial – ulcer recurrence (143). Reprinted with permission
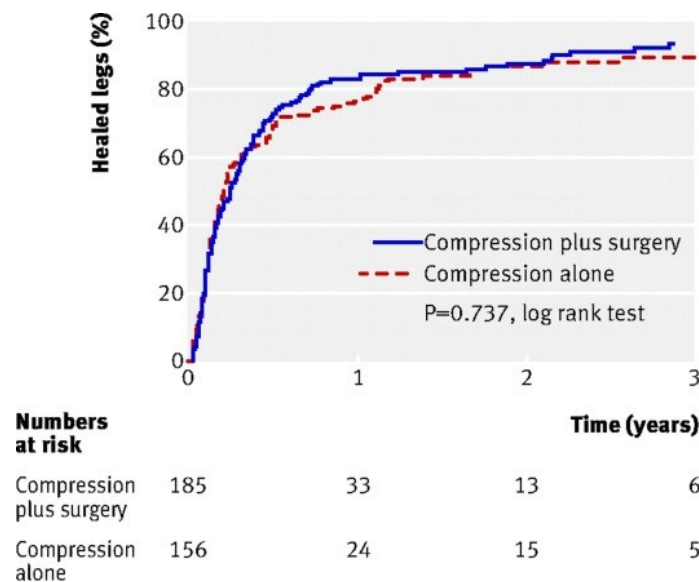
Figure 6. ESCHAR trial – ulcer healing (143). Reprinted with permission

1.9.2.4. The ESCHAR RCT – weaknesses

There were, however, several limitations to the ESCHAR study which may have affected the ability of the study the adequately assess the effects of saphenous surgery on ulcer healing. Firstly, as patients with both open and healed ulcers were included in the study there was not sufficient power to assess ulcer healing. The statistical power was reduced by a high crossover rate of the surgical arm patients, as one-third of those randomised to surgery declined their operation. In addition, those who consented to surgery waited seven weeks on

average for intervention, so did not receive an immediate benefit; by the time the intervention occurred, smaller ulcers might have healed with compression bandaging. Furthermore, some of the surgical procedures used high tie ligation alone under anaesthesia, without the vein being stripped, which would be deemed suboptimal when judged by current standards, which may have meant some legs were left with residual venous incompetence. Lastly, the study did not evaluate the impact of surgical intervention on patients' quality of life.

Therefore, it is likely that the benefits of treating superficial venous reflux were underestimated in this study, particularly in respect of ulcer healing. The high crossover rate highlights the need for a minimally invasive superficial venous treatment modality to increase compliance to surgery.

1.9.3. Endovenous techniques

In response to a perception of high recurrence rates and the need to reduce costs of open surgery, coupled with a growing patient desire for less invasive treatments, a range of novel, minimally invasive endovenous treatment options have been developed and have gained in popularity over the last 15 years, namely thermal and chemical ablation (144). These procedures differ from surgery by destroying the incompetent veins in situ via ultrasound guided cannulation, rather than removing them as per the open surgical techniques and can be performed in an outpatient setting using local anaesthesia, without the need the large groin incisions that ligations require. This is relevant to the older population of patients with VLUs, who can be frail with existing co-morbidities, plus the techniques do not require anti-coagulation therapy to be interrupted, which is often prescribed in this group of patients.

The majority of studies evaluating these techniques have been performed in C2 or C3 disease, where two-year truncal occlusion rates of up to 90% have been shown. With their minimally invasive nature, endovenous techniques are becoming increasingly popular for use in patients with open and healed ulceration, and indeed these have been recommended as the first-line treatment for truncal reflux by NICE (10) (145)

Each of the endovenous modalities has advantages and disadvantages and will be discussed in the following sections.

1.9.3.1 Endothermal ablation

The use of endothermal ablation was first reported in the late 1990s and includes endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and, less commonly, steam ablation.

All thermal ablation procedures work via insertion of a fiber or catheter into the incompetent vein, which is heated to a high temperature, causing the collagen in the walls to contract - effectively stripping the endothelium and destroying the lumen. Thickening of the vein wall, coupled with contraction of the lumen and fibrosis of the vein, results in permanent occlusion. The blood, therefore, must return to the heart via the remaining superficial and deep veins, reducing venous hypertension (146). Thermal ablation methods require the use of a generator to power the ablation and therefore are costly than methods which do not.

1.9.3.1.1   Endovenous laser ablation (EVLA)

EVLA works by a laser generator that emits monochromatic light which is transmitted to the tip of the fiber and absorbed by haemoglobin or water in the lumen where it is converted into heat energy, creating steam bubbles at the tip of the catheter. The steam causes damage to the wall as detailed above and, as it is localized, poses no risk of air embolism. Both diode and YAG laser fibers are used with varying wavelengths, delivering the laser continuously or discontinuously, and unlike in RFA the diode does not contact the vein wall (147). Successful ablation relies on delivery of an optimal amount of energy (80 to 100J/cm), which is dependent on both the power and catheter pull-back velocity which can result in temperatures of up to 700^0C (148).

The Food and Drug Administration (FDA) approved the technique in 2002, allowing its use to expand, although it does require the provider to be fully accredited in the procedure, and to have a protected secure room and use of laser goggles. The technique also requires the use of tumescent anaesthesia to reduce the complications associated with thermal energy, such as pain, skin burns and nerve damage; tumescent anaesthesia itself may be uncomfortable for many patients (145). As well as reducing pain, the tumescence allows improved wall contact by compressing the vein onto the catheter, reducing the cooling effect of blood as well as preventing thermal energy from transferring to the surrounding tissue, thus minimizing damage.

1.9.3.1.2   Radiofrequency ablation (RFA)

RFA was approved by the FDA in 1999, three years prior to EVLT. The most commonly used Covidien Venefit™ procedure involves insertion of the Covidien ClosureFast™ catheter into the vein which does not require the continuous pull back in EVLA and previous RFA VNUS Closure Plus™ catheters. An electrical current is passed through a coil at the catheter

tip, applying heat to the vein wall directly in segments. This allows a consistent heat of around 120^0C to be applied to 3cm or 7cm vein segments for 20 seconds depending on the catheter used, resulting in protein degradation. Despite the lower temperatures, tumescent anaesthesia is also required for this procedure due to side effects such a paresthesia and skin burns (149).

1.9.3.1.3 Steam

Endothermal ablation by steam was introduced in France in 2008 and works via injection of an electrically heated catheter to insert pulsed steam into the refluxing vein. The steam condenses at the end of the catheter causing heat to be transferred to the wall of the vein with a constant heat of 120^0C and is considered to have similar occlusion rates and post-operative pain as EVLA (150).

1.9.3.2. Chemical ablation

Chemical ablation for varicose veins using a liquid sclerosant was first described in 1855 but only grew in popularity in the mid-20th century. The side effects and recurrence rates meant that it was not widely used, but as foam sclerotherapy was developed in the early 21st century the technique was revived (151).

1.9.3.2.1. Ultrasound guided Foam Sclerotherapy (UGFS)

The foam is made by combining a liquid sclerosant, usually sodium tetradecyl sulfate (STS) or polidocanol (POL), with air or gas via the Tessari technique. When injected under ultrasound guidance, the foam displaces the blood within the vein, allowing the sclerosant greater contact with the vein wall than its liquid counterpart and with greater occlusion rates (152). Unlike endothermal techniques, UGFS requires neither a generator nor tumescence anaesthesia, making it cheaper to use and resulting in better patient satisfaction (145).

1.9.3.2.2. Mechanochemical Endovenous Ablation (MOCA)

Mechanical Occlusion with Chemical Assistance (MOCA) uses the ClariVein® catheter to inject a liquid sclerosant in combination with mechanical endothelial damage from a rotating wire. Firstly, the motorised spinning catheter tip causes venospasm and damages the venous endothelium; this is followed by injection of liquid sclerosant. The damage is less pronounced than with endothermal ablation and may result in less pain for the patient. Again, neither a generator nor tumescence is required (153).

1.9.3.2.3. Endovenous Chemical Occlusion - cyanoacrylate

VenaSeal Adhesive (previously known as Sapheon Glue) involves injecting small amounts of cyanoacrylate every 3cm along the vein from the catheter. The area is then compressed to physically occlude the vein, resulting in fibrosis. Again, neither a generator nor tumescence is required (154).

1.9.3.3. *Relevant research – endovenous interventions*

Despite the widespread acceptance of endovenous modalities, few prospective studies have been published reporting outcomes after endovenous treatment in patients with leg ulcers, with much of the research being performed in varicose veins.

Two prospective cohort studies of foam sclerotherapy to note include one which treated 130 patients with chronic venous ulceration by UGFS achieving 1 to 2-month healing rates of 82% (155). The other treated 186 leg ulceration patients with UGFS reporting 24 week ulcer healing rates of over 70%, with excellent patient acceptability of treatment, leading the authors to conclude that endovenous ablation is an excellent alternative to surgery (156).

Another 2012 study compared compression alone with surgical ablation of axial and perforator reflux using EVLA or foam in 95 ulcers and found that time to ulcer healing was faster in the surgical arm compared with the compression alone arm, with lower recurrence rates in the surgical arm. It should be noted that this study was not randomised and may have had considerable selection bias (157). More recently a retrospective cohort study of 170 patients with active or healed leg ulceration (195 legs) treated with EVLA, demonstrated excellent healing rates (all the ulcers healed between surgery and follow-up) and low recurrence rates of 16% (158).

To further add weight to the argument for treatment of superficial reflux by endovenous ablation, a private specialist vein unit conducted a 12-year retrospective study in 84 limbs, to assess healing in patients who either underwent surgical or endovenous interventions after previously only being offered conservative management with compression. Healing rates of 85% and a 98% clinical improvement rate were observed, suggesting a clear benefit of interventional management (159).

A 2013 Cochrane review identified no RCTs in patients with active or healed ulceration investigating the effect of superficial endovenous ablation on ulcer healing, recurrence or quality of life. The review noted an RCT by Viarengo et al demonstrating that EVLA favoured ulcer healing compared with compression alone, but this was excluded on the

grounds of a substandard quasi-randomisation method. The authors recommended that high-quality RCTs were needed to investigate the clinical and cost effectiveness of treating patients with chronic venous ulceration by endovenous thermal ablation (146) (160).

A similar review by Mauck et al (161) concluded that surgical and endovenous interventions may improve ulcer healing rates in addition to compression but noted a low level of available quality of evidence. It is worth recognising that this review decided to include the Viarengo study, in addition to an RCT comparing the effect of UGFS on ulcer healing compared with compression alone. This RCT found no difference in healing rates between the groups but the study failed to recruit and could not draw formal comparisons (162).

Interestingly, a 2017 retrospective cohort study studied subgroups of patients undergoing EVLA and found that recurrence rates were lower in patients without concomitant deep reflux compared with those with superficial reflux alone, which echoed the results of the ESCHAR study which suggested clinical benefit of intervention in both groups, albeit with an effect that was more pronounced in those with isolated superficial reflux (143) (163)

With small studies lending support to the hypothesis that early intervention to correct superficial venous reflux will promote ulcer healing and improve patient quality of life, it is clear that a large randomised trial is required to overcome a lack of quality level 1 evidence and influence clinical practice

1.9.4.   Patient acceptance of endovenous techniques

Unsurprisingly patient acceptance of endovenous treatments is excellent and reported complication rates are low due to the obvious less invasiveness nature of the intervention (164). A recent meta-analysis indicated that endovenous intervention outcomes are commensurable to open surgery with respect to technical success, but are associated with lower complication rates (of pain, infection, bruising) and quicker return to work (165). This was corroborated by Carradice et al. who also found that return to work or normal post-EVLA was quicker than post-surgery (4 days versus 14 days; P<0.001) (166).

1.9.5.   Current guidance lines of treatment

The 2013 NICE guidelines, based on a cost effectiveness analysis, recommend that the first line of treatment for SVI should be interventional. Endothermal ablation (including RFA and EVLA) should be considered firstly, followed by UGFS if the former is deemed unsuitable and finally surgery if both endothermal ablation and surgery are not deemed suitable options.

Conservative management by compression bandaging alone is only recommended if interventional treatment is not a viable option (10). It is important to note that the results of the analysis may be more relevant to those with earlier stages of CVI, rather than those with advance stages of ulceration.

The availability of the different treatment modalities across the UK varies between Trusts and is usually based on local funding. Foam is the cheapest of the interventions and therefore is more readily available than the costlier endothermal ablation, which is not accessible in some regions of the UK at the time of writing (109).

1.9.6. Pharmacological

Pharmacological agents are often used as adjuncts to treat venous ulceration and work by reducing the damage to the microcirculation while promoting ulcer healing. They are more commonly used in Europe and the USA than in the UK, where many are still unlicensed, and clinicians and guidelines still believe that pharmacotherapy should be offered as a treatment option to enhance ulcer healing. There is, however, limited evidence for the use of drugs in preventing recurrence (167). The most commonly investigated agents are discussed below.

1.9.6.1. Aspirin

Aspirin has been considered to improve ulcer healing due to its anti-inflammatory properties. A small RCT in the 1990s randomised 20 patients to OD 300mg of oral aspirin or placebo and saw 38% patients in the aspirin arm heal at 4 months versus none in the placebo arm. In addition, about half of the aspirin arm patients had notable reductions in ulcer size compared with a quarter in the placebo group (168). Years later, in 2012, another small RCT was conducted in Spain and found that time to healing was shorter in the aspirin arm than the placebo arm. A recent Cochrane review evaluating the efficacy of aspirin on ulcer healing, included both these RCTs and concluded that there is insufficient evidence to recommend aspirin use in venous ulceration (169) and therefore, the SIGN guidance does not recommend its use.

A recent RCT from a group in New Zealand, aspirin4VLU (Low dose aspirin as adjuvant treatment for venous leg ulceration: pragmatic, randomised, double blind, placebo controlled trial ClinicalTrials.gov NCT02158806), failed to detect any significant difference in ulcer healing or size reduction when comparing 150mg aspirin once daily versus placebo in 251 participants (170), but it should be noted that the dose was half of that in the previous RCTs. Another small RCT, the aspirin for venous ulcers (AVURT trial) (clinicaltrials.gov

NCT02333123) run by a group in the UK, aimed to build on the evidence base and randomised 100 participants to 300 mg of aspirin OD or placebo but the trial was stopped for failing to recruit.

1.9.6.2. Micronized purified flavonoid fraction (Daflon)

Micronized purified flavonoid fraction (Daflon) is a venoactive drug shown the improve oedema, leg heaviness and pain in patient with CVI (171). A meta-analysis of five RCTs concluded that Daflon can accelerate ulcer healing (172), and its use is popular in Europe (167). The quality of the included studies has been criticised however, and SIGN have concluded that there is insufficient evidence to recommend its use in VLU treatment and indeed, Daflon is not licensed for use currently in the UK (9).

1.9.6.3. Pentoxifylline

Pentoxifylline (400 mg three times daily) is recommended to as an adjunct therapy for VLU to improve ulcer healing (9, 111). Its use for venous ulceration is an unlicensed indication, although it is licensed in peripheral vascular disease. This recommendation is based on a Cochrane review, which showed that pentoxifylline improved healing rates by 21% (RR 1.56, 95% CI 1.14 to 2.13) if used as an adjunct to compression, compared with 23% when used in isolation (173).

1.9.6.4. Mesoglycan

Mesoglycan is a mixture of glycoaminoglycans extracted from animal sources and is used in a variety of venous disorders. It has been shown to improve ulcer healing in several studies but is currently not widely used in the UK (174, 175).

1.9.6.5. Antibiotics

The routine use of antibiotics in venous leg ulceration is not recommended unless there is evidence of a clinical infection, in which case Flucloxacillin or Clarithromycin are recommended (9, 111).

1.9.6.6. Statins (simvastatin)

A 2015 single site RCT conducted in the Philippines showed remarkable improvements in ulcer healing when patients were administered 40 mg daily simvastatin, in addition to compression (10-week healing rates were 100% versus 50% for ulcers ≤ 20 cm^2 [RR 0·10, 95% confidence interval (CI) 0·0141-0·707]) and 67% versus 0% for ulcers > 20 cm^2 [RR 0·33, 95% CI 0·132-0·840] (176). This study suggests statin use could be a cheap and easy to administer adjunct but requires further investigation in larger, multicentre trials.

1.9.7.   Physical treatments

There are a number of physical therapies that have been investigated for use as adjuncts in the treatment of venous leg ulceration.

Cochrane reviews of electromagnetic light, laser light and intra-red light, hyperbaric oxygen and negative pressures therapies did not find sufficient evidence to recommend their use in the treatment of venous leg ulcers (177) (178, 179) (180, 181). A Cochrane review protocol was released in 2018 to determine the effects of low-level light therapy (LLLT) for treating venous leg ulcers (182)

Intermittent pneumatic compression involves inflation and deflation of an airtight bag around the lower limb to improve circulation. This not been shown to improve healing with compression in situ but may have a role in those who cannot tolerate compression (183).

Skin grafting involves placing skin cells over the wound to stimulate new cell growth and closure of the wound. These cells may come from the patient's own skin, usually the thigh, or grown into a dressing using the patient's skin, or may come from a donor, which is known as an allograft. Some clinicians currently use skin grafts for large, non-healing ulcers. Bilayer artificial skin has been shown to improve healing when used with compression compared with dressing and compression alone but there is currently insufficient evidence to recommend any other types of skin graft at present (184).

1.10. Outcome measures

The primary goal of most clinicians involved in the care of patients with venous leg ulcers is to improve healing and prevent ulcer recurrence but RCTs involving VLU have been found to have considerable heterogeneity with respect to the outcome measures assessed (185). The following section will discuss some of these outcome measures in detail.

1.10.1. Healing

Venous ulcers often have prolonged healing times with some ulcers never healing (98, 99). Venous ulcers have been shown to have longer healing times than those without a venous component, with some taking over 10 years to heal. Shockingly, some studies even found patients with ulcers that have remained unhealed for over 60 years (99, 121).

The majority of patients are treated in the community, where healing rates are low compared with specialist clinics, for example, the six month community healing rate in the Scottish Leg Ulcer Trial was 45%, whereas specialised centres have demonstrated healing rates of up to 70% (9). A recent review paper similarly determined that 25% to 50% of leg ulcers have not healed by six months even with the best care available (79).

Other randomised trials using different methods of intervention, such as surgery, have shown similar 24-week healing rates of 60 to 65% and it is likely that the rates within the real-world population are significantly lower (141, 186).

A 2012 systematic review showed that time to healing is quicker in patients who wear compression versus no compression, may contribute to the high healing rates in specialist centres which are more likely to be experienced in applying compression (126).

Time to complete healing has been demonstrated as a high priority for those with ulcers and complex wounds (63), which aligns with our findings from Patient and Public involvement (PPI) work (*see section 2.3.1.*).

1.10.2. Recurrence

Unfortunately, venous leg ulcers are characterised by repeated cycles of ulceration and recurrence. Callam et al 1987 observed that two-thirds of venous leg ulcers recurrent, with one-third of those experiencing more than four episodes (121). As compression use and healing rates increase, so does the risk of recurrence. Recurrence rates have been estimated to

be 26% after 12 months and 31% after 18 months, with further increases over longer time periods. However, it should be noted that wide ranges in recurrence rates are seen, with 12-month recurrence rates between 26% and 69% in the literature (125, 130, 187).

Although the Dutch van Gent study did not show a difference in recurrence rates at 2 years for those treated with Subfascial endoscopic perforator surgery (SEPS) compared with those treated with compression (141), the 10-year follow-up reported that the recurrence rates were almost half in the surgical group - 48.9% versus 94.3% in the compression alone group (188). Inadequate assessment and suboptimal treatment are likely to contribute to poor outcomes, although severe underlying venous disease plays a significant role (189). Callam et al. showed that leg ulcers in patients from the most deprived social classes have protracted healing rates and higher recurrence rates (190).

1.10.3. Clinical success markers

As mentioned earlier the VCSS is currently the most utilised scoring system to classify venous disease and, therefore, is often used as a marker of clinical success.

The technical success of the endovenous intervention can also be utilised as a marker of clinical success, although it could be argued that this is only relevant in the presence of associated symptoms such as pain or ulcer recurrence. Technical success can be determined by performing a post-operative duplex Doppler and is often measured as the proportion of veins that have re-occluded or the presence of residual / recurrent truncal superficial venous reflux. The timing of the post-operative duplex is controversial and, therefore, there is no agreed time point at which this should be performed to assess the technical success of interventions, nor has this been validated to predict healing or recurrence (191)

1.10.4. Health outcomes

According to the World Health Organisation (WHO) quality of life encompasses several domains; physical, psychological, functional, and social (192). As discussed earlier, venous ulceration can greatly affect the quality of life of the patient and measuring quality of life is crucial when evaluating health technologies, so that common gains can be compared and inform policy makers to allow the technical success of a given intervention to be differentiated from a success outcome from a patient's perspective. It could be argued that

there is also an ethical obligation to include patient-reported outcomes in UK health research, as the National Health Service is publicly funded by tax payers.

1.10.4.1. Quality of Life impairment
It has been shown by both quantitative and qualitative studies that the quality of life in patients with venous leg ulceration is lower than the general population (70, 193). A 2007 study assessing the changes in SF-36 domains in patients with chronic leg ulceration found that those patients whose ulcers had healed during the follow-up period experienced less body pain, improved vitality, mental health, physical and emotional role functioning compared with the ulcers which remained unhealed (194).

A variety of generic and disease-specific tools have been used to assess patient reported outcome measures (PROMs) in patients with venous disease or venous ulceration which will be discussed below.

1.10.4.1.1 EQ-5D® (European Quality of Life-5 dimensions questionnaire, EuroQol Group, Rotterdam, The Netherlands)
EQ-5D® is a well-recognised, generic questionnaire used to measure health outcomes and Quality Adjusted Life Years (QALYs). The EQ-5D® encompasses two sections, one assesses the participant's mobility, self-care, ability to perform usual activities, pain / discomfort and anxiety / depression levels, used to calculate a health index on a score or 0 to 1 and the other records participants' self-rated health on a vertical score of zero to 100 (*see Table 3 and Appendix 1*).

1.10.4.1.2. 36-Item Short Form Health Survey (SF-36®) (Short Form questionnaire-36 items, standard U.K. Version 1.0) (QualityMetric, Lincoln, RI, USA)
The SF-36® is a generic quality of life tool used to determine physical and mental wellbeing. The physical domain measures physical functioning, physical role limitations, body pain and general health, whereas the mental dimension measures vitality, social functioning mental health role limitations and general mental health. Two separate physical / mental component summary scores are produced, in addition to the eight separate domain scores. Each score is measured on a scale of zero to 100 (worst to best) which represent the percentage of total possible score achieved (*see Table 3 and Appendix 2*).

1.10.4.1.3. Aberdeen Varicose Vein Questionnaire (AVVQ)
The Aberdeen Varicose Vein Questionnaire (AVVQ) comprises of a diagram where patients draw on their varicose veins followed by 12 questions, half of which require a response for

each leg. The scores range from zero to 100 (no effect to severe effect) (195) (see *Table 3 and Appendix 3*).

1.10.4.2. Validation of PROMS in venous disease

A review in patients with venous leg ulcers suggested that the generic EQ-5D® and SF-36® had good acceptability but did not appear to be fully responsive to patients with venous legs ulcers over time (196). Despite this, other studies have shown that the EQ-5D® and SF-36 had been validated in a variety of patient groups, including those with venous leg ulcers (197, 198).

The disease specific AVVQ is a validated patient-reported disease-specific health questionnaire to assess quality of life in patients with varicose veins (195). One systematic review in varicose vein patients determined that the AVVQ and the SF-36 were the most widely evaluated PROM in these patients (199).

The Charing Cross Venous Ulcer Questionnaire (CCVUQ) is a 21-question tool with four domains encompassing social interaction, domestic activities, emotional state, and aesthetics (200). The tool has subsequently been shown to have an error in scoring (namely questions 3 and 7) but this is easily rectified (201). The CCVUQ has been validated in several languages but still is not as widely utilised at the AVVQ (202, 203).

As mentioned earlier endovenous interventions have been shown to reduce pain and time to work compared with surgery, which should improve the quality of life. The ESCHAR trial did not measure quality of life in relation to surgical correction of venous reflux, but with respect to endovenous interventions; a recent systematic review by Sinha et al. showed comparable quality of life improvements between EVLA, RFA, sclerotherapy, and MOCA (204). There have been no studies to date investigating the quality of life of patients undergoing early endovenous ablation.

Table 3 - Summary of secondary outcome measures and quality of life tools used in EVRA study (205)

Details of outcome measure	Type of assessment	Range of scores	Comments
Venous Clinical Severity Score (VCSS)(25)	Physician assessed clinical severity evaluation	0 – 30	Higher scores indicate worse severity of venous disease
Aberdeen Varicose Vein Questionnaire(195)	Patient reported disease specific QoL	0 – 100ª	Higher scores indicate worse health related to varicose veins
EuroQol – 5 Dimension (EQ-5D-5L) (206)	Patient reported generic QoL	0 – 100 (health scale)	Consists of a health scale and health index (with higher scores indicating better health)
Short-Form 36 (SF-36) (198)	Patient reported generic QoL	0 – 100 (for each domain)	Eight scores covering different domains of health, with higher scores indicating better health

ªprevious studies have used 0.25SD as a clinically important difference (207)

1.10.4.3. Quality Adjusted Life Year (QALY)

QALYs are a commonly used health outcome for economic evaluations taking into account both the quantity and length of health-related quality of life (HRQoL) and indeed the National Institute for Health and Care Excellence (NICE) in the UK requires the use of QALYs for assessment of health technologies. Where QALYs are used as a cost outcome, it is known as a cost-utility analysis (CUA) (208).

QALYs are generated from health utilities, which are essentially preference weights where the preference is desirability. Utilities are measured on a scale of 0 (death) to 1 (full health), although states worse than death are possible and are indicated by a negative value. The scale is marked by intervals and therefore changes from 0.6 to 0.8 equates to the same change as 0.2 to 0.4 (208).

At present, NICE recommends using the crosswalk tariff (209) to convert the EQ-5D® values into utility score which essentially maps the 5-level EQ-5D® responses to 3 level values via the Dolan et al. tariff (210). There are other tariffs available, such as the EQ-5D-5L Devlin tariff (206). QALYs are derived by calculating the duration of time spent in a particular health state by the utility score.

NICE also recommends that discounting should be applied to QALYs past one year, to take into account costs and benefits over time, as health benefits in the here and now are preferential to benefits in the future. Currently the recommended discounting rate is 3.5%, with 1.5% for sensitivity analyses (211).

The Index values can be plotted onto a graph against the length of life in years, and overall QALYs and QALYs gained can be estimated from the area under the graph *(see Figure 7)*.
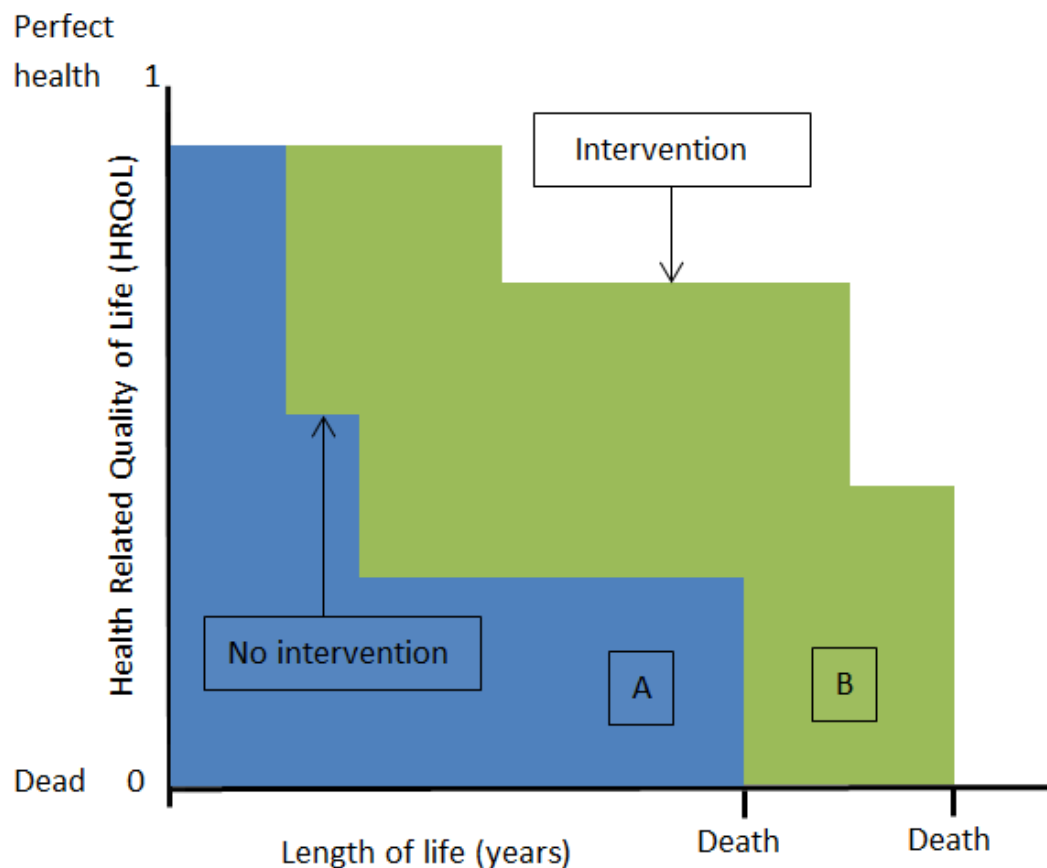
Figure 7 - QALYs calculated from area under graph. A = QALYs with no intervention, B=QALYs with the intervention

1.10.4.4. Health economic analysis

There are several different types of cost analyses: cost-benefit, cost-minimisation, cost-consequence and the most common when assessing health technologies; cost-effectiveness analyses (CEAs). Both of these compare the relative costs and relative effects of interventions and are usually expressed as a ratio, known as the incremental cost-effectiveness ratio (ICER):

$$(ICER) = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

The ratio numerator (C) is cost of the health gain (where C_1 is the cost of the intervention, C_0 is the cost of the comparator) and the denominator is the health gain (E) where E_1 is the health gain of the intervention and E_0 is the health gain of the comparator). If the health gain is measured in life years saved the analysis is known as a CEA whereas CUAs are where the

health gain is QALYs saved. The lower the ICER, the better the cost effectiveness - an intervention is considered 'cost effective' when its ICER is lower than the threshold set by decision makers. In the UK, NICE typically uses a threshold of £20 000 to £30 000 (€22 546–33 819) per QALY gained (211).

Health economic analyses can be performed from different perspectives, e.g. societal, healthcare system, individual hospitals or patients, with societal being the broadest and including loss of productivity or days off work, but this can be biased by the age or ability to work of the patient population who may be retired or unemployed. NICE currently recommends that analyses be performed from the perspective of 'NHS and personal and social services' which includes treatment-related costs (cost of interventions themselves and administering and monitoring including health resource visits) but excludes costs to the patients themselves. (211, 212).

1.10.4.5. Within-trial analyses

It is usual for several different economic models to be created during a within-trial analysis, each model based on its own assumptions, usually determined by literature, and therefore subject to some uncertainty. A base case analysis is the model which includes the preferred set of data and assumptions resulting in the most likely scenario (213). It is then common to perform sensitivity analyses with alternate data and assumptions to assess the degree of uncertainty. Examples of these include alternative methods of handling missing data, alternative preference weights / tariffs for health-related quality of life, and per-protocol analyses.

1.10.4.6. Current evidence

Until recently there were no published cost-effectiveness analyses for surgical procedures versus compression therapy, despite several studies evaluating non-surgical therapies (214). Epstein et al. used a Markov model (*Figure 8*) based on available RCT data to determine QALYs gained by open surgery, endothermal ablation and UGFS compared with compression alone, and found that surgery was more cost effective than compression alone. The study was inconclusive for endothermal ablation and UGFS due to the limited RCT evidence available evaluating these interventions and recommended further research in this area (215).
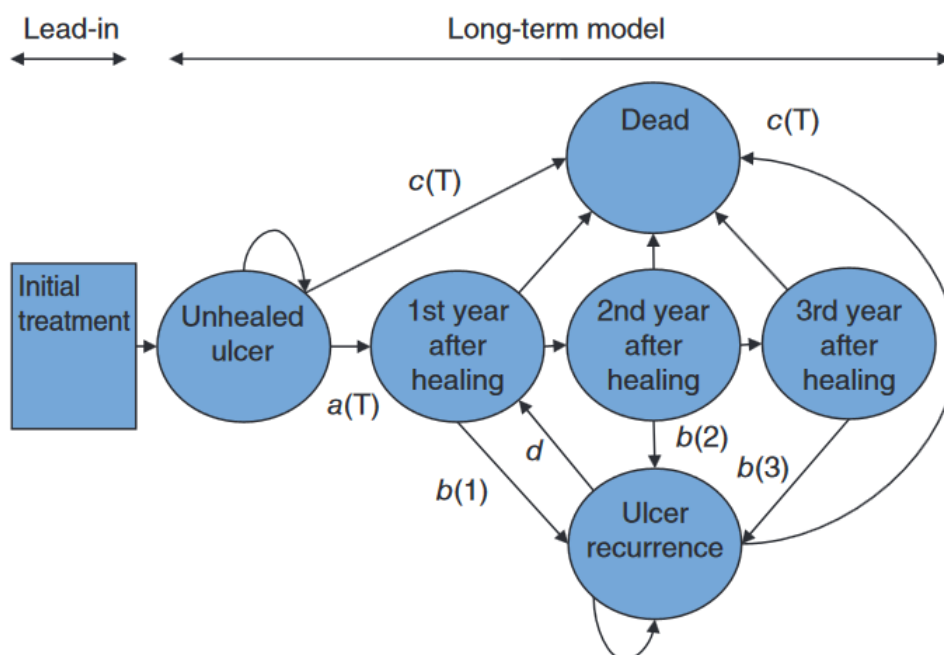
Figure 8 - Markov model used to evaluate treatments for superficial venous reflux in patients with chronic venous ulceration.

The lead-in period is six weeks, during which initial therapy is undertaken. Subsequent cycles in the long-term Markov model are 1 year. Transitions :a(T) is the rate of healing at time T;b (1),b(2) etc. are the rates of recurrence in the first, second, etc. year after healing; c(T) is the mortality rate at time T;d is the rate of healing after recurrence. Tunnel states for the fourth year and beyond after healing are included in the model but not shown in the figure. Figure reproduced from (215) with permission under the terms of the Creative Commons Attribution License.

1.11.   Summary of evidence and thesis rationale

Venous leg ulcers are open wounds that have a detrimental effect on the quality of life of patients. Treatment of the condition in the UK represents a substantial economic burden on the NHS and social care services, amounting to many hundreds of millions of pounds per year. Until recently, superficial venous reflux could only be treated by open surgery. Newer, endovenous techniques have been shown to be just as effective as open surgery in terms of clinical improvement but with reduced complications and pain. These techniques do not need to be performed under general anaesthesia and therefore may be more suitable for elderly patients with significant co-morbidities.

The most recent UK guidelines for varicose veins recommend early referral to a vascular service for diagnosis and first-line treatment by means of endovenous interventions, yet despite this there is evidence that there is considerable variation across the UK as to who qualifies for referral or treatment of varicose veins and leg ulcers, and hence a substantial proportion of patients are still treated in the community, with widespread acceptance that the management of these patients may be suboptimal (102, 108, 109).

Despite the evidence that the treatment of superficial venous reflux reduces recurrence in patients with venous leg ulcers, there is currently no level 1 evidence demonstrating reductions in time to healing or the cost effectiveness of early ablation (216) (146). With this void in evidence, the treatment of superficial venous reflux is often performed after ulcers have healed following conservative treatment involving compression bandaging. The danger of taking this approach is that once the ulcer is healed and the symptoms have resolved, patients may not be referred. The resulting untreated superficial venous reflux contributes to increased risk of ulcer recurrence, which is both costly for the health service and distressing for the patient. The previous RCT literature may have underestimated the clinical benefit of intervention, with recent prospective cohort studies of endovenous intervention in active leg ulceration clearly suggesting an adjuvant benefit compared with compression therapy alone in terms of healing rates. Time to healing has been highlighted as the most important endpoint to patients, as demonstrated in our PPI work and even a modest improvement in ulcer healing would significantly reduce the health service costs associated with the condition.

EVRA will be the largest randomised clinical study evaluating endovenous ablation treatments in patients with chronic venous ulceration. There is little evidence for the long-

term durability, intervention rates and patient acceptability of the endovenous techniques, which may be gained from longer term follow-up data and which will be essential to inform guidelines, and possibly identify groups of patients who may benefit most.

If the primary results of the EVRA trial show that early endovenous ablation reduces time to ulcer healing, it will create a strong rationale for the development of pathways to aid early referral and assessment of patients with chronic venous ulceration, but driving changes in healthcare practice is notoriously challenging, particularly when multiple health settings and funding systems are involved. Longer-term recurrence rates could add weight to the argument, and more likely to result in sustainable change in national clinical practice.

If the primary results of the EVRA trial do not demonstrate that early endovenous ablation reduces time to ulcer healing, it is possible that healthcare professionals and policy makers will conclude that early ablation offers no benefit, despite the evidence from the ESCHAR and cohort studies. In this era of austerity and cost savings, there is a danger that numbers of superficial venous interventions may even reduce due to 'cherry picking' of the evidence base. Evaluating the longer-term recurrence rates, quality of life and health economic data will allow a fuller analysis of treating superficial reflux in patients with venous ulcers.

As the incidence and prevalence of venous ulcers is likely to increase as a result of the ageing population, it is important to clarify the role and timing of superficial endovenous ablation in venous ulceration to guide treatment recommendations and referral pathways (11, 102).

1.12.   Aims of the thesis

The aim of this thesis is to determine:

1) The clinical, quality of life and cost effectiveness of early endovenous treatment of superficial venous reflux in addition to standard care, compared with standard care alone in patients with chronic venous ulceration via a randomised controlled trial (RCT)
2) The current standard of global management of venous leg management
3) The impact on the global management of venous leg ulceration following the results of the randomised controlled trial.

Chapter 2: EVRA Trial Methodology

2.1 Introduction

As detailed in *Chapter 1*, currently no level 1 evidence exists as to whether early endovenous ablation improves ulcer healing or affects quality of life and there are no published cost-effectiveness studies of endovenous procedures versus compression therapy.

2.2 Aim

The aim of this chapter is to describe the methods to determine the 12-month and longer-term clinical and cost effectiveness of early endovenous ablation of superficial venous reflux plus compression therapy compared with deferred endovenous ablation plus compression in patients with superficial venous ulceration.

2.3 Trial design

A multicentre, open arm, pragmatic, RCT with participants randomised 1:1 to either deferred (standard) therapy consisting of multilayer elastic compression therapy with deferred

endovenous ablation of superficial reflux once the ulcer has healed, or early endovenous ablation of superficial venous reflux in addition to multilayer elastic compression therapy.

2.3.1. Patient and Public Involvement (PPI)

There is an ethical obligation of researchers to include patients and the public in research and public involvement and indeed it has been shown to benefit research (219, 220). The '*INVOLVE Briefing notes for researchers: public involvement in NHS, public health and social care research*' were utilised to plan PPI input into the research design (221) notably patient consultation and patient collaboration.

Patient consultation

As detailed in *section 1.9.2.4*, the 2004 ESCHAR study suffered from a high crossover rate as 24% of patients randomised to surgery refused an operation which weakened the power of the study (143). It was assumed that the less invasive interventional modalities employed in the EVRA study would not have the same rate of refusal. To corroborate this assumption a small group of patients with active leg ulceration were consulted with the proposed trial design to see if they would be willing to undergo early intervention. Almost all the patients agreed they would have been willing to participate in the study, as they all wished to undergo intervention to heal their ulcer and the study offers the possibility of being treated sooner than standard care coupled with a less invasive strategy than open surgery.

Patient collaboration

A patient with healed leg ulceration was approached to join as a lay member co-applicant to assist in the design of the research study and ensure that the research question and outcomes were relevant to those affected by venous leg ulceration. Lay member involvement at the design stage helped the EVRA study team gain insight into:

- Patients' fears and lack of knowledge about procedure and options
- Thoughts on early referral and intervention "*my ulcer would have healed quicker if I had been referred and treated promptly as intervention had an immediate impact*".
- Deciding an appropriate primary outcome measure "*time to healing is the most important outcome, as the smell associated with the ulcer affected my social confidence*" as well as important secondary outcome measures including patient quality of life and ulcer free time.

- The frequency of follow-ups "*most patients would benefit from a 6-week clinic visit and monthly telephone calls to give them reassurance they were not lost in the system, as most patients are discharged out into the community post procedure*"

2.4 Sponsorship

The trial was sponsored by Imperial College London.

2.5 Ethical and research and development approvals

The National Research Ethics Service (NRES) Committee South West - Central Bristol granted a favourable ethical opinion on 15th August 2013 (reference number 13/SW/0199). Annual reports were submitted to this committee who confirmed that the ethical approval continued to apply.

The North-West London Clinical research network (CRN) granted study-wide governance approval in August 2013. Initial research and development (R&D) NHS approvals were granted at participating sites between October 2013 and March 2015, and for each substantial amendment. The study was granted the new Health Research Authority (HRA) approval on 30th June 2016.

2.6 Amendments to the protocol

After the initial approval, several substantial amendments to the trial protocol were made and are summarised in *Appendix 4.*

2.7. Trial outcomes

2.7.1. Primary outcome at 12 months

The primary outcome measure of this study at 12 months was time from randomisation to complete healing of ulcers on the reference leg, confirmed by a core lab blinded assessment. Healing was defined in the protocol as "*complete re-epithelialisation of all ulceration on the randomised leg in the absence of a scab (eschar) with no dressing required*".

2.7.2. Secondary outcomes at 12 months

- The proportion of ulcers healed at 24 weeks from randomisation.
- Ulcer recurrence at 12 months determined by participant-reported ulcer recurrence on the reference leg

- Ulcer-free time at 12 months determined by participant-reported ulcer recurrence on the reference leg

- HRQoL at six weeks, six months, 12 months using the ED-5D, SF-36 & AVVQ

- Participant-reported utility and resource use at 12 months

- The VCSS at six weeks.

- The presence of residual / recurrent truncal superficial venous reflux in the early ablation group at six weeks by means of a venous duplex.

- Health economic costs and associated QALYs at 12 months

2.7.3. Primary outcome at a median of 3.5 years

The primary outcome measure at a median of 3.5 years was time to the first ulcer recurrence on the randomised leg from the date of healing. Ulcer healing was defined as per *section 2.7.1* and recurrence was defined as "*any break in the skin lasting for more than two weeks duration on the reference leg, either self reported by the particpant or collected from the medical notes*".

2.7.4. Secondary outcomes at a median of 3.5 years

- Time to first recurrence on the randomised leg from the date of randomisation

- Proportion of ulcer recurrence at annual timepoints

- Time to ulcer healing from the date of randomisation

- Participant-reported ulcer recurrence periods and any subsequent healing to determine ulcer-free time were collected up to 5 years from randomisation (median 3.5 years) or until trial exit

- Time to healing of all recurrent ulcers from the date of healing

- Compliance to compression bandaging

- HRQoL at a median of 3.5 years using the ED-5D, SF-36 & AVVQ

- Health economic costs and associated QALYs at a median of 3.5

2.8. Sample size

2.8.1. Primary outcome

The sample size calculation for the 12-month outcomes was based on published 24-week ulcer healing rates. In the compression-alone arm of the ESCHAR study, 60% patients were

healed at 24 weeks (186), whereas the proportion of patients healed by 24 weeks in two prospective cohort studies evaluating the early endovenous ablation of superficial venous reflux was 82% (155, 156).

It was therefore assumed that the 24-week healing rate in the deferred (standard) group would be 60%. The desirable absolute clinical benefit associated with early endovenous ablation of superficial truncal reflux was estimated at 15%. The required sample size was calculated at 416 subjects (208 in each group, 254 healed leg ulcers in total), using the Freedman method (222) to identify a difference of 15% between the two groups at 24 weeks with 90% power, i.e. 75% healed at 24 weeks in the early intervention group at a two-sided alpha level of 5% (log-rank test). This calculation allowed for 10% dropout rate, but the target sample size was set at 450 participants to allow for additional protocol violations and unexpected withdrawals.

2.8.2. Longer term recurrence analysis.

The recurrence analysis was designed to provide a median follow-up of 3.5 years from randomisation of the main study, by collecting data from October 2018 and March 2019, and including all participants that that not formally withdrawn or died.

It was assumed at the time of design, that the total healing rate in EVRA trial at 12 months would be 90%, with an approximate 15% withdrawal or lost to follow-up. The sample size for the recurrence analysis, was therefore calculated at 344 participants (450*0.9*(1-0.15) =344).

In the ESCHAR trial, the reported four-year recurrence rates were between 40%-45% (the paper only reported the recurrence rates for two groups separately) (143). Assuming the recurrence rate in the EVRA participants would be similar to that in the ESCHAR trial, the recurrence rate by the end of October 2018 was estimated to be between 36% and 41% and therefore, the sample size was based on an anticipated recurrence rate of 38% by October 2018.

2.9. Site Feasibility and selection

Prior to selection, secondary care vascular departments completed feasibility questionnaires to confirm the number of patients with leg ulceration seen each month, estimated numbers of patients that would be eligible for the study and vascular scanning capacity. In total through the recruitment, 20 sites from the following NHS Trusts were selected to participate

throughout England: (*in alphabetical order*) Bradford Teaching Hospitals NHS Foundation Trust; Cambridge University Hospitals NHS Foundation Trust; Frimley Park Hospital NHS Foundation Trust; Gloucestershire Hospitals NHS Foundation Trust; Heart of England NHS Trust (now University Hospitals Birmingham NHS Foundation Trust); Hull & East Yorkshire Hospitals NHS Trust; Imperial College Healthcare NHS Trust; Leeds Teaching Hospitals NHS Trust; North Cumbria University Hospitals NHS Trust; North West London Hospitals NHS Trust; Plymouth Hospitals NHS Trust; Salisbury NHS Foundation Trust; Sheffield Teaching Hospitals NHS Foundation Trust; Taunton and Somerset NHS Foundation Trust; The Dudley Group NHS Trust; the Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust; the Royal Wolverhampton Hospitals NHS Trust; University Hospital Birmingham NHS Trust; Worcestershire Acute Hospitals NHS Trust; York Hospitals NHS Foundation Trust.

2.10. Recruitment procedure

2.10.1. Participant Identification Centres (PICs)
Prior to recruitment, trial and NICE guideline information was disseminated to general practitioner (GP) practices in each recruiting region. As per the July 2013 NICE guidelines on varicose veins, patients with venous ulcers were required to be referred from primary to secondary care as part of the standard care pathway (10). Primary Care trusts (PCTs) were set-up as Participant Identification Centres (PIC) sites displaying posters and leaflets and disseminating participant information sheets to patients.

2.10.2. Screening
Patients were screened from secondary care vascular, ulcer and tissue viability clinics in each recruiting site. Standard care involves a clinical assessment and colour duplex examination of patients presenting with a leg ulcer. Depending on the results of these tests, the patients were given a short leaflet containing a summary of the study and, if interested, then given the more detailed participant information sheet (PIS) to read.

The details of patients who were eligible for the trial but did not agree to participate, and patients with ulcers who were not eligible in the study were recorded anonymously on screening logs along with a minimal data set comprising of age, ulcer duration and venous duplex / ABPI findings if known and reason for non-inclusion.

2.11. Informed consent

Patients were provided with a PIS and given a minimum of 24 hours to consider their participation and were free to discuss the study with their family and / or GP. Patients were telephoned by the research nurse to discuss the study further and arrange a baseline visit for interested participants, where written informed consent was obtained. A copy of the participant information sheet informed consent (PISIC) was filed in the participant's hospital notes, and the local research file, and a copy was also given to the participant. A letter was also sent to the participant's GP with consent of the participant.

2.12. Baseline assessment

Once written consent was given by the participant, baseline assessments were performed to confirm trial eligibility and collect baseline characteristics in the case record forms (CRF).

2.12.1. Inclusion criteria

The inclusion criteria were as follows:

- Patient age $\geq$ 18 years
- Current leg ulceration duration of greater than six weeks, but less than six months duration
- Able to provide informed consent to participate in the study after reading the participant information documentation
- ABPI $\geq$ 0.8
- Superficial venous disease on colour duplex assessment deemed to be significant enough to warrant ablation by the treating clinician (either primary or recurrent venous reflux defined as retrograde flow >0.5 seconds in the superficial veins and >1second in the deep veins)

2.12.2. Exclusion criteria

The exclusion criteria were as follows:

- Presence of deep venous occlusive disease or other conditions precluding endovenous superficial venous ablation at the discretion of the treating clinician
- Patients unable to tolerate multilayer compression therapy. As concordance with compression therapy can be variable for patients at different times, patients who were generally concordant with compression, but unable to tolerate short periods were still deemed eligible

- Inability of the patient to receive prompt (within two weeks) endovenous ablation by recruiting centre

- Pregnancy

- Leg ulcer of non-venous aetiology as assessed by the treating clinician

- Patients deemed to require skin grafting as assessed by the treating clinician

2.12.3. Participant demographic and contact details

Data collected comprised of participant contact details, GP details, age, sex, ethnicity, and work status. Woman of child-bearing potential took urine pregnancy tests to confirm eligibility.

2.12.4. General medical and ulcer history

This included BMI, ABPI, medical history and current medications. An ulcer history was taken including any previous ulcers and interventions and any history of previous deep vein thrombosis recorded.

2.12.5. Ulcer duration and size

Ulcer duration on the randomised leg was determined by medical notes review and was confirmed by the participant. The total area of the ulcer/s was measured by placing 1cm^2 tracing square grids over each wound and tracing the outside perimeter with an indelible pen. The ulcers were also photographed using a Sony Cyber-shot DSC-WX60 16.2 Megapixel Digital Camera, incorporating a measuring scale. Tracing and ulcers were assigned trial numbers only and transferred to the core lab by the Imperial College file exchange. Image J was used to calculate an exact ulcer area from the tracings and photographs, and the most accurate measurement was taken as the total ulcer area (223)

2.12.6. Clinical Ulcer assessment - CEAP

A full basic CEAP (Clinical, Etiological, Anatomical and Pathophysiological) assessment was performed and recorded.

2.12.7. Clinical Ulcer assessment - VCSS

The baseline VCSS score was recorded each participant.

2.12.8. Suitability for intervention

Venous Duplex ultrasound scans were performed as per standard care at the randomising site, with patterns of superficial and deep venous reflux recorded and assessed by the treating clinician for suitability for ablation.

2.12.9. Participant completed questionnaires

Three baseline HRQoL questionnaires were administered prior to the participants being told of their treatment allocation:

- EQ-5D®
- SF-36®
- AVVQ

2.12.10. Reminder cards for ulcer healing

Participants were also provided with a reminder wallet card which contained the contact details of the local research nurse, with a reminder message to call the nurse when they thought their ulcer has healed.

2.12.11. Health resource diaries

Participants were provided with a health resource diary to collect any data related to contact with health professionals during the study.

2.13. Randomisation and treatment allocation

The statistician prepared separate randomisation lists for each centre prior to recruitment using randomly permuted blocks in two block sizes (ralloc command; Stata V14.2, StataCorp LLC, Texas, USA) and loaded onto the InForm™ (Oracle ® Health Sciences, USA) system. Allocation concealment was maintained by restricting the lists to the statistician.

Once the participants had consented and eligibility was confirmed, online randomisation was performed remotely by the research nurse in the InForm™ ITM (Integrated Trial Management) System which automatically assigned the next available treatment allocation in the appropriate randomisation list and allocated a unique trial number to the participant.

The randomisation ratio was 1:1 with participants allocated to either:

- Early (within two weeks) endovenous ablation of superficial venous reflux in addition to compression therapy
- Deferred (standard) therapy consisting of multilayer elastic compression therapy with deferred endovenous ablation of superficial reflux once the ulcer had healed

As the interventions relate to timing of the endovenous ablations, it was not possible to blind either the treating team or the participant to the treatment allocations.

2.13.1. Control group – deferred ablation

The deferred group received multilayer compression therapy alone with endovenous ablation of superficial reflux once ulcer healing had been confirmed (or at six months post randomisation or if clinical deterioration of the leg ulcer was observed). Duplex ultrasounds post intervention were performed at the discretion of the treating clinician.

2.13.2. Interventional group - early ablation

The interventional group received endovenous ablation of superficial truncal reflux within two weeks of randomisation, in addition to multilayer compression therapy. Duplex ultrasounds post intervention were performed at six weeks from randomisation.

2.14. Standardisation of interventions

2.14.1. Compression

There are a number of compression types available within the NHS and these vary on a Trust-by-Trust basis. The types of compression used in the trial therefore left to the discretion of the clinicians and health care professionals. Multilayer elastic (two, three or four layer), short stretch and hosiery compression were all deemed acceptable therapies. Compression hosiery was advised to be worn post healing, in line with local policy.

2.14.2. Endovenous interventions

Clinicians were required to ablate the main truncal reflux to the lowest point of incompetence and ablate significant residual or recurrent superficial reflux identified on the six-week duplex. However, as with compression, a wide range of endovenous ablation procedures are available and vary by Trust. EVLA or RFA, UGFS, MOCA, and cyanoacrylate glue closure were permitted for use in the study, performed alone or in combination at the discretion of the treating vascular specialist. Other factors not standardised were the site of cannulation and length of vein ablation, whether to ablate the sub-ulcer plexus or visible varicose veins, the location of the procedure and the timing of subsequent procedures.

2.15. Participant follow-up

All randomised participants were followed-up until either a median of 3.5 years after randomisation, the participant chose to withdraw from the study or death. As per standard care in the UK, participants received routine leg ulcer care in the community and / or hospitals in accordance with local policies.

The study design is summarised in *Figure 9*.

BASELINE VISIT
Consent & Randomisation
Clinical Assessment
Photo/Tracing of Ulcer
Quality of life questionnaire

Multilayer compression / stockings alone

Multilayer compression / stockings + EVRA

ENDOVENOUS ABLATION OF SUPERFICIAL REFLUX (within 2 weeks)

6 WEEKS
Quality of life questionnaire
Assessments of ulcer healing *

ENDOVENOUS ABLATION OF SUPERFICIAL REFLUX (once ulcer healed or at 6 months)

6/12 MONTHS
Self-completed quality of life questionnaire
Assessments of ulcer healing *

VERIFICATION VISIT
4 weekly photos of the ulcer**

MEAN 3.5 YEARS (2 to 5 YEARS)

Collection of:
Ulcer recurrence and healing***
Ulcer non-healing
Self-completed quality of life questionnaire
Intervention/re-intervention
Related adverse events

* Assessments of ulcer healing will be on going throughout the study follow-up period and will be performed by community nursing teams and research staff (at least every month)

**Once the research team has been informed by the patient that the ulcer has healed. Can occur any time during the 12 months.

***at each of these intervals if there has been an intervention / duplex scan performed the results of this will be recorded.

Figure 9 - Summary of EVRA study design (Gohel et al. 2019). Reprinted with permission.

2.15.1. Monthly telephone calls / follow up

Participants were contacted by the research nurses on a monthly basis for 12 months, by telephone to assess whether or not the reference ulcer had healed and once healed to confirm any recurrent ulcers. Utility and resource use data as well adverse and serious adverse events were also collected. If the participants informed the nurse that the ulcer had healed, an urgent verification visit was arranged within one week which involved a clinical assessment and digital photography of the healed leg, which was repeated weekly for four weeks, unless otherwise agreed by the trial manager. The Digital photographs were assigned pseudonyms by trial number only and transferred via a secure server to the trial manager for assessment in the core lab (*see 2.16. Assessment of trial outcomes*).

2.15.2. 6-week clinic visit

Participants were clinically assessed at six weeks post-randomisation to determine the area of the wound by photography and tracing or confirm healing if no wound present, document the VCSS and record the current compression regimens and resource use. Participant-reported HRQoL was collected via the EQ-5D®, SF-36 and AVVQ. All participants in the early arm were assessed by venous duplex to determine any residual superficial venous reflux to guide whether further interventions were required.

2.15.3. 6-month and 12 months

Additional participant reported HRQoL were collected via the EQ-5D®, SF-36 and AVVQ questionnaires sent by post.

2.15.4. Longer term follow-up (3.5 years)

All participants that had not withdrawn or died were contacted by telephone between October 2018 and March 2019 to collect longer-term healing and recurrence data up to five years (a median of 3.5 years). Other data collected at this visit included any further interventional treatments received, plus any adverse and serious adverse events related to these, and other resource use related to the ulcer or recurrences. Data was verified by medical notes wherever possible. Additional participant-reported HRQoL outcomes were collected via the EQ-5D®, SF-36 and AVVQ questionnaires sent by post at this time point.

2.16. Assessment of trial outcomes

2.16.1 Main trial primary outcomes up to 12 months – time to healing of the reference ulcer

The verification digital photographs were independently assessed by two vascular surgeons who were blinded to treatment allocation according to a predefined set of decision rules based on those utilised in VenUS IV (80) (see *Appendix 5*). Disagreements were resolved through discussion with a third reviewer.

If the whole leg, including the reference ulcer was deemed to have healed, the date of the photograph in which healing was recorded was taken to be the date of healing. If healing was confirmed at the first verification visit, the date of healing notification (by the participant or community nurse) was taken as the date of ulcer healing.

2.16.2 Main trial secondary outcomes up to 12 months

2.16.2.1. Proportion of healed ulcers

The proportion of ulcers healed at 24 weeks was reported to allow comparison with other published studies.

2.16.2.2. Ulcer free time (ulcer recurrence)

Participant-reported ulcer recurrence periods and any subsequent healing to determine ulcer-free time were collected up to 12 months from randomisation or until trial exit and verified using participant notes from recent clinic visits wherever possible.

2.16.2.3. Health-related quality of life

Health-related quality of life was measured at baseline, six weeks, six and 12 months using the EQ-5D®, SF-36 and AVVQ. Where necessary, reminder letters were sent by post to participants if the questionnaires had not been returned.

2.16.2.4. Venous Clinical Severity Score

The VCSS was assessed by the research nurse or treating clinician at baseline and the 6-week clinic visit.

2.16.2.5. Ablation success

The six-week venous duplex performed in the early ablation group was assessed by the treating clinician for the presence of residual / recurrent truncal superficial venous reflux. If the truncal veins were not fully occluded, further ablation procedures were arranged. Where the reflux was only present in tributaries or perforating veins, the decision whether or not to

perform additional endovenous interventions was left to the discretion of the treating clinician.

2.16.2.6. Safety monitoring of early ablation

In order to monitor the safety of early ablation, adverse events related to the endovenous procedures and all serious adverse events were collected.

Adverse events

The adverse events expected to be related to the interventions are summarised in *Table 4*. Adverse Events were reviewed and categorised by the Study Manager and Chief Investigator as procedural complications.

Table 4 - Adverse events expected to be related to the intervention

Systemic	Local
Allergic reaction req. local / no treatment	Bleeding requiring intervention
Migraine	Blistering of skin
Visual disturbance	Pressure damage
Fainting	Nerve damage
Cough / chest tightness	Deep vein thrombosis (DVT)
Systemic infection	Hematoma
Pulmonary Embolism (PE)	Participant reported paraesthesia
Transient ischaemic attack (TIA)	Pigmentation of skin
Stroke	Superficial thrombophlebitis (SVT)
	New ulcer
	Deterioration of ulcer
	Wound infection

Serious adverse events

Serious adverse events (SAE) were defined as those adverse events that: result in death, are life threatening, require in-patient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, result in congenital anomaly or birth defect, are cancer, or are other important medical events in the opinion of the responsible investigator (i.e. not life threatening or resulting in hospitalisation, but may jeopardise the

participant or require intervention to prevent one or more of the outcomes described previously) (224). All SAEs were reported to the sponsor within 24 hours of the research team becoming aware of the event, whether deemed by the local principal investigator to be related to the trial intervention or compression or not and reviewed by the Chief Investigator.

2.16.2.7. Health economic analysis
The methods for the health economic analysis are described in *section 2.19*.

2.16.3 Longer term follow-up to five years (median 3.5 years) primary outcome – time to first ulcer recurrence

The primary outcome measure was time to the first ulcer recurrence on the randomised leg from the date of healing. For the purposes of this study, ulcer healing was defined *'as complete re-epithelialisation of all ulceration on the randomised (reference) leg in the absence of a scab (eschar) with no dressing required'*. Recurrence was defined as '*any break in the skin lasting for more than two weeks duration on the reference leg, either self reported by the particpant or collected from the medical notes'*.

2.16.4 Longer term follow-up to five years (median 3.5 years) secondary outcomes

2.16.4.1 Time to the first ulcer recurrence on the randomised leg from the date of randomisation.
Time to first recurrence on the randomised leg from the date of randomisation was one of the secondary outcomes, with ulcer recurrence defined as per *section 2.16.3*.

2.16.4.2 Ulcer recurrence rate
Ulcer recurrence rate was defined as the proportion of participants who had an ulcer recurrence at a defined timepoint.

2.16.4.3 Time to healing of initial ulcer
Time to ulcer healing was defined as the time from the date of randomisation to the first ulcer healing on the randomised leg.

2.16.4.4 Ulcer free time (ulcer recurrence)
Participant-reported ulcer recurrence periods and any subsequent healing to determine ulcer-free time were collected up to 5 years from randomisation (median 3.5 years) or until trial exit and verified using participant notes from recent clinic visits wherever possible.

2.16.4.5 Time to healing of recurrent ulcers

Healing of any recurrent ulcers was defined as the time between the date of the recurrence and the date of the healing of the recurrent ulcer. This could happen multiple times per participant and all the recurrent ulcers will be included the analysis.

2.16.4.6 Health-related quality of life

Health-related quality of life was collected at one further timepoint up to five years (a median follow-up of 3.5 years) by the EQ-5D®, SF-36 and AVVQ. Where necessary, reminder letters were sent by post to participants if the questionnaires had not been returned.

2.16.4.7. Health economic analysis

The methods for the health economic analysis are described in *section 2.19*.

2.17. Participant withdrawal

Participants were free to withdraw from the study at any time without stating a reason, but efforts were made to identify the reason for withdrawal if possible. Participants who expressed a wish to withdraw from data collection were asked to confirm if they agreed to the study teams retaining their existing trial data, and accessing trial-related NHS data, and this was documented in the participant notes. Participants who declined endovenous ablation remained in the trial as per protocol, unless they specifically withdrew their consent.

2.18. Statistical methods

All trial analyses were carried out on an intention-to-treat basis (ITT) (i.e. all participants remained in the group allocated at randomisation) using Stata version 14.2, with a per-protocol sensitivity analysis.

Distributions and outliers of continuous variables were determined by histograms, and boxplots and mathematical transformations were applied, when appropriate, in order to render the continuous variables normally distributed. Any continuous variables that followed an approximately normal distribution were summarised using means and standard deviations, whereas skewed continuous variables were summarised using medians and inter-quartile ranges. Frequencies and percentages were used to summarise categorical variables. All hypothesis testing was planned to be two-tailed with a 5% significance level and no adjustment for multiple testing.

2.18.1. Baseline characteristics

Baseline characteristics for all randomised participants were summarised by treatment group; ulcer duration was calculated as the difference between the date of randomisation and the date the ulcer appeared (based on medical records and participant recall).

2.18.2. Trial completion

Reasons for trial exit were as follows: completed study (to 12 months and 3.5 years), participant lost to follow-up, withdrawal or death.

2.18.3. Main trial statistical analysis for outcomes up to 12 months– primary endpoint

The primary outcome was time from randomisation to complete ulcer healing and the null hypothesis was that there was no difference in time to ulcer healing between the deferred and early ablation groups was tested using a Cox proportional hazards model with a random effect adjustment for potential centre effects. Kaplan-Meier survival curves were presented with the effect of participant age, ulcer size at baseline, and duration of time to ulcer healing investigated as a subsidiary analysis.

Censoring of participations occurred at the date of the last follow-up if they were lost to follow-up, withdrew or had died before primary ulcer healing. As the follow-up time was 12 months after randomisation, censoring of participants with an unhealed primary ulcer occurred at this time.

2.18.4. Main trial statistical analysis for outcomes up to 12 months – secondary endpoints

2.18.4.1 Recurrence / ulcer free time to 12 months and 24-week ulcer healing rate

The proportion of ulcers healed at 24 weeks and associated 95% confidence intervals were obtained from the Kaplan-Meier analysis. The effect of early intervention on ulcer-free time was categorized and analysed using appropriate regression methods to adjust for potential confounders.

The 12-month ulcer-free time (in days) in those who had completed follow-up to 12 months was calculated as total follow-up time (i.e. 12 months) less the total duration of ulcers, including the primary ulcer and any subsequent recurrences.

2.18.4.2. Quality of Life

The AVVQ was scored according to the manual (195). The SF-36 was scored using QualityMetric Health Outcomes™ Scoring Software 4.0 for the physical health and mental health dimensions, and all eight scales, including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy / fatigue, emotional wellbeing, social functioning, pain, and general health. The index-based values ('utilities') were calculated by the EQ-5D-5L Crosswalk Index Value Calculator downloaded from the EQ-5D® official website.

Line plots for both the early and deferred study groups were used to illustrate trends in the AVVQ score, SF-36 and EQ-5D-5L over time. The means and 95% CI of means were calculated at each time point, including baseline, six weeks, six months, 12 months after randomisation. Differences in HRQoL scores and overall p-values for the difference in HRQoL scores by study group at each time point were calculated using mixed models of time, age, ulcer size and duration as fixed effects, and study centre and participants as random effects.

2.18.4.3. Markers for Clinical Success VCSS

The VCSS at baseline and six weeks were summarised using boxplots for both groups. If the changes in VCSS between the early and deferred arms were normally distributed they were compared using the t-test whereas if they were not normally distributed these were investigated using an appropriate non-parametric test.

2.18.4.4. Markers for Clinical Success CEAP

Any changes in the clinical component in the CEAP score at six weeks post randomisation from baseline were reported. The chi-square test was used to compare the two groups.

2.18.4.5. Safety data

The AEs and SAEs were provided in a tabular format by group. AEs were summarised by description and outcome and SAEs were summarised by SAE reason, frequency, severity, and relationship to treatment, outcome and expectedness.

2.18.5 Sensitivity analysis

A per-protocol analysis for both primary and secondary outcomes was performed as a sensitivity analysis which excluded participants with protocol deviations.

2.18.6 Missing Data

Imputation of missing data was not used for the primary endpoint of time to healing, or the secondary endpoints of 24-week healing rate and ulcer-free time. Multiple imputation of the quality of life measures and measures of clinical success was performed using chained equations as a sensitivity analysis and the extent of missing data was reported.

2.18.7. Longer term follow-up to five years (median of 3.5 years) statistical analysis

The analyses were performed on an intention-to-treat basis with a subsidiary per-protocol analysis as per the main study. As the withdrawal rates could have been dependent on the treatment effect (and therefore cause systematic difference between the two arms), the analyses were adjusted for the most influential predictors to report as the primary results as follows:

- Age
- Ulcer size
- Ulcer chronicity

2.18.7.1. Longer term follow-up to five years (median of 3.5 years) primary endpoint

The hypothesis was that there is no difference in the time to first recurrence from the time of first ulcer healing, between the control and intervention groups was tested using a Cox regression model with study centre as a random effect. Kaplan-Meier survival curves and the log-rank test result were presented.

Both unadjusted and adjusted (by age, ulcer size and ulcer duration) Hazard Ratios (HR) and their 95% Confidence Interval (CI) were presented with the adjusted results were taken as the

primary results. For Cox regression models the proportionality assumptions were assessed graphically using diagnostic plots.

2.18.7.2. Longer term follow-up (3.5 years) secondary endpoints

2.18.7.2.1. Time to ulcer healing
As per the primary outcome, the hypothesis that there is no difference between time to ulcer healing from randomisation between the control and intervention groups was tested using an unadjusted and adjusted Cox model with study centre as a random effect. Again, the adjusted results were taken as primary and the same adjustment factors were made. Kaplan-Meier survival curves and the log-rank test result and HR with 95% CI were also presented and this, again will be repeated in the per-protocol population.

2.18.7.2.2. Ulcer recurrence rate
The ulcer recurrence rate was obtained from the Kaplan-Meier analysis of the primary outcome and the rates in each arm will be tabulated for appropriate time points (1 year, 2 years, 3 years and 4 years from randomisation) with associated 95% confidence intervals.

2.18.7.2.3. Ulcer free time
A Cox regression model was used, adjusted for center, patient age, ulcer size, and ulcer chronicity, as mentioned, as well as length of follow-up (as a fixed effect) to test the hypothesis that there was no difference in ulcer-free time between the early-intervention and deferred-intervention groups. The adjusted results were taken as primary. Where participants were deceased, withdrawn or lost to follow-up, ulcer free time was calculated as the time from randomisation until last follow-up.

As a sensitivity analysis, the analysis of ulcer free time was repeated using all the participants, irrespective of length of follow up to give a very conservative estimate of the treatment effect.

2.18.7.2.4. Healing of recurrent ulcer
All of the recurrent ulcers were included the analysis using a Cox regression with centre as a random effect and adjusted as previously described. Kaplan-Meier survival curves and the log-rank test result and HR with 95% CI were also presented for visualisation.

2.18.7.2.5. Incidence rate of recurrent ulcer
The incidence rate of recurrent ulcers (ulcers per person-years) and incidence rate ratios with 95% CIs were calculated.

2.18.7.2.6. Quality of life

The AVVQ was scored according to its manual and the SF-36 was be scored using Health Outcome Scoring Software 5.1 for the physical health and mental health dimensions, and all eight scales.

Quality of life measurements were presented using line plots for each study arm to illustrate trends in AVVQ score, SF-36 and EQ-5D-5L over time. A three-level mixed model was used to explore changes in HRQoL over time and assess the difference between the two intervention groups using grouped centre and participant as random effect.

2.19. Health economic analysis

2.19.1. Main within-trial economic analysis to 12 months

The health economic analysis was a 'within-trial analysis' comparing early versus deferred endovenous ablation for superficial venous truncal reflux in patients with venous ulceration. The primary outcome measure was the QALY at 12 months. The analyses were performed from the perspective of the NHS and personal and social services (PSS) in accordance with NICE methods guidance (211) within the 12 months. A cost-utility analysis was performed and no subgroup analyses were undertaken.

The total cost per participant aimed to only include items related to the endovenous ablation procedure or venous leg ulcer. The price year was 2015/16 and no discounting was applied as the follow up was 12 months. The study was reported according to guidelines for economic evaluation using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (225).

The results of the analyses were presented as estimates of mean incremental costs, effects, and, incremental cost per QALY. Sensitivity analysis were conducted using Monte-Carlo simulation to test the robustness of the results to alternative assumptions about model structure, assumptions and input data. The results of the base case and sensitivity analyses were presented as mean estimates and as cost-effectiveness acceptability curves (CEACs).

2.19.1.1 Data

Resource use data were collected in the CRF from the monthly telephone calls or clinic visits and from the postal HRQoL questionnaires. The healthcare resources collected in the study and the assumptions made in the economic analysis are presented in *Appendix 6 Table S1*.

The EQ-5D-5L questionnaire was administered to participants at baseline, six weeks, six months and 12-months post-randomisation to calculate the health state utilities.

2.19.1.2 Ulcer-related resource use

The analysis of resource use was designed to only include those that related to the ulcer as patients with leg ulcers are usually elderly with significant comorbidities and therefore may have many healthcare visits unrelated to the ulcer. Free text was used to collect the reasons for the use of healthcare resources and treatments received, which was reviewed to assess whether these were ulcer related. Pre-specified ulcer-related resource use included ulcer care,

skin care, leg care, venous procedures, angiography, infection, rehabilitation, DVT and related key words (see *Appendix 6 Table S1*).

Total health care costs were tabulated but only ulcer related resource use was included in the total cost per participant. It was assumed that all district nurse visits, primary care visits, physiotherapy and occupational therapy were definitely or probably ulcer related. Any inpatient or day-case admissions, or outpatient consultations costs relating to non-ulcer related resource use, were also excluded from the mean cost per participant, as well as out of pocket expenses and time lost from usual activities.

2.19.1.3 Unit costs

Resource use costs were calculated by multiplying resource use by unit costs obtained from England and Wales Healthcare Resource Group (HRG) costs, published literature, and manufacturers' list prices for catheters and disposable kit (*Appendix 6 Table S2*).

2.19.1.4. Handling of missing data

The extent and pattern of missing data were assessed to decide how to handle the missing data. Costs and EQ-5D-5L index were set to zero after the date of death. The base-case analysis only used complete cases in an ITT analysis. A complete case was defined as completing all the EQ-5D® questions at baseline, six weeks, six months and 12 months, and did not withdraw from the study before 12 months.

In the sensitivity analysis, multiple imputation using chained equations by regression ensured '*missingness at random*' (226). This technique considers missing costs as predictable from the observed data, plus or minus a random error. If participants were lost to follow-up, the costs were imputed at each month following the loss, with imputation of the EQ-5D-5L index if this was missing. Rubin's rules were used to analyse ten imputed datasets, and this was considered sufficient to give stable results allowing for Monte-Carlo error (226).

2.19.1.5. Cost-effectiveness analysis

Five sensitivity models were constructed:

1) Complete cases with bootstrap standard errors and cross-walk EQ-5D-5L tariff (Base case, Model 1)

2) Complete case with bivariate normal standard errors and cross-walk EQ-5D-5L tariff (Model 2)

3) Multiple imputation with bivariate normal standard errors and cross-walk EQ-5D-5L tariff (Model 3)

4) Complete case with bootstrap standard errors and EQ-5D-5L tariff estimated by Devlin et al. (206) (Model 4)

5) Per-protocol analysis, based on Model 1 which excluded patients with protocol deviations related to their treatment (Model 5)

QALYs were estimated for each participant to 12-months as the area under the curve of EQ-5D-5L index values. The ICER was calculated, and the probability that early ablation was more cost-effective than deferred ablation was estimated at different cost-effectiveness thresholds using two methods.

The base-case analysis used bootstrapping to estimate the confidence intervals, with 1000 Monte Carlo resamples with replacement. The base-case economic analysis uses the crosswalk tariff (209) which is an algorithm that maps the EQ-5D® 5-level responses to the three-level responses, and then values those health states using the original EQ-5D® 3-level tariff developed by Dolan et al. (210). This tariff was available from the EuroQol group website and was recommended by NICE at the time of these analyses (227).

Bivariate normal regression has been suggested as a method to account for variation between the study sites (for example, patient case-mix, clinical practice, and unit costs). This approach was used to estimate the mean total QALY per participants and the difference in mean total costs, including the baseline EQ-5D-5L in the QALY regression Monte Carlo resamples (Manca et al., 2005). Direct regression approach models costs and QALYs as separate dependent variables, each with error terms following normal distributions (228). For the bivariate normal regression, the differences in cost and differences in QALYs between the treatment arms were estimated using a system of seemingly unrelated regression (SUR) equations (229). With this approach, the cost for each individual is assumed to be linearly related to the randomised treatment variable and an error term, and the QALY for each

individual is assumed to be linearly related to the randomised treatment variable, baseline EQ-5D and an error term. The major difference between SUR and direct regression is that the error terms for costs and QALYs in the SUR are assumed to be correlated, so that they follow a bivariate normal distribution with zero means and a specific covariance matrix so that the cost and effects equations are related through their error terms. This is advantageous to direct regression as it allows modelling of costs and effects, whilst also allowing alternate sets of covariates in the two equations to be included. It also allows correlations to exist at participant level, between costs and effects, which improves the efficiency of the estimation process when this correlation is different from zero (230) (231).

The bootstrap was used only for the analysis of complete cases, as bootstrap combined with multiple imputation can be very computationally demanding. The model for multiple imputation therefore also the bivariate normal approach (232).

As an alternative sensitivity analysis, an alternative five-level tariff recommended by Devlin et al. was used on the complete case, bootstrap model (206).

2.19.2. Longer term follow-up (3.5 years) within-trial economic analysis

The health economic 'within-trial analysis' up to five years (median of 3.5 years) was also performed from the perspective of the NHS and personal and social services (PSS) in accordance with NICE methods guidance over a three-year horizon (211). Again, a cost-utility analysis was performed, and no subgroup analyses were undertaken. The primary outcome measure was the QALY at a median of 3.5 years.

The total cost per participant aimed to only include items related to the endovenous ablation procedure or venous leg ulcer. The price year was 2017/18 and discounting was applied at 3.5% according to UK Government guidelines (233).

Resource use items in hospital and community care related to the treatment of venous ulceration, adverse events or complications are collected by case note review and questionnaires completed at baseline and at a median of 3.5 years. Resource use was multiplied by UK unit costs obtained from published literature, NHS reference costs, and manufacturers' list prices to calculate overall costs. Participant costs and time lost from work and usual activities was reported as a secondary analysis (societal perspective).

2.19.2.1 Data

Resource use data were collected in the CRF from at one timepoint between October 2018 and March 2019 by telephone calls to the participants or by case note review. The EQ-5D-5L was also collected at this timepoint. Utilities and QALYs were calculated from the EQ-5D-5L questionnaire using the cross-walk tariff recommended by NICE and, as a sensitivity analysis, alternative published tariffs (206).

2.19.2.2 Ulcer related resource use

Unlike the 12-month outcomes, only resource use related to the treatment of venous ulceration, adverse events or complications was collected by case note review and participant recollection as it was unfeasible to collect total resource use from participant recollection. The healthcare resources collected in the study were classified into four categories and the associated assumptions made are presented in *Appendix 6 Table S3*.

2.19.2.3 Unit costs

Resource use costs were calculated by multiplying resource use by unit costs obtained from England and Wales Healthcare Resource Group (HRG) costs, published literature, and manufacturers' list prices for catheters and disposable kit (*Appendix 6 Table S4)*. Currency conversions from GBP (£) to euros (€) were calculated to the rate applicable at the time of conversion (£1 = €1·1273; exchange rate 20 September 2018).

2.19.2.4 Handling of missing data

The extent of missing data was assessed and appropriate methods to handle missing data were applied. As stated below, multiple imputation was not performed.

2.19.2.5. Cost-effectiveness analysis

Unlike the 12-month outcomes which utilized the complete cases, this analysis was performed using mixed (normal longitudinal) models to account for the differing follow-up time of each participant, which can cause complex censoring patterns (and therefore a complete base analysis would not work as too much data would be lost). This allowed all available data to contribute to the total mean cost estimate, avoiding the need to censor participants with missing data at various timepoints. Sensitivity analysis were carried out to test the robustness of results to alternative assumptions, although multiple imputation was unnecessary because of the mixed model. The bivariate normal longitudinal model would be too complex and was also not performed.

The difference in mean total cost was then estimated over the 3 years in the base-case, and 4 years and 5 years in sensitivity analyses, and discounting was applied. Confidence intervals for these estimates were calculated using the lincom command in STATA.

As per the 12 month outcome, the utility indices were calculated from the EQ-5D-5L questionnaire using the NICE recommended "crosswalk" tariff (209), and as a sensitivity analysis, an alternative published tariff was employed (206). The index values were also then analysed using a linear mixed model, with age, ulcer size and ulcer duration as control variables and used to calculate the mean and difference in QALYs. The incremental cost-effectiveness ratio was calculated and compared to UK decision making thresholds at the time of analysis (£20,000 – 30,000 in the United Kingdom).

Uncertainty in mean costs and QALYs were quantified using bootstrapping. There were no planned subgroup analysis.

Three sensitivity models were constructed:

1) Bootstrap standard errors and cross-walk EQ-5D-5L tariff (Base case, Model 1)
2) Bootstrap standard errors and EQ-5D-5L tariff estimated by Devlin et al. (206) (Model 2)
3) Per-protocol analysis, based on Model 1 which excluded participants with protocol deviations related to their treatment (Model 3)

2.20. Database and data processing

2.20.1. InForm™ database
The trial database utilised was InForm™ - an electronic data-capture system built around an Oracle database which allows the research nurses at each site to enter data remotely. A computer-generated audit trail records who entered the data, plus the date and time of entry plus any subsequent amendments. InFormTM sits on a server behind a firewall connected to the Imperial College Storage Area Network (SAN) and is managed by the Imperial College Information and Communication Technologies (ICT) team, which ensures the data is regularly backed up.

2.20.2. Data queries and cleaning
The InFormTM system includes pre-specified range checks and validation rules for data entry to help ensure data accuracy. During the recruitment and follow-up phases, inconsistent, implausible or missing data were queried with the local sites. Quality control checks were

performed on the first two CRFs and participant questionnaires entered at each site to ensure the accuracy of data input and ensure that data entry processes had been understood. Ongoing data checks using source data verification were performed at each monitoring visit.

Following the data collection stage, the data was cleaned to ensure that missing or unknown values were labelled accurately, to flag inconsistent or spurious data. All comments were reviewed to ensure they did not conflict with the entered data. The primary endpoint, final ulcer healing dates, entered into the database were double checked by an independent data checker. All outstanding queries were resolved prior to the database hard lock.

2.21. Assessing impact of the EVRA trial

To assess any potential impact that the EVRA study may have on the management of ulceration worldwide, health professionals will be surveyed to determine the current management strategies. This methodology and results will be discussed further in *Chapter 3*, with further assessment post release of the trial results discussed in *Chapter 6*.

Chapter 3: Global Management of Leg ulceration – Service evaluation (pre EVRA results)

3.1 The requirement for a survey-based approach

The various guidelines that exist for the referral and management of chronic venous disease, including venous ulceration, are difficult to implement and often suffer from a lack of compliance due to lack of training or local funding models, or conflicting guidelines (111, 234, 235).

As it would be impossible to review and fully assess the management of venous disease worldwide due to logistical and funding constraints, surveying a sample of the vascular community is a suitable methodology (236).

3.2 Questionnaires as tool

Surveys have been used in clinical research since the 1800s. The advantages of this method are that the data is based on real-word observations, it is cheap to administer, uses a sample of the population to make inferences about the wider community and, therefore, assuming a suitable design, is likely to be representative. The main challenges are ensuring a high response rate and ensuring adequate completion (237).

A good research survey should be simple and appropriate for its use and demonstrate both reliability (i.e. the ability to produce results) and validity (i.e. measure what it intends to).

There are different methods by which validity (content, criterion and construct) and reliability (test retest, split half and interrator) can be achieved, and different types of survey require that methods be tailored as required – ultimately the validation process reduces bias and ensures quality data (238).

3.3 Global secondary care survey of venous leg ulceration management questionnaire – pre EVRA trial

3.3.1 Introduction

As discussed previously, standard care in the UK at the time of writing, utilises compression bandaging to heal the ulcer, followed by interventions to correct the reflux and prevent recurrence. This evidence-based practice is supported by the results of the ESCHAR trial, which showed that surgical intervention can reduce the rate of ulcer recurrence. The guidelines also recommend referral to a vascular service within two weeks of ulceration (10, 186).

Current venous ulceration guidelines in the USA were developed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system, which makes recommendations based on the quality of evidence, the harm/benefit ratio and patient preference (*Table 5*). These guidelines recommend further investigation by a specialist upon presentation with an ulcer and have a weak Grade 2, level C recommendation for the treatment of reflux prior to ulcer healing based on the results of some cohort studies (11, 155, 156).

Table 5 - GRADE recommendations based on level of evidence. Adapted with permission (11).

Grade	Description of recommendation	Benefit vs risk	Methodologic quality of supporting evidence	Implications
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burden, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burden, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burden, or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risk and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risk and burden	RCT*s with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefit and risk, and burdens; Risk, benefit, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; Other alternatives may be reasonable

Unfortunately guidelines can be difficult to implement and are not always followed, for example, Sheldon et al. found that the implementation of NICE guidelines is highly variable and is dependent on professional and financial support which can results in disparate care across the UK (240).

A 2005 UK survey of venous ulcer centres found that the organisation of care can be variable (241). Although this survey was carried out prior to the establishment of CCGs, a lack of standardisation still exists with respect to the management and referrals of patients with venous leg ulceration, especially as CCGs were in-part intended to enable local differentiation (110).

3.3.2 Aim

The aim of this section is to determine the standards of global management of patients with venous leg ulceration in secondary care prior to the publication of the EVRA RCT results.

3.3.3 Methods

An online, 26 question survey was created to evaluate the current global clinician management of venous leg ulceration. The survey was classed as a service evaluation according to the HRA decision tool (http://www.hra-decisiontools.org.uk/research/) and therefore did not require HRA /ethical approval.

A short, simple design was utilized with a voluntary, opt-in consent by completion of the questionnaire completed by an anonymous link via Qualtrics Survey Platform (https://imperial.eu.qualtrics.com/jfe/form/SV_3TTDnB4SWCXCaC9) which is quick to load so not to affect completion rates. The survey used adaptive questioning and was distributed over three pages. The survey allowed respondents to review and change their answers via the 'back' button and was equipped with a completeness check before the questionnaire could be submitted however this could be overruled. Cookies were used to assign a unique user identifier to each respondent computer and set on each page. Jeavons et al. (1998) found that respondents stopped completing surveys when asked to supply their email address or complete a complex grid design. In 2013, Couper et al. found that this remained true and that a simple grid design can improve response rates and, therefore, the grid collecting intervention choice was placed near the end of the questionnaire and the email address for follow-up was placed as the last question (242) (243).

A focus group of three clinicians were asked to identify important and appropriate questions to include. The questions posed requested the number of patients with leg ulceration seen and referral times from primary to secondary care, whether Ankle brachial pressure index (ABPI) and duplex ultrasound assessments were performed, compression therapy utilised, and whether endovenous interventions or surgery were performed and if so the methods and timing of these. Respondents were also asked their opinion on whether intervention affects healing and recurrence and whether the results of the EVRA study would influence their practice. The survey is detailed in *Appendix 7*.

The questionnaire underwent five rounds of revision after initial review by vascular surgeons, and was piloted externally on a further five surgeons to confirm appropriate content and face validity (244). A meta-analysis of response rates from web-based surveys showed that higher

response rates can be obtained by pre-contacting participants, personalising the correspondence and following up respondents with a reminder (245). Pre-contacting was not used as distribution was via societies, but correspondence was personalised wherever possible and respondents were followed up with a reminder email.

The survey was circulated by the following societies to approximately 15000 participants using the following national and international mailing lists:

- American Venous Forum (AVF)
- American College of Phlebology (ACP)
- Veith Symposium
- Venous-lymphatics World International Network foundation, ONLUS
- Vascular Society of Great Britain & Ireland (VSGBI)
- Venous Forum UK
- Venous news / Charing Cross Symposium
- The Australasian College of Phlebology (ACP)
- International Union of Phlebology (UIP)
- Venous Association of India (VAI)
- European Venous Forum (EVF)
- European Society of Vascular surgery (ESVS)
- Turkish / Mexican / Baltic mailing lists

Reponses were collected over a four-month period (November 2017 to February 2018). The results have been reported in accordance with the CHERRIES checklist for a survey type service evaluation. (Eysenbach, 2004)

Microsoft Excel was used to determine normality and analyse the results. The results did not follow a normal distribution and were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text was categorised by common themes for the ease of interpretation.

3.3.4 Results

3.3.4.1 Responses

799 responses were received from 86 countries with an approximate response rate of 5%. As some respondents did not answer all questions, the total number of responses are stated in each section.

Table 6 details the baseline characteristics of the respondents and *Figure 10* depicts the global responses by country.

Table 6 - Respondent baseline characteristics. Adapted from (239)

Characteristic	Respondents (n=799)
Age (years)	**(n=798)**
Under 30	10 (1.3%)
30 to 39	113 (14.2%)
40 to 49	222 (27.8)
50 to 59	280 (35.1)
Over 60	173 (21.7%)
Clinician Type	**(n=799)**
Vascular surgeon	552 (69.1%)
Phlebologist	115 (14.4%)
General surgeon	51 (6.4%)
Dermatologist	10 (1.3%)
Family medical practitioner	3 (0.4%)
Specialised vascular nurse	15 (1.9%)
Other	53 (6.6%)
Gender	**(n=798)**
Female	112 (14.0%)
Male	681 (85.3%)
Prefer not to say	5 (0.6%)
Region of Practice*	**(n=799)**
United Kingdom	128 (16.0%)

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Europe (excluding UK)	331 (41.4%)
North America	172 (21.5%)
Central America	16 (2.0%)
South America	48 (6.0%)
Australasia	19 (2.4%)
Africa	12 (1.5%)
Asia	59 (7.4%)
Middle East	14 (1.8%)
Area of Care	**(n=798)**
Primary / Community	147 (18.4%)
Secondary / district general/ county hospital	232 (29.1%)
Academic / teaching	316 (39.7%)
Other	102 (12.8%)

*Albania (n=3) , Argentina (n=11), Australia (n=15), Austria (n=6), Bangladesh (n=1), Belarus (n=4), Belgium (n=9), Bosnia (n=1), Brazil(n=26), Bulgaria (n=5), Canada (n=5), Caribbean (n=3), Central America (n=6), Chile (n=3), Colombia (n=3), Costa Rica (n=1), Croatia (n=1), Cyprus (n=1), Czech Republic (n=4), Denmark (n=5), Ecuador (n=2), Egypt (n=3), El Salvador (n=1), Estonia (n=1), Finland (n=1), France (n=11), Georgia (n=2), Germany (n=21), Greece (n=12), Honduras (n=2), Hong Kong (n=1), Hungary (n=1), Iceland (n=1), India (n=27), Indonesia (n=1), Iran (n=1), Ireland (n=8), Israel (n=4), Italy (n=49), Japan (n=5), Jordan (n=2), Kenya (n=1), Kosovo (n=1), Kuwait (n=1), Latvia (n=7), Lebanon (n=3), Lithuania (n=10), Luxembourg (n=1), Mexico (n=14), Moldova (n=2), Morocco (n=1), Nepal (n=1), Netherlands (n=15), New Zealand (n=4), Nicaragua (n=2), Norway (n=7), Pakistan (n=2), Panama (n=1), Paraguay (n=1), Peru (n=2), Poland (n=15), Portugal (n=18), Romania (n=2), Russia (n=22), Saudi Arabia (n=1), Senegal (n=1), Serbia (n=4), Slovakia (n=4), Slovenia (n=4), South Africa (n=3), South Korea (n=11), Spain (n=23), Sri Lanka (n=1), Sweden(n=20), Switzerland (n=6), Taiwan (n=3), Thailand (n=4), Tunisia (n=1), Turkey (n=9), United Arab Emirates (n=2), Uganda (n=1), Ukraine (n=9), United Kingdom (n=128), USA (n=153), Missing (n=19)
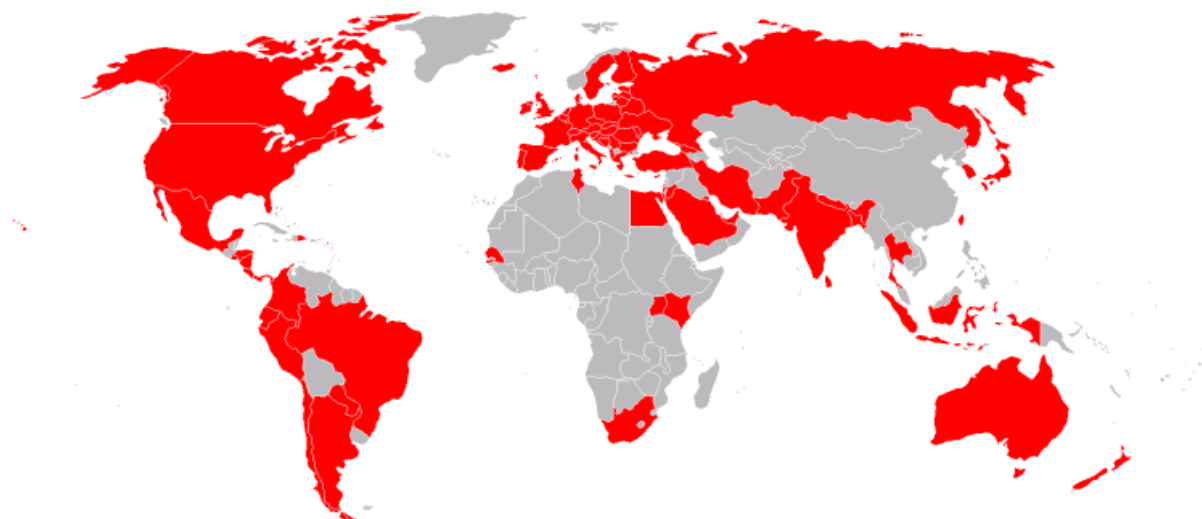
Figure 10 – Respondents by country

3.3.4.2. Patients seen each month with open leg ulceration

Table 7 details the number of patients seen with open leg ulceration each month. Globally, and within the UK, the median number of patients with open ulceration each month was reported as 10 (IQR 5 to 20).

Table 7 - The number of patients with open ulceration seen each month globally

Patients with open ulceration seen / month	n = 797
Less than 10	334 (41.9%)
10 to 30	381 (47.8%)
More than 30	71 (8.9%)
Not known	11 (1.4%)

3.3.4.3. Average referral time from primary to a specialised vascular service

Table 8 details the average referral time from primary care to a specialised vascular service. Globally, the overall median referral time was six weeks (IQR 2 to 12). In the UK, the median referral time was eight weeks (IQR 6 to 12).

Table 8 - Average wait time for patients with chronic venous leg ulceration to be referred from primary care / GP to a specialised vascular centre

Average referral wait time	n = 797
Less than six weeks	248 (31.1%)
six weeks to six months	251 (31.5%)
More than six months	42 (5.3%)
Not known	256 (32.1%)

3.3.4.4. ABPI performed or arranged

Figure 11 details whether an ABPI was performed or arranged at first visit, both globally and within the UK. Of the global respondents, 61% typically performed an ABPI. Those who didn't reported that they relied on a physical exam (palpable pulses), review of symptoms, or results of a duplex ultrasound. UK respondents were slightly more likely to perform an ABPI.
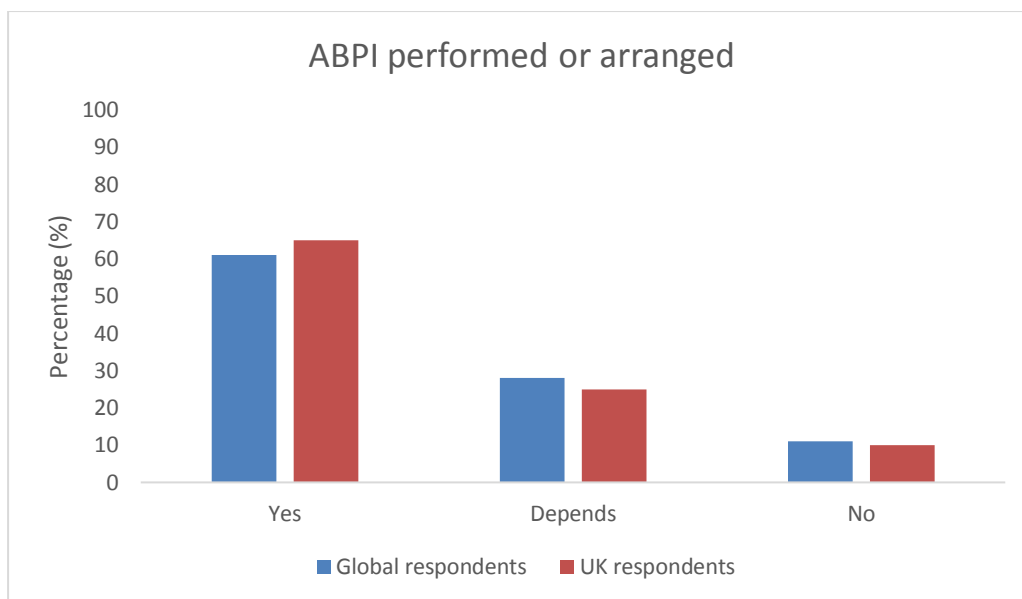
Figure 11 - APBI performed or arranged at first visit (global n=786, UK n=127)

3.3.4.5. *Venous duplex performed or arranged*

Figure 12 details whether venous duplex was performed or arranged for patients presenting with a leg ulcer. Of the global respondents, 84% typically performed a venous DUS on those presenting with a leg ulcer. Those who did not, stated that they mostly replied on an arterial assessment or physical exam. UK respondents were slightly more likely to use other factors to decide whether they would perform a venous duplex.
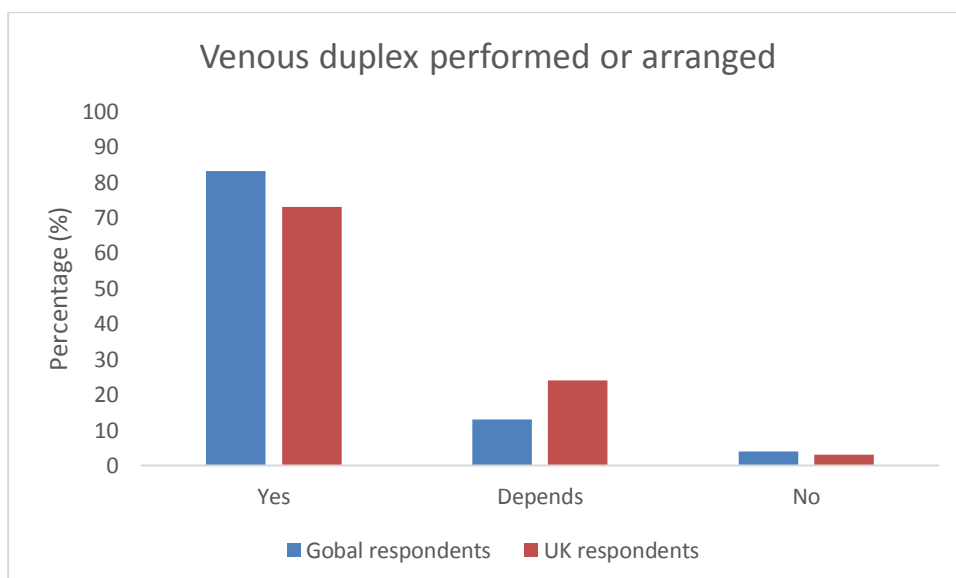
Figure 12 - Duplex ultrasound performed or arranged on patients presenting with a leg ulcer (global n=793, UK n=127)

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3.3.4.6. Compression therapy prescribed

Globally, 95% of the respondents prescribed compression if not contraindicated, with 51% prescribing compression bandages, 31% prescribing stockings and 18% prescribing other types (*Figure 13 & Figure 14*). The results were similar in the UK, although bandages were the preferred compression type.
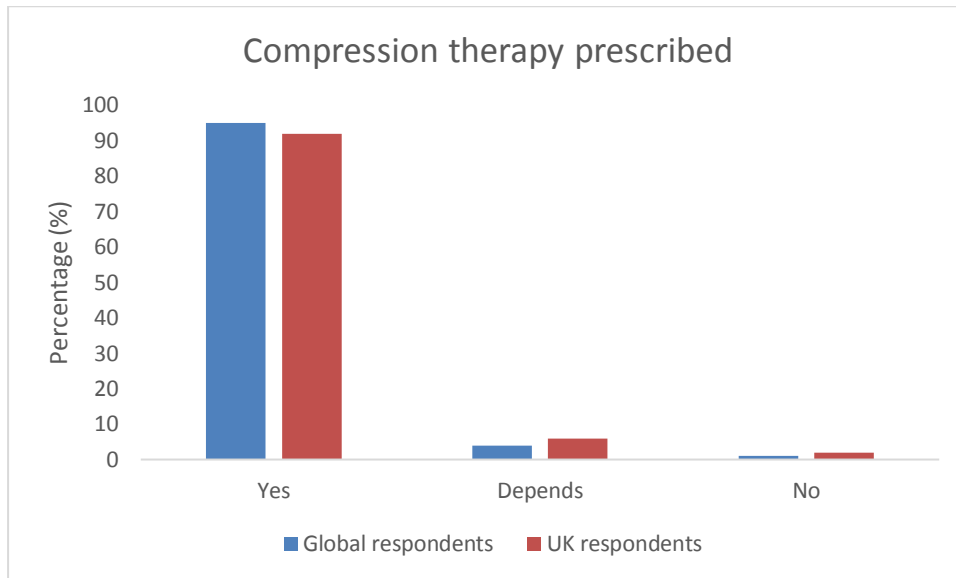
Figure 13 - Compression prescribed if not contraindicated (global n=793, UK n=127)
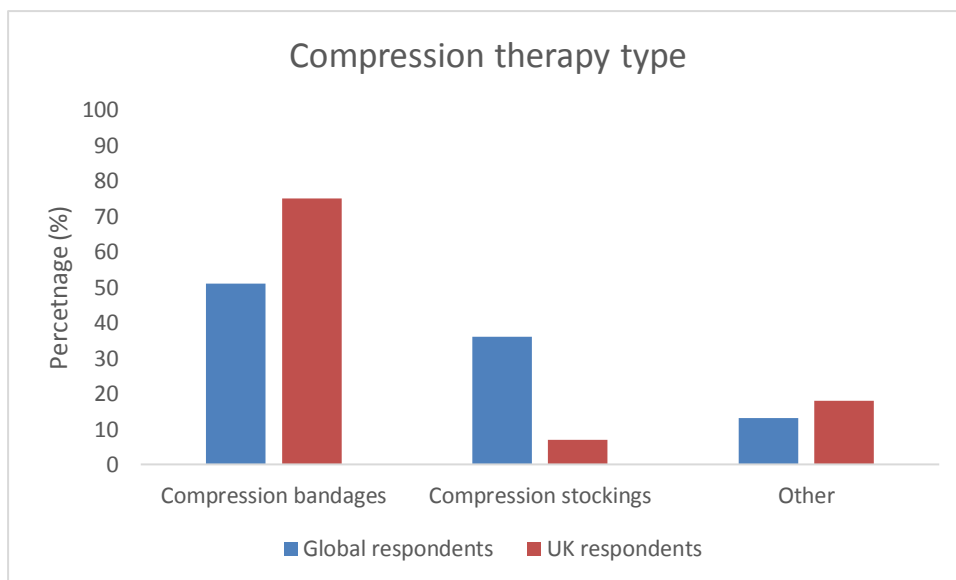
Figure 14 - Compression type prescribed (global n=776, UK n= 123)

3.3.4.7. Opinion on whether the treatment of superficial truncal venous reflux by endovenous intervention or surgery benefit ulcer healing in patients with chronic venous ulceration

78% of the global respondents thought that the treatment of superficial truncal venous reflux by endovenous intervention or surgery benefits ulcer healing in patients with chronic venous ulceration *(Figure 15)*. Less of UK respondents reported that they thought the intervention benefits ulcer healing and a higher proportion thought it depends on other additional factors.
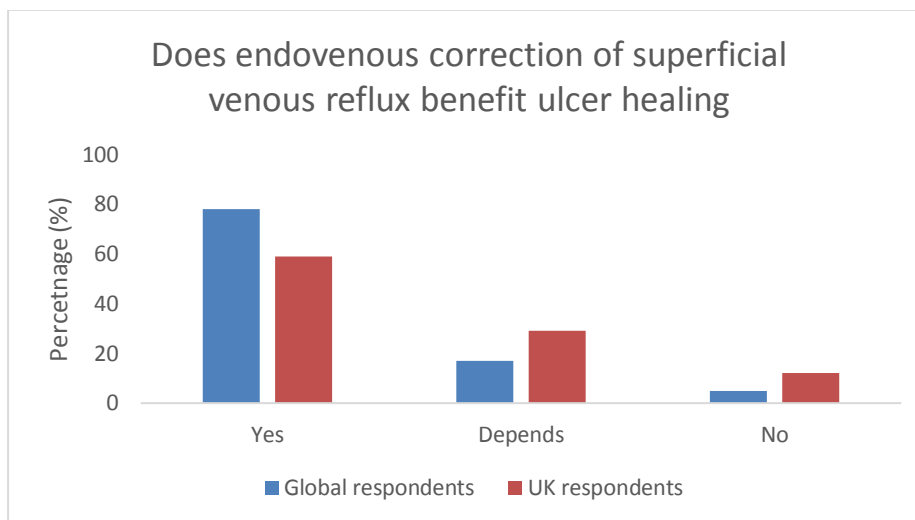
Figure 15 - Opinion on whether treatment of superficial truncal venous reflux by endovenous intervention or surgery benefits ulcer healing in patients with chronic venous ulceration (global n=787, UK n = 126).

3.3.4.8. Opinion on whether the treatment of superficial truncal venous reflux by endovenous intervention or surgery benefit ulcer recurrence rates in patients with chronic venous ulceration

80% of the global respondents thought that the treatment of superficial truncal venous reflux by endovenous intervention or surgery benefits recurrence rates in patients with chronic venous ulceration (*Figure 16*). A slightly higher proportion of the UK respondents thought intervention can benefit ulcer recurrence.
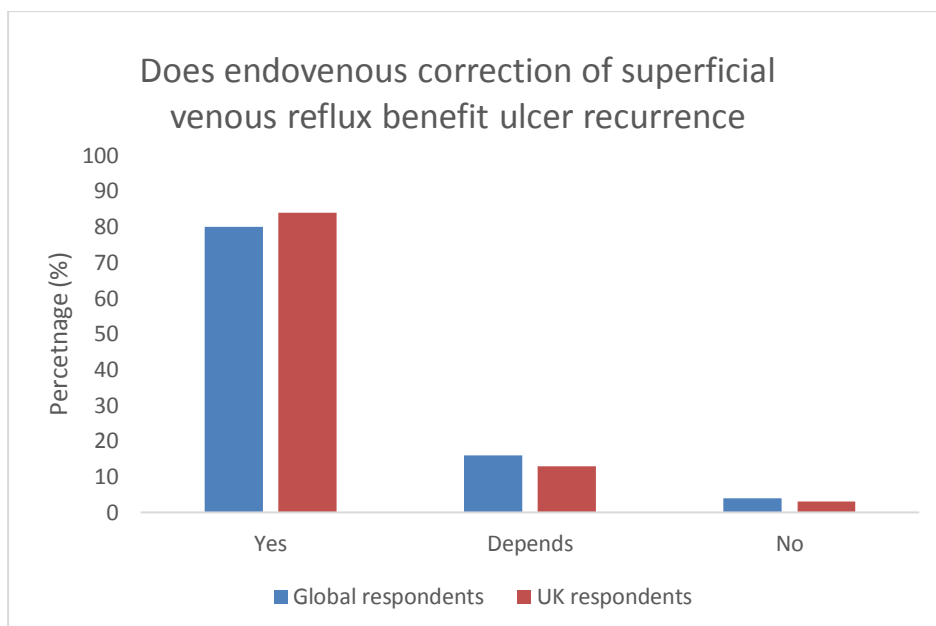
Figure 16 - Opinion on whether treatment of superficial truncal venous reflux by endovenous intervention or surgery benefits recurrence in patients with chronic venous ulceration (global n=787, UK n = 126).

3.3.4.9. Intervention timing

Figure 17 shows the timing of endovenous intervention or surgery. Of the global respondents, 59% reported that they usually perform endovenous intervention or surgery prior to ulcer healing, with 19% after and 19% depending on the individual circumstances (3% do not perform intervention). In the UK, 50% of respondents usually performed endovenous intervention or surgery prior to ulcer healing, with 24% after and 20% depending on the individual circumstances (6% do not perform intervention).
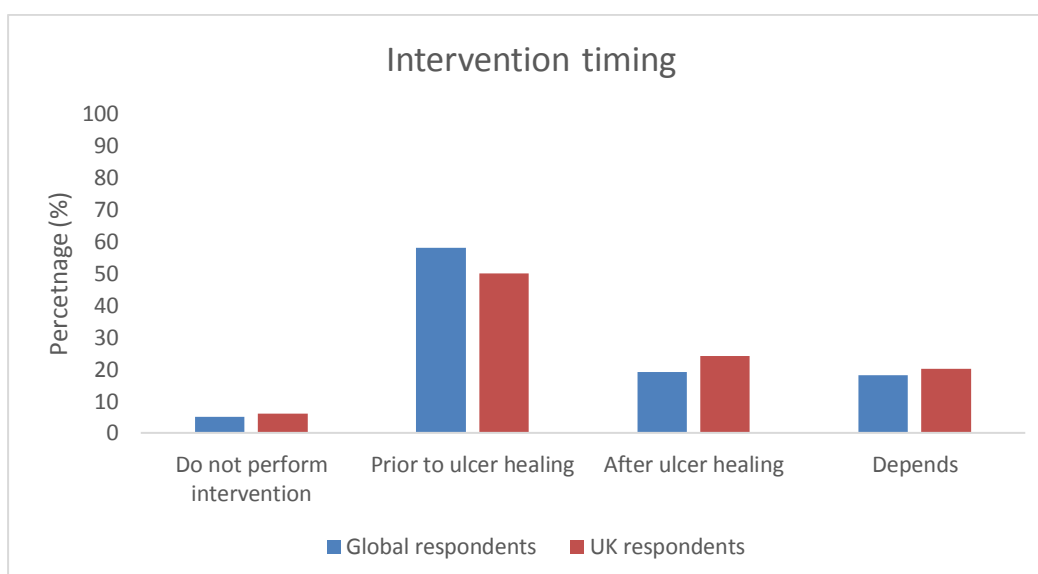
Figure 17 - Timing of endovenous or surgical interventions (global n=785, UK n= 125). Adapted from (239)

3.3.4.10. Intervention strategy preferences

Globally, endothermal ablation alone was the most utilised method of intervention, followed by a combination of foam and endothermal, followed by foam alone and open surgery. MOCA, glue and combinations of these were the least utilised *(Table 9)*.

Table 9 - Interventional strategies employed to treat truncal superficial venous reflux in patients with active leg ulceration. Adapted from (239)

Interventional Strategy	Always	Mostly	Sometimes	Never	Total (n)
Foam alone	3.5%	8.4%	51.2%	36.9%	549
Endothermal ablation alone	14.6%	38.3%	34.7%	12.5%	583
Mechanochemical Endovenous Ablation alone	1.2%	5.0%	22.2%	71.6%	514
Glue alone	0.2%	1.2%	15.9%	82.7%	504
Open surgery alone	4.2%	17.0%	43.4%	35.4%	553
Foam and Endothermal ablation combination	9.7%	22.3%	40.6%	27.4%	547
Foam and Mechanochemical Endovenous Ablation combination	0.9%	2.6%	16.9%	79.5%	508
Foam and Glue combination	0.0%	1.2%	10.9%	87.9%	506
Open surgery and foam	1.5%	6.7%	33.5%	58.3%	537
Other method not stated:	2.1%	3.2%	5.8%	88.9%	380

Globally, cost and clinician preference appear to be the driver to use foam alone and open surgery, whereas guidelines were the driver for utilising endothermal ablation alone, foam alone or a combination of the two. Clinician preference drove using endothermal alone and endothermal ablation and foam combination, whereas patient preference drove those using endothermal ablation alone and foam alone *(*

Table 10*)*.

Table 10 - Reasons for interventional strategy preference. Adapted from (239) .

Interventional Strategy	Cost	Guidelines	Clinician Preference	Patient Preference	Availability of Equipment	Other	Total (n)
Foam alone	17.7%	16.9%	27.1%	15.8%	13.1%	9.4%	679
Endothermal ablation alone	6.7%	28.8%	30.2%	14.7%	15.9%	3.8%	894
Mechanochemical Endovenous Ablation alone	10.9%	8.8%	27.5%	13.1%	23.4%	16.3%	320
Glue alone	10.9%	8.7%	20.7%	13.5%	22.6%	23.6%	275
Open surgery alone	12.9%	15.5%	33.1%	12.5%	14.9%	11.0%	562
Foam and Endothermal ablation combination	7.4%	19.6%	38.5%	12.4%	13.8%	8.4%	623
Foam and Mechanochemical Endovenous Ablation combination	10.8%	7.3%	27.7%	8.5%	19.6%	26.2%	260
Foam and Glue combination	11.7%	7.2%	22.5%	7.6%	20.9%	30.1%	249
Open surgery and foam	13.8%	13.6%	34.3%	11.7%	11.7%	14.9%	376
Other method not listed:	6.5%	10.3%	24.3%	7.5%	5.6%	45.8%	107

3.3.4.11. Assessing technical success

Of 647 global respondents, 73% reported performing a duplex ultrasound post intervention to assess technical success *(Figure 18).* Those who didn't usually cited lack of resources or that they truly believe in their technique. Some reported that performing a post-interventional duplex was dependant on whether symptoms had resolved, whether the ulcer had healed or not, or if any complications were apparent. In the UK, only 38% of respondents (n=105) stated that they perform a duplex ultrasound post intervention to assess technical success. All of those who did only performed one duplex in total, usually between one and six weeks.

Of those who performed a post-interventional duplex (n=473), 48% performed only one, 16% performed two, 9% three and 3% four and 6% more than four *(Figure 19).* With respect to

timings (n=473), 42% performed the first post-intervention duplex one-week post intervention, 32% between one and six weeks, and 9% post six weeks (*Figure 20*).
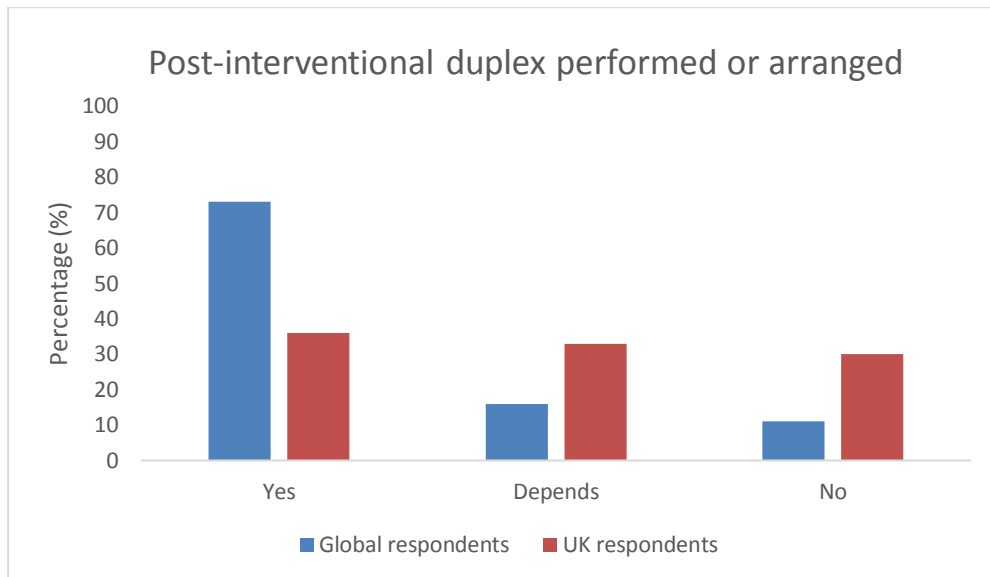
Figure 18 - Percentage of respondents who performed or arranged a post-interventional duplex ultrasound (global n=647, UK n = 105)
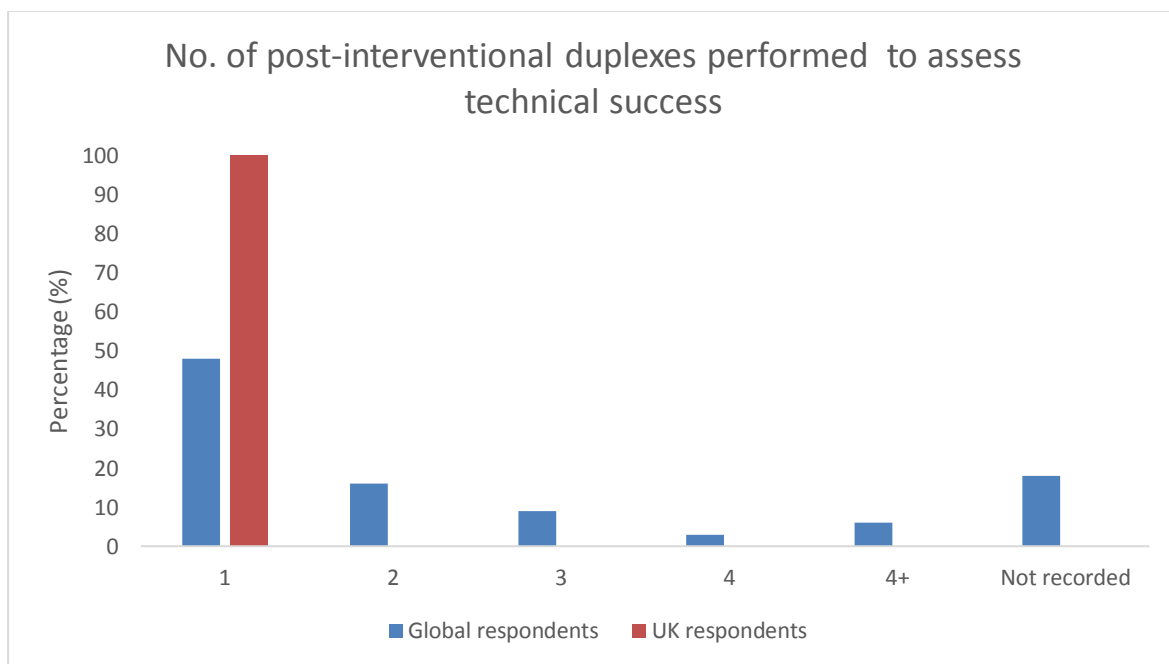
Figure 19 - Number of post interventional duplex ultrasounds performed by clinicians to access technical success who perform a post-interventional duplex (global n=473, UK n=25)
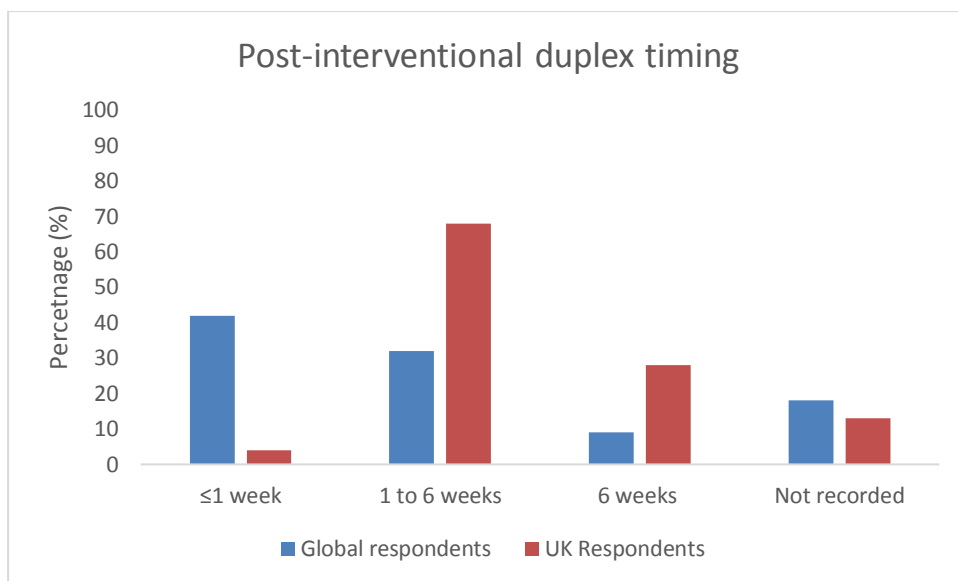
Figure 20 - Timing of post-interventional duplex ultrasound scan by clinicians who perform a post-interventional duplex (global n=473, UK n=25)

3.3.4.12. Importance of outcome measures

Global outcome measures of intervention were ranked by clinician perceived importance (1 = most important; 6 = least important) and are summarised in *Table 11*.

Table 11 - Intervention outcome measures ranked in order of importance (n=582)

Outcome	Rank					
	1	2	3	4	5	6
Ulcer healing	66.5%	26.1%	6.4%	0.3%	0.5%	0.2%
Ulcer recurrence	8.9%	41.9%	41.6%	5.3%	1.7%	0.5%
Quality of life	22.2%	26.6%	38.5%	9.9%	2.2%	0.5%
Cost	1.0%	3.0%	7.2%	48.9%	36.3%	3.4%
Number of reinterventions	0.7%	1.9%	5.3%	34.5%	55.3%	2.2%
Other (specify)	0.7%	0.3%	1.0%	0.9%	3.9%	93.1%

Ulcer healing was the most important intervention outcome measure cited, followed by preventing ulcer recurrence and optimizing the quality of life of patients whereas cost and

number of reinterventions were considered less important. Most respondents did not specify 'other' important outcomes but those who did have been categorised in *Table 12*.

Table 12 – Other important outcome measures specified

'Other important outcome measures'	n	%
Complications	5	11.9%
Patient satisfaction with cosmetic results	15	35.7%
Return to work / social	4	9.5%
Symptom relief	7	16.7%
Technical success	5	11.9%
Other	6	14.3%
No 'other' specified	541	
Total	**583**	

3.3.4.13. Changing practice

Figure 21 shows the percentage of respondents who reported they would change practice with respect to the timing of intervention if the EVRA study results were to show that early intervention improves ulcer healing; Of 681 global respondents, 46% stated that they would now treat prior to ulcer healing, 37% stated that they would not change practice but already treated prior to ulcer healing, 6% would not change practice and currently treat after ulcer healing and 11% said it would depend on other factors.

Similarly, in the UK, of 114 respondents, 50% respondents stated they would change their practice 36% stated that they would not change practice but already treated prior to ulcer healing, 4% would not change practice and currently treat after ulcer healing and 10% said it would depend on other factors.
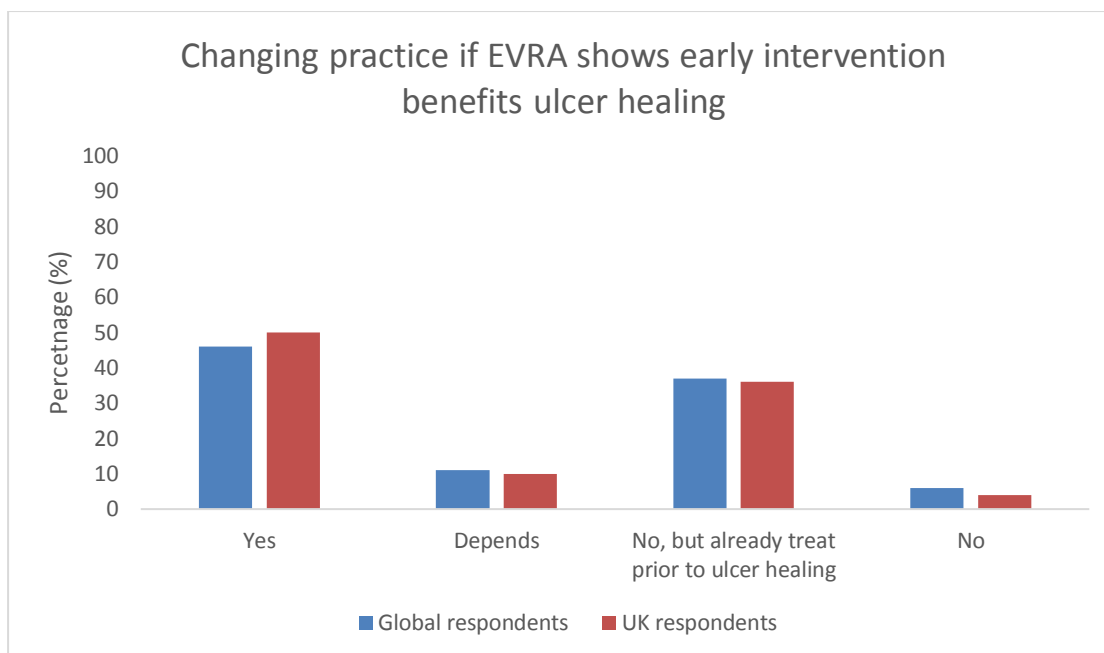
Figure 21 – Percentage of respondents who would change their practice if the EVRA trial showed that early ablation improves ulcer healing (global n= 681, UK n=114)
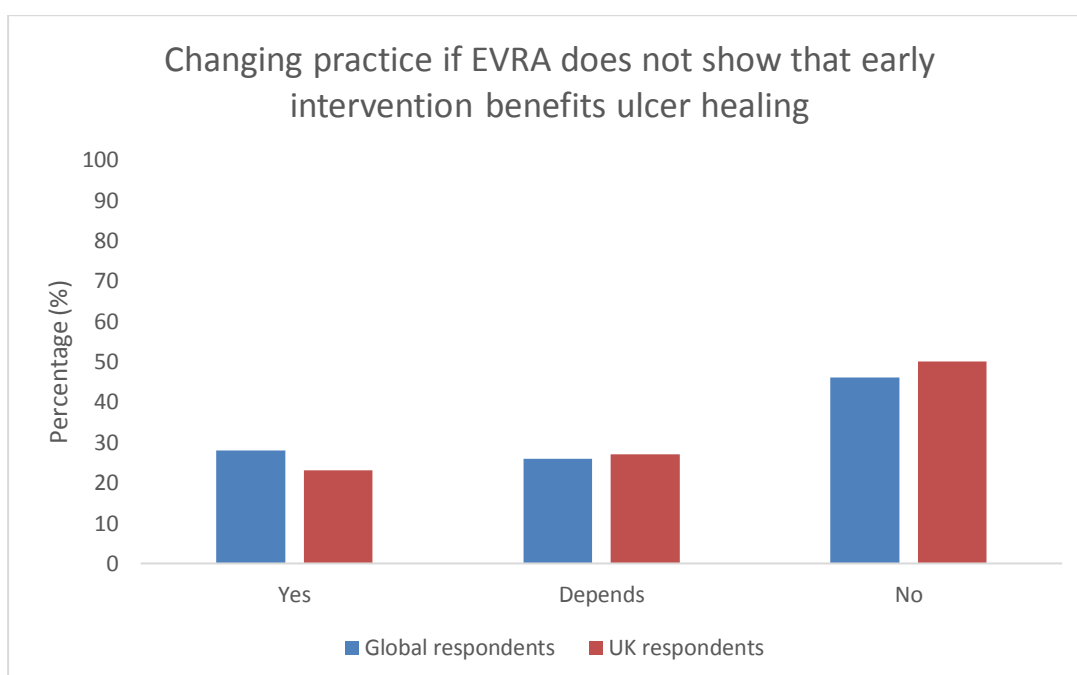
Figure 22 - Percentage of respondents who would change their practice if the EVRA trial showed that early ablation does not improve ulcer healing (global n= 676, UK n=114)

Of 676 global respondents, 46% said a negative result would not change their practice with respect to timing of intervention. Reasons cited were that they were confident early ablation does improve ulcer healing, and it is already proven to reduce recurrence. 26% said changing practice would depend on other factors, such as individual sub-group analyses, quality of life improvements and personal assessment of the overall quality of trial. 28% said they would

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most likely change practice – for reasons such as insurance no longer covering the interventions or the aim to be less aggressive in treatment (*Figure 22*).

3.3.4.14. Barriers to changing practice

Table 13 lists the barriers cited by the global respondent clinicians to changing practice if they wished to do so. The majority (78%) did not list any barriers or stated that there were none. Cost was the biggest barrier to practice change, followed by insurance, kit availability and local guidelines or procedure reimbursements.

Table 13 - Barriers to changing practice

Reason	Respondents (%) n =799
N/A or none	622 (77.9%)
Cost	67 (8.4%)
Insurance / reimbursement	35 (4.4%)
Kit availability / training	26 (3.3%)
Local Guidelines / CCGs / NHS	19 (2.4%)
Primary / secondary care integration & referral issues	11 (1.4%)

3.3.5 Discussion

The survey results show that the referral and management of venous ulceration is disparate globally, despite level 1 evidence that surgical correction of truncal superficial venous reflux can reduce the risk of recurrence and level 2 evidence that endovenous ablation can improve ulcer healing (143). The results echo the findings of van der Velden et al. who also demonstrated global variation in the management of patients with superficial venous disease (246) which is likely a result of the difficulty of implementing guidelines, coupled with variation in the uptake of guidelines (247, 248).

It should be noted that there was no discrimination between new and recurrent ulcers in the survey responses, but if we take the UK data as an example, the median number of patients seen per month in the UK was reported to be 10 (IQR 5 to 20), which would indicate that a small proportion of patients with leg ulceration are actually referred to secondary care, (based on the assumption that there are approximately 278 000 patients with open leg ulcers, and that each vascular surgeon in the UK (approximately 425) sees 120 patients each year (65). Indeed, Hospital Episode Statistic (HES) data (2016/17) notes only 3,736 admissions for people with varicose veins and ulceration as the primary diagnosis. It is likely that a proportion of patients referred to secondary care are being seen by other multidisciplinary teams, such a dermatologists, podiatrists and pain clinics (249).

The overall median referral time was six weeks (IQR 2 to 6). In the UK, the median referral time from primary care to a specialised vascular service was eight weeks (IQR 6 to 12) despite the NICE guidelines recommending referral within two weeks (10). These appear to be unjustified treatment delays which may impact on ulcer healing times (68) and, indirectly, to the important clinical, quality of life and financial burden of venous leg ulceration.

Only 61% of the global respondents reported that they always perform an ABPI at the first visit. In the USA only just over half of respondents performed an ABPI, despite the American guidelines recommending that an ABPI is performed on all venous leg ulcer patients (Grade 1, level B) (11, 17, 114). While in the UK, the NICE guidance for varicose veins does not advocate performing an ABPI (in contrast to the CKS for venous leg ulcers which does), 65% of the UK respondents reported always performed an ABPI (10, 111).

Both US and UK guidelines advocate the use of DUS to confirm the diagnosis and extent of truncal reflux and indeed the majority of respondents performed a venous DUS on those presenting with a leg ulcer. Those who did not, stated that they mostly relied on an arterial

assessment or physical exam, which might be deemed suboptimal. Perhaps surprisingly, nearly three quarters of the respondents perform duplex ultrasound post intervention to assess technical success, despite this not forming part of standard care in the UK or USA (191). The majority of respondents reported that usually perform only one duplex post intervention, but interestingly a third reported routinely performing more than one, with a small proportion performing more than four. Although not examined in detail by this survey, it is likely that this practice is related to the availability of funding to perform these assessments in different healthcare systems (e.g. nationalised versus private). With respect to timing of the first post-intervention duplexes, the majority were performed within one week or between one and six weeks.

Of the global respondents, nearly all prescribed compression if not contraindicated as advocated by the American guidelines (11). In contrast, the UK guidelines only recommend the use of compression bandages if interventional treatment is not suitable or post intervention.

The interventional strategies utilised varied greatly. Endothermal ablation alone appeared to be the most utilised method, followed by a combination of foam and endothermal, followed by foam alone and open surgery. MOCA, glue and combinations of these were the least utilised. The UK recommends endothermal ablation as the first-line treatment, but kit availability varies amongst Trusts, with foam widely utilized due to its low cost. Indeed, cost appears to be the driver to use foam alone and open surgery, whereas guidelines were the driver for utilising endothermal ablation alone, foam alone or a combination of the two.

Of 785 global respondents, only three fifths reported that they usually perform endovenous intervention or surgery prior to ulcer healing, despite American guidelines recommending that intervention is performed in active ulceration to improve ulcer healing (Grade 2, level C) and prevent recurrence (Grade 1, level B). Interestingly in the UK, half of the respondents treat prior to ulcer healing, despite no level 1 evidence suggesting a benefit to healing. It is perhaps likely this is due to clinician perception that intervention improves ulcer healing that once patients are referred, intervention is performed to prevent recurrence.

It is possible that the proportion of patients treated prior to ulcer healing will change once the results from the EVRA trial are published. Indeed, nearly half of the respondents stated that they would change practice with respect to intervention timing if the EVRA study results show that early intervention improves ulcer healing, with surprisingly only a small number of

clinicians reporting barriers to changing practice. There is no doubt that issues exist with respect to referrals from primary to secondary care, resulting in a number of patients not receiving interventional treatment despite the evidence that this can prevent ulcer recurrence (110, 143, 186, 248). It will be interesting to see if the results of the EVRA trial influence practice in reality.

Ulcer healing was the most important outcome of superficial intervention cited, followed by ulcer recurrence and the quality of life, with cost playing a less important role, perhaps indicating more patient centered care globally, perhaps especially in those countries with private health insurance.

The study is limited by the response rate. It was impossible to determine the exact response rate, as some surgeons were listed across several society mailing lists and were even listed several times within the same lists with different email addresses. It is estimated that the response rate was at least 5% and although this is a low rate, there were 799 overall responses from 86 countries. In the UK, 128 vascular surgeons responded to the survey; as there are approximately 450 consultant vascular surgeons registered with the Vascular Society of Great Britain & Ireland, nearly a third of the total vascular surgeons responded. As not all the surgeons will specialise in venous ulceration it is likely the representation is higher than anticipated (250).

Other potential limitations include selection bias for only targeting society members, although it would be almost impossible to contact clinicians who were not members of these societies for data protection reasons. Response bias may have existed due to internet access, and to language barriers as the survey was only circulated in English (so only English-speaking health professionals could complete) and it is likely language barriers would have existed limiting comprehension of the questions in some cases. It is also possible that the respondents did not answer truthfully but the anonymous completion link option should have limited this.

3.3.6 Conclusion

This survey highlights that global leg ulcer care is inconsistent, with a clear need to develop a robust pathway for patients with leg ulceration. The reasons for the variation are multifactorial, including local funding availability, access to healthcare, differences in training and education, and inconsistent referral pathways coupled with a lack of level 1

evidence that early intervention improves ulcer healing. Resurveying the participants after the publication of the EVRA results may give an indication of the impact of the RCT.

3.4 UK primary care survey of venous leg ulceration management and referral - pre EVRA trial

3.4.1. Introduction

The majority of patients with venous leg ulceration are treated in primary care by community, district and practice nurses, with general practitioners as the first point of contact. However, although we know district nurses can spend as much as 50% of their time caring for CVU, there is a lack of centralised data regarding the number of patients treated in primary care and who is providing the care (103). This, coupled with patients retaining their notes so that they are not readily available for the different health care providers to access, makes it difficult to ascertain the current standards of leg ulcer management.

Studies looking at the provisions of care within the UK during the late 1990s found high variability in the type of care practitioner that first examined the patient, how a venous ulcer was diagnosed and the training provided for both administering compression therapy and measuring the ABPI (249, 252). Despite attempts to improve the model of care since then, it appears that, in reality little has changed (248).

More recently, the venous leg ulcer CKS was designed to inform primary care practitioners on the management and referral of patients with venous leg ulceration (111) and is aligned with the NICE guidelines for varicose veins with respect to referral to a vascular service (10).

Unfortunately, most CCGs have individual leg ulcer referral pathways which leads to great geographic variation in terms of trigger points for (e.g. ulcer duration, wound reduction) and where to refer (e.g. vascular service, leg ulcer service, tissue viability). Furthermore, some CCGs may not recommend referral to a vascular service despite the evidence-based guidance and therefore patients are largely treated in the community with disparate care.

The Department of Health used to collect data on who referred patients to community nurses, with their last report in 2004 detailing that over half of referrals were made by general practitioners, with 22% being made by hospital staff and 28% by other sources (249). There

is little available data on the vascular referral rates of patients with venous ulceration to a vascular surgeon, but *Table 14* suggests that less than 3% of patients diagnosed with venous ulceration are referred to a vascular surgeon, so there is significant work to do to increase this proportion. Indeed HES data from 2015/2016, found that of 33,460 admissions for varicose vein related procedures, 1,978 were coded as having leg ulcer, which is a low proportion compared to the numbers of patients with active leg ulcers estimated from Guest et al. (65, 253).

Table 14 - Referral Rates 2001 to 2006 for patients with venous leg ulceration from the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) databases (249)

	CPRD	THIN
Patients with a VLU diagnosis	16920	14568
Patients with a VLU diagnosis who receive any a referral of any kind within 12 months	6287 (37%)	4195 (29%)
Patients with a VLU diagnosis who received a leg ulcer related referral* (as % of all patients)	2075 (12%)	2347 (16%)
Patients with a VLU diagnosis who received a leg ulcer referral to a vascular surgeon* (as % of all patients)	304 (1.8%)	380 (2.6%)

* Dermatologist/ dermatological clinic/dermatology special interest GP; Vascular surgeon; Podiatrist/chiropodist/foot care; Specialist leg ulcer or tissue viability services; Pain management/ pain clinic/ pain management nurse; Nursing/ community/practice/district/community matron

In summary, it is difficult to determine how patients are managed and referred from Primary care currently in the UK.

3.4.2. Aim

The aim of this section is to determine the standards or referral and management of patients with venous leg ulceration in primary care prior to the release of the EVRA RCT results.

3.4.3. Methods

An online, 14-question survey was created to evaluate the current UK management of venous leg ulceration in primary care. The survey was classed as a service evaluation according to the HRA decision tool (http://www.hra-decisiontools.org.uk/research/) and therefore did not require HRA /ethical approval.

The questions probed the number of leg ulcer seen per month, the personnel responsible for managing leg ulcers, whether and ABPI and/or duplex ultrasound is performed and the

process for arranging the latter, and whether they prescribed compression bandaging for those not contraindicated. They were asked about the referral process for patients with open leg ulceration and timelines if so, and whether the EVRA results would amend practice with respect to referrals processes. The survey was reviewed by a community/public health nursing lecturer involved in the NHS national wound care strategy program. Additionally, it was reviewed by two independent district nurses and one vascular nurse specialist and underwent five rounds of revisions before being piloted externally on a further five primary care professionals to confirm appropriate content and face validity (244). All were deemed to have expert knowledge of venous leg ulceration in addition to an understanding of research methodology. The questionnaire is detailed in *Appendix 8*.

As per the global clinician survey, a short, simple design was utilized, with a voluntary, opt-in consent by completion of the questionnaire by an anonymous link via Qualtrics Survey Platform (https://www.qualtrics.com) which was quick to load. The survey used adaptive questioning and was distributed over four pages. The survey allowed respondents to review and change their answers via the 'back' button and was equipped with a completeness check before the questionnaire could be submitted however this could be overruled. Cookies were used to assign a unique user identifier to each respondent computer and set on each page.

The survey was circulated in the UK only to approximately 800 participants via local and national networks (the wound research network and the tissue viability society), including social media to primary care professionals, including GPs, community nurses and district nurses.

Reponses were collected over a four-month period (November 2017 to February 2018). Microsoft Excel was used to determine normality and analyse the results. The results did not follow a normal distribution and were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text was categorised by common themes for the ease of interpretation.

3.4.4. Results

90 responses were received, an approximate response rate of 10%. *Table 15* details the respondent breakdown of primary care giver type. As some respondents did not answer all questions, the total number of responses are stated in each section.

Table 15 - Respondent primary care giver type. Two respondents did not complete this question. Adapted from (251).

Care giver type	Respondents (n=88)
GP	2 (2.3%)
Practice nurse	19 (21.6%)
Community nurse	10 (11.4%)
District nurse	4 (4.6%)
Tissue viability nurse	37 (42.0%)
Other	16 (18.2%)

3.4.4.1. Patients seen each month with open leg ulceration

Table 16 details the number of patients seen with open leg ulceration each month. The median number of patients seen was 20 (IQR 5 to 30).

Table 16 - The number of patients with open ulceration seen in primary care institutions each month. Adapted from (251).

Patients with ulceration seen / month	n = 90
Less than 10	27 (30.0%)
10 to 30	26 (28.9%)
More than 30	26 (28.9%)
Not known	11 (12.2%)

3.4.4.2. Caregiver who primarily manages leg ulcers in the respondent centre

Figure 23 details the caregiver who manages the leg ulcers in the respondent centre.
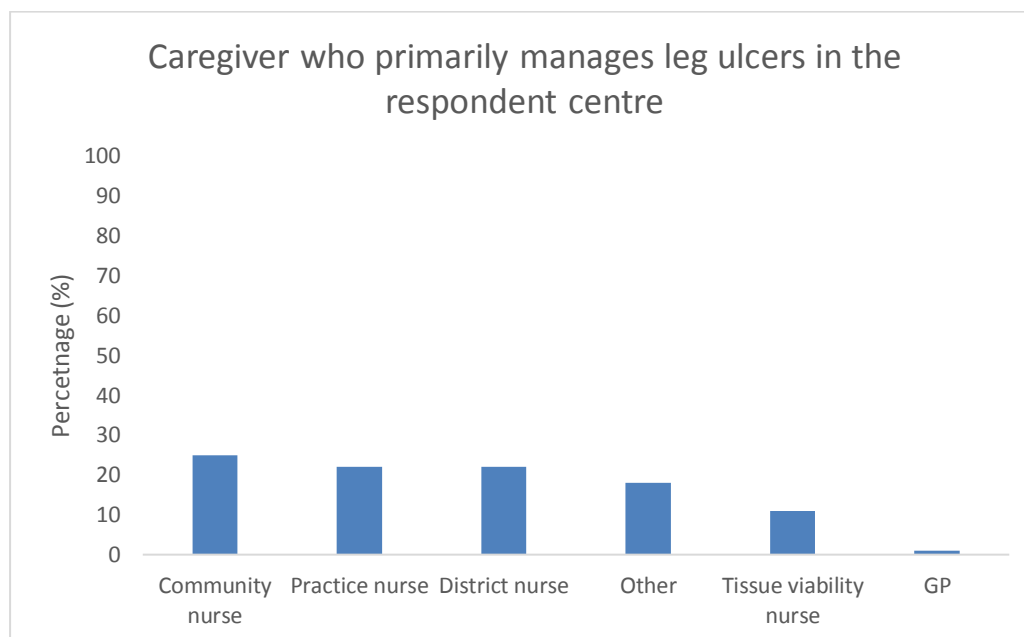
Figure 23 - Caregiver who primarily manages leg ulcers in the respondent centre (n=90). Adapted from (251).

3.4.4.3. ABPI performed or arranged

Of 90 respondents, 54% reported that they performed or arranged an ABPI at first visit, 25% reported that they that they do not perform an ABPI at first visit as they do not have the capacity / time, or do not have access to a Doppler and 21% reported that it depended on factors such a time and capacity or patient history (*Figure 24)*.
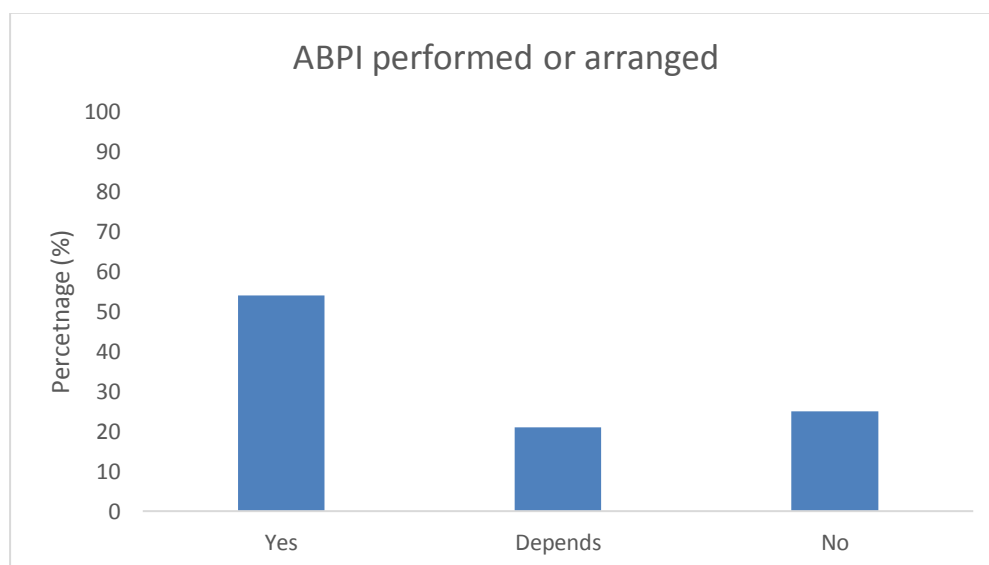
Figure 24 - APBI performed or arranged at first visit (n=90)

3.4.4.4. Venous duplex performed or arranged

Figure 25 details whether venous duplex was performed or arranged for patients presenting with a leg ulcer. Of the 90 respondents, 13% performed a venous DUS on those presenting with a leg ulcer, whilst 62% did not and 25% said it depended on other factors.
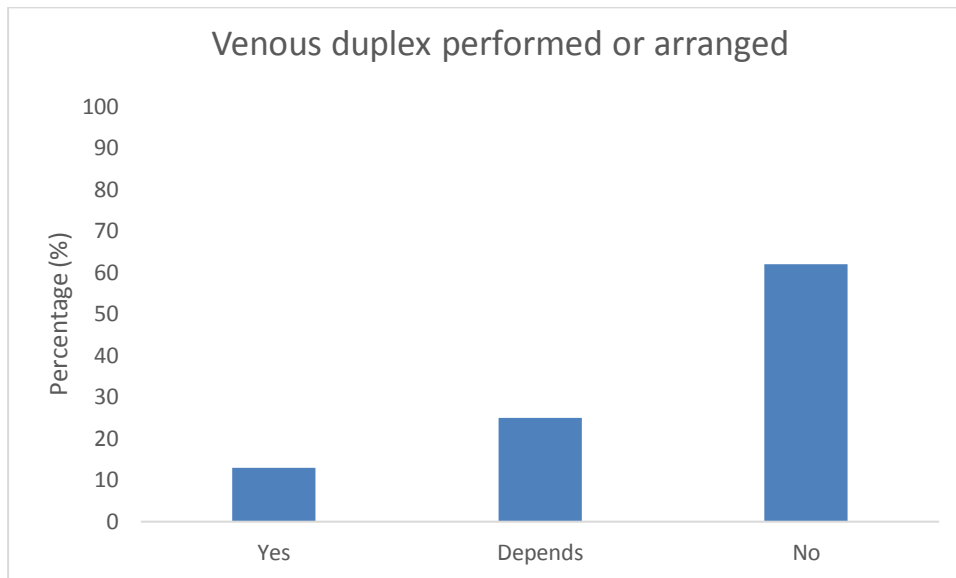
Figure 25 - Duplex ultrasound performed on patients presenting with a leg ulcer (n=90)

Of those who usually perform a duplex ('yes' or 'depends'), 24% refer to a provider to perform a duplex which they interpret and use to manage the patient, 48% refer to a provider who performs and interprets the duplex, 15% perform and interpret the duplex themselves which they use to manage the patient, and 12% refer to a provider to perform a duplex which they use to refer the patient for management.

3.4.4.5. Compression therapy offered

82% reported offering compression therapy to patients with open leg ulceration, with 10% stating it is depended on the ABPI or patient choice, and 8% stated that they did not offer compression therapy due to lack of training and capacity (*Figure 26*).
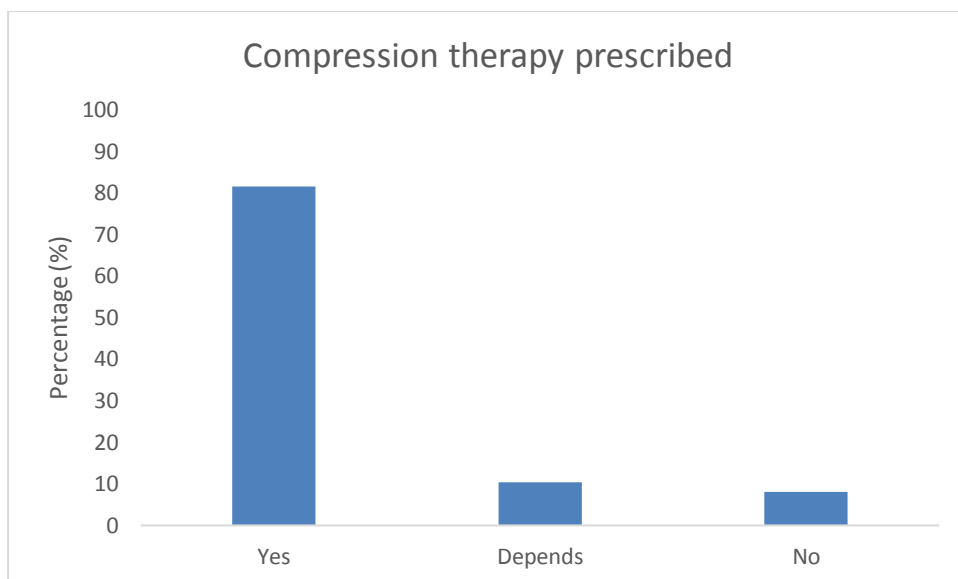
Figure 26 - Compression therapy offered (n=90)

Of 78 respondents who offer compression therapy, 72% reported the use of compression bandages, 4% compression stockings and 24% use others such as hosiery (*Figure 27*).
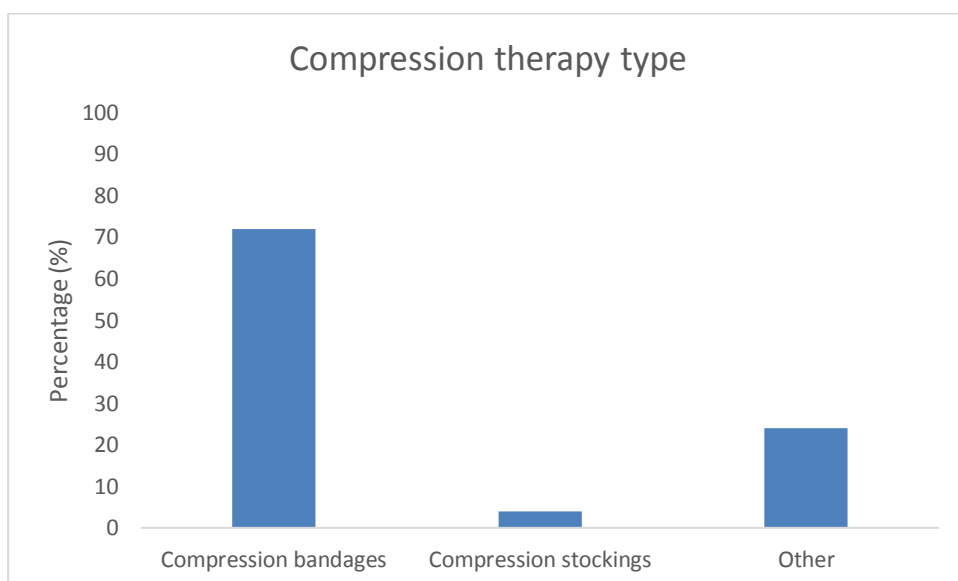
Figure 27 - Type of compression therapy used (n=78)

3.4.4.6. Referral to a vascular service

Of 68 respondents, 32% reported that they routinely refer patients with open leg ulceration to a vascular service, with 53% stating that this would depend on certain factors, such as if the patient was responding to compression, or GP agreement and 14% reported that they never refer (*Figure 28*).
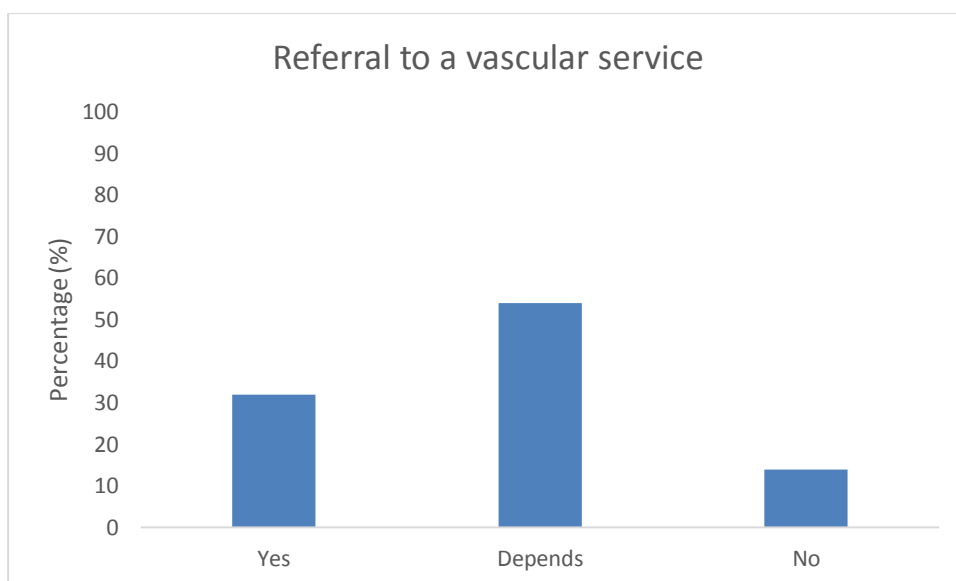
Figure 28 - Percentage of patients referred to a vascular service (n=68)

Those who referred to a vascular service, reported that the median time for referral was four weeks (IQR 2 to 8), with the breakdown as illustrated in *Table 17*.

Table 17 - Average wait time for patients with chronic venous leg ulceration to be referred from primary care / GP to a specialised vascular centre. Adapted from (251).

Average referral wait time / weeks	n = 68
Less than six weeks	25 (36.78%)
Six weeks to six months	23 (33.82%)
More than six months	8 (11.76%)
Not known	12 (17.65%)

3.3.4.7. Changing practice

Of 72 respondents, 57% stated that they would change practice with respect to referral if the EVRA study results were positive, with 8% stating they would not and 35% stating that this would depend on other factors such a vascular service capacity and clinical commissioning group (CCG) approval to refer (*Figure 29*).
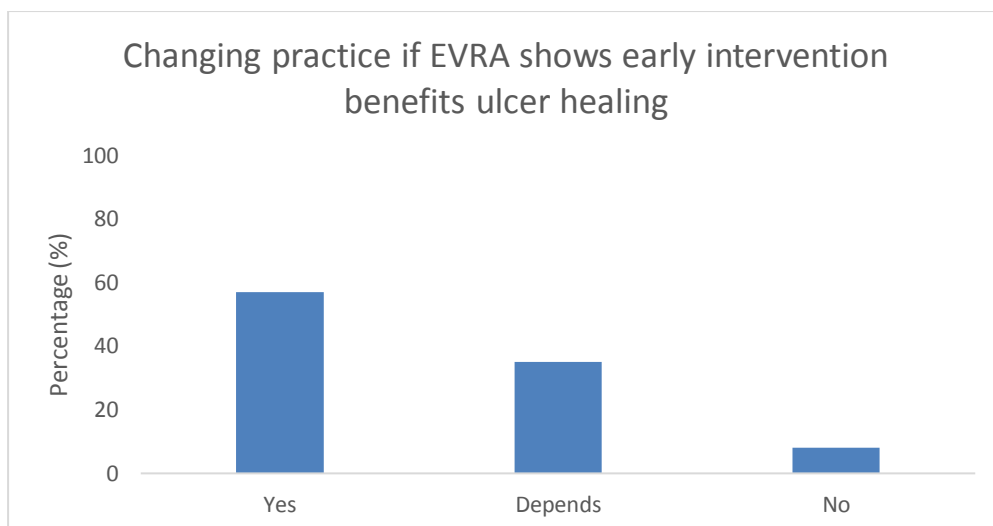
Figure 29 - Percentage of respondents who would change their practice if the EVRA trial showed that early ablation improves ulcer healing (n=72)

Of the 72 respondents, 14% said they would change practice if the EVRA results did not show that early intervention improves ulcer healing, 26% said changing practice would depend on other factors, such as whether they thought it would help recurrence, and 60% of respondents said a negative result would not change their practice with respect to referral (*Figure 30*).
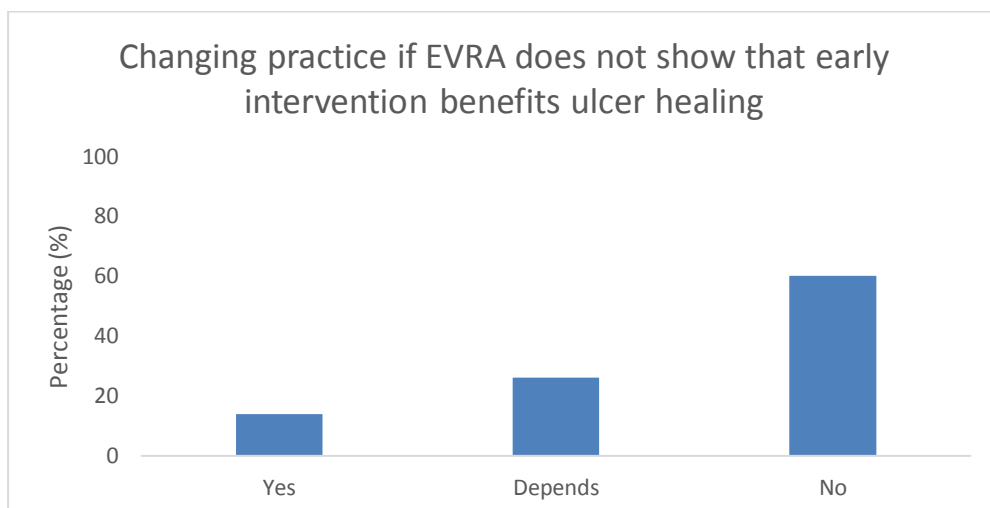
Figure 30 - Percentage of respondents who would change their practice if the EVRA trial showed that early ablation does not improve ulcer healing (n=72)

3.3.4.8. Any additional comments provided

The comments were reviewed for recurrent themes and found that lack of training in how to manage patients with venous leg ulceration was frequently highlighted, especially relating to the cause of leg ulcers, as these are often treated as a simple wound (with dressings) or as a lymphatic problem that would not be addressed by venous surgery. A high variation in skill

level, usually resulting from lack of funds and resources at certain clinics, was also highlighted - as was a need for clarity regarding referral and treatment pathways. Most often, direct referrals to vascular centres can only be made by the GP, and not by the district or tissue viability nurses, and there was a belief that there were waiting times for clinic appointments once patients were referred to vascular centres.

Some respondents raised conflicting issues, such as secondary care consultants encouraging conservative over interventional treatment once referred, or surgeons only accepting referrals for ulcers with an underlying arterial cause. Interestingly, some respondents highlighted that the recent CQUIN for wound assessment (107) had led to the community and district teams not being able to cope with the increased demands for secondary care referrals.

3.4.5. Discussion

The survey results demonstrate disparity in the management of patients with venous ulceration in the primary care setting, coupled with a lack of clear guidelines and evidence to guide the referral and treatment of these patients. This is perhaps, unsurprising, given the variety of health professionals who care for leg ulcer patients.

Surprisingly just over half of the respondents stated that they performed an ABPI, which is higher than the 16% noted by Guest et al. (65) but this could be due to responder bias. Regardless, this demonstrates non-compliance with the NICE CKS guidance and as 82% reported routinely prescribing compression, this is potentially worrying, although it is possible that an ABPI has been performed previously or elsewhere. This practice also indicates that a substantial proportion of patients with arterial disease not being diagnosed and urgently referred for investigation. The survey found as did Guest et al, that a proportion of patients are not placed into compression at all, despite this being the gold standard of wound management.

Unsurprisingly, only a small number of respondents reported that they routinely perform a DUS, which reflects either the lack of availability of a DUS, lack of training in primary care or lack of resources. Although performing or arranging a DUS would allow the diagnosis of venous disease, due to the need for these to be performed by a highly trained specialist it is unlikely this skill would be prevalent in a community setting. Unfortunately, this will

inevitably result in practitioners having limited knowledge regarding a patient's underling condition, resulting in delays to any necessary treatment.

The median number of patients with active leg ulceration reported to be seen in primary care was double those reported to be seen by secondary care clinicians (20 versus 10), which may emphasise the lack of referrals to vascular centres, and indeed, only a third of respondents reported routinely referring patients with open leg ulceration to a specialist vascular service and half of the respondents stating that the decision would depend on different factors, such as the length of current treatment and the condition of the ulcer. Unfortunately, the survey did not capture other services or departments that the patients might be referred to, but it is clear that the NICE guidelines and CKS (109, 111) are not being followed with respect to the referral of patients with non-healing leg ulcers, despite most CCGs allowing this (254). This is not dissimilar to many other specialities where it has been demonstrated that it can be difficult to implement of NICE guidance due to barriers such as poor clinician engagement and financial pressures (255). Free text comments support this finding detailing a need for clarity regarding the referral pathway in addition addressing the issues of who can and cannot refer patients. With district, community and practice nurses predominantly managing care it is interesting that responses highlighted the need for a GP to send the referral. Responses also revealed a belief that referral to a vascular specialist may not always be helpful due to a perception of conservative treatment plans and lengthy waiting times for clinic appointments. For those who do routinely refer patients, interestingly the reported perceived time for a referral from primary to secondary care was half that than reported by the secondary care clinicians in the UK, although it is difficult to determine how precise these estimates are. Encouragingly over half of respondents stated that a positive outcome in the EVRA trial would result in a change in practice, however a third stated this would depend on other factors such as the capacity of local vascular services so it is difficult to determine how possible this would be.

The two-year CQUIN scheme 2017-2019 (107) was launched in November 2016 with the intention "*to deliver clinical quality improvements and drive transformational change*" by incentivising community services to improve the assessment of wounds and result in better patient and system outcomes. This approach does not encourage referrals to secondary care, but as a holistic wound assessment is likely to increase the time spent with each patient and it is possible that if capacity is reached in the community, clinics' referrals to secondary care may increase. The House of Commons held a debate in November 2017 entitled, '*Improving*

the standard of wound care in the NHS' chaired by Rt Hon. Lord Hunt of Kings Heath, which highlighted the need for strategies to improve wound outcomes (256), with a follow-up meeting held in early 2018 to formulate a strategic plan. It will be interesting to see if these initiatives impact leg ulcer outcomes in practice or affect the number of referrals to secondary care.

The main limitation of this study was the low response rate, and a low representation of GPs, which is a result of the difficulty in accessing the contact details of primary care professionals. It is possible that the survey is subject to responder bias of those who have a special interest in leg ulceration and therefore it is unclear if the data collected represents national practice, although the previously published data by Guest et al, however would suggest that it does.

Overall the findings of this study reflect the challenges of community health professionals and highlighted potential barriers for change. These include, the ability for community and district nurses to refer directly to a vascular service, the requirement for improved communication between primary and secondary care, and clarity of treatment and referral pathways, as well as the funding and training required in primary care in order to administer ABPIs and perform a full wound assessment. Although improving the understanding of front-line staff is essential, it is also imperative that they are equipped with the appropriate resources to apply this understanding to practice. If improvements are not made, nursing time constraints and financial pressures faced by local CCGs will continue to cause care inequalities for CVU patients.

Now the EVRA study results have been published providing evidence that early intervention for venous reflux results in an improvement in healing. it would be interesting to re-survey a larger number of primary care practitioners to gain an understanding of the impact of the publication.

3.4.6. Conclusion

The primary care survey showed a diversity of assessment, referral and treatment pathways with a clear need to develop evidence-based guidelines for patients with leg ulceration and clear referral pathways into second care so that the underlying cause can be determined, and

intervention performed as necessary. Robust, level 1 evidence may improve practice, but this may only occur in practitioners with specialist interest in leg ulceration and those who will engage in recently published research. To reduce delays, it is imperative that more is done to increase the awareness and understanding of current best practice guidelines with regards to referral as the two-week referral timeline outlined by NICE is often not met.

Chapter 4: EVRA main trial results up to 12 months – Clinical

4.1. Screening and recruitment

Screening for recruitment commenced in October 2013 and was completed at the end of September 2016, with 6555 patients screened for potential inclusion the trial. Of these, 6105 failed inclusion / exclusion criteria or declined to participate, with 450 (7.4 per cent) randomised. The reasons for exclusion are presented in the CONSORT Diagram, *Figure 31*.

Figure 31 - CONSORT diagram of the study population. The cumulative number of participants who had withdrawn, died, had failed to comply with the protocol or had been lost to follow-up by each time point are presented (205)

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al*. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

4.2. Study site recruitment

Initially, ten sites were activated for recruitment, each with a recruitment target of 24 participants / month. A further 11 sites were activated as it became apparent that recruitment was slower than anticipated, and in October 2015 the target per site was reduced to 13 participants / month, adding an additional eight months to the recruitment period. In total 21 sites participated in the study, with one site failing to recruit any participants.

4.3. Follow-up

The last recruited participant completed follow-up on 28th September 2017. 402 participants attended the 12-month follow-up, with a median follow-up time for both the deferred and early ablation groups of 365 days (364-370). The cumulative number of participants who had withdrawn, died, failed to comply with the protocol or been lost to follow-up can be seen in *Figure 31.*

4.4. Ineligible participants

Six ineligible participants were randomised, with two in the early ablation group (one with leg ulceration of greater than six months duration and one with no active ulceration) and four participants in the deferred ablation group (two participants with leg ulceration of greater than six months duration, one with no active leg ulceration and one participant with deep venous occlusive disease). Ineligible participants were included in the ITT analysis, but excluded from the per-protocol analysis.

4.5. Baseline characteristics of participants by trial group

The baseline characteristics, including medical history, current medication, ulcer history and baseline compression therapy are summarised in *Table 18, Table 19 & Table 20.* The two study groups were well matched with respect to baseline characteristics, including the potential prognostic factors of ulcer duration, ulcer size, participant age and previous history of DVT in the randomised leg.

Slightly more males than females were randomised (55 per cent versus 45 per cent). The mean participant BMI was 30.3 kg/m^2 which is clinically obese by definition.

Table 18 - Baseline characteristics between the early (EVRA) and deferred (standard) ablation group (205)

	Early	Deferred
	n=224	n=226
Age[a]	67.0 (15.5) [n=224]	68.9 (14.0) [n=226]
Height[a]	171.9 (11.1) [n=220]	170.5 (10.8) [n=220]
Weight[a]	89.5 (25.6) [n=218]	88.8 (24.1) [n=219]
BMI[a]	30.1 (7.8) [n=218]	30.4 (7.4) [n=219]
Gender		
Female	97 (43.3%)	106 (46.9%)
Male	127 (56.7%)	120 (53.1%)
Smoking		
Current	23 (10.3%)	19 (8.4%)
Former	86 (38.4%)	101 (44.7%)
Never	115 (51.3%)	106 (46.9%)
Ethnicity		
White	206 (92.0%)	208 (92.0%)
Mixed	1 (0.4%)	0 (0.0%)
Asian	11 (4.9%)	12 (5.3%)
Black	3 (1.3%)	5 (2.2%)
Chinese	0 (0.0%)	0 (0.0%)
Other	3 (1.3%)	1 (0.4%)
EQ-5D®		
Health state score	70.2 (17.7) [n=222]	70.1 (17.1) [n=225]
Index value	0.7 (0.2) [n=222]	0.7 (0.2) [n=226]
SF-36		
Physical function	37.3 (12.0) [n=223]	37.5 (12.5) [n=225]
Role-Physical	39.0 (12.2) [n=223]	39.7 (12.1) [n=224]
Body pain	41.3 (11.1) [n=223]	41.6 (11.9) [n=224]
General Health	45.8 (9.2) [n=223]	46.0 (9.8) [n=225]
Vitality	48.2 (10.2) [n=222]	47.8 (10.6) [n=224]
Social Functioning	42.6 (12.4) [n=223]	42.4 (13.5) [n=224]
Role-Emotional	42.7 (13.8) [n=222]	43.7 (13.6) [n=224]

	Early	Deferred
Mental Health	49.2 (10.3) [n=222]	49.3 (10.7) [n=224]
Physical Component Summary	38.5 (9.9) [n=222]	38.8 (10.8) [n=223]
Mental Component Summary	49.2 (10.9) [n=222]	49.4 (11.6) [n=223]
Total AVVQ	44.1 (9.0) [n=200]	44.3 (8.7) [n=192]

Data presented as frequency (percentage) for categorical variables and mean (SD) for continuous variables.

[a]*Presented as mean (SD)*

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

Table 19 - Summary of medical history and concurrent medication(205)

	Early	Deferred
	N=224	N=226
Previous pregnancy[a]		
Yes	85 (87.6%)	91 (85.9%)
History of DVT in pregnancy (yes)	1 (1.2%)	2 (2.2%)
No	12 (12.4%)	15 (14.2%)
Hormone therapy[a]		
None	66 (29.5%)	71 (31.4%)
Previous HRT	16 (7.1%)	15 (6.6%)
Current HRT	1 (0.4%)	3 (1.3%)
Previous OC	21 (9.4%)	21 (9.3%)
Current OC	2 (0.9%)	1 (0.4%)
Previous Rheumatoid disease		
No	204 (91.1%)	212 (93.8%)
Yes	20 (8.9%)	14 (6.2%)
Previous DVT in either leg		
No	206 (92.0%)	203 (89.8%)
Yes	18 (8.0%)	23 (10.2%)
Previous DVT in trial leg		
No	206 (93.3%)	203 (93.4%)
Yes	15 (6.7%)	15 (6.6%)
Current antiplatelet therapy		
None	172 (76.8%)	179 (79.2%)
Aspirin	49 (21.9%)	44 (19.5%)

Clopidogrel	5 (2.2%)	5 (2.2%)
Other	1 (0.4%)	0 (0%)
Current anticoagulation therapy		
None	196 (87.5%)	189 (83.6%)
Warfarin	25 (11.2%)	32 (14.2%)
New oral anticoagulants	2 (0.9%)	4 (1.8%)
Other	1 (0.4%)	1 (0.4%)
Current Steroids		
No	211 (94.2%)	220 (97.4%)
Yes	12 (5.8%)	6 (2.7%)
Current Trental (pentoxifylline)		
No	224 (100%)	226 (100%)
Yes	0 (0%)	0 (0%)
Diabetes		
No	190 (84.8%)	198 (87.6%)
Yes	34 (15.2%)	28 (12.4%)

Data presented as frequency (percentage)

[a]*Female only*

HRT Hormone replacement therapy; DVT Deep vein thrombosis; OC Oral contraception

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

Table 20 - Summary of ulcer history and baseline compression (205)

	Early	Deferred
	n=224	n=226
Previous ulcer (yes)		
No	106 (47.3%)	108 (48.0%)
Yes	118 (52.7%)	117 (52.0%)
Ulcer dressing		
NA	64 (28.6%)	55 (24.3%)
Inadine™	28 (12.5%)	25 (11.1%)
Other	131 (58.5%)	146 (64.6%)
Missing	1 (0.4%)	0 (0%)
Baseline Compression		
None[a]	3 (1.3%)	7 (3.1%)
KTwo	32 (14.3%)	29 (12.8%)

Three-layer bandage	42 (18.8%)	41 (18.1%)
Four-layer bandage	59 (26.3%)	59 (26.1%)
European short stretch	43 (19.2%)	36 (15.9%)
Stocking	42 (18.8%)	53 (23.5%)
Other	2 (0.9%)	1 (0.4%)
Missing	1 (0.4%)	0 (0%)
Time of wearing		
Day & night	196 (87.5%)	185 (81.9%)
Day only	25 (11.2%)	39 (17.3%)
Missing	3 (1.3%)	2 (0.9%)

Data presented as frequency (percentage).

[a]*for participants not treated with compression at baseline, compression therapy was commenced at randomisation*

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

Table 21 summarises the baseline ulcer characteristics. The participant ulcer duration was slightly greater in those randomised to early ablation; median (IQR) of 3.2 months (2.3-4.2) versus a median (IQR) of 3.0 months (1.7-4.2) in the deferred group. The median (IQR) ulcer size in the early ablation group was 2.4 cm^2 (1.0-7.1) and 2.9 cm^2 (1.1-8.2) in the deferred ablation group.

Two of the ineligible participants had a healed ulcer at the time of randomisation (confirmed after randomisation). The ineligible participant with deep venous occlusive disease was confirmed to have both deep vein reflux and outflow obstruction by baseline duplex ultrasound scan. In general, ulcer characteristics were well matched between the two groups.

Table 21 - Characteristics of current ulcer (205)

	Early	Deferred
	n=224	n=226
Ulcer duration (months) [a,b]	3.2 (2.3-4.2)	3.0 (1.7-4.2)
Trial ulcer leg		
Right	107 (47.8%)	115 (50.9%)
Left	117 (52.2%)	111 (49.1%)
Ulcer location		

Lateral	92 (41.1%)	93 (41.2%)
Medial	116 (51.8%)	118 (52.2%)
Circumferential	9 (4.0%)	7 (3.1%)
Missing	7 (3.1%)	8 (3.5%)
Ulcer size (cm²) [b][c]	2.4 (1.0-7.1)	2.9 (1.1-8.2)
Duplex Scan: Deep Vein		
Normal	150 (67.0%)	157 (69.5%)
Abnormal[d]	74 (33.0%)	69 (30.5%)
Reflux	74 (100%)	69 (100%)
Outflow obstruction	0 (0%)	0 (0%)
CEAP Score		
Clinical signs – grade		
C_5	1 (0.4%)	1 (0.4%)
C_6	224 (99.6%)	225 (99.6%)
Clinical signs – presentation		
Asymptomatic	0 (0%)	0 (0%)
Symptomatic	224 (100%)	226 (100%)
Etiologic classification		
Primary	217 (96.9%)	214 (94.7%)
Secondary	7 (3.1%)	12 (5.3%)
Deep	0 (0%)	0 (0%)
No venous cause	0 (0%)	0 (0%)
Anatomic distribution		
Superficial	220 (98.2%)	221 (97.8%)
Perforator	3 (1.3%)	3 (1.3%)
Deep	1 (0.4%)	2 (0.9%)
Pathophysiologic dysfunction		
Reflux	224 (100%)	226 (100%)
Obstruction	0 (0%)	0 (0%)
Both	0 (0%)	1 (0.4%)
No venous cause	0 (0%)	0 (0%)
VCSS Score[b]	15 (14-18)	16 (14-18)
Palpable pedal pulses		
No	15 (6.7%)	14 (6.2%)
Yes	209 (93.3%)	212 (93.8%)

Data presented as frequency (percentage) for categorical variables and median (IQR) for continuous variables
[a]*ulcer duration as reported by participant*
[b]*presented as median (interquartile range)*
[c]*ulcer size evaluated using digital planimetry from standardized digital photographs by assessor blinded to intervention group*
[d]*defined as presence of retrograde flow in common femoral, femoral or popliteal veins >1seconds duration after augmentation. A participant can have both deep vein reflux and obstruction*

The patterns of superficial truncal venous reflux at baseline can be seen in *Table 22*.

Table 22 - Summary of truncal venous reflux patterns at baseline (205)

	Early	Deferred
	n=224	n=226
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[a]	11 (4.9%)	15 (6.6%)

Data presented as frequency (percentage)

[a]*accessory saphenous, perforator vein or tributary vein reflux*

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

4.6. Interventions

Endovenous strategies and timings of the first ablation are summarised in *Table 23*. In the deferred group 55 participants did not undergo ablation by 12-months. Of these, 19 participants died, withdrew, or were lost to follow-up from the study and 36 participants completed the study (27 participants with healed ulcer and nine participants with unhealed ulcer at 12-months) (*Table 24*). In the early ablation group, seven participants did not undergo endovenous ablation, including one participant who had their procedure abandoned before completion. The most common interventional strategy was UGFS alone (47%), followed by endothermal ablation alone (29%).

In the early ablation group the majority of participants (90.6%) underwent ablation within two weeks of randomisation. In the deferred ablation group, one participant was treated before two weeks and five participants were treated prior to ulcer healing between two weeks and six months.

Table 23 - Summary of endovenous ablation procedures performed (205)

	Early	Deferred
	n=224	n=226
Interventional ablation Type		
No ablation	6 (2.7%)	55 (24.3%)
Endothermal only[a]	71 (31.7%)	54 (23.9%)
UGFS only[b]	111 (49.6%)	100 (44.3%)
Mechanochemical ablation (MOCA) only	5 (2.2%)	1 (0.4%)
Endothermal[a] and UGFS[b]	27 (12.1%)	16 (7.1%)
MOCA and UGFS[b]	3 (1.3%)	0 (0%)
Abandoned ablation	1 (0.5%)	0 (0%)
Timing of first ablation procedure[c]		
No ablation	6 (2.7%)	55 (24.3%)[d]
Within 2-weeks	203 (90.6%)	1 (0.4%)
Before ulcer healing	*200*	*1[e]*
After ulcer healing	*3*	*0*
Between 2 and 4-week	9 (4.0%)	1 (0.4%)
Before ulcer healing	*9*	*1[e]*
After ulcer healing	*0*	*0*
Between 4-weeks and 6-months	6 (2.7%)	103 (45.6%)
Before ulcer healing	*4*	*4[e]*
After ulcer healing	*2*	*99*

After 6-months	0 (0%)	66 (29.2%)
Before ulcer healing	*0*	*19*
After ulcer healing	*0*	*47*

Data presented as frequency (percentage)

[a]*endovenous thermal ablation procedures included laser and radiofrequency ablation*

[b]*UGFS to treat tributary veins or sub-ulcer venous plexus performed as per the standard technique of the treating clinician*

[c]*timing of first endovenous ablation only. Timing of any additional ablations was left to the discretion of treating clinicians*

[d]*Of the 55/226 (24.3%) of participants in the deferred ablation group who were not treated by 12 months post randomization, the ulcer was healed in 27, not healed in 9 and the remaining 19 participants had either died (n=7), withdrawn (n=7) or were lost to follow-up (n=5). For the 27 participants with healed ulcers, 16 participants declined ablation, 3 were no longer deemed to be suitable for ablation (as decided by the treating clinician), 6 were on the waiting list for ablation and may have been treated after 12 months and for the remaining 2 participants, the reasons for not receiving ablation are unclear*

[e]*Reasons for ablation before ulcer healing in 6 participants in deferred ablation group were: clinical deterioration of ulcer (n=3); participant request for ablation (unwilling to continue with deferred ablation strategy) (n=2); participant treated early in error (n=1).*
Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al*. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

Table 24 - Summary of participants not having endovenous ablation

	Deferred	Early
	n=55	n=6
Completion of the study		
Yes	36 (65.5%)	2 (33.3%)
Ulcer healed by 12 months	27	2
Ulcer unhealed by 12 months	9	0
No	19 (34.5%)	4 (66.7%)
Withdrawal	7	3
Death	7	1
Other	5	0

4.7. Primary outcome – ulcer healing

The Kaplan-Meier Curve for time to ulcer healing can be seen in *Figure 32*. Two participants were healed at the time of randomisation and therefore ineligible for the study so were not included in the survival analysis.

The median healing time was 56 days (95% CI 49-66) in the early group versus 82 days (95% CI 69-92) in the deferred ablation group.
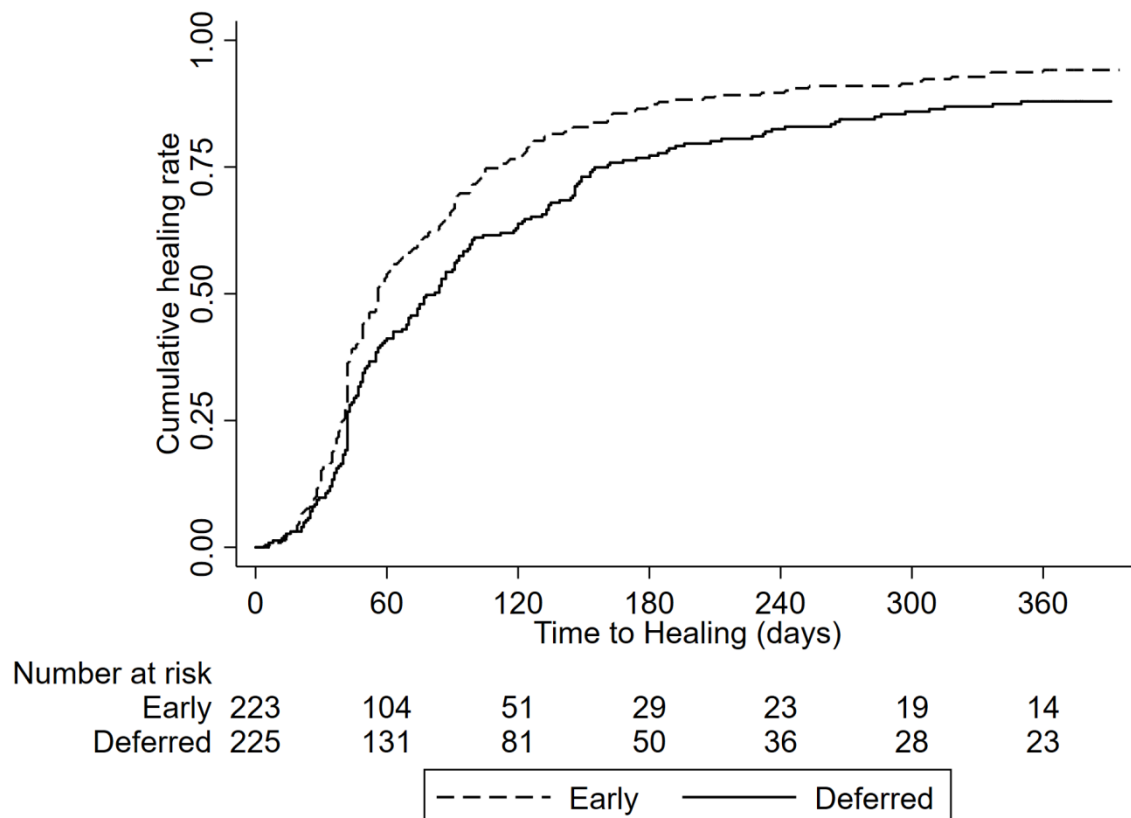
Figure 32 - Kaplan-Meier curve showing ulcer healing time in the early and deferred ablation groups (p=0.001, log rank test). Ulcer healing rates were greater in participants randomised to early ablation (205).

Adapted from N Engl J Med Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, et al. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

The Cox model proportional hazards assumptions were verified with visual and numerical methods and did not detect a violation (*Figure 33*).

Test of proportional-hazards assumption

Time: Time

	rho	chi2	df	Prob>chi2
1b.treat	.	.	1	.
2.treat	0.01161	0.06	1	0.8118
age	0.08768	3.12	1	0.0772
1b.size_c	.	.	1	.
2.size_c	0.09074	3.40	1	0.0652
3.size_c	0.11952	5.76	1	0.0163
4.size_c	0.12940	6.40	1	0.0114
1b.duratio~c	.	.	1	.
2.duration_c	−0.01932	0.15	1	0.6968
3.duration_c	0.05013	1.05	1	0.3060
4.duration_c	0.03871	0.62	1	0.4318
global test		15.38	8	0.0521

e)
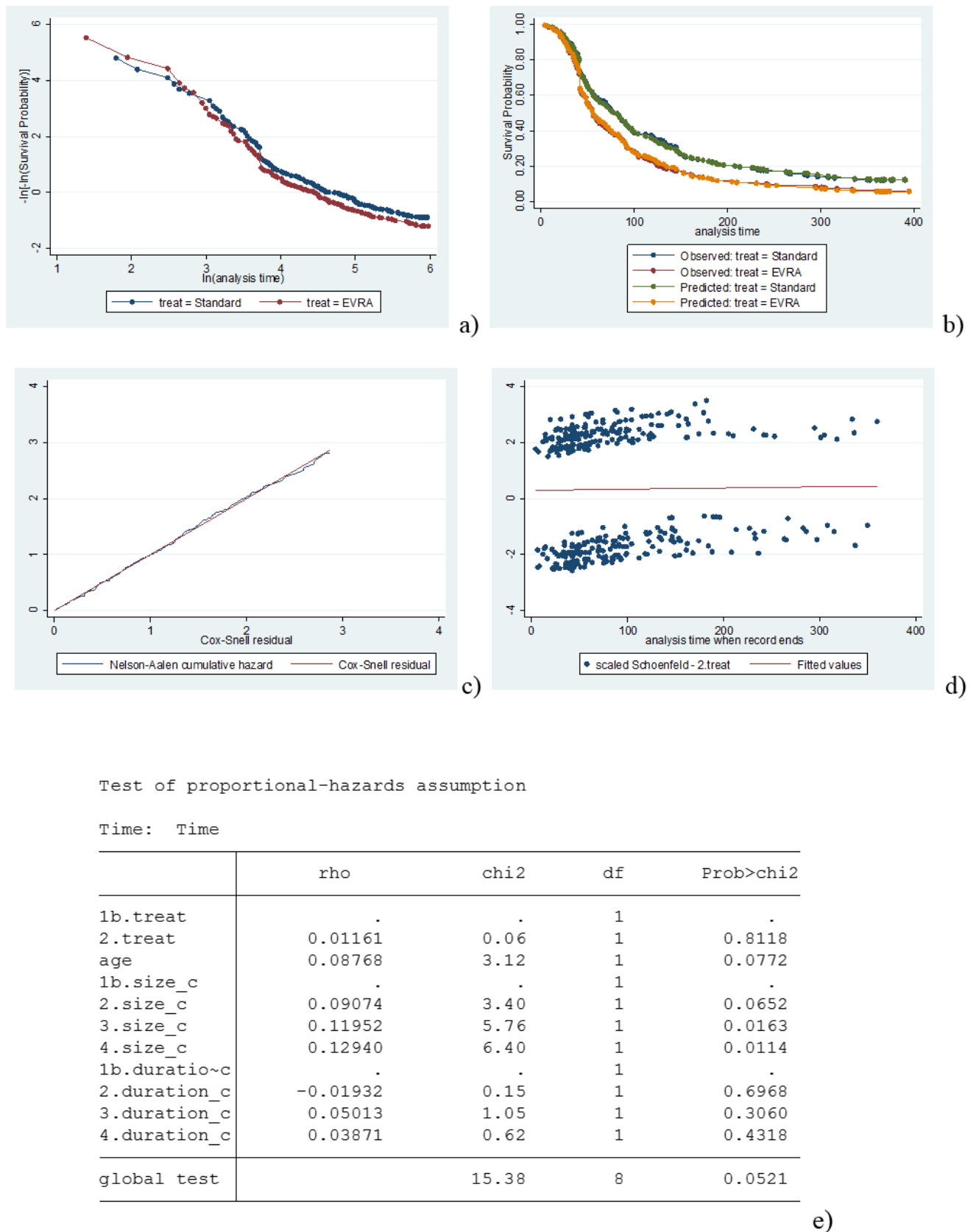
Figure 33 - Proportional Hazards Assumption Evaluation by a) log-log plot of survival; b)Kaplan-Meier and predicted survival plot; c) Nelson-Aalen cumulative hazard function versus the Cox-Snell residuals; d) Scaled Schoenfeld residuals plot; e) Test of proportion

The Cox proportional hazards regression results can be seen in *Table 25*. The HR in the early ablation group for ulcer healing in the unadjusted model (with study centre as a random effect) was 1.38 (1.13-1.68) (p=0.001) compared with participants randomised to deferred ablation. Once adjusted for age, ulcer duration, and ulcer size at baseline in the adjusted model, the HR was 1.42 (1.16-1.73) (p=0.001).

Table 25 -Time to ulcer healing in participants with venous ulceration (Cox regression model)

	N^a	n^a	Unadjusted model [b]		Adjusted model[c]	
			HR (95% CI)	p value	HR (95% CI)	p value
Treatment						
Deferred group	226	194	Ref		Ref	
Early group	224	210	1.38 (1.13-1.68)	0.001	1.42 (1.16-1.73)	0.001
Age (years)	448	402	1.00 (0.99-1.00)	0.25	1.00 (0.99-1.01)	0.69
Ulcer duration (months)						
1st Quartile (0.9-2.2)	113	102	Ref		Ref	
2nd Quartile (2.3-3.1)	114	101	1.01 (0.77-1.33)	0.96	1.00 (0.76-1.33)	0.97
3rd Quartile (3.1-4.2)	111	105	1.11 (0.85-1.47)	0.44	1.14 (0.86-1.51)	0.35
4th Quartile (4.2-8.4)	112	96	0.75 (0.56-0.99)	0.04	0.79 (0.59-1.05)	0.10
Ulcer size (cm^2)						
1st Quartile (0.4-1.5)	113	108	Ref		Ref	
2nd Quartile (1.6-2.9)	112	108	0.79 (0.61-1.04)	0.09	0.72 (0.55-0.95)	0.02
3rd Quartile (3-7.5)	113	101	0.52 (0.40-0.69)	<0.001	0.51 (0.38-0.67)	<0.001
4th Quartile (8-235)	112	87	0.31 (0.23-0.41)	<0.001	0.29 (0.22-0.39)	<0.001

[a]N: total number of participants; n: number of participants with healing ulcer

[b]Adjusted by centre (centre included in the model as a random effect)

[c]Adjusted by centre, age, ulcer size and duration (centre included in the model as random effect and age, ulcer size and duration as fixed effects).

Figure 34 depicts the adjusted Cox regression model HR for pre-planned specific subgroups. The results were consistent in the majority of the subgroups analysed except that by BMI, ulcer size and ulcer chronicity, where an interesting pattern was observed. The BMI HR in the early group in underweight participants was less than those in the other three groups. For the subgroup analysis by ulcer size, the HR was consistent for participants with ulcer size in the 1st to 3rd quartile. However, in participants with ulcer size in the 4th quartile, the observed effect of early intervention disappeared (HR: 0.99 (0.62-1.56)). For the subgroup analysis by ulcer chronicity, early intervention did not make a different to ulcer healing compared with standard treatment in the 1st and 2nd quartiles, but the HR in the early arm increased across the quartiles of ulcer chronicity. However, this study was not powered to investigate any interactions and thus the above findings will need further studies to confirm.

Subgroup	No. of Pts	Hazard Ratio (95%)
BMI		
Underweight	63	1.04 (0.56-1.93)
Normal	49	2.07 (0.85-5.06)
Overweight	144	1.52 (1.06-2.18)
Obesity	179	1.39 (1.00-1.94)
Age		
<50 yrs	54	2.22 (1.06-4.67)
50-70 yrs	165	1.49 (1.04-2.14)
>70yrs	229	1.28 (0.97-1.70)
Gender		
Male	245	1.37 (1.03-1.83)
Female	203	1.40 (1.04-1.88)
Smoke		
Never	219	1.53 (1.14-2.05)
Current	42	2.67 (1.15-6.22)
Former	187	1.23 (0.89-1.70)
Ulcer Size		
1st Quartile	112	1.53 (1.02-2.30)
2nd Quartile	112	1.24 (0.82-1.88)
3rd Quartile	112	2.66 (1.69-4.19)
4th Quartile	112	0.99 (0.62-1.56)
Ulcer Duration		
1st Quartile	113	0.87 (0.56-1.35)
2nd Quartile	114	1.35 (0.90-2.03)
3rd Quartile	110	1.79 (1.16-2.77)
4th Quartile	111	2.19 (1.43-3.36)
DVT		
No	418	1.52 (1.24-1.88)
Yes	30	0.58 (0.18-1.86)
Rheumatoid Arthritis		
No	414	1.38 (1.12-1.71)
Yes	34	1.73 (0.69-4.33)
Anti-platelet Therapy		
No	100	1.29 (0.81-2.05)
Yes	348	1.49 (1.18-1.88)
Previous Ulcer		
No	214	1.55 (1.15-2.10)
Yes	233	1.41 (1.06-1.87)
EQ5D		
1st Quartile	112	1.50 (0.94-2.40)
2nd Quartile	114	1.75 (1.15-2.66)
3rd Quartile	121	1.24 (0.83-1.86)
4th Quartile	99	1.86 (1.17-2.93)
Total		
	448	1.42 (1.16-1.73)

Figure 34 - Forest plot of subgroup analysis for primary outcome.

The healing advantage in pre-specified subgroups was consistent with the overall healing benefit observed with early ablation. The broken line indicates overall HR for ulcer healing in entire study population.(205). Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

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Figure 35 shows the HRs for the endovenous strategies in the early ablation group, compared with deferred ablation. The MOCA only group, endothermal & UGFS, and MOCA & UGFS groups are merged into one group as 'other ablation' as they were small groups. The HRs for the groups of endothermal only, UGFS only and other treatment were consistent.

Subgroup	No. of Pts	Hazard Ratio (95%)
Treatment Type		
Deferred Arm	225	Reference
Early Arm-No treatment	6	0.95 (0.38-2.41)
Early Arm-Endothermal alone	70	1.61 (1.18-2.20)
Early Arm-Foam alone	111	1.34 (1.04-1.73)
Early Arm-Other	36	1.43 (0.99-2.06)
Total		
	448	1.42 (1.16-1.73)

0.0   1.0   2.0   3.0

Deferred Better   Early Better
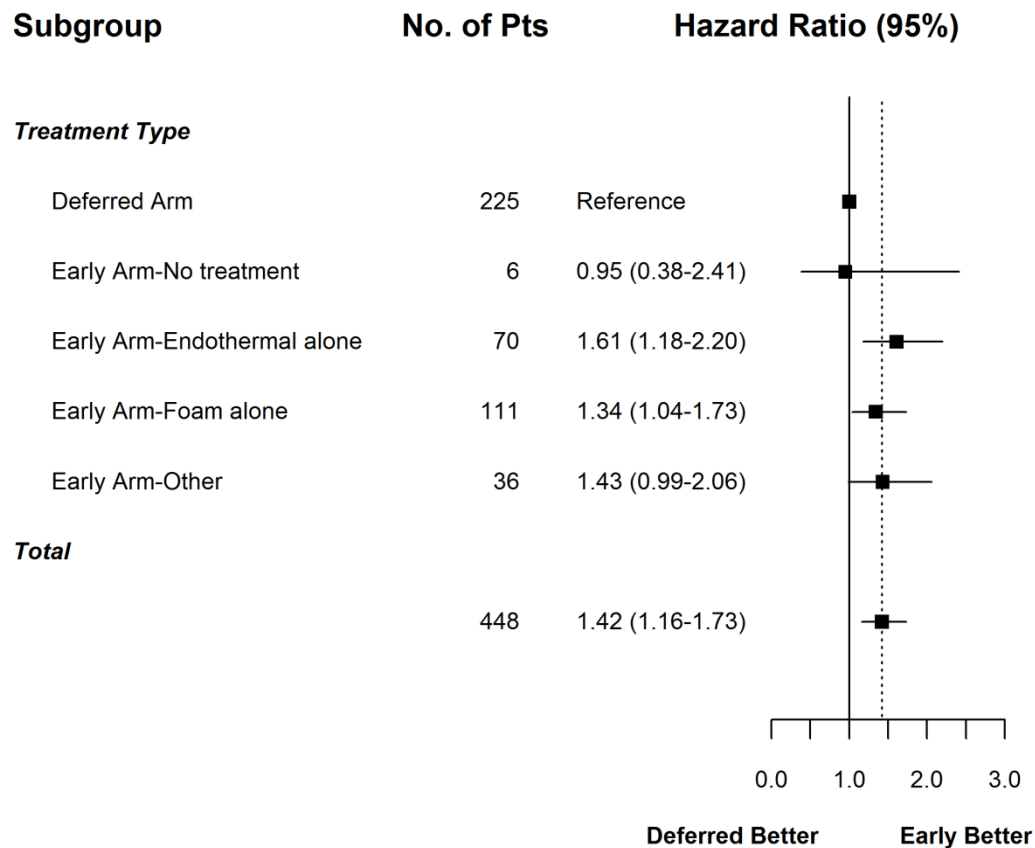
Figure 35 - Forest plot of different endovenous ablation techniques for primary outcome (205) The healing advantage in pre-specified subgroups treated with different ablation techniques was consistent with the overall healing benefit. The broken line indicates overall hazard ratio for ulcer healing in entire study population.

4.8. Secondary outcomes

4.8.1. Ulcer-free time to 12-months

407 of the 450 participants attended the 12-month follow-up visit and therefore were included in the analysis of ulcer-free time to 12-months (203 participates in the deferred group and 204 in the early ablation group). The median and IQR ulcer-free time to 12-months was 278 days (IQR: 175-324) and 306 days (240-328) for the deferred and early ablation groups respectively.

The ulcer- free time to 12 months did not follow a normal distribution and as a few of the participants had zero ulcer-free time, mathematical transformation was not possible. The ulcer-free time was therefore categorised into quartiles, with ordinal regression to assess the treatment effect (*Table 26*). The OR for being in a higher quartile in the unadjusted analysis was 1.60 (1.13-2.27) for the early ablation group. The adjusted model (age, ulcer duration and size) was 1.54 (1.07-2.21) with p=0.02.

The results of ordinal logistic regression by different subgroups are shown in *Figure 36*. The results are consistent across different subgroups with observed patterns similar to those seen in the subgroup analysis by ulcer size and duration.

Table 26 - Ordinal logistic regression for ulcer-free time to 12 months (quartiles) in participants with venous ulceration (217)

	Unadjusted model [a]		Adjusted model [b]	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Treatment				
Deferred group	Ref		Ref	
Early group	1.60 (1.13-2.27)	0.009	1.54 (1.07-2.21)	0.02
Age (years)	0.99 (0.98-1.00)	0.14	1.00 (0.98-1.01)	0.57
Ulcer duration (months)				
1st Quartile (0.9-2.2)	Ref		Ref	
2nd Quartile (2.3-3.1)	0.87 (0.53-1.44)	0.59	0.94 (0.56-1.56)	0.80
3rd Quartile (3.1-4.2)	0.94 (0.57-1.55)	0.82	0.96 (0.58-1.60)	0.89
4th Quartile (4.2-8.4)	0.55 (0.33-0.92)	0.02	0.64 (0.38-1.08)	0.10
Ulcer size (cm^2)				
1st Quartile (0.4-1.5)	Ref		Ref	
2nd Quartile (1.6-2.9)	0.50 (0.30-0.82)	0.006	0.48 (0.29-0.79)	0.004
3rd Quartile (3-7.5)	0.23 (0.14-0.39)	<0.001	0.23 (0.14-0.39)	<0.001
4th Quartile (8-235)	0.09 (0.05-0.16)	<0.001	0.10 (0.06-0.17)	<0.001

[a] *Adjusted by centre (centre included in the model as a random effect)*

[b] *Adjusted by centre, age, duration and size (centre included in the model as random effect and age, ulcer duration and size as fixed effects)*

Subgroup	No. of Pts	Odds Ratio (95%)
BMI		
Underweight	58	1.01 (0.35- 2.93)
Normal	44	5.51 (1.18-25.78)
Overweight	134	2.13 (1.10- 4.14)
Obesity	160	1.13 (0.64- 2.01)
Age		
<50 yrs	42	1.64 (0.44- 6.14)
50-70 yrs	154	1.69 (0.92- 3.09)
>70yrs	211	1.36 (0.82- 2.26)
Gender		
Male	224	1.73 (1.05- 2.84)
Female	183	1.33 (0.78- 2.28)
Smoke		
Never	203	1.64 (0.98- 2.75)
Current	36	4.63 (1.12-19.13)
Former	168	1.41 (0.79- 2.52)
Ulcer Size		
1st Quartile	105	1.65 (0.79- 3.42)
2nd Quartile	100	1.51 (0.71- 3.20)
3rd Quartile	104	2.93 (1.29- 6.63)
4th Quartile	98	0.98 (0.45- 2.15)
Ulcer Duration		
1st Quartile	101	0.91 (0.41- 2.00)
2nd Quartile	102	1.88 (0.90- 3.93)
3rd Quartile	101	2.01 (0.94- 4.29)
4th Quartile	103	2.16 (1.04- 4.50)
DVT		
No	418	1.66 (1.14- 2.41)
Yes	26	0.38 (0.07- 2.08)
Rheumatoid Arthritis		
No	375	1.40 (0.97- 2.04)
Yes	32	8.00 (1.47-43.66)
Anti-platelet Therapy		
No	97	1.95 (0.88- 4.34)
Yes	310	1.61 (1.06- 2.45)
Previous Ulcer		
No	193	1.61 (0.93- 2.77)
Yes	214	1.78 (1.07- 2.95)
EQ5D		
1st Quartile	98	1.98 (0.89- 4.41)
2nd Quartile	102	1.29 (0.61- 2.73)
3rd Quartile	115	1.56 (0.78- 3.11)
4th Quartile	91	1.80 (0.77- 4.23)
Total		
	407	1.54 (1.07- 2.21)

Deferred Better   Early Better

Figure 36 - Forest plot showing the treatment effect on ulcer-free time by pre-defined sub-groups (217)

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The OR for the treatment effect on ulcer free time by type of endovenous ablation is shown in *Figure 37*. The ORs are consistent in the endothermal only and foam only groups, while the OR in the 'other' treatment group is 1.06 (0.56-2.02) but the lack of treatment effect here may be due to the small number in the 'other' treatment group.
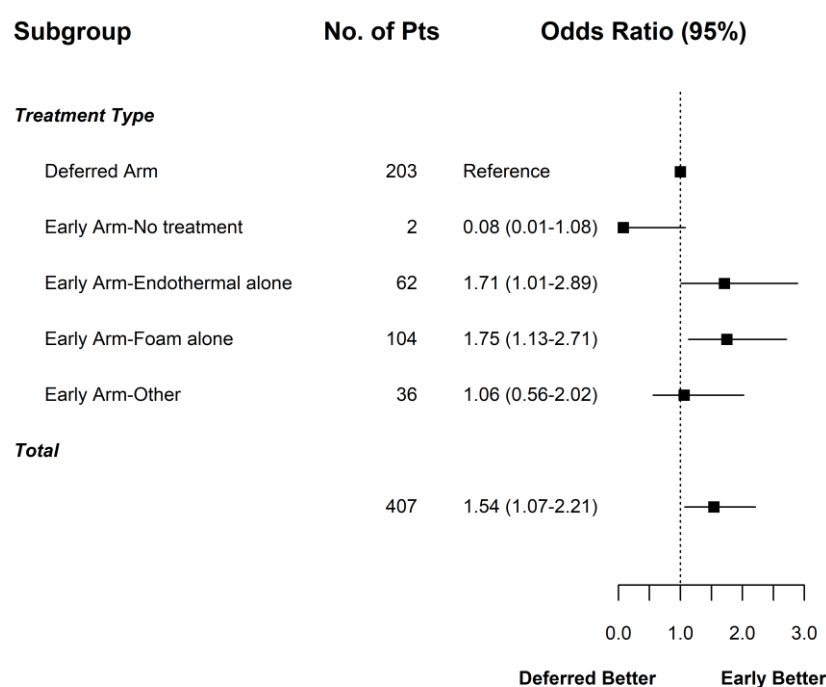
Figure 37 - Forest plot showing the treatment effect on ulcer-free time by different ablation techniques (217)

4.8.2. Ulcer healing at 12 weeks and 24 weeks

The unadjusted Kaplan-Meier time-to-event ulcer healing analysis showed that the healing rates (95% CI) at 24 weeks were greater in the early ablation group (85.6% [80.6–89.8] compared with the deferred ablation group (76.3% [70.5-81.7]). *(Table 27)*

A post-hoc analysis allowed comparison with other published studies. The 12-week ulcer healing rates (95% CI) were 63.5% [57.2-69.8] in the early ablation group versus 51.6% [45.2-58.3] in the deferred group.

A total of 404/450 (89.7%) randomised participants had healed by 12 months post-randomisation (210/224 [93.8%] in early, and 194/226 [85.8%] in deferred ablation groups respectively), with an increase of 7.9% percentage points in the early group [95% CI 2.3-13.5].

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Table 27 - Summary of 12-week and 24-week ulcer healing and ulcer free time (217)

	Early	Deferred
	n=224	n=226
12-week ulcer healing [a]	63.5%	51.6%
	(57.2%-69.8%)	(45.2%-58.3%)
24-week ulcer healing [a]	85.6%	76.3%
	(80.6%-89.8%)	(70.5%-81.7%)
No. of participants with a healed ulcer at 12 months	210 (93.8%)	194 (85.8%)
No. of participants with recurrent ulcer[b]	24 (11.4%)	32 (16.5%)
Ulcer free time (days)	306 (240-328) [n=204]	278 (175-324) [n=203]

Data presented as frequency (percentage) for categorical variables and median (IQR) for continuous variables

[a]*Data presented as estimation by KM curve (95%CI)*

[b]*Proportion of participants with ulcer healed at 12 months*

4.8.3. Quality of life

The HRQoL data at baseline, week six, month six and month 12 for the two study groups is summarised in *Appendix 6 Tables S5, S6, and Figure S1, 2 & 3*. The AVVQ has scores ranging from zero to 100, with zero representing the best score, and 100 the worst score, while for EQ5D and SF36, the higher the score, the better the HRQoL.

The AVVQ, EQ-5D-5L index value and SF36 baseline scores were similar in early and deferred ablation groups. There was a significant difference in AVVQ scores between the treatment groups over time (p<0.001) with lower mean scores, suggesting better disease-specific HRQoL, in the early ablation group. There was also a significant difference over time in EQ-5D® Index value between the treatment groups (p=0.03), again with more favourable scores in those randomised to early ablation, and in SF-36 body pain (p=0.05) but little difference between the groups for the other generic HRQoL measures. Overall, there was a decreasing trend of HRQoL score across time was observed for both deferred ablation and early groups. The HRQoL data with multiple imputation of missing values which produces similar values.

There was no control for multiple testing, and therefore these results should be interpreted with caution.

4.8.4. VCSS and technical success

4.8.4.1. VCSS

The clinical success at six weeks with respect to the VCSS is shown in *Table 28 and Figure 38*. VCSS scores at baseline for both groups were similar. The VCSS evaluates changes in venous disease over time, with lower scores indicating a better clinical condition. Early ablation was associated with a lower VCSS score at week 6 compared with deferred ablation.

The number of participants with change of CEAP status from C6 to C5 is 106 (47.3%) in the early ablation group and 72 (31.9%) in the deferred group which corresponds directly with ulcer healing.

Table 28 - Summary of VCSS at six weeks after randomisation (217)

	Early	Deferred	p value
	n=224	n=226	
VCSS total			
Baseline	15.8 (3.3) [n=223]	15.7 (3.1) [n=226]	0.62[a]
Week 6	10.5 (4.7) [n=218]	12.6 (4.4) [n=210]	<0.001[a]
Clinical classification downgrade (C6 to C5)			
Yes	106 (47.3%)	72 (31.9%)	0.001[b]
No	112 (50.0%)	139 (61.5%)	
Missing	6 (2.7%)	15 (6.6%)	

Data presented as mean (SD) or frequency (percentage)

[a] p value for t-test

[b] p value for Pearson's chi-squared test
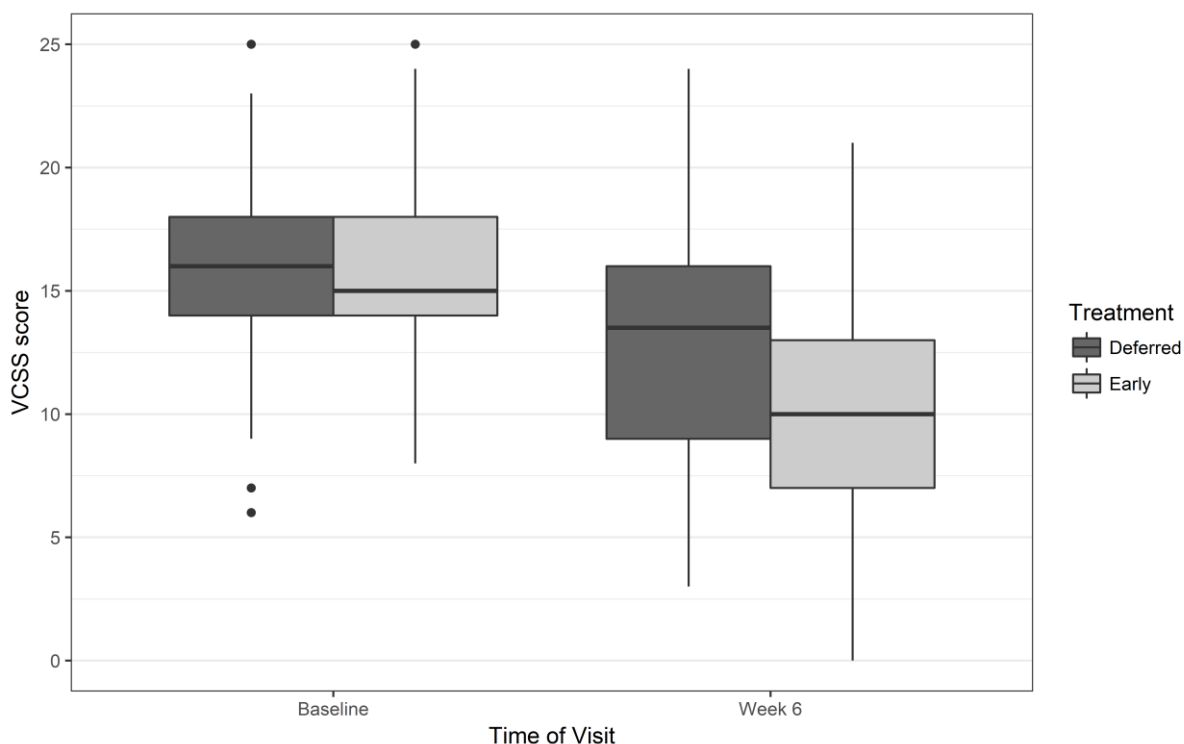
Figure 38 - Summary of VCSS in early and deferred ablation groups: VCSS at baseline and six weeks after randomisation (217)

4.8.4.2. Technical success

The post-ablation duplex ultrasound scans at six weeks in the early arm showed that treated segments were completely ablated in 179/215 (83.3%) of scanned participants and 74.8% of legs had no evidence of residual reflux.

4.8.5. Safety assessment

4.8.5.1. Adverse events

The total number of ablation procedures for each group within 12-months and associated related adverse events are shown (*Table 29)*. 218 (97.3%) participants underwent at least one ablation treatment in the early group, compared with 171 (75.7%) in the deferred group.

The procedural complications after endovenous ablation are summarised in *Table 30*, with DVT and pain being the most common complications post-ablation. The vast majority of DVTs were identified on duplex scans performed one-week post ablation and were in crural veins / asymptomatic.

Table 29 - Summary of adverse events (217)

	Early	Deferred
	n=224	n=226
Total number of procedures	269	203
Total number participants having a procedure	218 (97.3%)	171 (75.7%)
No. of surgical procedures		
1	173 (79.4%)	147 (86.0%)
2	39 (17.9%)	17 (9.9%)
3	6 (2.8%)	6 (3.5%)
4	0 (0%)	1 (0.6%)
Total number of AEs	117	130
Total number participants with AE	67 (29.9%)	83 (36.7%)
Description of AE		
Systemic	7 (6.0%)	6 (4.6%)
Local	110 (94.2%)	124 (95.4%)
Outcome		
Recovered	111 (94.9%)	111 (85.4%)
Not yet recovered	6 (5.1%)	19 (14.6%)
Death	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)

Data presented as frequency (percentage)

Table 30 - Summary of complications after endovenous ablation (217)

	Early	Deferred
	n=28	n=24
Allergic reaction requiring local or no treatment	5	3
Bleeding requiring intervention	2	1
Cough / chest tightness	0	1
DVT	9[a]	3 [b]
Infection [c]	3	5
Oedema	1	0
Pain	6[d]	6
Participant reported paraesthesia	1	1
SVT	1	4

4.8.5.2. Serious Adverse events

The total number of serious adverse events per arm are summarised in *Table 31*.

There were three SAEs in the deferred arm that were possibly, probably or definitely related to the ablation procedures and four in the early ablation group. All of the SAEs were expected and were are categorised using MEdDRA version 20.0 (*Table 32*).

Table 31 - Summary of serious adverse events (217)

	Early	Deferred
	n=224	n=226
Number of participants undergoing an ablation procedure	218 (97.3%)	171 (75.7%)
Total number of procedures	269	203
Total number of SAEs	43	55
Number of participants with SAE	30 (13.4%)	35 (15.5%)
Serious reason		
Death	3 (7.0%)	4 (7.3%)
Life threatening	0 (0%)	0 (0%)
Persistently disabling	0 (0%)	0 (0%)
Hospitalisation required	38 (88.4%)	50 (90.9%)
Congenital abnormality	0 (0%)	0 (0%)
Other	2 (4.7%)	1 (1.8%)
Frequency		
Single Episode	32 (74.4%)	49 (89.1%)
Intermittent	1 (2.3%)	1 (1.8%)
Frequent	1 (2.3%)	0 (0%)
Continuous	7 (16.3%)	5 (9.1%)
Unknown	2 (4.7%)	0 (0%)
Severity		
Mild	3 (7.0%)	4 (7.3%)

Moderate	17 (39.5%)	23 (41.8%)
Severe	18 (41.9%)	20 (36.4%)
Life threatening or disabling	5 (11.6%)	8 (14.6%)
Relation to procedure		
Not related	38 (88.4%)	51 (92.7%)
Unlikely	1 (2.3%)	1 (1.8%)
Possible	1 (2.3%)	3 (5.5%)
Probable	1 (2.3%)	0 (0%)
Definite	2 (4.7%)	0 (0%)
Outcome		
Recovered	36 (83.7%)	46 (83.6%)
Not yet recovered	1 (2.3%)	1 (1.8%)
Death	6 (14.0%)	8 (14.6%)
Unknown	0 (0%)	0 (0%)
Expectedness[a]		
Expected	4 (100%)	3 (100%)

Data presented as frequency (percentage) [a]Expectedness is reported among all SAEs that are possibly, probably or definitely related to procedure (n=7)

Table 32 - MedDRA coding of the expected and related serious adverse events (217)

Treatment allocation	System Organ Classes Term	Preferred Term	Lowest Level Term
Early	Musculoskeletal and connective tissue disorders	Pain in extremity	Leg pain
Early	Surgical and medical procedures	Vascular compression therapy	Compression dressing application
Early	General disorders and administration site conditions	Peripheral swelling	Swelling of legs
Early	Skin and subcutaneous tissue disorders	Skin ulcer	Leg ulcer
Deferred	Injury, poisoning and procedural complications	Laceration	Laceration of head
Deferred	Infections and infestations	Urinary tract infection	Urinary tract infection
Deferred	Infections and infestations	Infected skin ulcer	Infected skin ulcer

4.9. Protocol deviations

There were 89 protocol deviations in early group from 59 participants compared with and 74 from 58 participants in the deferred ablation groups (*Table 33*).

Treatment-related protocol deviations were excluded from the per-protocol analysis. There were 38 protocol deviations (involving 32 participants) related to trial treatment in the early group and 32 (involving 31 participants) in the deferred ablation group, hence 63 participants were excluded from the per protocol analysis.

Table 33 - Summary of protocol deviation (217)

	Early	Deferred
	N=89[a]	N=74[b]
Number of participants with protocol deviation	59	58
Deferred ablation in early group	17 (19.1%)	0 (0%)
Non-concordance with bandaging	9 (10.1%)	12 (16.0%)
Early ablation in deferred group	0 (0%)	16 (21.3%)
Other	63 (70.8%)	46 (62.2%)
FU visit missing/late	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[c] (22.2%)	0 (0%)

[a]*Includes 38 that were treatment related (Deferred 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))*

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

[c]*abnormal scan (n= 1), deferred reporting of healing (n=1), 1 ablation not completed for technical reason (n=1), 1 ablation outside 2 weeks (n= 4), no ablation (n= 5), other (n= 2)*

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

4.10. Sensitivity analysis (per-protocol)

The per-protocol analysis Kaplan-Meier curve included 387 participants, as 63 participants with treatment-related protocol deviation were excluded (*Figure 39*). As participants in the deferred group experienced poorer healing, the difference was less pronounced than the ITT analysis (*Figure 40 & Table 34*).

The 24-week ulcer-healing rate in the deferred group was 76.3% in the ITT analysis and 82.6% in the per-protocol analysis. After adjusting for covariates in the Cox regression in the per-protocol, analysis the HR for time to healing associated with early compared with deferred ablation was 1.31 (1.06-1.63) with p = 0.01 (*Table 35*). Despite the less severe nature of the ulcers in the deferred intervention, participants in the per-protocol analysis early ablation still experienced more rapid ulcer healing.
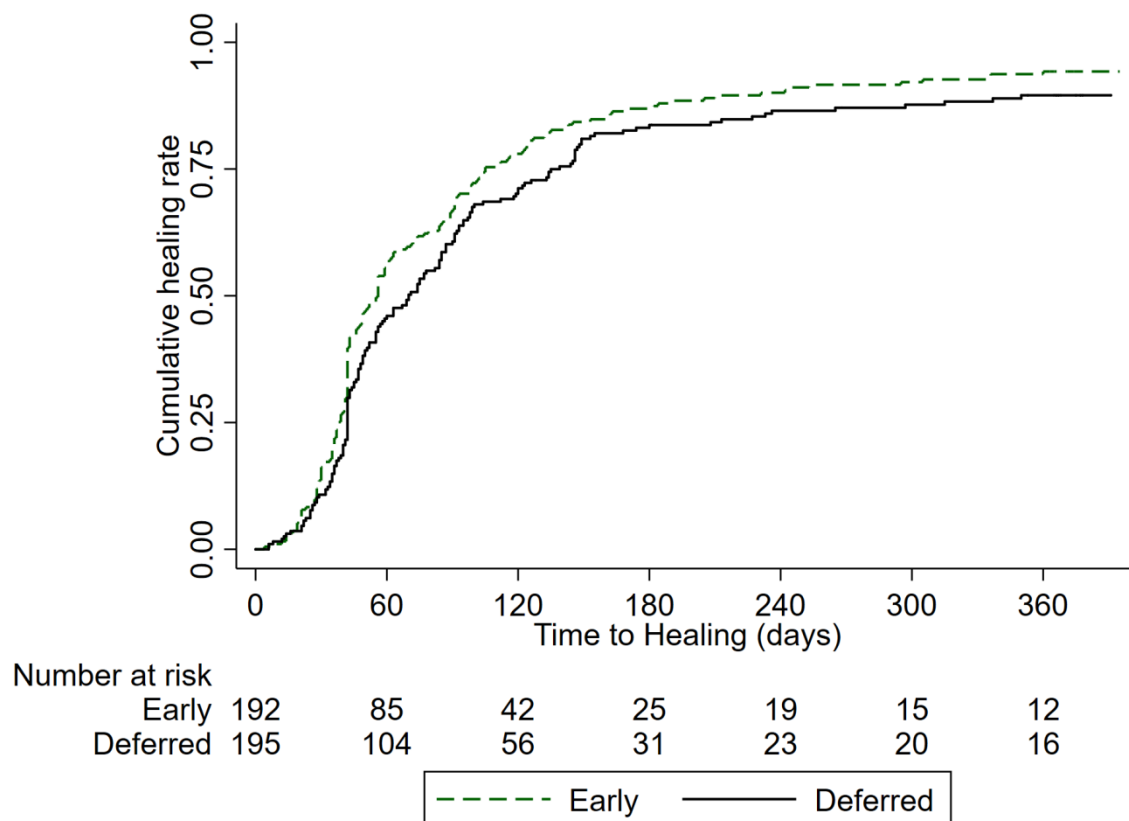
Figure 39 - Per protocol analysis (excluding participants with a protocol deviation) Kaplan-Meier curve showing ulcer healing in the early and deferred (standard) ablation groups (p=0.04) (217)
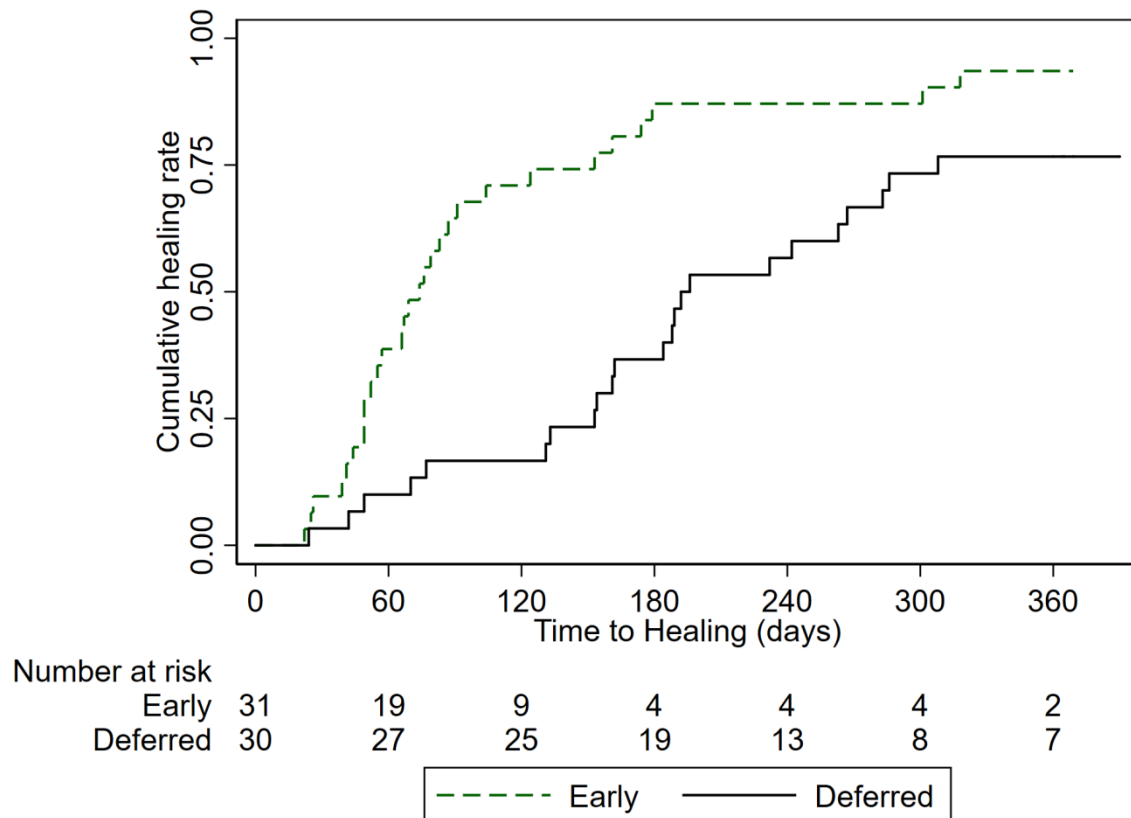
Figure 40 - Kaplan-Meier curve showing ulcer healing time in the early and deferred ablation groups among participants with protocol deviations (p<0.001) (217)

Table 34- Per-protocol analysis for 12-week and 24-week ulcer healing rate and ulcer-free time (217)

	Early	Deferred
	N=192	N=195
12-week ulcer healing rate[a]	63.9%	57.0%
	(57.1%-70.6%)	(50.2%-64.1%)
24-week ulcer healing rate[a]	86.4%	82.6%
	(81.1%-90.8%)	(76.8%-87.6%)
Number of participants with healed ulcer at 12 months	180 (93.8%)	170 (87.2%)
Number of participants with recurrent ulcer[b]	23 (12.8%)	28 (16.5%)
Ulcer-free time (days)	309 (240-329)	286 (213-325)
	[n=177]	[n=176]

Data presented as frequency (percentage) for categorical variables and median (IQR) for continuous variables

[a]*Data presented as estimation by KM curve (95%CI)*

[b]*The proportion reported among participants with ulcer heal at 12 months*

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Table 35 - Per-protocol analysis for time to ulcer healing (Cox regression model) (217)

	N[a]	n[a]	Unadjusted model[b]		Adjusted model[c]	
			HR (95% CI)	p value	HR (95% CI)	p value
Treatment						
Deferred group	195	170	Ref		Ref	
Early group	192	180	1.25 (1.01-1.55)	0.04	1.31 (1.06-1.63)	0.01
Age (years)	387	350	0.99 (0.98-1.00)	0.02	1.00 (0.99-1.01)	0.56
Ulcer duration (months)						
1st Quartile (0.9-2.2)	101	91	Ref		Ref	
2nd Quartile (2.3-3.1)	101	92	1.02 (0.76-1.37)	0.88	1.03 (0.77-1.39)	0.83
3rd Quartile (3.1-4.2)	96	91	1.09 (0.81-1.46)	0.56	1.14 (0.85-1.53)	0.38
4th Quartile (4.2-8.4)	89	76	0.74 (0.54-1.00)	0.05	0.84 (0.61-1.15)	0.27
Ulcer size (cm^2)						
1st Quartile (0.4-1.5)	98	94	Ref		Ref	
2nd Quartile (1.6-2.9)	96	93	0.80 (0.60-1.07)	0.13	0.76 (0.57-1.03)	0.07
3rd Quartile (3-7.5)	98	88	0.50 (0.37-0.67)	<0.001	0.50 (0.37-0.67)	<0.001
4th Quartile (8-235)	95	75	0.30 (0.22-0.40)	<0.001	0.29 (0.21-0.41)	<0.001

[a]N: total number of participants; n: number of participants with healing ulcer

[b]Adjusted by centre as fixed effects

[c] Adjusted by centre, age, ulcer size and duration as fix effects

4.11. Discussion

The EVRA study showed that early endovenous ablation of superficial venous reflux as an adjunct to compression therapy in patients with venous leg ulceration was associated with significantly shorter time to healing compared to compression therapy alone, and patients had longer ulcer free time up to 12 months.

The EVRA study was pragmatic, and therefore designed to be have broad inclusion and exclusion criteria, coupled with interventional strategies determined by the surgeons to ensure that the study was as unrestrictive as possible.

The screening data collected gives an indication of the generalisability of the study. Despite only a 7% inclusion rate of participants which may indicate low generalisability, it is important to note the reasons why patients were not included in the study. Firstly, the largest excluded group (n=1772) were patients who had ulcers present for more than six months in duration (27%). This was mainly due to delays in referrals from primary to secondary care and secondary care waiting lists. It has already been suggested that early ablation may have an even greater effect on longer ulcer durations and with streamlining of the referral process to ensure early ablation this group may no longer exist. The second largest group excluded were 10% of those screened whose ulcers had healed by randomisation (n=610). Again, this was mainly due to delays in referral, plus this group has been shown to benefit from intervention to prevent recurrence (143)

It could be argued that the 'did not have an ulcer' group should not have been included on the screening logs. This group mainly included those who had an open wound on their leg that upon investigation was not considered to have an underlying venous or arterial cause, such as dermatological issues or simple bites. It would be helpful to have more insight into why 8% of patients screened were excluded based on 'clinical decision', but unfortunately this data was not collected. It appears that 67% (n=4410) of those screened would have been eligible for superficial intervention. The other 2145 deemed ineligible has various reasons for being contraindicated for ablation; arterial disease (n=873), other ulcer (n=393), no venous disease (n=378), insufficient venous reflux (n=267), deep venous occlusive disease (n=199), unable to adhere to compression (n=35). It is therefore likely that the study results are more generalisable than they initially appear and indeed the baseline characteristics of the trial participants are representative of the target leg ulcer population, when compared with other published studies (68, 80, 139).

Interestingly, the healing rates reported in the deferred arm at 12 (51.6%) and 24 weeks (76.3%) were higher than those previously found in other studies evaluating the effect of compression but are consistent with systematic reviews which have reported that the use of compression therapy can double the chances of a venous ulcer healing (126, 257). It is likely that this was as a result of the highly skilled vascular research staff administering high levels of good quality compression, which are likely to exceed the quality and consistency of standard care across the country, which can vary considerably due to lack of funding and resource (102, 103, 105). Despite the superior healing rates found in the deferred ablation arm, a shorter time to healing was still displayed in the early group, so it is likely that the difference may be more pronounced in the real-world scenario with the suggestion that the UK is currently only achieving healing rates at 12 months of 47% (65).

The additional advantage of an early endovenous ablation strategy over compression alone is that it can usually be administered by a single treatment, for example, 79.4% of the participants required only one procedure, and therefore patient acceptability and compliance is likely to be higher than compression therapy. From our data it is also evident that patients are more willing to undergo the intervention earlier when they have an open ulcer. Once the ulcer is healed and no longer symptomatic, it appears that they are less likely to attend for the intervention, which could mean that the ulcer is more likely to recur.

The recurrence rate in the early arm at 12 months was 5% points less than the deferred arm, but as the trial demonstrated faster healing in the early arm, it is possible that the true effect of early intervention on recurrence is underestimated at 12 months as those who heal earlier, have longer in which to recur.

The inclusion criteria for the trial was designed with an upper limit of six months in duration, as not only does ulcer duration appears to be an independent factor related to ulcer healing, but there were concerns that the investigators would lose equipoise at six months as it may be unethical to withhold treatment from those who did not heal after six months of conservative compression bandage therapy. The sub-group analysis results should be interpreted with caution as they were not powered to detect interactions but there was an observable trend for a greater benefit from early intervention as the ulcer duration increases across the quartiles. Further studies are required to investigate the effect of early ablation on ulcer durations longer than six months.

4.11.1 Intervention related complications

The most commonly reported intervention-related complications were DVT and pain. The DVT rate was higher than reported previously in the literature but upon investigation it appears that six were infra-popliteal (with four identified during routine scans one-week post intervention as per local care in that site) and these sub-clinical DVTs would likely not be detected without such investigation.

Ninety-eight SAEs were reported over the course of the study, which is to be expected given the age and comorbidities of the study population, but only seven were deemed to be possibly, probably or definitely related to the ablation procedures (four in the early arm and three in the deferred arm) and this was not clinically significant.

4.11.2 Health related quality of life

Early ablation led to a meaningful improvement in disease-specific (AVVQ) and general HRQoL (EQ-5D® Index Value), and body pain (SF-36 Body Pain), over the follow up period. The differences were most pronounced at six weeks and six months post randomisation, which is consistent with more rapid healing but these differences, appeared to narrow at 12 months. It will be interesting to see if any differences in quality of life are seen in the longer term.

4.11.3. Strengths and limitations of the EVRA RCT

4.11.3.1 Strengths

Sample size and loss to follow-up

The study recruited the target sample size of 450 participants and at least 254 events occurred (healed legs) to ensure that the study was adequately powered, resulting in the EVRA study being the largest RCT to evaluate the effect of early endovenous ablation of superficial venous reflux on ulcer healing. Over 12 months, 31 (7%) participants were lost to follow-up or withdrew and 12 died, which did not exceed the 10% estimated dropout rate.

Missing data

Due to the low withdrawal rate, there was relatively little missing data with respect to the primary and secondary outcomes.

The health outcomes suffered from some missing data, due to attrition over time but this is usually expected and accounted for in the sensitivity analysis by multiple imputation and did not result a marked difference from the base case analysis.

In total 24% of participants had some costs of ED-5Q missing data over the 12 months. Although the base case only included those with complete data, the sensitivity analyses used multiple imputation to include all participants and again, the results did not differ greatly.

Verification visit and blinded outcome assessment
As the study was a surgical trial (involving intervention timing) it was impossible to blind the treatment allocation from the research team or the participants. A key strength of the study, however, was the assessment of the primary outcome, performed by independent assessors who were blinded to the treatment allocation.

4.11.3.2 Limitations

Recruitment
Recruitment was slower than anticipated, mainly due to the lack of referrals from primary care and large proportions of patients with chronic ulcers over six months in duration. It is unlikely that this contributed to bias but reflects the current difficulties encountered within the NHS.

Centre, endovenous modality and compression variations
As with most RCTs, there were variations of practice between the recruiting sites, most notably in this trial with the choice and availability of endovenous modality and compression therapies and variability between individual surgeons. To address this, we stipulated core ablation principals, stratified by centre and included centre as a random effect in the Cox regression analysis.

The study was not powered to compare the different ablation modalities with respect to ulcer healing, which may be relevant because of the significant differences between the procedures with respect to cost. The common ablation technique utilised in this trial was ultrasound-guided sclerotherapy (46.9% of cases), most likely reflecting its low cost and versatility Foam sclerotherapy has been shown to have lower occlusion rates of 51% at 12 months (258). Although it is acknowledged that thermal ablation of truncal superficial reflux may result in better occlusion rates (259) (260), there have been several studies demonstrating good ulcer healing outcomes with foam (155, 156). Longer term analysis could shed light on whether differing rates of venous occlusion impact the rates of ulcer recurrence.

Superficial venous reflux patterns
The superficial venous reflux patterns and presence of deep venous incompetence varied amongst participants at baseline but overall the results support the current literature

demonstrating the benefit of treating superficial venous reflux even in the presence of concomitant deep venous incompetence (34, 186, 261).

Post-ablation Duplex

A post-ablation Duplex ultrasound at six weeks was required only for participants of the early arm, whereas the post-ablation strategy for the deferred arm was as per standard care. It is possible that this led to more frequent repeat ablations and hence a higher success in the early arm at 12 months, but this is only relevant to the longer-term recurrence rates and not the primary outcome of ulcer healing.

Ulcer recurrence

A limitation of the recurrence data collection is that it was mostly participant reported and therefore may be subject to inaccuracies. Data were verified by hospital and primary care notes wherever possible to minimise this. The 12-month follow-up period was too short to give meaningful recurrence data as there is a potential bias against the early ablation group, but with the median follow-up at 3.5 years we anticipated that this bias will diminish.

4.12. Conclusion

The EVRA RCT showed that early endovenous ablation of superficial venous reflux in addition to compression therapy was associated with shorter time to ulcer healing of venous leg ulcers than compression alone.

Chapter 5: EVRA main trial results up to 12 months – Health Economics

5.1. Resource use and total cost analysis

The number of ablation procedures and overall subsequent resource use in the 450 randomised participants is summarised in *Appendix 6 Table S7 and Figure 41*. The total mean cost per participant was calculated over 12 months and excluded any participants who terminated the study before 12 months, but those who died during the year were included in the cost analysis with costs set to zero after the date of death. In total 419 participants completed 12 months of the study or died; 211 in the deferred ablation group (226 randomised, less 15 withdrawals or lost to follow up) *versus* 208 in the early group (224 randomised, less 16 withdrawals or lost to follow up). (*Figure 31 CONSORT*).

The total mean cost over 12 months was very similar in the two study groups: £2514 (SD 2770) (€2834 (SD 3123)) for 208 participants randomised to early ablation versus £2516 (SD 3242) (€2836 (SD 3655)) for 211 participants in the deferred ablation group.

Greater initial costs were incurred in the early ablation group due to the early intervention because a greater proportion of participants had ablation by 12 months. Despite the study protocol allowing participants in the deferred group to have a procedure once the ulcer was healed, many were not treated (55/226 had no intervention in the deferred arm compared with 7/224 in the early arm at 1 year) (*Appendix 6 Table S7*). Reasons for not performing ablation procedures were not consistently captured but both participant and clinician preferences seemed to have played a role.

Despite the greater initial costs in the early ablation group, these were offset by fewer consumables used and the lower costs from having fewer district nurse visits due to quicker

wound healing (*Appendix 6 Table S7*). Other resource use was similar across the two groups (*Figure 41*).
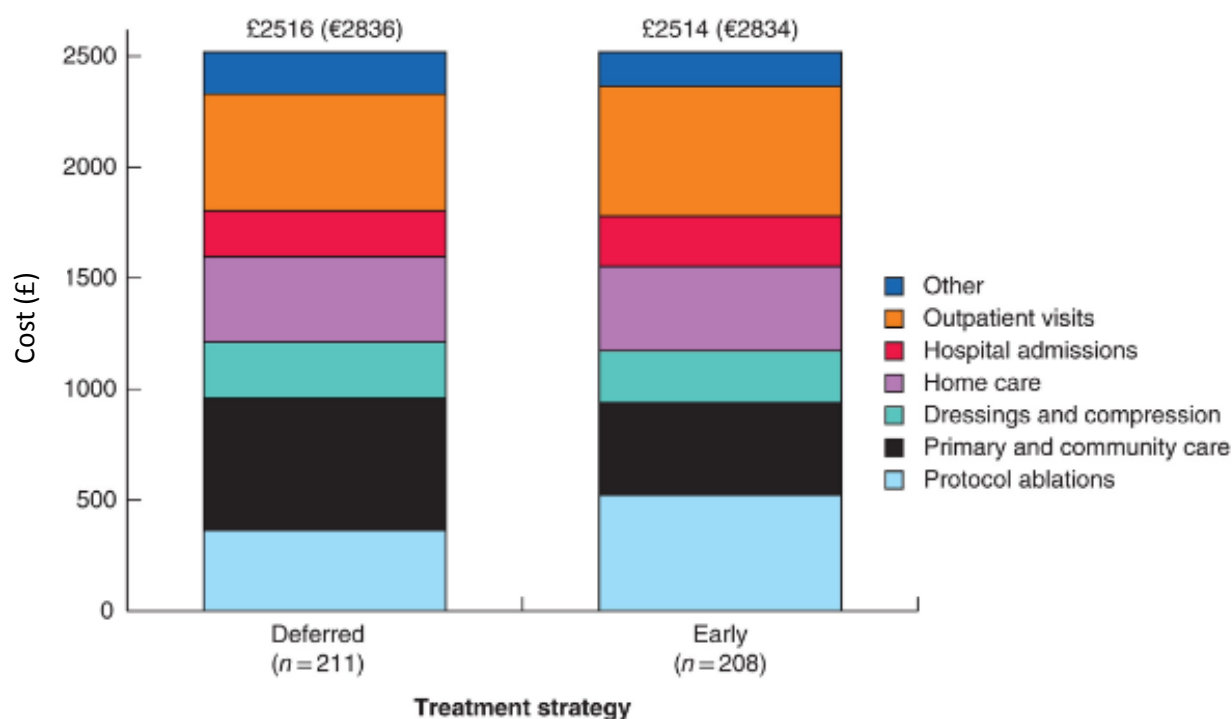
Figure 41 - Mean NHS and personal social services costs of early versus deferred strategies over 12 months, for participants with complete data on costs £ N=208 (early) and N=211 (deferred). From (231) with permission.

Table 36 shows the total number of vein procedures, including those reported in the monthly telephone follow-up. To avoid double counting, a record was assumed to be duplicated if a participant reported the same procedure in the same month in both the CRF and the telephone follow-up.

Table 36 - All varicose vein ablation procedures recorded in the study (217)

Number of procedures	Early (n=224)	Deferred (n=226)
No procedure	7	55
≥ 1 procedure	218 (97%)	171 (76%)
≥ 2 procedures	68 (30%)	51 (23%)
≥ 3 procedures	38 (17%)	21 (9%)
≥ 4 procedures	6 (3%)	7 (3%)
5	0	1 (<1%)

5.2. Cost-effectiveness analysis

The cost-effectiveness analysis uses data on both total costs and QALYs over 12 months. *Table 37* summarises the pattern of missing data, which was similar in both arms (23% in the early arm and 24% in the deferred arm).

31 (7%) participants had missing data for costs (due to withdrawal or protocol deviation), whereas (16%) had some missing data at 12 months for EQ-5D-5L, mainly due to withdrawal, or partial completion of questions in the HRQoL questionnaires at each follow up. Overall, 24% (106 of 450 participants) had some missing EQ-5D® or cost data over the year and hence a total of 344 /450 (76%) of participants were included in the complete case cost-effectiveness analysis.

Table 37 - Pattern of missing data (217)

Randomised	Early ablation n=224	Deferred ablation n=226	Total n=450
Any missing cost data over the year	16 (7%)	15 (7%)	31 (7%)
Missing EQ-5D-5L at baseline	2 (<1%)	0 (0%)	2 (<1%)
Missing EQ-5D-5L at 6 weeks	13 (6%)	18 (8%)	31 (7%)
Missing EQ-5D-5L at 6 months	36 (16%)	31 (14%)	67 (14%)
Missing EQ-5D-5L at 12 months	36 (16%)	36 (16%)	72 (16%)
Any missing data over the year	51 (23%)	55 (24%)	106 (24%)
Complete cases	173	171	344

Table 38 shows the results of the cost and QALY regressions for the cost-effectiveness analysis.

In the complete case analysis (Model 1), the mean difference (early less deferred) in cost per participant was £163 (SE 318) (€184(358)), the difference in QALY at 12 months was 0.041 (SE 0.017) and the ICER was £3976 (€4482)/ QALY. There was an 89% probability that early venous surgery is cost-effective at the current 'willingness to pay' threshold of £20,000 (€22 546)/ QALY (*Figure 42*). Assuming bivariate normality to estimate standard errors gave

very similar results (Model 2). There was a significant negative correlation between costs and QALYs, indicating that participants with a worse quality of life were also those who tended to incur greater healthcare costs (correlation –0.294, p<0.001).

Missing data were imputed (Model 3) so that all 450 participants were included. The mean difference in total cost was -£72 (SE 290) (−€81(327)) – early intervention was cheaper at 12 months, and the mean difference in QALY over 12 months was 0.058 (SE 0.018). There was a 99% probability of early intervention being cost effective at a threshold of £20,000 (€22 546)/ QALY.

Using alternative tariff values for the EQ-5D-5L resulted in a slightly smaller difference in QALY between the treatment groups, but the ICER was similar to the base case (Model 4).

The per-protocol analysis (Model 5) used the same approach as Model 1, but excluded the protocol deviations (n=117, 59 in early group and 58 in the deferred group). Of these, 46 had both a protocol deviation and missing data at 12 months, hence 273 participants were included in the analysis (344 with complete data at 12 months, less 71 (117-46) protocol deviations). The ICER in this model was £8679 (€9784)/ QALY.

Table 38 - Regression results for cost-effectiveness analysis. Adapted from (231) with permission.

Coefficient	Model 1 (base case)[a]	Model 2[b]	Model 3	Model 4	Model 5
	Complete case (N=344), with bootstrap standard errors (1000 samples) & crosswalk EQ-5D tariff	Complete case (N=344), with bivariate normal standard errors & crosswalk EQ-5D tariff	10 multiple imputations (N=450), with bivariate normal standard errors & crosswalk EQ-5D tariff	Complete case (N=344) with bootstrap standard errors & Devlin EQ-5D-5L tariff	Per-protocol compliers (N=273) with bootstrap standard errors
Difference in cost, mean (SE), p-values	163(318), p=0.607	163 (322), p=0.612	-72 (290), p=0.803	163 (322), p=0.612	486 (326), p=0.137
Difference in QALY, mean (SE), p-value	0.041 (0.017), p=0.017	0.041 (0.018), p=0.024	0.058 (0.018), p=0.002	0.033 (0.016), p=0.039	0.056 (0.019), p=0.003
ICER (£/QALY)	£3976	£3976	n/c	£4939	£8679
(€/QALY)	€4482	€4482	n/c	€5568	€9784

[a] Base-case or primary analysis.
[b] Estimated correlation of residuals between cost and quality-adjusted life-years (QALYs) in the bivariable normal model: −0·294 (P < 0·001). n/c ICER is not computable as early intervention is estimated to cost less and deliver greater QALY gain than deferred intervention
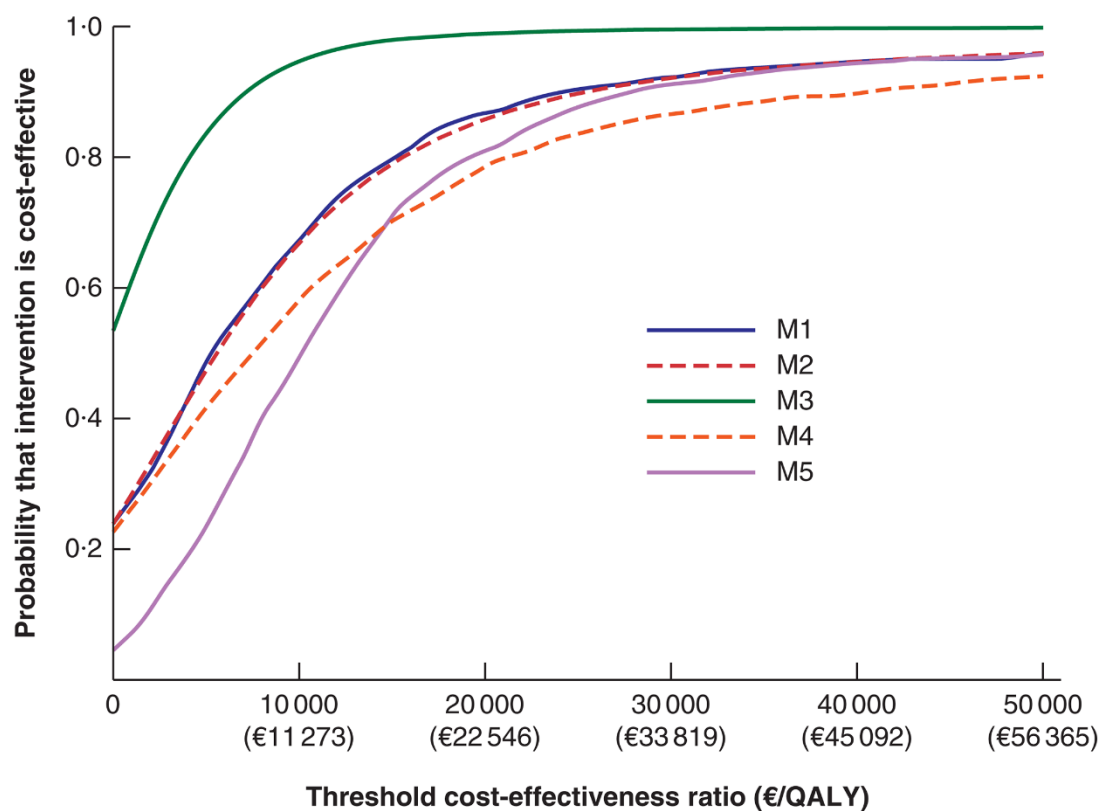
Figure 42 - Cost-effectiveness acceptability curves for each model. M1: complete case model; M2: complete case using bivariate normal model; M3: multiple imputation; M4: alternative EQ-5D-5L tariff; M5: Per-protocol. Reproduced from (231) with permission.

5.3 Discussion

This economic analysis compared early versus deferred endovenous ablation for the treatment of superficial venous reflux in participants with venous leg ulcers. The complete case analysis showed little difference in total mean cost per participant over 12 months between early and deferred ablation (mean difference £163 [SE 318] (€184(358); p=0.607). The greater initial mean cost of the early ablation strategy was mostly offset by the reduced cost of treating unhealed leg ulcers. There is however a substantial and statistically significant gain in QALY over 12 months, with a mean difference of 0.041 (SE 0.017), p=0.017. The ICER of early ablation at 12 months was therefore £3976 (€4482)/ QALY, compared with deferred ablation, with a high probability (89%) of being more cost effective at conventional UK WTP thresholds (£20,000 per QALY). Sensitivity analyses using alternative statistical models gave qualitatively similar results.

Interestingly, QALY gain over 12 months between early and deferred ablation strategies was found to be larger than those reported in a recent systematic review comparing studies that evaluated the costs and benefits of complex wound interventions (214).

Whilst the EVRA trial detected some trends for clinical benefit across pre-defined sub-groups, it was not powered to detect any meaningful differences, and hence the cost effectiveness study did not evaluate the cost benefit across the sub-groups, such as specific endovenous interventions and more research is required in this area.

Despite the difference in HRQoL appearing to narrow at 1 year, results from the longer-term follow-up (*See Chapter 7*) are required to see if the early ablation cost gains are maintained. The ESCHAR trial showed that surgery, in addition to compression to treat superficial venous reflux, reduced the recurrences rates compared to compression alone (143). If the early ablation strategy also results in lower recurrence risk in addition to reducing the time to healing, then an even more pronounced cost-effectiveness may be observed over the lifetime of the patient (231).

The strengths of the health economic analysis were the low rates of missing data and that it was performed from the NICE recommended perspective of 'NHS and personal and social services'. The main limitations were using the average costs of each intervention and using assumptions for some costings rather than actual data and that the findings are only generalisable to the UK, as the model is not translatable to other healthcare systems globally.

Chapter 6: Global Management of Leg ulceration – Service evaluation (post EVRA results)

6.1 Global secondary care survey of venous leg ulceration management questionnaire – post EVRA trial

6.1.1 Introduction

As previously discussed in *Chapter 1,* the UK NICE guidelines for varicose veins was introduced in 2013 and recommends the referral of patients with open ulceration to a specialised vascular centre within two weeks to diagnose the underlying aetiology. Unfortunately, this seems to have made little impact on the number of patients being referred (110, 248). Davies et al. hypothesised that this may be due to four main reasons; economic, gaps in the training and education of primary care providers, lack of patient awareness of available treatments and the absence of an evidence base underpinning the guidelines to encourage early diagnosis, referral and intervention (263). Likewise, other global guidelines do not steer clinicians with respect to referral for assessment, presumably because of the lack of level 1 evidence to guide policy makers (17, 114).

The EVRA trial 12-month results were published in the New England journal of Medicine (NEJM) on 24th April 2018, with dissemination via regional, national and international conferences throughout the year, with the aim to share the results as widely as possible. The results were also publicised by social media, including the NIHR dissemination channels. As the EVRA trial is the first RCT to provide level 1 evidence to show that an early intervention strategy is cost effective that can reduce the time to ulcer healing it has the potential to strengthen guidelines and change practice with respect to the management of patients with leg ulceration.

6.1.2 Aim

The aim of this section is to determine the standards of global management of patients with venous leg ulceration in secondary care four to six months after the release of the EVRA RCT results to see if the trial has impacted practice, particularly with respect to the timing of the intervention.

6.1.3 Methods

An online, 11 question survey was created and distributed as per the methods detailed in *section 3.3.3* using local, national and international mailing lists. Again, a focus group of three clinicians were asked to identify important and appropriate questions to include. Themes included: referral time from primary to secondary care and time to intervention, knowledge of the NICE guidelines, understanding of the EVRA study trial results and the impact these may have on practice. The survey then underwent five rounds of revisions and was piloted externally on a further five surgeons to confirm appropriate content and face validity.

Outcomes of interest were the average referral waiting time (defined as the time between a patient's first presentation to primary care for a venous ulcer to the date that they were referred to a vascular service), time to vascular clinic review (defined as the time between the patient first being referred to vascular clinic to first being seen in vascular clinic), and whether they currently perform superficial intervention before or after ulcer healing and the wait times to do this. Clinician demographics were collected and respondents were probed about whether they were familiar with the NICE guideline for varicose veins and referral recommendations and the EVRA trial and 12-month outcomes and whether these have influenced practice with respect to timing of intervention, and if applicable barriers to doing so. Clinicians were also asked if the cost effectiveness would influence their clinical decision and opinions on whether early intervention will affect longer term recurrence rates. The survey is detailed in *Appendix 9*.

Reponses were collected over a four-month period (September 2018 to December 2018). Microsoft Excel was used to determine normality and analyse the results. The results did not follow a normal distribution and were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text was categorised by common themes for the ease of interpretation. The Mann-Whitney U test was used in SPSS to compare differences between the UK and global responses.

6.1.4. Results

6.1.4.1 Responses

In total, 664 responses were received from 78 countries with an approximate response rate of 4.4%.

Table 39 details the baseline characteristics of the respondents and *Figure 43* depicts the global responses by country. As some respondents did not answer all questions, the total number of responses are stated in each section.

Table 39 - Respondent baseline characteristics. Adapted from Heatley et al (262)

Clinician Type	Respondents (n=662)
Vascular surgeon	491 (74.2%)
Phlebologist	68 (10.3%)
General surgeon	38 (5.7%)
Interventional Radiologist	16 (2.4%)
Vascular nurse specialist	12 (1.8%)
Dermatologist	5 (0.8%)
Interventional Cardiologist	4 (0.6%)
Consultant vascular nurse	3 (0.5%)
Family medical practitioner	1 (0.2%)
Plastic Surgeon	0 (0%)
Aesthetic Practitioner	0 (0%)
Tissue Viability Nurse	0 (0%)
Other	24 (3.6%)
Region of Practice*	**(n=660)**
Europe (excluding UK)	252 (38.2%)
North America	152 (23.0%)
United Kingdom	108 (16.4%)
South America	62 (9.4%)
Asia	39 (5.9%)
Australasia	24 (3.6%)
Africa	16 (2.4%)
Central America	4 (0.6%)

Middle East	3 (0.5%)
Area of Care	**(n=657)**
Academic / teaching	369 (56.2%)
Secondary / district general / county hospital	127 (19.3%)
Primary / Community	94 (14.3%)
Other	67 (10.2%)

*Algeria (n=1),Albania (n=2) , Argentina (n=10), Australia (n=19), Austria (n=7), Bahrain (n=1), Bangladesh (n=1), Belarus (n=1), Belgium (n=12), Bolivia (n=1), Bosnia (n=1), Brazil(n=40), Bulgaria (n=7), Canada (n=6), Chile (n=1), China (n=1), Colombia (n=4), Costa Rica (n=1), Croatia (n=3), Cuba (n=1), Czech Republic (n=4), Denmark (n=2), Ecuador (n=2), Egypt (n=5), El Salvador (n=1), Finland (n=4), France (n=5), Georgia (n=1), Germany (n=22), Greece (n=12),Honduras (n=1), Hong Kong (n=1), Hungary (n=3), India (n=11),Indonesia (n=2), Iraq (n=1), Ireland (n=6), Israel (n=4), Italy (n=37), Japan (n=2), Kenya (n=1), Kosovo (n=1),Kuwait (n=1), Latvia (n=2), Lithuania (n=3), Malaysia (n=1), Mexico (n=19), Monaco (n=1), Montenegro (n=1), Netherlands (n=8), New Zealand (n=5), Norway (n=4), Pakistan (n=2), Palestine (n=1), Paraguay (n=1), Peru (n=1), Poland (n=8), Portugal (n=23), Romania (n=3), Russia (n=9), Serbia (n=3), Slovakia (n=5), Slovenia (n=6), South Africa (n=8), South Korea (n=1), Spain (n=20), Sri Lanka (n=2), Sweden(n=10), Switzerland (n=5), Taiwan (n=1), Thailand (n=9), Turkey (n=6), Ukraine (n=3), United Kingdom (n=108), USA (n=127),Uruguay (n=1), Missing (n=3)

Figure 43 - Respondents by country

6.1.4.2. Average referral time from primary care

Table 40 details the average referral time from primary care to a specialised vascular service. The overall median referral time was six weeks (IQR 2 to 12). This was longer in the UK, median time eight weeks (IQR 4-14 weeks), p=0.02 (Mann-Whitney U).

Table 40 - Average global wait time for patients with chronic venous leg ulceration to be referred from primary care / GP to a specialised vascular centre

Average referral wait time	(n=659)
Less than six weeks	312 (47.3%)
Six weeks to six months	293 (44.5%)
More than six months	49 (7.4%)
Not known	5 (0.8%)

6.1.4.3. Average waiting time to be seen in clinic once referred

Table 41 details the average waiting time to be seen in clinic once referred. The overall median waiting time was two weeks (IQR 1 to 4), increasing to four weeks in the UK (IQR 2 - 6), p<0.01 (Mann-Whitney U).

Table 41 - Average global wait time for patients with chronic venous leg ulceration to be seen in clinic once referred

Average wait time	(n=664)
One week or less	282 (42.5%)
Between one and six weeks	283 (42.6%)
Between six weeks and six months	92 (13.9%)
More than six months	7 (1.1%)

6.1.4.4. Familiarity with the EVRA Trial and results.

Of 659 respondents 69% reported that they were aware of the EVRA trial and 63% were familiar with the results.

Figure 44 shows the timing of endovenous intervention or surgery. Of 656 global respondents, 77% reported that they usually perform endovenous intervention or surgery prior to ulcer healing, with 20% performing it after healing and 3% not performing intervention. Of 107 UK respondents, 65% reported usually performing endovenous intervention or surgery prior to ulcer healing, with 30% after healing and 5% not performing intervention at all.
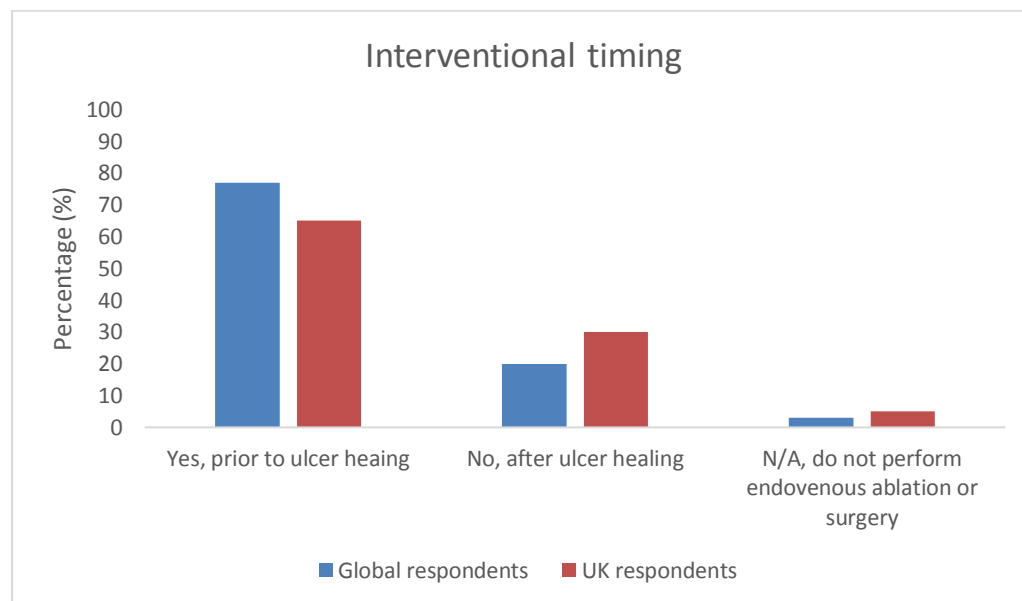
Figure 44 - Intervention timing (global n=656, UK n=107)

Of the 507 global respondents who treat prior to ulcer healing, 45% recorded that they would aim to perform the intervention immediately. For those who did not aim to treat immediately, the median aim-to-treat-time was three weeks (IQR 2 to 4). Only 28% of respondents were actually able to perform the intervention immediately and for those who could not, the median reported time to actually treat was four weeks (IQR 2 to 5).

In the UK, 33% of the 70 respondents who treat prior to ulcer healing recorded that they aim to perform intervention immediately. For those who did not aim to treat immediately, the median reported aim-to-treat-time was four weeks (IQR 2 to 6). Only 13% of respondents were able to perform intervention immediately, and those who could not reported an actual median time to treat of six weeks (IQR 4 to 8) (See *Figure 45*).

181
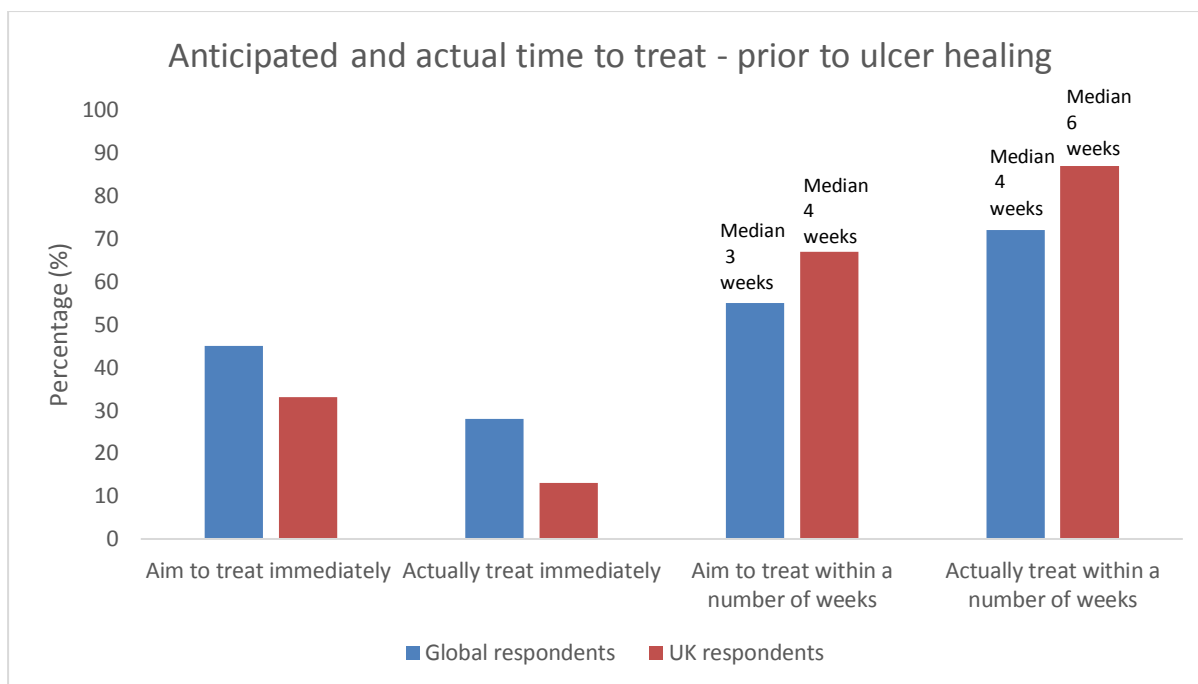
Figure 45 - Anticipated and actual time to treat – prior to ulcer healing (global n=507, UK n=70)

Figure 46 depicts the anticipated and actual time to intervene for those who treat after ulcer healing. Of the 129 global respondents who treat after ulcer healing, 39% would aim to perform the intervention immediately after healing. For those who did not aim to treat immediately, the median reported aim time from healing was four weeks (IQR 2 to 4). Only 22% of respondents recorded that they would actually be able perform the intervention immediately after healing and for those who could not, the median reported time from healing to actually treat was four weeks (IQR 4 to 8).

In the UK, of the 32 respondents who treat after ulcer healing, only 16% would aim to treat immediately after ulcer healing. For those who did not aim to treat immediately, the median recorded aim time from healing was four weeks (IQR 3 to 5.25). Only 3% of respondents were able perform the intervention immediately and for those who could not, the median time from healing to actually treat was eight weeks (IQR 4 to 10).
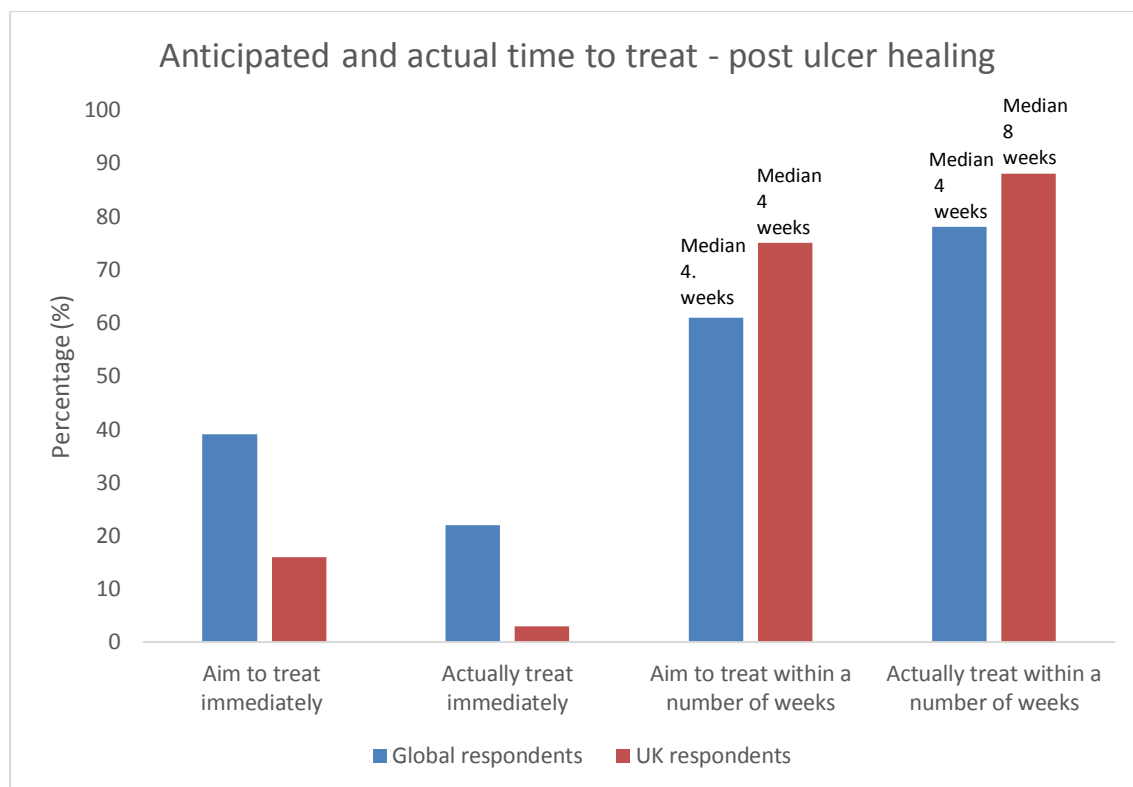
Figure 46 - Anticipated and actual time to treat – post ulcer healing (global n=129, UK n=32)

6.1.4.6. Changing practice

Figure 47 shows that 30% (n=195) of global respondents (n=637) reported that they have changed practice with respect to the timing of intervention based on the results of the EVRA study, 418 (66%) had not and 24 (4%) did not answer the question. Of those have not changed practice, 46% (n=192) of the respondents stated that they would like to and 4% (n=24) did not answer the question. Of the 51% (n=226) who have not changed practice and would not like to do so, 91% reported that they already treat prior to ulcer healing, 4% stated other reasons for not changing practice, 3% were not convinced by the trial results and 2% did provide a reason.

In the UK, 48% of respondents stated that they have changed their practice with respect to the timing of intervention based on the EVRA results and 52% have not. Of those who have not, 42% (n=22) indicated that they would like to. Of the 54% (n=28) of UK respondents who have not changed practice and would not like to, 93% stated that they already treat prior to ulcer healing and 7% stated having other reasons not to amend the timing of intervention.
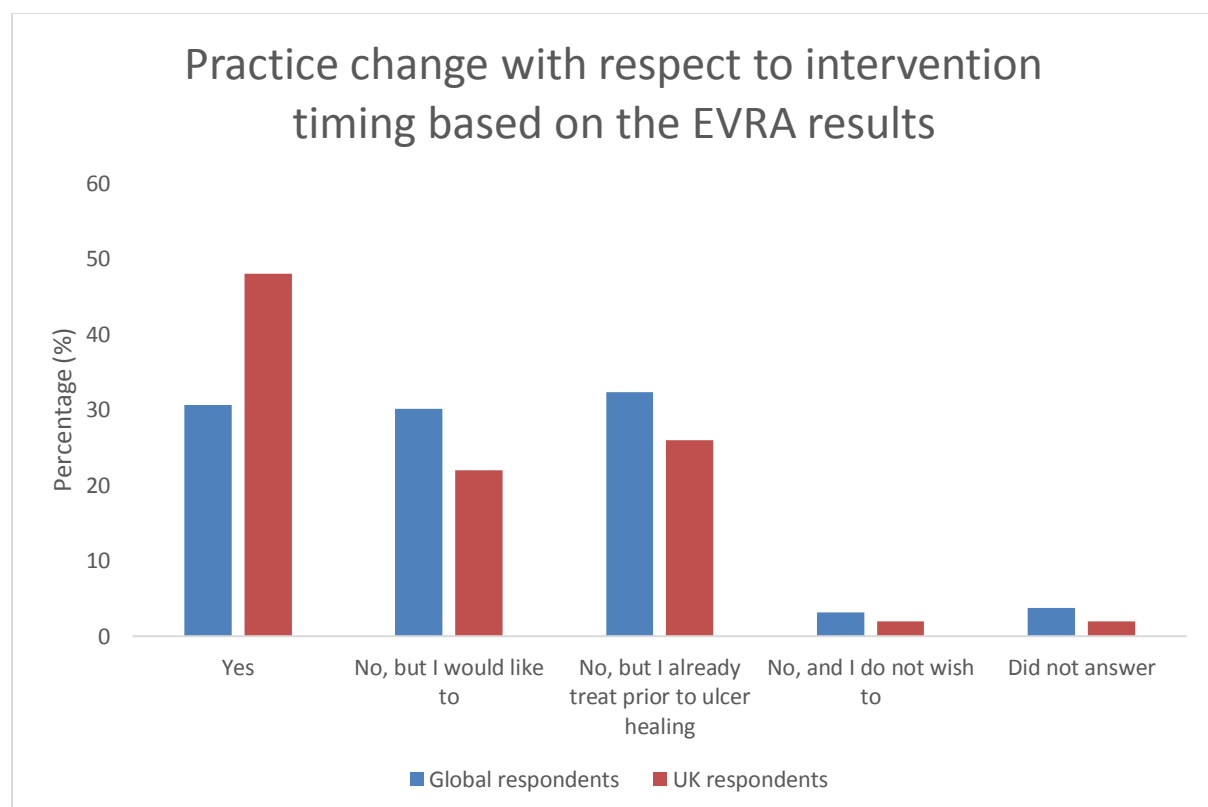
Figure 47 - Practice change with respect to intervention timing based on the EVRA results (global n=637, UK n=100)

6.1.4.7. Barriers to changing practice

As per *section 6.1.4.6*, 195 global respondents stated they had changed practice with respect to the timing of intervention based on the results of EVRA study. *Figure 48* details the barriers faced by the respondents in changing practice. Respondents could select more than one barrier and therefore 347 barriers were recorded in total.

Figure 48 - Barriers faced to change practice with respect to timing of intervention for those who have already changed practice (n=347). Adapted from (262).

As per *section 6.1.4.6*, 192 respondents stated they had not changed practice with respect to the timing of intervention based on the results of EVRA study but would like to. *Figure 49* details the barriers the respondents think they would face in changing practice. Respondents could select more than one barrier and therefore 347 barriers were recorded in total.
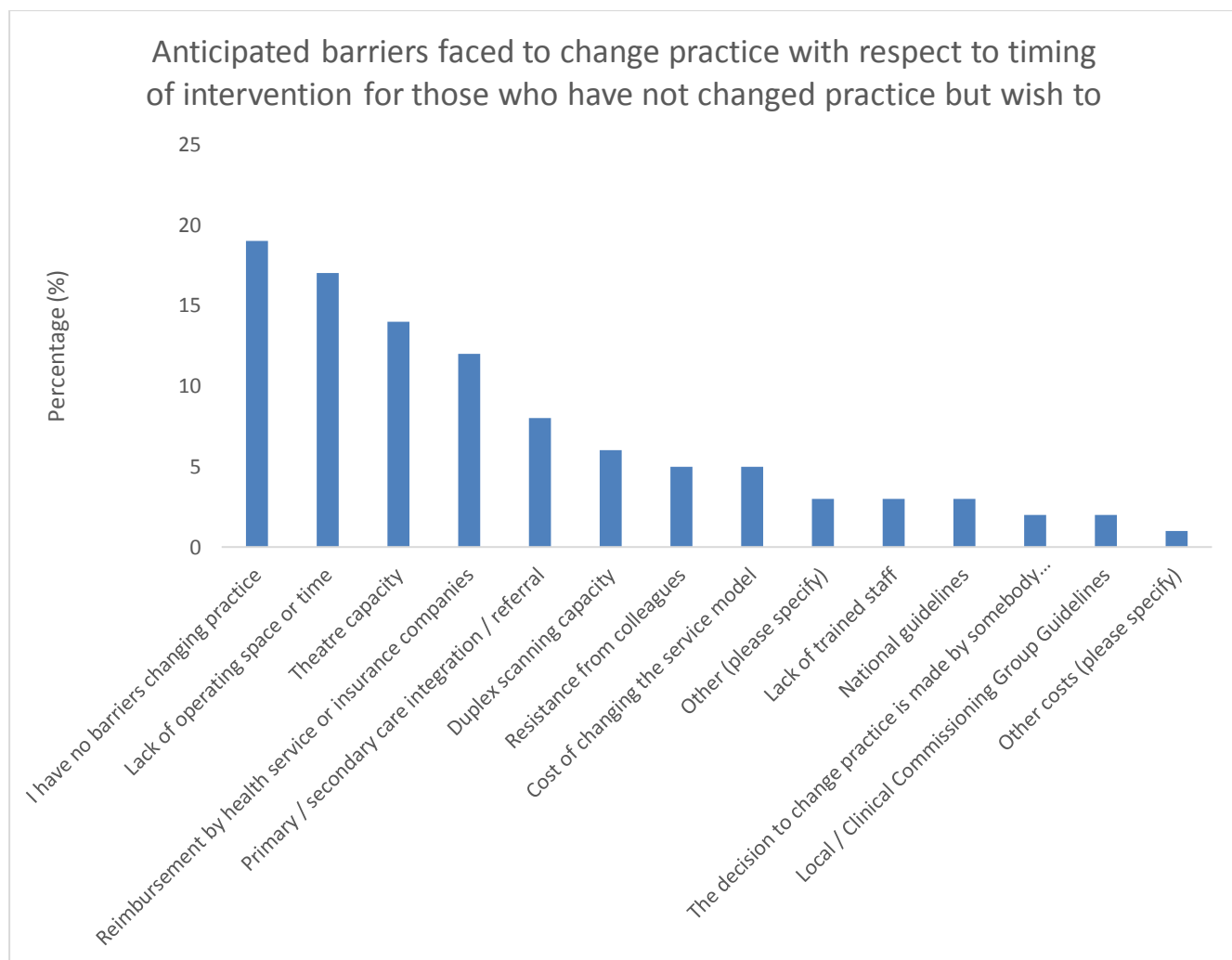
Figure 49 - Anticipated barriers faced to change practice with respect to timing of intervention for those who have not changed practice but wish to (n=347)

6.1.4.8. Cost effectiveness of early intervention

Sixty-two percent of respondents stated that the cost effectiveness results would alter how they made clinical decisions and 30% said they would not. Four percent stated that this would depend and 4% said the decisions are made by someone else such as the CCG (*Figure 50*).
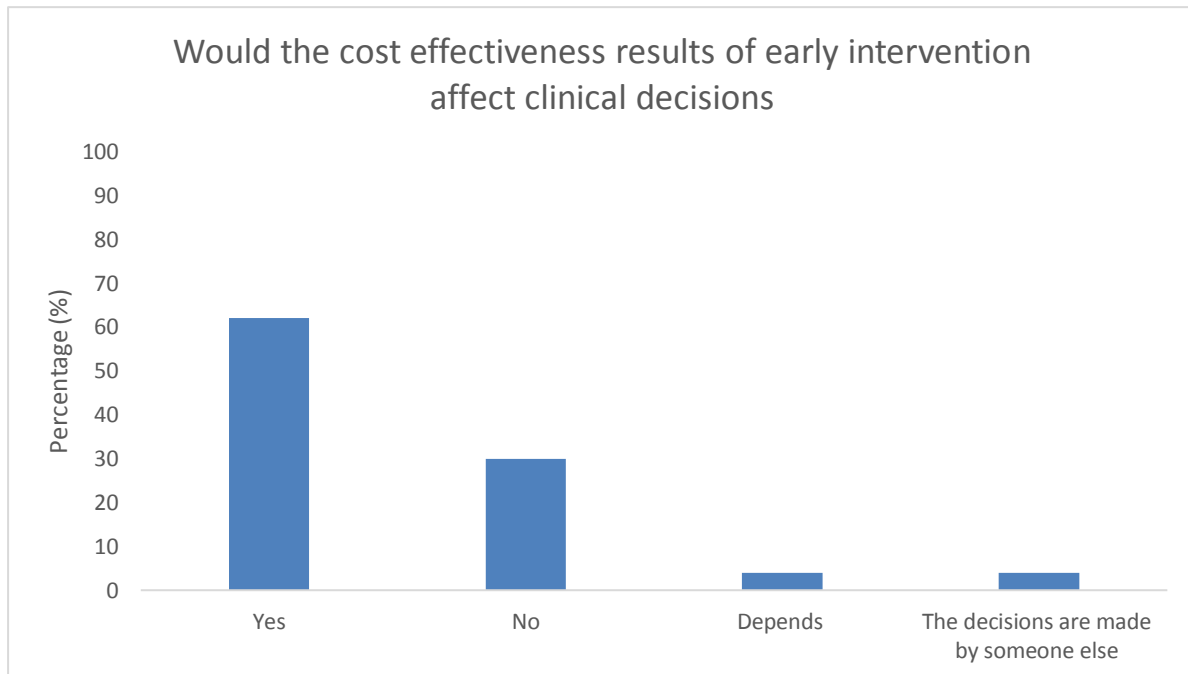
Figure 50 - Whether the cost effectiveness results of early intervention would affect how clinical decisions are made (n=630)

6.1.4.9. Opinion of whether early endovenous ablation will affect long term venous ulcer recurrence rates?

Of 627 respondents, 82% thought that early intervention will reduce longer term recurrence rates, 0.32% thought it would increase them, 13% thought there would be no effect and just under 4% thought it would depend on other factors such as the age of the ulcer, or extent of deep disease (*Figure 51*).

Opinion of whether early endovenous ablation will affect long term venous ulcer recurrence rates
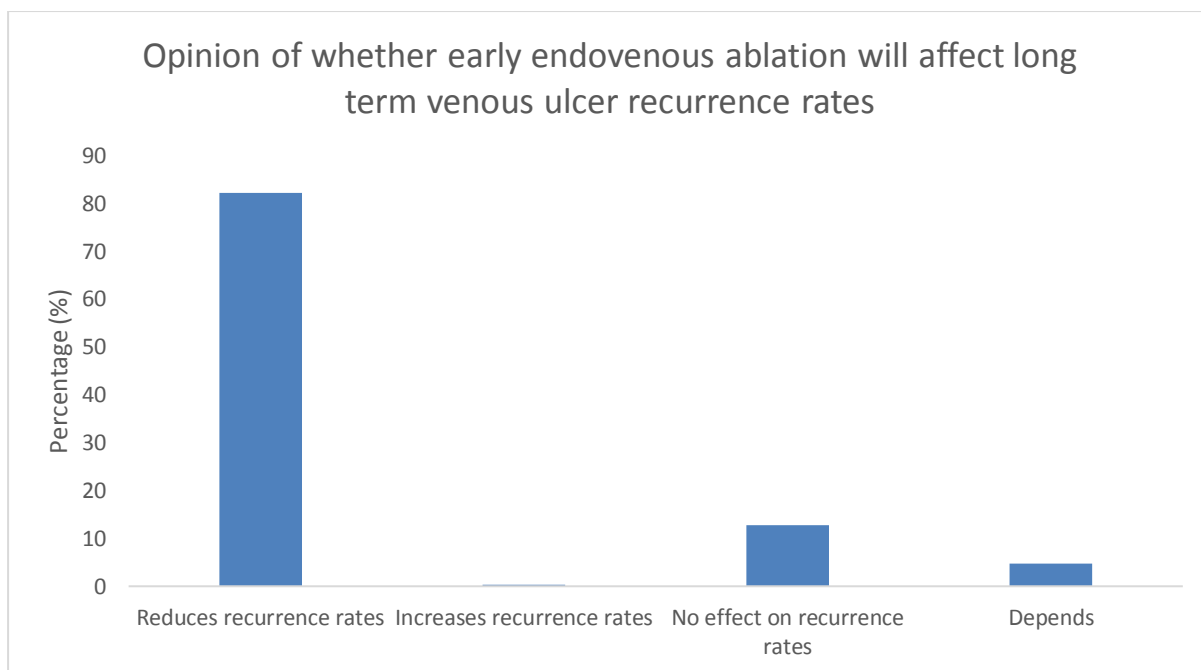
Figure 51 – Opinions on whether early ablation affect long term recurrence rates (n=627)

6.1.5. Discussion

The global management of patients with leg ulceration has previously been shown to be inconsistent (239).

In total, 664 responses were received from this survey. The proportions of clinician type and region of practice were very similar to the pre EVRA questionnaire, meaning that comparisons between the clinician surveys can be made.

The average referral times from primary to secondary care was the same as previously reported (239), indicating that the EVRA study results have made no impact on this. Once referred, there were additional waiting times reported to be seen in clinic, resulting in an overall median time to be seen as eight weeks globally and 12 weeks within the UK, which is a protracted time to seen for intervention, especially as early intervention has now been shown to improve ulcer healing (205) and is clearly longer than the recommendations issued by NICE (10).

Despite the wide dissemination of the EVRA results, less than two thirds of respondents reported being familiar with them, but 8% more respondents reported that they now perform endovenous ablation or surgery prior to ulcer healing, compared to prior to the EVRA results (15% more in the UK) indicating that there has been some practice change with respect to the timing of intervention. Interestingly, nearly a third of global (and nearly half of UK) respondents reported that they had changed practice. The majority of respondents recorded that they thought early intervention would reduce longer term recurrence rates, with only a small percentage citing they thought it would make no difference.

Despite nearly half of all respondents wanting to treat patient with open ulceration immediately from the first clinic visit, less than a third were able to achieve this. For those who did not treat immediately, the actual median time to treat was one week more than anticipated globally and two more weeks in the UK. This indicates that clinicians are mostly unable to treat as promptly as they wish and overall median time from primary care referral to first treatment is seven weeks globally and 12 weeks in the UK, probably reflecting the constraints of the national health service versus privatised health care systems globally. This is supported elsewhere where it is suggested that the UK is perhaps undertreating patients with chronic venous disease (264)

A minority of clinicians chose to perform intervention after ulcer healing. Although evidence from the randomised EVRA trial indicates that intervention can improve ulcer healing (205) this is not reflected in the UK (10), European (114), or American guidelines (11).

The proportions of the anticipated or actual barriers to changing practice were very similar, with the majority of the respondents reporting no barriers, however the three most cited were lack of operating time or space and theatre or duplex capacity accounting for nearly half of the stated barriers to change together. These barriers may explain why the clinicians were often unable to treat as promptly as they wish, and why there are protracted waiting times for referral from primary to secondary care.

Interestingly only small percentage of respondents cited costs associated with early intervention, changing the service model or lack of reimbursements from insurance companies and indeed, about 30% of the respondents reported that the cost effectiveness of early intervention would not alter how they made clinical decisions. It would be interesting to see the longer-term cost effectiveness results of the EVRA study and how these may influence practice.

The study is subject to the same limitations described for the pre-EVRA clinician surveys (*see section 3.3.5*), with 135 less responses received than the pre-EVRA survey. The lower response rate is thought to be due to time constraints preventing repeated chasing of non-responders. Despite this, the survey still gives a good overview of the current global management of patients with venous leg ulceration.

An 'Evidence-Based Interventions: Consultation Document' was published by NHS England, NHS Clinical Commissioners, the Academy of Medical Royal Colleges, NHS Improvement and the National Institute for Health and Care Excellence in July 2018 (265). This document suggested that surgery should no longer be performed in patients with varicose veins. Although the intention of the document was to highlight that other procedures such as endovenous ablation are now preferable to traditional surgery for most patients with varicose veins, and also to reduce inequalities in the provision of varicose vein interventions across England, it was widely reported in the media with the message that treatment of varicose veins is merely cosmetic and ineffective. This was potentially damaging to equality of access for needy patients and to the huge NHS cost burden of venous ulcers resulting from untreated varicose veins and may affect the number of patients with leg ulcers being referred for treatment despite being related to patients with varicose veins alone. The UK venous form

wrote to the authors to clarify that the majority of patients in the UK now have their varicose veins treated by the newer endovenous techniques (and not by surgical stripping), following the NICE recommendations of 2013 (10) and that traditional surgery is still appropriate for some patients (NICE has concluded that it is highly cost effective compared to non-interventional treatment). NICE CG168 recommends other treatments such as endothermal ablation or foam sclerotherapy should be considered first – not because traditional surgery is ineffective, but because the other treatments are less invasive and may have additional advantages. It is currently unclear if this document or the subsequent clarifications may have impacted the number of referrals patients with leg ulcers to secondary care for intervention.

The survey was only performed six months after the results of the EVRA RCT were published, hence any effects may become more pronounced with time. As this survey evaluates subjective clinician preferences on how venous ulceration is managed, additional work evaluating objective measure should be performed.

6.1.6. Conclusion

This survey has provided insights into the current management of venous ulceration and the potential impact the EVRA study may have had on this. Although many clinicians are aware of the trial, there may be a number of barriers to implementing the findings to clinical practice, including significant variation in the healthcare structures in each geographical region. Given the low response rate, a more in-depth evaluation of the barriers to achieving and delivering best practice care should be performed in each local area.

6.2 UK primary care survey of venous leg ulceration management and referral - post EVRA trial

6.2.1. Introduction

The EVRA trial results were published on 24th April 2018, with dissemination via nurse-read magazines such as Wounds UK (267) and the Nursing Times (268) and presented at national conferences such as the Tissue Viability Society and the Society for Vascular Nurses, plus regional study days for district and community nurses.

Following on from the 2017 House of Common's debate, a meeting called by Rt Hon. Lord Hunt of Kings Heath in May 2018 called for the development of a national wound care strategy programme (NWCSP). The aim of the programme is to improve assessment, treatment and healing of wounds of the lower leg and surgical acute wounds, as well as the assessment and prevention of pressure ulcers by research, education and training, and collecting wound related data via a NHS digital national community services outcome datasets (256). It is likely that this strategy will take some time to implement, but it is important to note that it focuses on care in the community and does not currently address referrals to specialist centres for intervention. The programme stated, however that "*national care pathways for wounds must be established to cover the complexity and variety of wounds, using evidence-based health economic data and academic and clinical expertise*".

There was also an aim to increase the workforce by recruiting an extra 5000 district nurses by 2019, mainly by increasing the number of UK training places by 25% and potential for increased pay via Agenda for Change pay deals (269). In May 2018 Health Minister Stephen Barclay announced that hard-to-recruit nursing disciplines such as district nursing would be offered a £10 000 'golden hello' to post-graduate students. It is not clear if this was implemented, nor the number of district nurses increased, at least this is not evident by early 2021.

6.2.2. Aim

The aim of this section is to determine the standards of referral and management of patients with venous leg ulceration in primary care after the release of the EVRA RCT results.

6.2.3. Methods

An online, 11 question survey was created and distributed as per the methods detailed in *section 3.4.3*. To ensure the appropriateness of questions the survey was reviewed by several experts in the field of venous leg ulceration, who also have expertise in research methodology. This was circulated via local and national networks, such as the Tissue Viability Network (TVN) and the Wounds Research Network (WREN). The survey was attached to the monthly email correspondents that is forwarded out to the regular mailing list. At the time WREN had approximately 300 of subscribers on their mailing list and 500 subscribed to the mailing list of the Tissue Viability Network. The survey was also posted on the Royal College of Nursing (RCN) District and Community Nursing Forum Facebook group which had approximately 5500 members at the time. The questions aimed to determine whether they were familiar with the EVRA trial and results, if they are able to refer patients with leg ulceration directly to a vascular service and if not, who is responsible. They were also probed about what percentage of patients with open and healed ulceration are referred to specialised vascular centre and the anticipated wait times if so. Opinions were sought on the recommendation that all patients with leg ulceration should be referred to a vascular service. The survey is detailed in *Appendix 10*.

Reponses were collected over a four-month period (September 2018 to December 2018). Microsoft Excel was used to determine normality and analyse the results. The results did not follow a normal distribution and were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text was categorised by common themes for the ease of interpretation.

6.2.4. Results

6.2.4.1 Responses

In total, 643 responses were received, an approximate response rate of 10%. As some respondents did not answer all questions, the total number of responses are stated in each section.

Table 42 details the respondent breakdown of primary care giver type.

Table 42 - Respondent primary care giver type. Adapted from (266)

Care giver type	Respondents (n=642)
GP	7 (1.1%)
Community nurse	311(48.4%)
District nurse	246 (38.3%)
Tissue viability nurse	35 (5.5%)
Practice nurse	19 (2.9%)
Specialist nurse	13 (2.0%)
Other	11 (1.7%)

6.2.4.2 Familiarity with the EVRA Trial and results.

Of the 643 respondents, only 14% had heard of the EVRA trial and 8% were familiar with the results.

6.2.4.3 Direct referrals to a specialised vascular service.

Table 43 shows how leg ulcer referrals must be made to a specialised leg ulcer service.

Table 43 – How leg ulcer referrals must be made to a specialised vascular service (n=593). Adapted from (266)

Referrals	Respondents (n=593)
Can refer patients directly	149 (25.1%)
Referrals must be made by GP	410 (69.1%)
Referrals must be made by someone else	25 (4.2%)
N/A – GP and can refer	9 (1.5 %)

Figure 52 shows that of the 149 respondents who can refer directly, 34% were community nurses, 43% district nurses, 7% other, 9% tissues viability nurses and 7% practice nurses. Of

the 25 respondents who stated that the referral must be made by someone else, 68% were districts nurses, 28% were community nurses and 4% were Tissue viability nurses. Of the 410 who stated referrals must be made by the GP, 41% were community nurses, 49% district nurses, 4% other, 4% tissues viability nurses and 1% practice nurses.
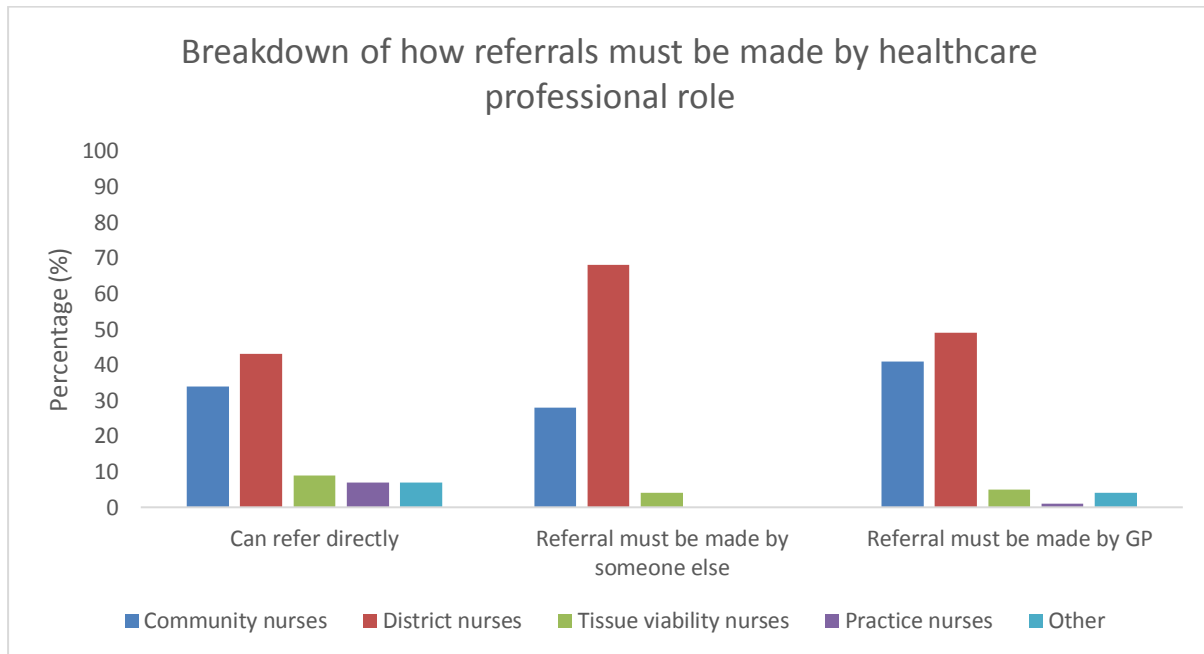
Figure 52 - Breakdown of how referrals must be made by healthcare professional role

6.2.4.4 Frequency of referrals to a specialist vascular centre prior to the EVRA results (open venous ulceration)

Of the 589 respondents 2.6% reported never referring, 28% reported referring rarely and 47% reported referring sometimes. 20.2% reported referring frequently and 2.2% reported they would always refer *(Figure 53)*.
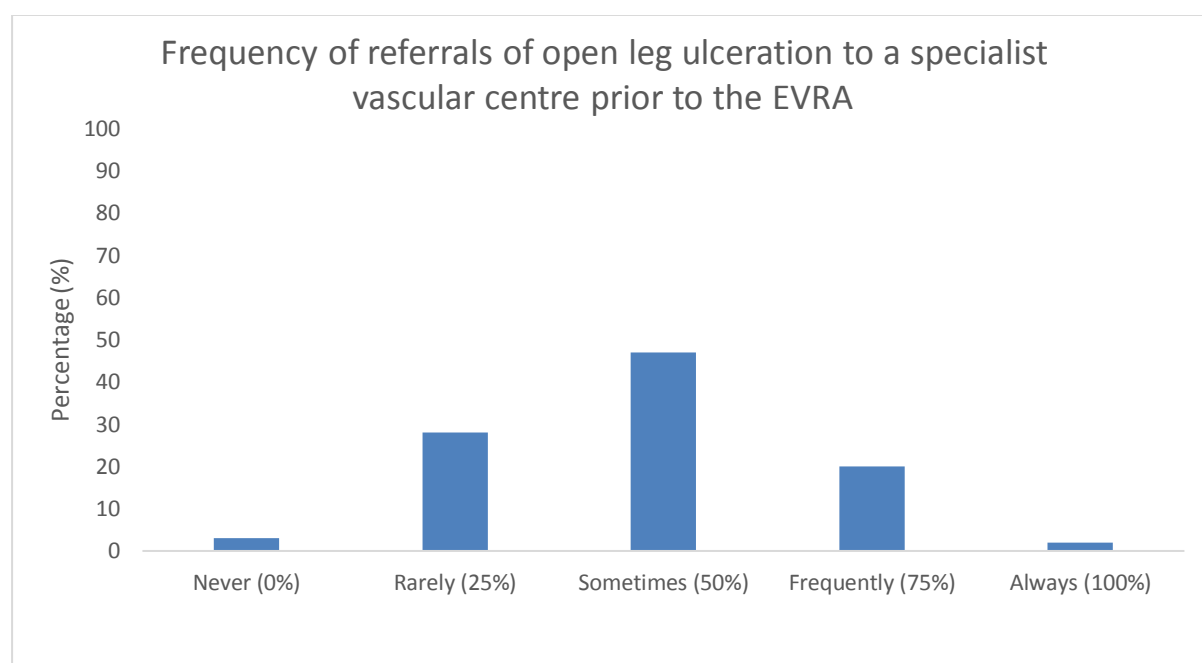
Figure 53 Frequency of referrals of open leg ulceration to a specialist vascular centre prior to the EVRA RCT (n=589)

6.2.4.5 Frequency of referrals to a specialist vascular centre prior to the EVRA results (healed venous ulceration)

When asked how often they would of referral patients with healed venous leg ulceration to specialist vascular centre prior to the EVRA results of 588 responses we received the following responses; 38.3% would never refer, 47.3% would rarely refer, 11.4% would sometimes refer, 2.2% would frequently refer and 0.9% would always refer (*Figure 54*).
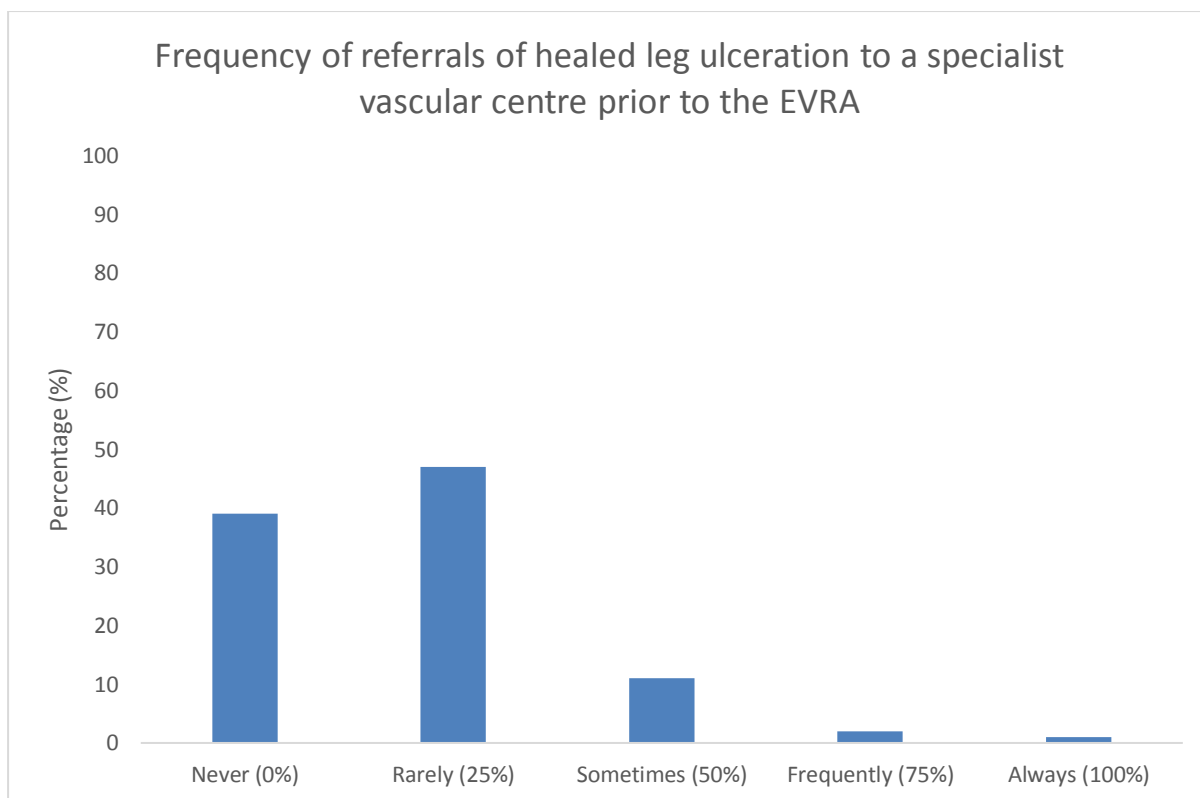
Figure 54 - Frequency of referrals of healed leg ulceration to a specialist vascular centre prior to the EVRA RCT (n=588)

6.2.4.6. Average waiting time to be seen in clinic once referred

Figure 55 details the assumed average waiting time to be seen in clinic once referred. The overall median waiting time was eight weeks (IQR 4 to 12). Of 444 respondents 29.3% assumed less than six weeks, 68.5% assumed six weeks to six months and 2.3% assumed more than six months.
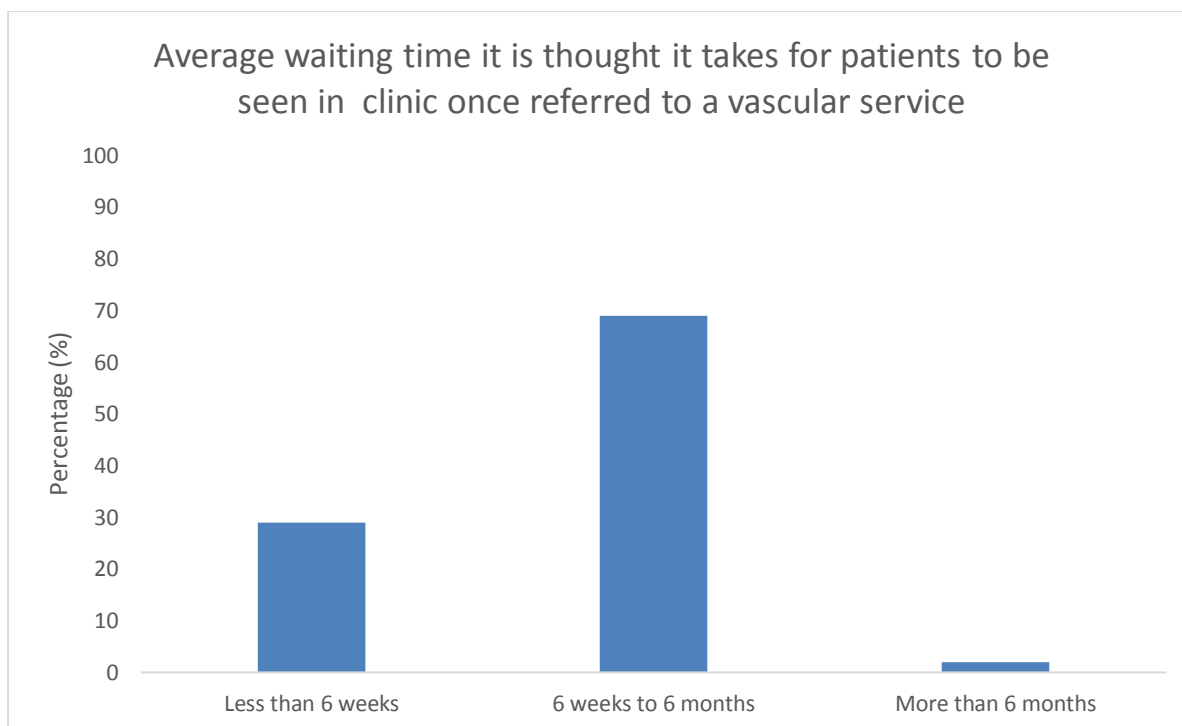
Figure 55 - Average waiting time respondents anticipate it takes for patients to be seen in clinic once referred to a vascular service (n=444)

6.2.4.7 Changing practice

Figure 56 shows 29% of respondents reported that they will change their practice with respect to referral to a specialised vascular service based on the results of the EVRA study and have no barriers to this. Of the 45% (n=198) who stated that they would like to refer earlier but the decision is made by someone else, 85% recorded that it was the GP's decision, 5% the tissue viability nurse, 8% other and 2% not stated. Of the respondents, 11% would like to change practice but face certain barriers (*see section 6.2.4.8*). Only 12% reported that they already refer promptly.
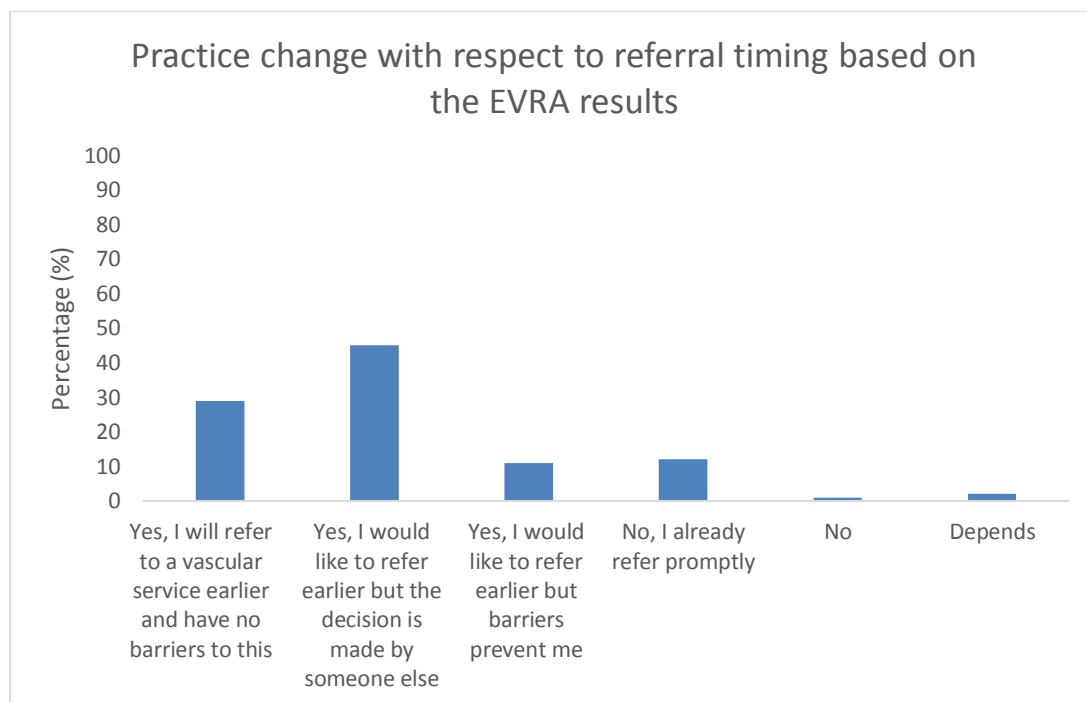
Figure 56 - Practice change with respect to referral timing based on the EVRA results (n=444). Adapted from (266)

6.2.4.8 Barriers to changing practice

The main barriers stated for changing practice were local referral pathway and policies, the capacity of vascular clinics and waiting times, and training/confidence of the primary care professionals and availability of equipment such as dopplers, plus time restrictions to perform the ABPI (*see Figure 57*).
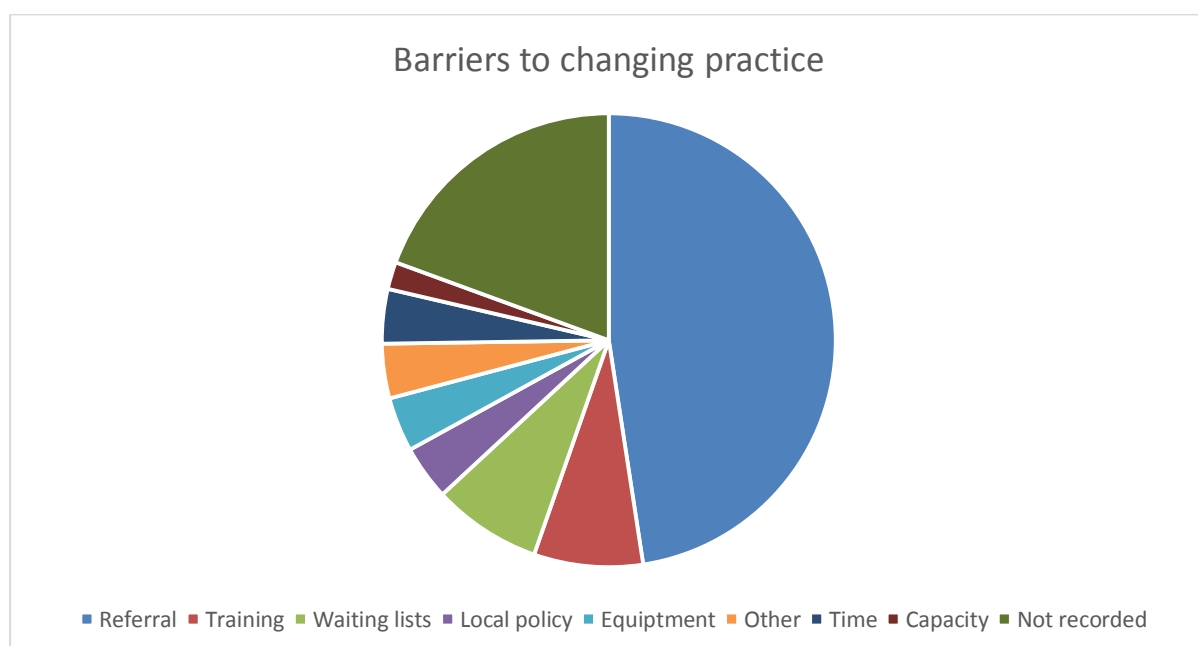
Figure 57 - Barriers to changing practice with respect to referral to a vascular service (n=49)

6.2.4.9. Familiarity of the NICE varicose veins: diagnosis and management clinical guideline [CG168]

Of 450 respondents 59% had heard of the NICE varicose veins: diagnosis and management clinical guideline [CG168] and 43% were aware of what the guideline says with respect to referral to a vascular centre.

6.2.4.10. Views on the recommendation that all leg ulcers should be referred to a vascular service for assessment and treatment

Of 449 respondents, 19% ranked the recommendation to refer all leg ulcer patients from zero to four (i.e. strongly disagree to disagree), 14% ranked the recommendation as five (neither agree or disagree), and 67% gave a score of 6 to 10 (i.e. agree to strongly agree), including 20% of respondents giving the strongest agreeance to the recommendation *(Figure 58)*.
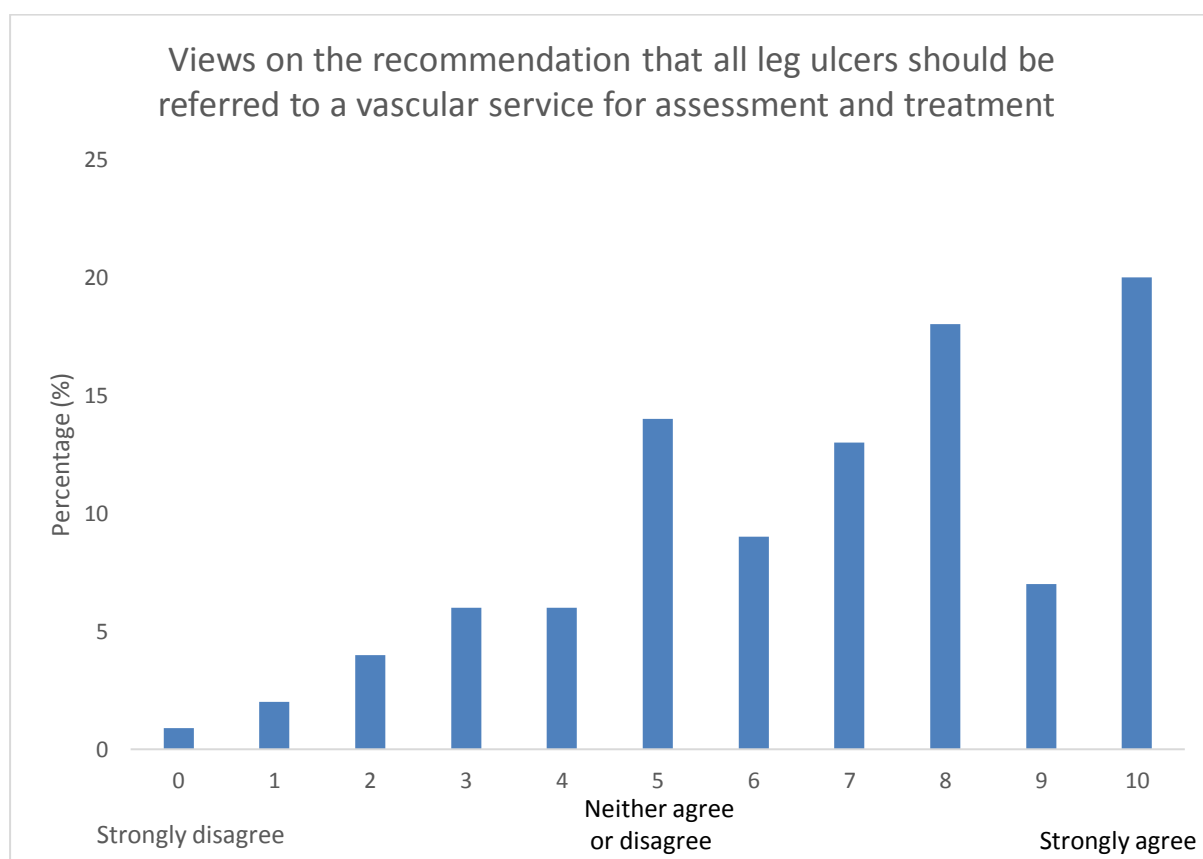
Figure 58 - Views on the recommendation that all leg ulcers should be referred to a vascular service for assessment and treatment (n=449)

6.2.5. Discussion

The number of responses (n=643) received was 7-fold higher than the number received for the primary care survey pre EVRA results and therefore is more likely to be representative of UK practice. Identification of social media groups who had a high number of district and community nurse members was the main reason for this.

Only a quarter of respondents reported that they could refer patients with a leg ulcer directly to a specialised vascular service with the remaining 75% requiring that referrals must be made by a GP, indicating a level of complexity. It appears that some district, community and tissue viability nurses can refer directly, whereas some must refer via the GP, so the ability is not role dependant and appears to be determined by local referral pathways. It is clear that GPs therefore, act as the gatekeepers for the referral of patients into secondary care. Unfortunately, GPs were not represented in this survey and therefore their views and referral criteria have not been explored.

Despite 43% of respondents reporting that they were aware of the NICE recommendations for referral (10), only a tiny proportion of respondents stated that patients with open leg ulceration were always referred to a vascular centre, with only a fifth 'frequently referring' and about half 'sometimes referring' these patients. The proportion of patients that were routinely referred was less than those reported in the pre-EVRA survey (20% vs. 32%). Over a third of patients were rarely and never referred which may be a reflection of the local CCG pathways. Interestingly less than 1% reported always referring patients with a healed leg ulcer with only another 2% frequently referring. In fact, the majority of patients with a healed leg ulcer were reported as rarely or never being referred despite the evidence from the ESCHAR trial (186) and NICE guidelines (270) recommending this. Perhaps, another factor affecting referrals is the assumed waiting time for patients to be seen in clinic, which was a median waiting time of eight weeks.

Just under a third of respondents reported that they would change practice with respect to referral timing and had no barriers to this, but perhaps, unsurprisingly, nearly half of respondents reported that although they would like to change practice, the decision to was made my someone else, with the majority reporting this was the GPs decision. To encourage changes in practice, the publication of NHS England's Commissioning for Quality and

Innovation CCG indicator specifications for 2020–2021 now includes the need for a comprehensive wound assessment and referral to a vascular specialist (271).

Training is also an apparent barrier and only 59% of respondents were aware of the NICE varicose veins: diagnosis and management clinical guideline [CG168] and less than half were aware of what the guideline recommends regarding referral to a vascular clinc. Despite this gap in knowledge, the majority of respondents thought early intervention would reduce recurrence and agreed that the idea of referring all patients will a leg ulcer to a specialist vascular service was a good policy, with less than a fifth disagreeing.

Overall the total number of responses was encouraging, although this only represents a small proportion of the professionals caring for patients with leg ulcers (approximately 1% of the community nurse population and 8% of the district nurse population) and GP were not represented. More detailed work is required to understand the referral processes of GPs as the surveys clearly highlight that they often remain responsible for this.

6.2.6. Conclusion

There is evidence in many cases that local referral pathways restrict the referral of patients with leg ulceration. Although these patients are managed in the community, many practitioners are powerless when it comes to referral to a vascular service despite wishing to refer patients promptly. It does not appear that the EVRA results have impacted the pathways, and work is needed to overcome the various barriers faced by primary care professionals to implement best practice.

Chapter 7: EVRA follow-up to five years (median of 3.5 years) Results – Clinical and health economics

7.1. Data collection

The EVRA study (205) found that 95% of ulcers in the early arm and 85% in the delayed arm experienced had healed by 12 months (*see Chapter 4*). With 344 participants (182 in the early arm and 162 in the delayed arm), the study has 82% power to detect an absolute difference in recurrence rate of 15% (30% early arm vs 45% delayed arm) and 97% power to detect an absolute difference in recurrence rate of 20% (30% early arm vs 50% delayed arm).

All living EVRA participants who had not formally withdrawn from follow-up by 12 months (n=422) were contacted by telephone between October 2018 and April 2019 to collect primary and secondary outcome data as described in *Sections 2.16.3 & 2.16.4*. Data was verified by hospital notes wherever possible. The final telephone follow-up was completed on 28th March 2019. Data was collected over the telephone and from medical notes or from medical notes alone from 399/422 participants (94.5%) still participating at one year (*Figure 59),* with a median follow-up period from randomisation of 1286 days (IQR 1038 to 1531 days) in the early-intervention group and 1287 days (IQR 1063 to 1519 days) in the deferred-intervention group. No participants died as a result of intervention and mortality was similar between the two groups (*Figure 60*).

In total, 510 endovenous interventions were performed (283 in the early arm compared with 227 in the deferred arm). In the early group, 203/224 (90.6%) were treated by early endovenous intervention within two weeks, and 97.3% of participants in this arm were treated in total. In contrast, 171/266 (75.6%) of participants in the deferred arm were treated within 12 months and 79.1% were treated in total (*Table 44*).

6555 Patients assessed for eligibility

6105 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** 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** Deep venous occlusive disease
- **71** Unable to provide consent
- **35** Unable to adhere to compression therapy
- **9** Had other reason

450 Randomized

226 Randomized to deferred-intervention group

224 Randomized to early-intervention group

12 mo
- **10** Patients withdrew from study
- **8** Patients died
- **5** Lost to follow-up

12 mo
- **1** Patient did not adhere to protocol
- **5** Patients withdrew from study
- **4** Patients died
- **10** Lost to follow-up

422 To be contacted for extended follow-up

3-5 y
- **8** Patients died
- **7** Lost to follow-up
- **10** Telephone follow-up
- **30** Medical records review
- **160** Telephone and medical records review

3-5 y
- **1** Patient withdrew from the study
- **10** Patients died
- **16** Lost to follow-up
- **11** Telephone follow-up
- **26** Medical records review
- **162** Telephone and medical records review

208 Included in intention-to-treat analysis for time to ulcer recurrence

218 Included in intention-to-treat analysis for time to ulcer recurrence

Figure 59 - updated CONSORT diagram to include participants follow-up at a median of 3.5 years. From Gohel et al. 2020 (218)

204
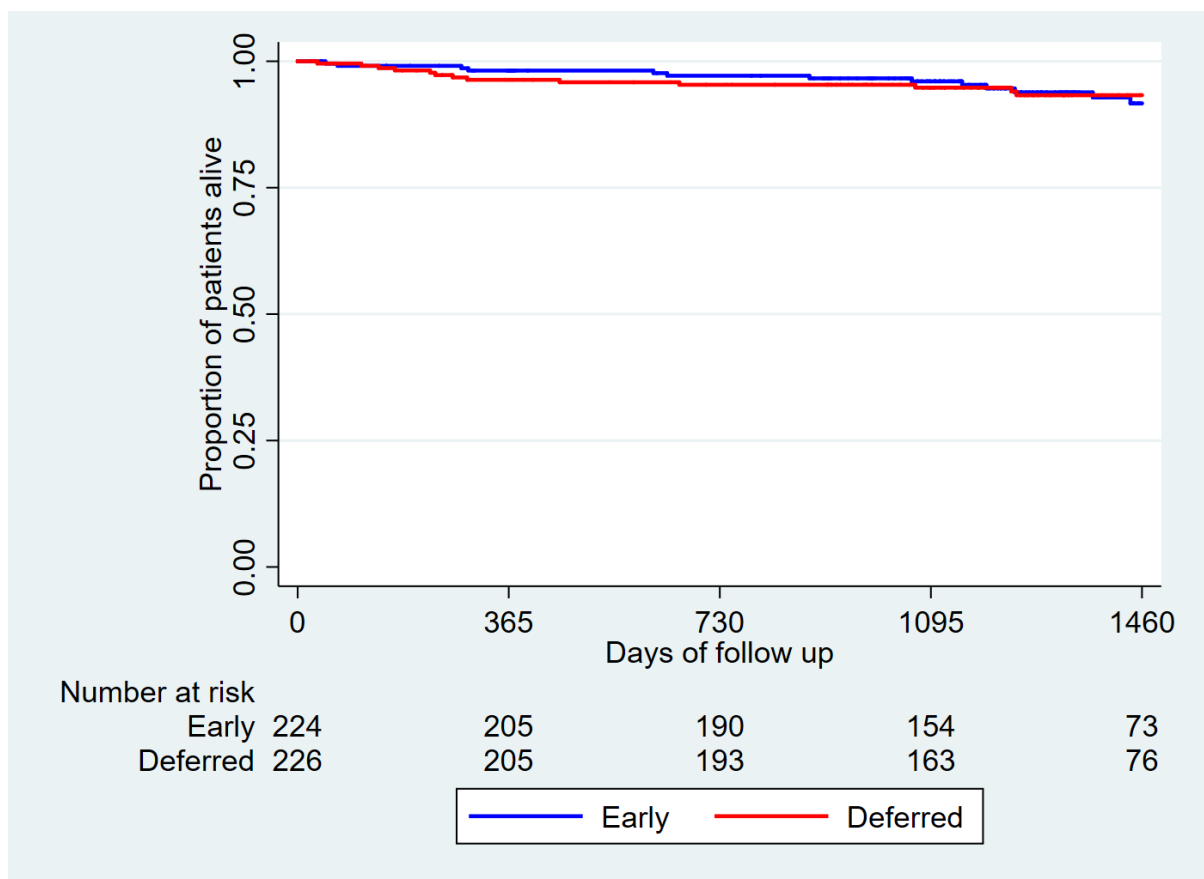
Figure 60 - Mortality rates across the follow-up period. Adapted from Gohel et al. 2020 (218)

Table 44 - Timing and number of endovenous interventions. Adapted from Gohel et al. 2020. (218)

Timing of first endovenous treatment (from randomisation)	Early intervention (n=224)	Deferred intervention (n=226)
Within 2 weeks	203 (90.6%)	1 (0.4%)
Between 2 weeks and 12 months	15 (6.7%)	170 (75.2%)
After 12 months	0 (0.0%)	8 (3.5%)
No treatment	6 (2.7%)	47 (20.8%)
Total numbers of procedures	283	227
Number of procedures per participant		
1	164	144
2	43	23
3	11	11
4	0	1

7.2. Primary outcome – time to first ulcer recurrence (from date of healing)

Of 426 participants whose leg ulcer had healed, 121 (28.4%) experienced at least one recurrence during follow-up. In total, there were 175 episodes of recurrent ulceration during the follow-up period (72 in the early-intervention group [56 participants] and 103 in the deferred-intervention group [65 participants]). *Table 45* details the number of recurrences experienced by the participants. The majority of participants experienced only one recurrence over the follow-up period.

Table 45 - The number of recurrences experienced by each participant

		Early	Deferred
		N=56	N=65
No. of recurrences	**1**	43 (77%)	38 (58%)
	2	11 (20%)	16 (25%)
	3	1 (2%)	10 (16%)
	4	1 (2%)	1 (2%)

The unadjusted cox regression model for time to first recurrence from ulcer healing can be seen in *Appendix 6 (Table S8)*.

The primary result, adjusting for participant age, ulcer size and ulcer chronicity, was similar in the early-intervention group and the deferred-intervention group (hazard ratio for ulcer recurrence, 0.82; 95% confidence interval [CI] 0.57 to 1.17; P=0.278). (*Appendix 6 Table S9 & Figure 61*)
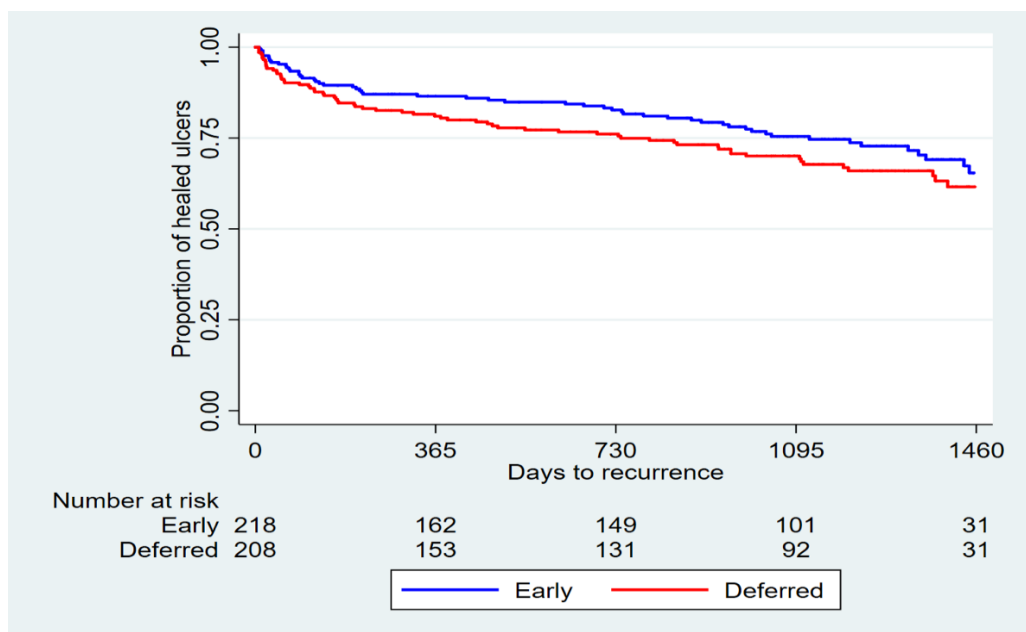
Figure 61 – Kaplan-Meier curve showing time to first ulcer recurrence (from date of healing). Log rank test: p=0.196. Adapted from Gohel et al. 2020 (218)

7.3 Secondary outcomes

7.3.1. Time to first recurrence (from randomisation)

Calculating the time to first ulcer recurrence from randomisation instead of from date of healing did not affect the results in both the unadjusted (hazard ratio 0.84 95% CI 0.59 to 1.12, P=0.326) (*Appendix 6 Table S10.*) or adjusted models (hazard ratio 0.86 95% CI 0.60 to 1.24, P=0.426) (*Appendix 6 Table S11 & Figure 62*).
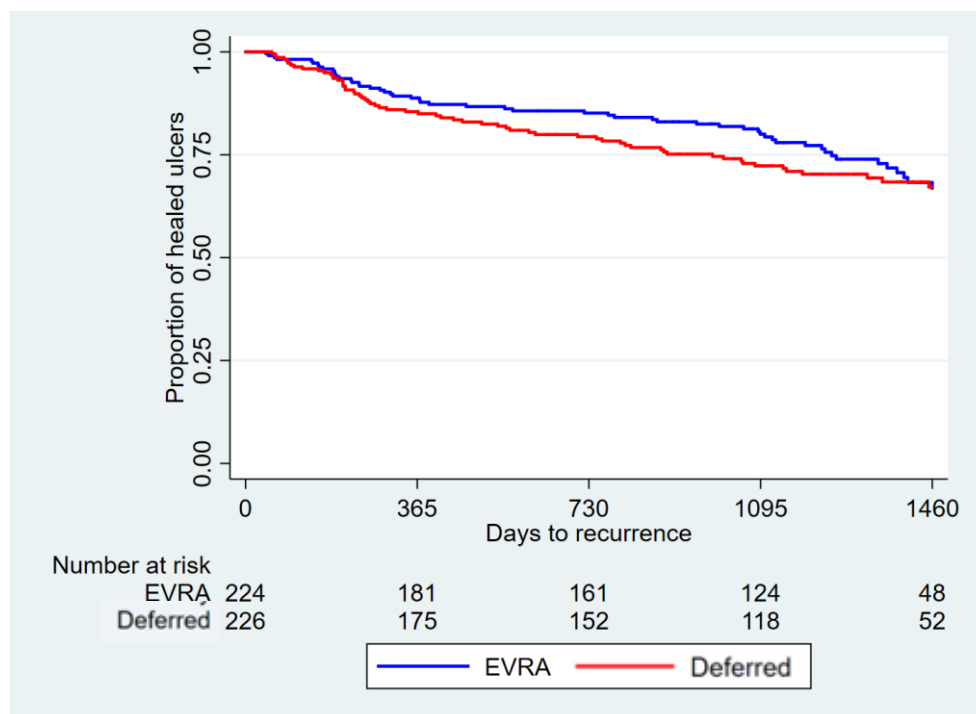
Figure 62 - Kaplan-Meier curve showing time to first recurrence (from randomisation), Log rank test: p = 0.342. Adapted from Gohel et al. 2020 (218)

7.3.2. Time to ulcer healing (from randomisation)

Time to ulcer healing was shorter in the early-intervention group for primary ulcers in both the unadjusted (*Appendix 6 Table S12*) and adjusted cox models (hazard ratio 1.36; 95% CI 1.12 to 1.64, p=0.002) (*Appendix 6 Table S13 & Figure 63).* This analysis also included primary ulcers that healed after 12 months unlike the analysis in Chapter 4.
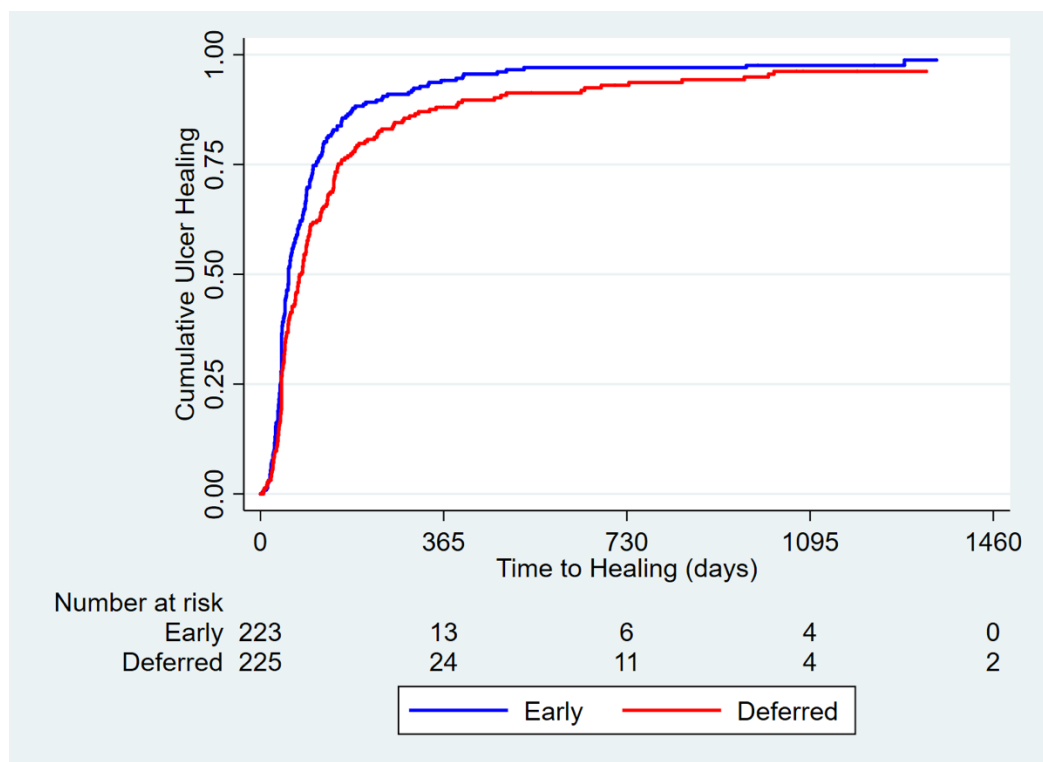
Figure 63 - Kaplan-Meier curve showing time to ulcer healing (of index ulcer), logrank test: p = 0.0016. Adapted from (218)

Among the 450 patients, there were 2 ineligible patients with ulcer healed at the time of randomisation, and the data of the two patients does not contribute to the survival analysis. Includes all ulcers that healed within the study period.

7.3.3. Ulcer Recurrence Rate (from ulcer healing, including first recurrence only)

At one-year ulcer recurrence rates from ulcer healing were 13.5% (95% CI 9.5 to 18.9) in the early group compared with 19.0% (95% CI 14.2 to 25.1) in the deferred group. At four years, these were 34.6% (95% CI 26.7 to 44.0) and 38.4% (95% CI 30.8 to 47.2) respectively (*Table 46*).

Table 46 - Recurrence rates (from ulcer healing) per year. Taken from Kaplan-Meier curve Fig 63. Adapted from Gohel et al. 2020 (218)

Study group	Follow-up	N*	Recurrences	Cumulative Recurrence rate	95% CI
Early-intervention group	1 Year	162	28	13.48%	9.51% to 18.94%
	2 Years	150	7	17.28%	12.71% to 23.26%
	3 Years	102	12	24.56%	18.99% to 31.41%
	4 Years	32	8	34.6%	26.7% to 44.04%
	5 Years	1	1**	-	-
Deferred-intervention group	1 Year	154	38	18.98%	14.18% to 25.13%
	2 Years	132	9	23.9%	18.52% to 30.53%
	3 Years	93	10	29.95%	23.92% to 37.1%
	4 Years	32	8	38.42%	30.81% to 47.18%
	5 Years	1	0	-	-

*number of participants successfully followed-up for ulcer recurrence at each time period post randomisation.
**1 participant in the early intervention group had a recurrence reported beyond 1 year and 1 participant had unreported healing time so is not included.

7.3.4. Ulcer Recurrence Rate (from randomisation, including first recurrence only)

At one-year ulcer recurrence rates from randomisation were 11.2% (95% CI 7.67 to 16.29) in the early group compared with 14.53% (95% CI 10.44 to 20.01) in the deferred group. At four years, these were 33.2% (95% CI 25.81 to 41.92) and 32.9% (95% CI 26.33 to 40.54) respectively (

Table 47).

Table 47 - Recurrence rates (from randomisation) per year.

Study group	Follow-up	N*	Recurrences	Cumulative Recurrence rate	95% CI
Early-intervention group	1 Year	181	24	11.23%	7.67% to 16.29%
	2 Years	162	7	14.86%	10.68% to 20.48%
	3 Years	126	9	20%	15.04% to 26.32%
	4 Years	48	14	33.16%	25.81% to 41.92%
Deferred-intervention group	1 Year	175	31	14.52%	10.44% to 20.01%
	2 Years	154	12	20.61%	15.7% to 26.78%
	3 Years	118	13	27.7%	22.02% to 34.49%
	4 Years	52	6	32.87%	26.33% to 40.54%

*number of participants successfully followed-up for ulcer recurrence at each time period post randomisation.

7.3.5. Incidence of recurrence

In the early intervention group, ulcers recurred at a rate of 0.107 per person years (PY), compared with 0.162 per PY in the deferred-intervention group (72 ulcers recurred in a total of 675.5 years of follow-up in the early arm vs. 103 ulcers in the deferred-intervention group during 636.0 years). The Incidence Rate Ratio (IRR) was therefore 0.658 (95% CI: 0.480 to 0.898, p=0.003) and was significant.

7.3.6. Healing time of first recurrence

The unadjusted cox regression model for time to healing of first recurrence can be seen in *Appendix 6 Table S14*.

Adjusting for participant age, ulcer size and ulcer chronicity, time to healing of first recurrence was similar in the early-intervention group and the deferred-intervention group (hazard ratio for ulcer recurrence, 0.91; 95% confidence interval [CI] 0.61 to 1.35; P=0.644) (*Appendix 6 Table S15 & Figure 64*).
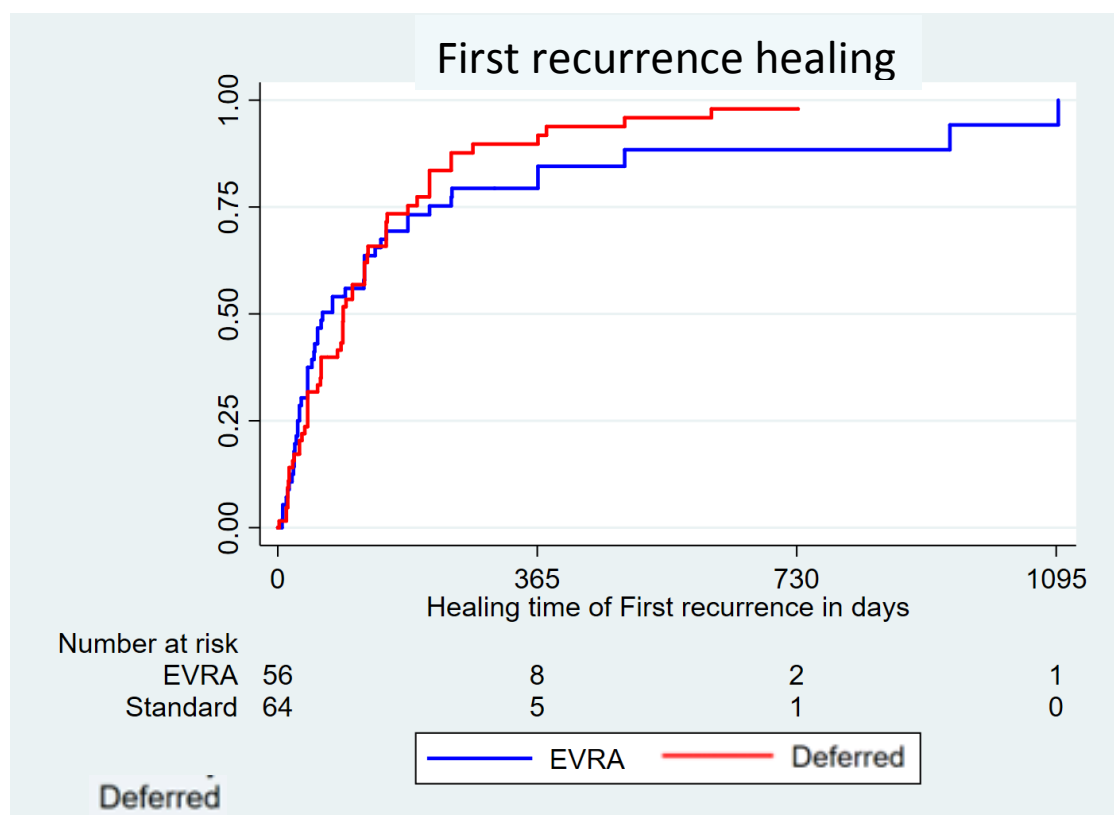
Figure 64 - Kaplan-Meier curve showing healing time of first recurrence.

One patient was excluded due to unknow ulcer healing date and 1 was excluded due to it was not possible to determine if their ulcer was healed or not from the data. Mann – Whitney U test: p = 0.875

7.3.7. Healing time of recurrent ulcers - all ulcers

The median time to healing of all recurrence ulcers was 63 days in the early arm and 96 days in the deferred arm (p = 0.338, Mann-Whitney U test).

There was also no clear difference in the time to healing of recurrent ulcers between the early-intervention group and the deferred intervention group (hazard ratio for healing including all ulcer recurrences (1.10; 95% CI 0.79 to 1.54, P=0.576) (*Appendix 6 Table S16 & Figure 65*)
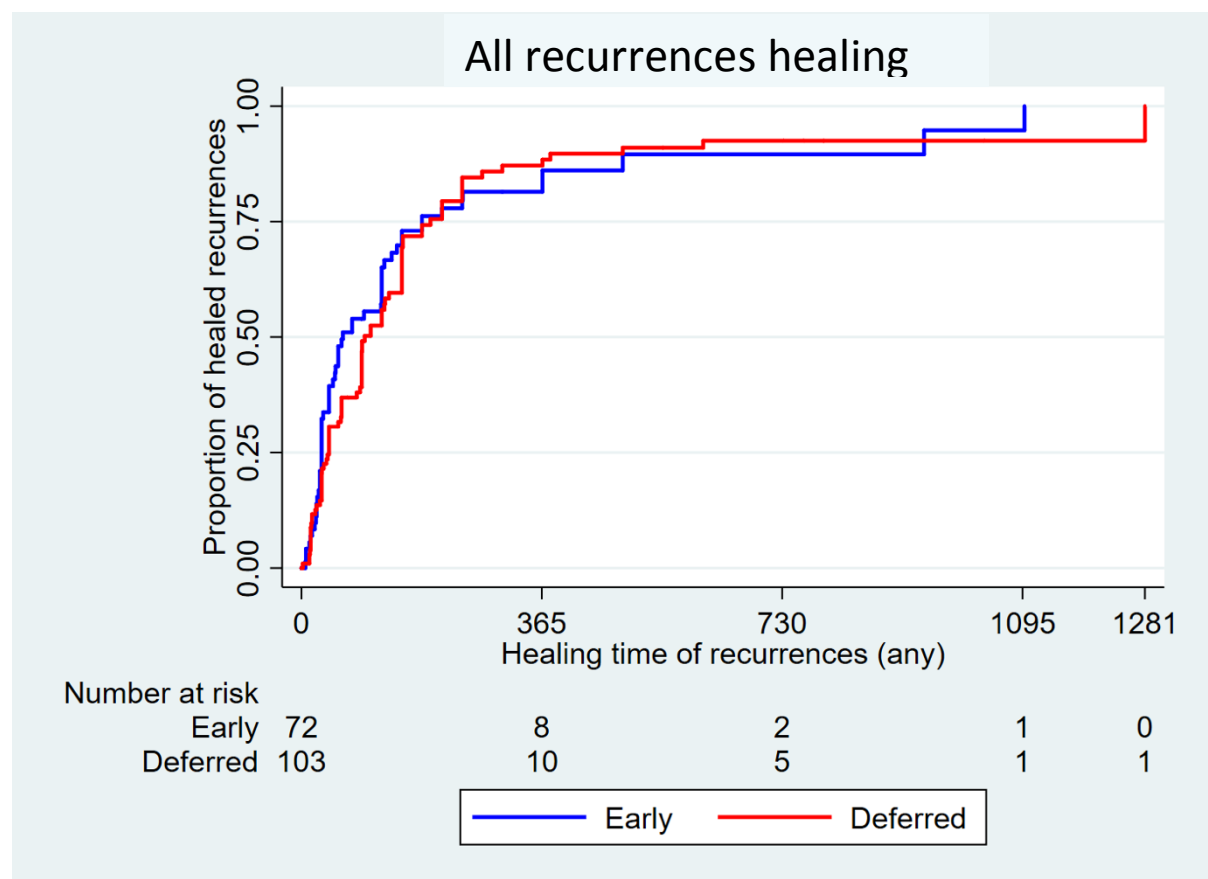
Figure 65- Kaplan-Meier curve showing healing of all recurrent ulcers (including which did not heal till the end of follow up). From Gohel et al. 2020 (218)

There were 175 recurrent ulcers (N=72 in Evra, N=103 in deferred) including which those which did not heal during the follow-up from 121 patients* (N=56 in Evra, N=65 in standard). *1 patient was excluded due to unknow ulcer healing date. Mann – Whitney U test: p = 0.338.

7.3.8. Ulcer free time

The ulcer free time in the early arm was 1137 days (IQR 860 to 1411) and 1090 days (IQR 625 to 1364) in the deferred arm. *Appendix 6 Table S17* shows the unadjusted cox model, which shows no difference between the group (hazard ratio for greater ulcer free time 0.88; 95% CI 0.73 to 1.06. P=0.170). There was also no difference between the groups in the adjusted cox model (adjusting for follow-up period, participant age, ulcer size and ulcer chronicity), (hazard ratio for greater ulcer free time 0.84; 95% CI 0.69 to 1.02. P=0.072) (*Appendix 6 Table S18*). The Kaplan-Meier can be seen in *Figure 66*.
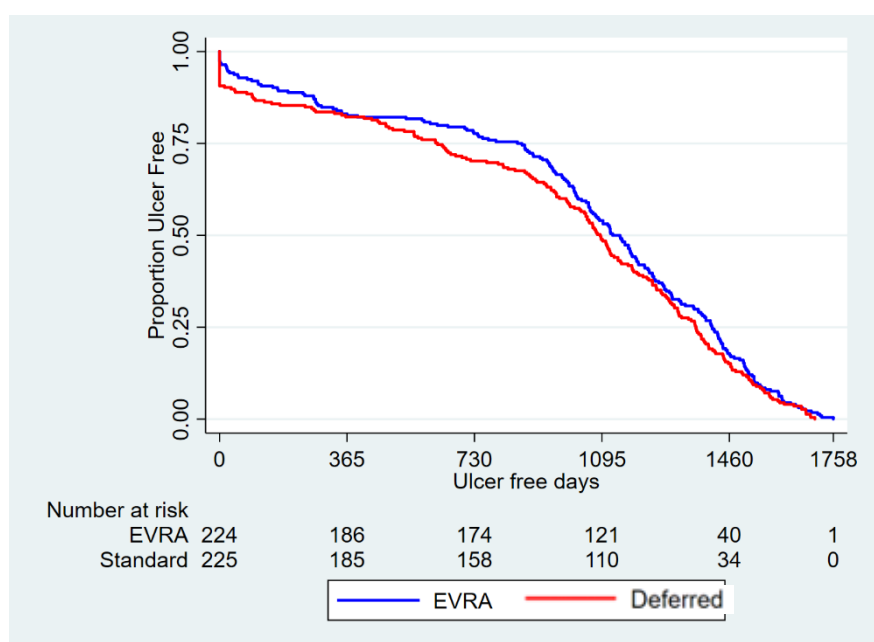
Figure 66 - Kaplan-Meier curve showing ulcer free time

7.3.9. Quality of life results

The AVVQ, EQ-5D-5L and SF-36 domains were similar in the two groups *(Appendix 6 Table S19)*.

7.4. Sensitivity analysis (per-Protocol)

For the sensitivity analysis, participants with treatment related protocol deviations were excluded as per *Table 48*.

	Early	Deferred
	N=27	N=34
Number of participants with protocol deviation	24	33
Deferred ablation in early group	17	-
Non-concordance with bandaging	10	12
Early ablation in deferred group	-	22

Figure 67 shows that there was no significant different between early and deferred intervention with respect to time to first recurrence from healing in the per-protocol analysis. The unadjusted (HR 0.86; 95% CI 0.59 to 1.26. P=0.45) (*Appendix 6 Table S20*) and adjusted (HR 0.90; 95% CI 0.61 to 1.3. P=0.59) (*Appendix 6 Table S21*) models were similar.
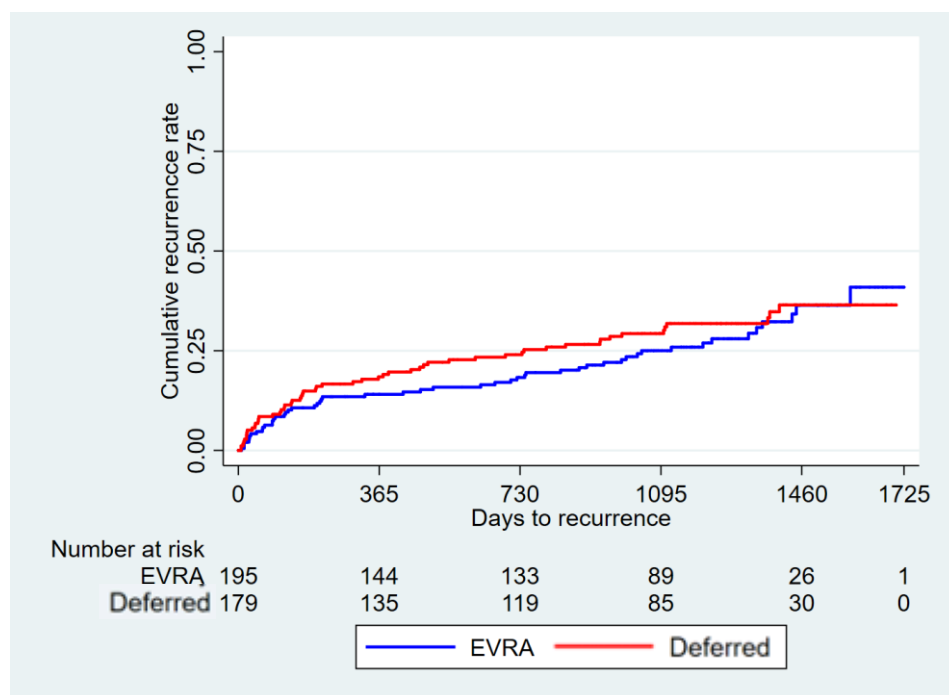
Figure 67 - Kaplan-Meier curve showing time to first recurrence (from healing), per-protocol. Patients with treatment related PDs are excluded. Adapted from (218)

Figure 68 shows that there was no significant different between early and deferred intervention with respect to time to ulcer healing in the per-protocol analysis. The unadjusted (HR 1.15; 95% CI 0.94 to 1.41. P=0.17) (*Appendix 6 Table S22*) and adjusted (HR 1.17; 95% CI 0.95 to 1.43.) (*Appendix 6 Table S23*) models were similar.
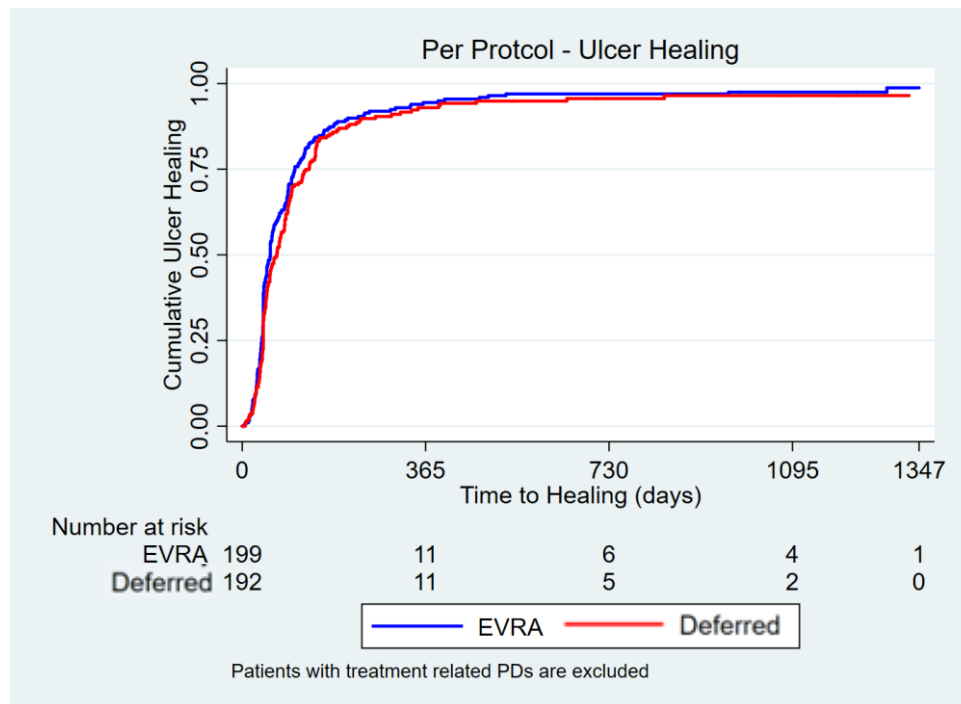
Figure 68 - Kaplan-Meier curve showing time to ulcer healing from randomisation, per-protocol. Patients with treatment related PDs are excluded. Adapted from (218)

7.5. Health Economics

7.5.1. Main analysis.

The resource use from each study arm is summarized in *Appendix 6 Table S24* and per patient undiscounted costs at three years are summarised in *Table 49.*

Table 49 - Undiscounted costs per patient at 3 years in each treatment group. From Gohel et al. 2020 (218)

Resource	Deferred, £	EVRA. £	Difference, £	95% CI	
Procedure	413	539	126	-186	439
Dressings & compression	607	507	-100	-265	65
Hospital and community services	2426	2255	-171	-1208	865
Medicine	28	26	-2	-38	35
Total	3493	3329	-164	-1295	967

Participants in the early intervention arm experienced more QALYs on average after three years (mean difference in QALY 0.073; 95% CI -0.06 to 0.20) and early intervention was the cheaper than deferred ablation, with the discounted total mean cost of this strategy at three years being -£155 (95% CI -£1262 to £953). With a greater QALY benefit and lower mean cost, early intervention is clearly the dominant strategy (*see Appendix 6 Table S25 & Figure 69*).
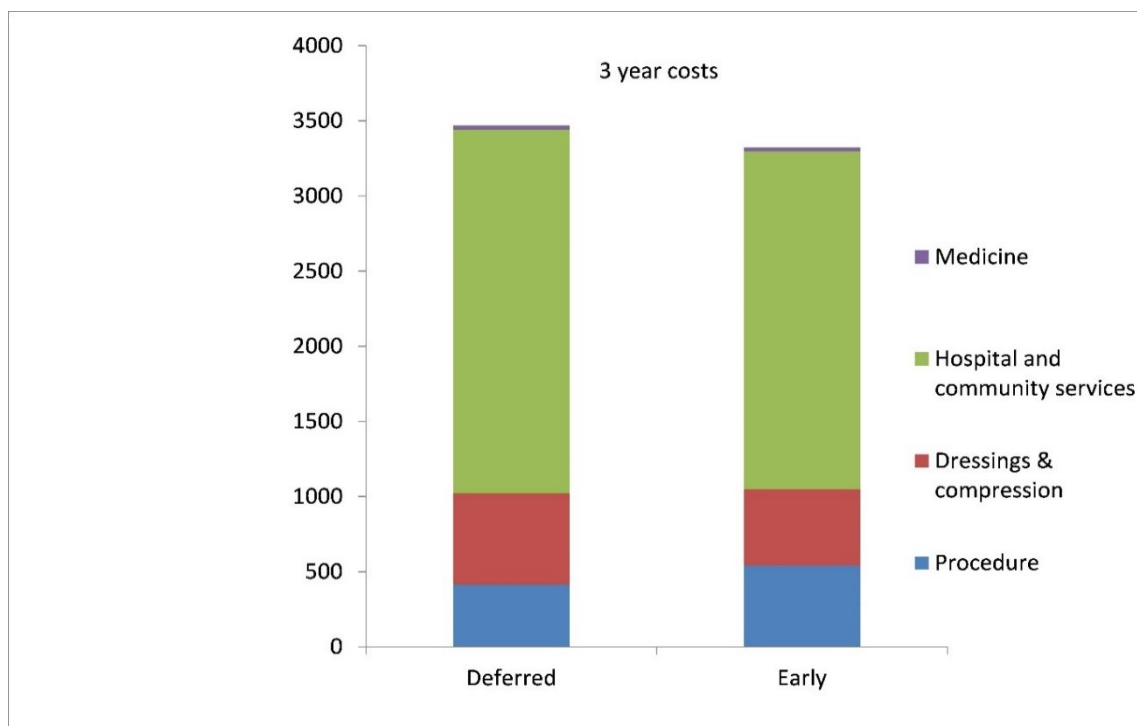
Figure 69 - Mean cost per participant at 3 years (in £). Adapted from (218)

7.5.2. Per-protocol analysis

Findings were similar for 4-year and 5-year horizons (*Appendix 6 Table S25*) and with a per-protocol analysis where the incremental cost-effectiveness ratio at 3 years was £2,265 per QALY (*Appendix 6 Table S26*). The difference in QALYs was smaller at 3 years using an alternative tariff for EQ-5D-5L (*Appendix 6 Table S25*).

The sensitivity analysis using Monte Carlo simulation can be seen in *Figure 70.* This demonstrated that early intervention was 91.6% likely to be cost-effective at a willingness-to-pay threshold of £20,000 per QALY and 90.8% at a threshold of £35,000 per QALY (*Figure 71*).
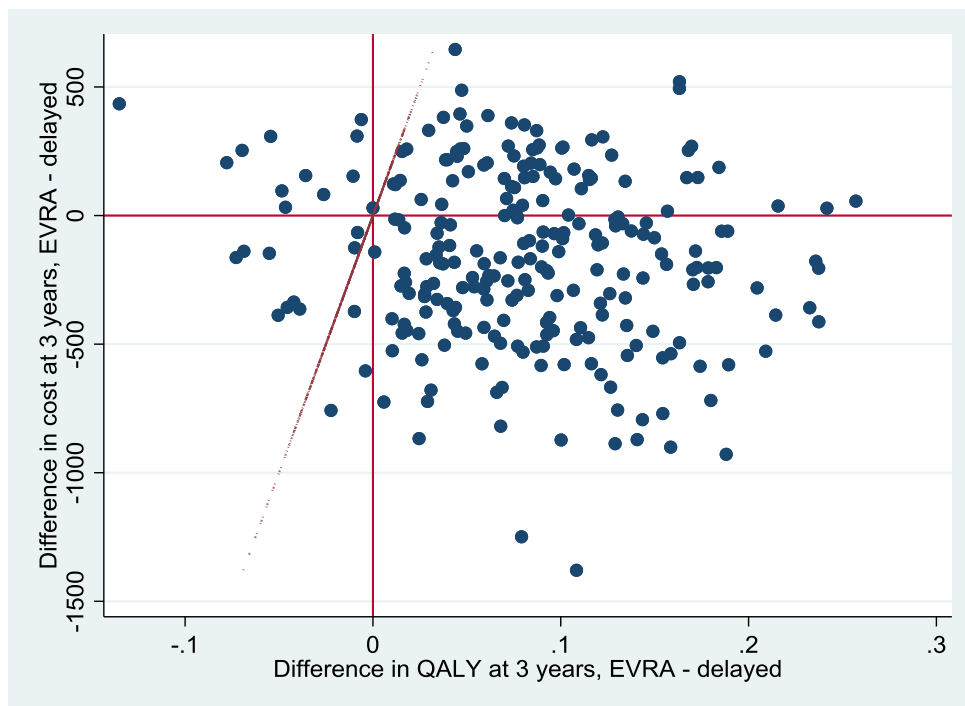
Figure 70- Sensitivity analysis using Monte Carlo simulation. Dashed line shows the threshold for cost-effectiveness at a willingness to pay of £20,000 per QALY. (218)
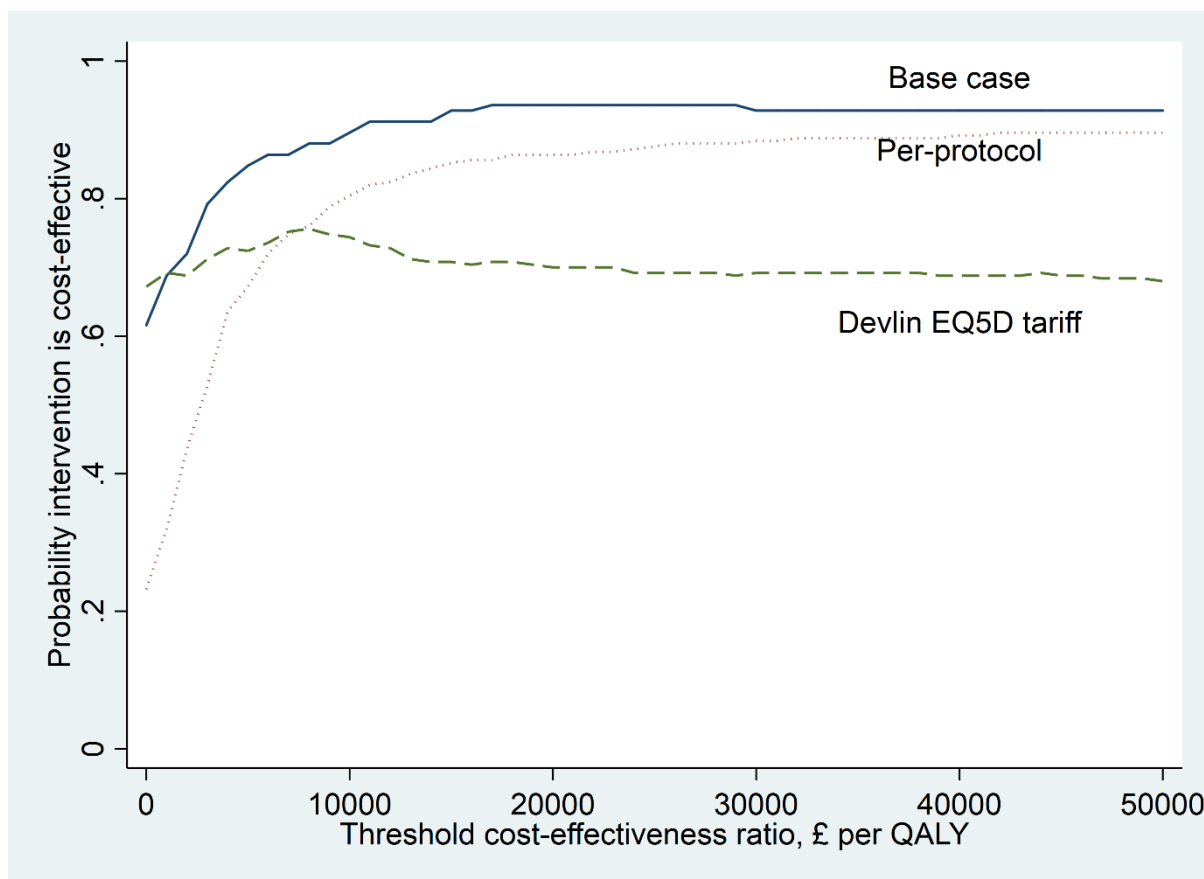
Figure 71 - Cost-effectiveness acceptability curve at 3 years. Adapted from (218)

7.6. Discussion

The 3.5-year outcomes show the incidence of ulcer recurrence to be lower in the early intervention group but indicates that early intervention does not affect the time to recurrent ulceration or time to healing of recurrent ulcers. Shorter time to ulcer healing shown at 12 months was sustained up to a median of 3.5 years.

The ulcer recurrence incidence rate in the early arm showed a significant reduction compared to the deferred arm so it's possible that delays in intervening could lead to some preventable recurrence events. The HR of 0.82 may also indicate that intervening early may reduce ulcer recurrence, although no significant difference between the arms was observed with respect to time to first ulcer recurrence. The study was only powered to detect differences in ulcer recurrence rates of 15 percentage points or greater, meaning that a smaller difference cannot be excluded. Potentially, a larger RCT may be required to evaluate this further.

Interestingly, those treated by the early ablation strategy underwent more interventions than the those in the deferred arm (76% of the deferred-intervention group compared with 97% of the early arm). It is likely this was due to the routine 6-week post ablation duplex ultrasound performed in the early group, which would have identified any treatable residual reflux and potentially those in the deferred arm might 'get lost in the system' or are less likely to want to undergo intervention once their ulcer has healed and they are asymptomatic.

The four-year ulcer recurrence rates in both EVRA arms were slightly higher to those found in the surgical arm of the ESCHAR trial but were considerably lower than the compression alone arm (36, 143). As ultrasound guided foam sclerotherapy was the most utilised method of endovenous intervention, it may have meant accounted for the higher recurrence rates as there is some evidence of greater recanalization rates compared to endothermal ablation of open surgery (207, 259). Regardless, it appears that treatment of superficial venous reflux is more essential than the actual modality.

The health economic analysis clearly supports early interventions as a treatment strategy, resulting in higher QALYs and lower mean costs which are likely to influence policy makers in most global healthcare systems.

Due to funding constraints, the major limitation to this portion of the trial is the method of a single telephone follow-up utilising patient recollection, which is likely to introduce some bias. However, this should be similar between both arms and the majority of participants

were seen for clinical follow-up in the research sites, resulting in clinical notes to which the telephone data was verified against.

In summary, the lower observed recurrent ulcer incidence rate in the early-intervention group and health economic benefits reinforce the conclusions from the 12-month results, that a policy of early endovenous ablation of superficial venous reflux would be highly beneficial for both patients and healthcare providers.

Chapter 8: Final discussion and conclusions

8.1. Final discussion

Compression bandaging for the treatment of venous leg ulceration has been in use for centuries, with surgery routinely utilised within the last 100 years or so. The introduction of Duplex ultrasonography in the 21st century has paved the way for less invasive, endovenous interventions to treat these patients, with ulcer healing rates equivalent to surgical techniques, but without the need to general anaesthesia. This has resulted in an increase in the number of patients that can benefit from the different endovenous modalities, allowing clinicians to be flexible in their approach to their management.

It was thought that the introduction of the NICE guidelines for varicose veins would improve the number of patients being referred for correction of the underlying venous disease, yet to date little improvement has been seen in this area (110, 248, 249).

The EVRA trial was the first multicentred RCT to assess the effect of early endovenous ablation for superficial venous reflux on ulcer healing in participants with venous ulceration. Global venous guidelines (10, 11) recommend surgical correction of superficial venous reflux in order to reduce recurrence based on the results of the ESCHAR study (36, 143). Prior to this study, no level-1 evidence existed on the effect of the timing of intervention on time to ulcer healing, and this may be the reason there are no clear pathways for early referral and assessment of patients with venous ulceration. The superior healing rates demonstrated in the compression only arm when compared to current real-life healing rates, the improved outcomes often seen in clinical trials (272, 273)

The RCT also showed that intervening early prior to ulcer healing accelerated ulcer healing and resulted in more ulcer-free time over the 12 months and reduced the ulcer recurrence incidence rates over the longer term, as well as being cost effective. The outcomes beyond four years, however, are not known.

Overall the RCT results suggest that patients with superficial venous ulceration can benefit from a strategy of early assessment and ablation, in addition to standard compression therapy with respect to accelerated ulcer healing. The mean ulcer duration of participants in the study was 3.2 months, and therefore it is likely that an even greater benefit may be seen if patients are treated within two weeks of diagnosis. As previously discussed, considerably more than

7% of patients would be suitable and benefit from intervention if the NICE guidelines stipulating referral after two weeks were adhered to (10).

However, in order to implement this strategy, considerable changes are required to the current care pathways, along with ensuring consistent dissemination of relevant study results, educating community nurse staff and conducting audits of current practice. It is imperative that secondary care centers are able to cope with the increased number of referrals, especially with respect to capacity and availability of both vascular scientists to scan and diagnose venous ulceration and vascular surgeons to perform interventions.

The global surveys indicate that the majority of vascular specialists face few barriers to adopting an early strategy, and as over 90% of those in the early ablation group were treated within two weeks, implementation in an NHS setting appears highly feasible. As the benefits to ulcer healing, recurrence and cost effectiveness have been shown regardless of the modality of intervention used, this further strengthens the ease of implementation within global healthcare systems and is not limited by local funding. It is perhaps possible to establish pathways similar to the two-week cancer referral system, which would improve care and reduce geographical inequalities.

It is, however, important that existing barriers for change in both primary and secondary care are properly understood. Although the surveys gave a brief overview of some of the barriers faced in relation to the referral pathways and an early treatment strategy, further work should be performed in this area. Interviewing both primary and secondary care professionals in depth, as well as leg ulcer patients and their carers might provide a better understanding of motivation for such referrals and the challenges faced.

The management of ulceration surveys showed a diverse array of assessment, diagnosis, referral and treatment pathways, both globally and within the UK. It's been well documented that community teams are often limited by their access to specialist equipment and training, in addition to time restraints to treat patients and the ability to refer patients without involving GPs (274).

The global clinician survey also suggested that demonstrating a cost-effective benefit would influence their practice. Despite the apparent ease for clinicians to treat patients prior to ulcer healing, it is clear that theatre and duplex scanning capacity still need to be considered, and the referral of patients from primary care to these teams remains a sticking point, further

highlighted by the baseline three-month ulcer duration of patients included in the EVRA study. With less than 30% of patients diagnosed with venous ulceration being referred to a vascular surgeon, there is significant work to do to increase this proportion (248). The primary care surveys indicate that, at least in the UK, GPs are the majority gatekeepers with respect to referral to secondary care and may act as a major barrier to referral. The current vision by the Royal College of General Practitioners is that all UK GPs will become '*expert generalists*' by 2022, with the expectation that patients with long-term conditions such as leg ulceration will see improvements under this model, although this can only be achieved with greater investment into primary care services (274).

It is doubtful that the diagnosis of venous incompetence by duplex ultrasound can be routinely performed by community and district nurse teams as it requires highly skilled personnel, especially given that the ability to even perform ABPIs in the community is limited, nursing numbers are decreasing and access to experience and training is limited. Although the early intervention strategy has been shown to be highly cost effectiveness once patients reach the vascular specialists, it could be argued that the results do not support such a change in primary care practice from a cost-effectiveness standpoint, as large numbers of patients would have to be referred and scanned at considerable expense to find a small proportion of people who are suitable for early endovenous ablation, but given that the results show a clear benefit to patients, it seems unethical to withhold early assessment and intervention. It is possible that if community teams had channels to easily refer directly patients for a diagnostic duplex, the patients requiring intervention for venous disease could then be referred to a specialist vascular team and those without venous disease could continue to be managed in the community so to ease the total number of referrals (274).

It is not simply enough to update the guidelines with this new evidence base and expect change, the message regarding referral of patient with open leg ulceration has been clear for several years. As discussed, guidelines are often not followed and although the reasons for this are unclear, it is possible that GPs are simply not aware of them, or they may prefer others specifically developed for leg ulcers such as SIGN which recommend referral after 12 weeks. In Australia, for example, it has been reported that less than a fifth of practice nurses use the best practice guidelines to inform treatment (275).

It is possible that renaming and redeveloping the NICE guideline for varicose veins (or creating a standalone leg ulcer guideline in the UK) to include venous leg ulcers or

superficial venous insufficiency, or encompassing chronic venous disease as a whole, as the European guidelines do, may ensure that patients suffering from repeated periods of recurrence are quickly referred back to a specialize service rather than getting lost in the system. It is possible though that the addition of another guideline might overwhelm professionals, another consideration is that developing and updating guidelines is expensive (somewhere in the region of £500K for a NICE guideline) and therefore it would be hard to justify this within the current climate of austerity, when they simply might be ignored (248).

It is also clear that enhanced communication and referral pathways between primary and secondary care are required, and it is yet to be seen if the NHS Five Year Forward View and Commissioning for Quality and Innovation (CQUIN) scheme 2017-2019 will have improved communication and wound outcomes (106, 107).

It was recently suggested that at least in the UK, there is a lack of national direction from the Department of Health (248), and therefore it is possible that the National wound care strategy programme (NWCSP) introduced in late 2018 with the aim to "*improve the quality of wound care provision across England by reducing unwarranted variation, improving safety and optimising patient experience and outcomes*" may improve the situation. Indeed, at the time of writing, the program had pushed for the creation of the most recent CQUIN for 2020 to 2021 which will measure performance in the community to ensure that patients diagnosed with a leg ulcer documented are referred to vascular services for assessment for surgical interventions (276). Another important aim of the NWCSP is to educate health professionals regarding the referral and management of leg ulceration and are currently in the early stages of creating and disseminating elearning modules to those in both primary and secondary care (personal communication, Sarah Onida, NWCSP committee member). Education in this area is crucial to improving the situation.

In late 2019 the All-Party Parliamentary Group on Vascular and Venous Disease published a report entitled '*Venous Leg Ulcers, A Silent Crisis*' setting out a vision with a three pronged approach to help ensure effective diagnosis and management of venous leg ulceration, review and improve commissioning of services and ensure workforce capacities are adequate and barriers between primary and secondary care are reduced (277). This report may finally thrust the issues surrounding venous leg ulceration into the limelight.

Ultimately the centers involved in the study may have insight into how to bring about change and future work could focus on a cluster or implementation study involving the trial centers

and the primary care and GP services that refer patients to them. The major challenge of a cluster study would be the difficulty in identifying the leg ulcer population prior to commencing the trial and therefore an implementation study might be simpler to conduct. This would involve several practices in which all patients presenting with a leg ulcer over one year being referred to a specialised vascular clinic for rapid intervention and calculating leg ulcer days saved and modelling the total cost of implementation to help convince CCGs that the strategy is worthwhile in order to implement clear referral pathways (276).

Finally, the importance of educating patients about the underlying cause of their venous leg ulceration and their rights to be referred to a vascular service for diagnosis and treatment should not be overlooked. Many studies have shown improved outcomes when patients are educated appropriately, so this should be considered when implementing a strategy for change as it may also impact the numbers of patients being referred and treated for their venous disease (278, 279)

8.2 Overall conclusions

The global management of patients with ulceration is disparate globally. Early endovenous ablation of superficial truncal reflux in addition to compression therapy accelerates the healing of venous leg ulcers compared with deferred ablation and reduces the IRR of ulcer recurrence. At three years, early ablation results in a cost saving, plus significant gains in QALYs compared with deferred ablation. Therefore, early ablation has a very high probability of being cost-effective at NICE willingness to pay thresholds. A strong argument for the commissioning of fair and accessible services for patients with venous leg ulceration therefore exists, but the barriers to the referral and early intervention must be properly explored and understand in order to successfully implement the strategy.

Chapter 9: Future work

The RCT subgroup analysis to investigate any differential treatment effects with respect ulcer duration showed a trend for increased treatment effect (ulcer healing) at the 3rd and 4th quartiles for ulcer duration and therefore is would be interesting to evaluate the benefit of early ablation for superficial venous reflux in patients with venous leg ulceration of greater than six months duration. The study also did not investigate in detail the optimal technique and the extent of eradication of superficial venous incompetence in patients with venous ulceration so this could be explored further.

Currently, the NHS does not routinely investigate and treat venous outflow obstruction in patients with venous leg ulceration, although stenting to correct non-thrombotic and post-thrombotic deep venous occlusive is on the rise. Despite the excellent healing rates were demonstrated from the use of compression therapy and superficial venous ablation, it's possible that a role for deep venous stenting exists in some of these patients with respect to ulcer healing and recurrence, yet further research is required (280, 281).

With respect to adopting early intervention, an implementation study may be the best approach to convince policy makers that the strategy is worthwhile, feasible and cost effective and a survey to GPs to determine whether they are familiar with the current guidelines with respect to referral, whether they agree with them and the criteria for GP referral to a vascular centre. In depth interviews with a variety of health care professionals involved in the management of patients with venous ulceration, and patients themselves should be conducted to determine the barriers to implementation of the early intervention strategy and ways to overcome these.

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Appendix 1 – European Quality of Life-5 dimensions questionnaire (EQ-5D)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state 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 ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today
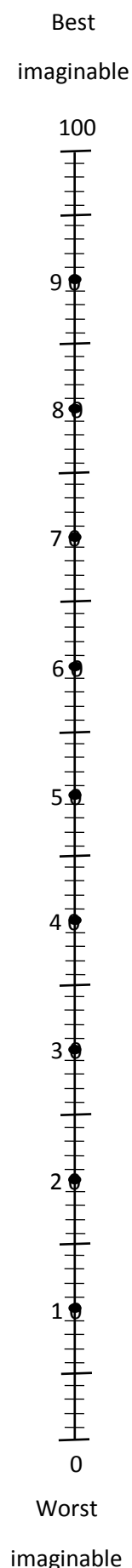
Best

imaginable

100

9 0

8 0

7 0

6 0

5 0

4 0

3 0

2 0

1 0

0

Worst

imaginable

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Best imaginable

100

90

80

70

60

50

40

30

20

10

0

Worst imaginable

Your own health state today

The score here would be 40

The score here would be 4
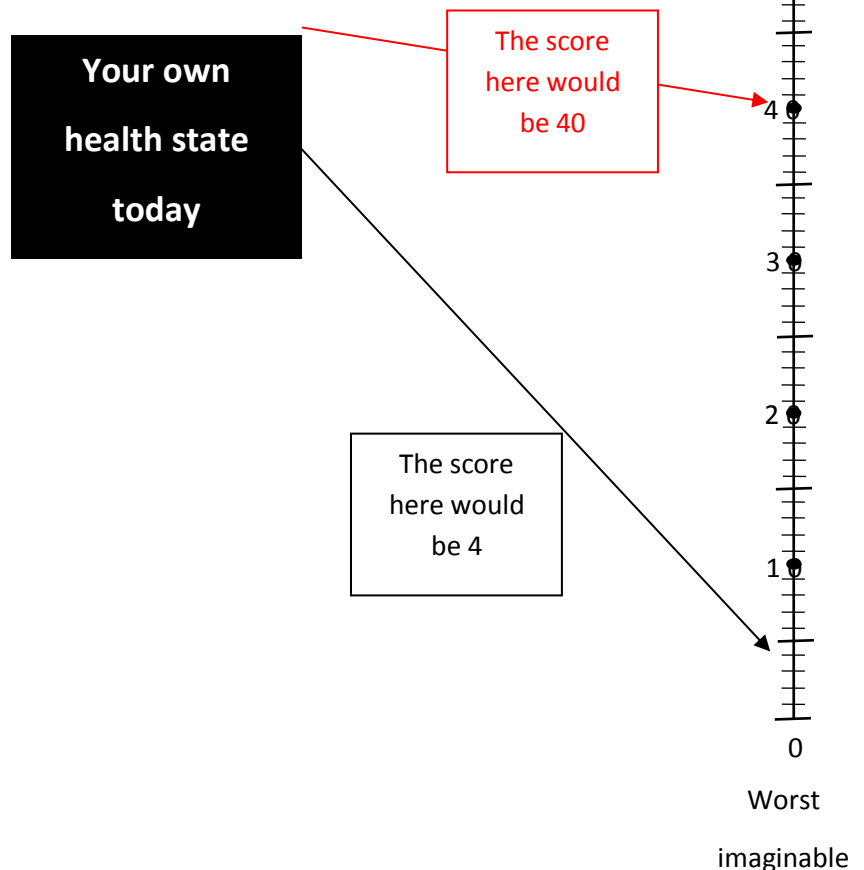
Health Questionnaire – SF-36
English version for the UK

The SF-36 form must be completed at <u>baseline</u> and then at <u>6 weeks, 6 months and 12 months</u>.

<mark>Please tick the relevant box to indicate:</mark>

Baseline ☐

6 week follow-up ☐

6-month follow-up ☐

12-month follow-up ☐

Date of questionnaire completion: ☐☐ ☐☐/☐☐

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1.   In general, would you say your health is:

(circle one)

Excellent 1

Very good..2

Good 3

Fair 4

Poor 5

2.   <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

(circle one)

Much better now than one year ago 1

Somewhat better now than one year ago 2

About the same as one year ago 3

Somewhat worse now than one year ago...4

Much worse now than one year ago..5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

<div align="right">(circle one number on each line)</div>

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **half a mile**	1	2	3
i. Walking **one hundred yards**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

<div align="right">(circle one number on each line)</div>

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)? (circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? .... (circle one)

Not at all..1

Slightly..2

Moderately 3

Quite a bit...4

Extremely 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

(circle one)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe..6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all...1

A little bit 2

Moderately 3

Quite a bit...4

Extremely...5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10.   During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)

All of the time..1

Most of the time…………………………………………………………….......2

Some of the time...3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Thank you!

Aberdeen Varicose Veins Questionnaire (AVVQ)

The AVVQ form must be completed at <u>baseline</u> and then at <u>6 weeks, 6 months and 12 months</u>.

<mark>Please tick the relevant box to indicate:</mark>

Baseline ☐

6 week follow-up ☐

6-month follow-up ☐

12-month follow-up ☐

Date of questionnaire completion:

☐☐ ☐☐ ☐☐

dd/mm/yy

Please answer all 13 questions

<div style="border:2px solid black; padding:10px; text-align:center; width:40%; margin:auto;">
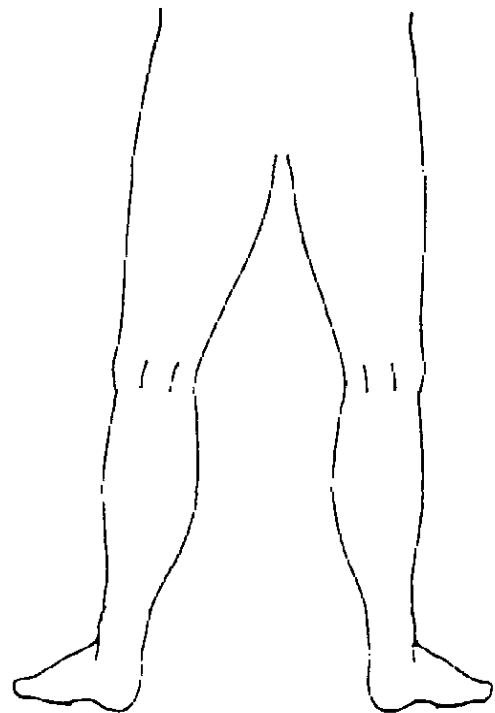
YOUR VARICOSE VEINS

</div>

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

Legs viewed

from front
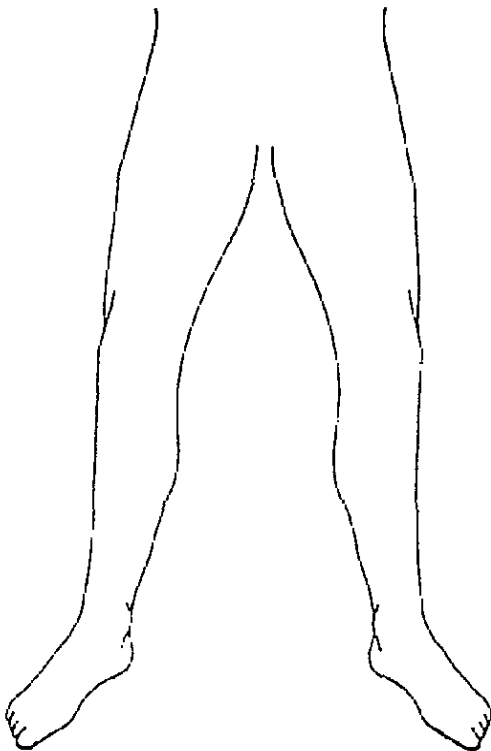
Legs viewed

from back

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 (e.g. causing you
to sit with your feet up whenever possible)   ☐

Severe ankle swelling (e.g. 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 ☐

259

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 ☐

Appendix 4– Summary of substantial amendments made to the trial protocol after initial approval

Protocol Version	Date	Amendments
V5.0	06/04/2017	To incorporate the HTA funding extension to the trial to allow for the collection of longer-term follow-up during October 2018 and March 2019. Revisions to the health economics section to reflect updated NIHR guidelines.
V4.0	16/03/2016	To correct sample size from 500 participants to 450 participants which was originally calculated erroneously. To allow for a reduction in the number of photo verification visits performed if the core lab confirms the ulcer is healed.
V3.0	10/03/2014	Revised to display posters, leaflets and disseminate participant information sheets in primary care sites.
V2.0	06/01/2014	Revision to provide a clearer definition of ulcer healing to clarify that healing cannot be assume if a scab is present. Statistics and Data Analysis section amended for clarity of per-protocol analyses. Serious adverse event section amended for clarity. Intervention section amended to clarify that participants can be offered intervention in the standard care (compression arm) if their ulcer has not healed at 6 months.
V1.0	19/06/2013	N/A – Original Protocol.

Appendix 5 – Decision rules for verification of the primary outcome measure

Verification of ulcer healing will be by clinical assessment and digital photography, to be repeated weekly for 4 weeks. The digital images will be evaluated by 2 blinded expert assessors in order to ascertain the date of healing, which will be considered the primary healing end-point. Disagreements will be resolved through discussion with involvement of a third blinded expert reviewer if necessary.

a) If the two blinded assessors agree that the reference ulcer has healed at the first photograph, the date of healing notification (by patient or community nurse) will be taken as the date of ulcer healing. If the two blinded assessors agree that the reference ulcer has healed at subsequent photographs the date of those photographs will be used as the date of healing. If the two blinded assessors agree that the reference ulcer has healed at the first photograph but the ulcer reoccurs at subsequent photographs, the date of healing from the first photograph will be used and the re-occurrence will be noted in the eCRF. Patient's may undergo intervention for venous reflux after the first point the ulcer is confirmed healed (they do not have to wait until all 4 photos are verified.

b) If the two assessors say Unsure/Unsure then the ulcer has not healed at that point and the next photo graph will be assessed.

c) If the two blinded assessors disagree as to whether the reference ulcer has healed, there will be the following combinations with regards to healing:

1) <u>Yes/Unsure</u>

If the two assessors state Yes/Unsure then the ulcer has healed, using the date provided by the assessor who said 'yes' or if the first photograph, the date of healing notification will be used.

2) <u>No/Unsure.</u>

If the two assessors state No/Unsure then the ulcer has not healed.

3) <u>Yes/No</u>

If the two assessors state Yes/No = 3rd assessor will be consulted and will decide if the ulcer is healed or not. The 3rd assessor's decision will be final. If they are unsure whether the ulcer has healed, the ulcer will be considered unhealed.

d) If no photographs of the reference ulcer are available, the unblinded date the treating nurse / GP recorded will be used if available.

e) If the [treating] nurses state that the wound is healed and stop taking photographs but blinded assessors says the wound is not healed then we will consider the wound healed.

f) If photos are taken of a participant for more than 12 months and the date of healing occurs beyond 12 months post-randomisation, the participant will be regarded as unhealed at 12 months.

g) Photos taken after a large interval of time has elapsed (i.e. one month or more) since the due date of the last healed photo (post-healed photo 4) will not be included in the blinded outcome assessment.

Appendix 6 – Statistical tables

Table S 1 - Resource use items collected in the study and assumptions made in the 12-month outcome analysis. Adapted from (217) with permission.

Resource use	Description
Trial vein ablation procedures	Time in operative theatre was recorded and the type of procedure (UGFS, RFA, EVLA or MOCA). Participants could have more than one trial vein ablation procedure. Staff procedure costs were calculated f rom the time in operative theatre (recorded in the CRF) multiplied by standard unit costs (see *Appendix 6 Table S2*)
Dressings and bandages for wound healing	Dressings: Classified in the CRF as NA (non-adherent) dressing, Inadine™ (iodine impregnated), or other. For estimating costs, it was assumed two dressing changes per week until wound healing. Compression: The CRF recorded if the participant used compression bandages, stockings or no compression. If bandages, it was assumed that they were changed at each dressing change Participants who used compression stockings were assumed to own two pairs (one to wash and one to wear), and both were replaced every three months (personal communication Karen Dhillon, November 2017).Bandages were assumed to have been used if the CRF did not state which mode of compression was applied (as these are the most common type of compression therapy in use).
Compression therapy to prevent recurrence after wound healing	The costs of compression therapy post healing were estimated in line with local policy. For estimating costs, it was assumed stockings were changed every three months (personal communication, Karen Dhillon, vascular research nurse, 18/05/2017).
Visits to a district nurse or primary care nurse	All these visits were included in the total cost, for any reason
Visits from a district nurse	All these visits were included in the total cost, for any reason.
Hospital admissions (inpatient and day case)	The trial collected data on the reason for the admission and any procedure undertaken as free text. Admissions were classified as "vein-related" if one of the text fields included one of these key word fragments: "leg ulcer vein rf abla evlt evla sclero screlo vnus foam ugfs angio rehab physio conval skin antibio sepsis septic infection dvt" (the list takes account of spelling errors in the text field) Vein ablation procedures were identified if one of the text fields included one of the following keywords: "vein rf abla evlt evla sclero screlo vnus foam ugfs". Admissions were cross-checked against trial procedures so as not to double-count the same event. The exact date of the admission was not recorded in the admissions CRF, only the month after randomisation. It was assumed that if two vein ablation procedures occurred in the same month, then they were duplicate records.
Outpatient visits	Outpatient visits were recorded, along with free text indicating the reason for the consultation and any procedure undertaken. Outpatient visits were classified as "not vein-related" if the reason for

the consultation or the procedure contained one of these key words: "tia hernia aaa asth aneurysm ankle opthal arthritis breast bowel bereavement eye breath carpal cpap cancer chest colorectal diab diet head ent endoscopy endocrin fall fracture gynae gastro heamat hearing heart hyperdermic immuno testic kidney knee lung lymph facial nasal oncol ortha ortho urology pacemaker parkinson pessary cateract rheuma renal respiratory reveal recell rhemat spinal sleep wrist thumb shoulder abdo aorta deaf memory migrane ovary" (note that ReCell and Randomized EValuation of the Effects of Anacetrapib through Lipid-modification (REVEAL) are other concurrent clinical trials)

Vein procedures in outpatients were identified if one of the text fields included one of the following keywords: "sclero foam ugfs".

Outpatient visits were cross-checked against trial procedures so as not to double-count the same event. The exact date of the outpatient consultation was not recorded in the CRF, only the month after randomisation. It was assumed that if two vein ablation procedures occurred in the same month, then they were duplicate records.

Visits to and from the GP	All these visits were included in the total cost, for any reason
Use of antiplatelet and anticoagulant medicines	The CRF recorded the drug used each month, but did not record the dose. It was assumed that doses (taking account age, gender and weight) were as recommended by the British National Formulary(282).
Physiotherapy and occupational therapy	All these visits were included in the total cost, for any reason
Home care visits (auxiliary nursing)	All these visits were included in the total cost, for any reason
Home help visits for (personal care)	All these visits were included in the total cost, for any reason
Out of pocket, informal care and personal expenses	Time lost from work and normal activities, informal care and whether out-of-pocket expenses were incurred were recorded in the CRF. These were tabulated but not included in the NHS and PSS total costs.

Table S 2 - Unit costs for the 12-month outcomes. Adapted from (231) with permission.

Resource	Unit Cost £	Assumption	Source
Index procedure			
Staff procedure costs			
EVLA	£5.49 / minute	Assumed same cost / minute for RFA	Brittenden 2015(259)
UGFS	£4.67 / minute	Assumed same cost / minute for MOCA	Brittenden 2015(259)
Disposable kit or catheter prices			
EVLA	£238.60		Angiodynamics (personal communication Caley Kitchen Territory Manager – Vascular; 14/02/2018). List price catheter £200. Generator £22000- Assuming 2-year life, 600 procedures in total, cost of capital 3.5% per year. This gives an annuity cost per procedure of £38.60
RFA	£543		Medtronic list price. Personal communication (Harriet Ellis, vascular nurse specialist, 16/11/2017). Includes generator rental
MOCA	£375		Vascular Insights list price. Personal communication (Harriet Ellis, vascular nurse specialist, 16/11/2017)
Other theatre consumables and anaesthetic			
EVLA	£66		Brittenden 2015(259)
RFA	£66		Assumed same cost as EVLA
UGFS	£50		Brittenden 2015(259)
MOCA	£50		Assumed same cost as UGFS
Other costs of vein ablations (pre-procedure and recovery)			
EVLA	£72		Brittenden 2015(259)
RFA	£72		Assumed same cost as EVLA
UGFS	£42		Brittenden 2015(259)
MOCA	£42		Assumed same cost as UGFS
Consumables ulcer healing			

Resource	Unit Cost £	Assumption	Source
Urgo KTwo compression bandages	£7.84	Assumed changed 2 times per week until healing	NHS supply chain(283)
Ulcertec compression stockings	£27.10	Assumed two pairs changed every 3 months until healing	NHS supply chain(283)
Ulcer dressing		Assumed changed 2 times per week until healing	
NA dressing	£11.20 for 40		NHS supply chain(283)
Inadine™ 9.5x9.5cm	£15 for 25		NHS supply chain(283)
Atrauman® dressing	£10.89 for 30	Assumed used if no other information provided	NHS supply chain(283)
Consumables after healing to prevent recurrence			
Class 2 compression stocking	£31.27	Assumed changed every 3 months	NHS supply chain(283)
Admissions to hospital (other than vein procedures)			
Overnight stay without procedure	£265 / night		Reference cost 2015-16, Excess bed day: Peripheral Vascular Disorders with CC Score 2-4(284)
Spinal surgery	£4142	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Shoulder replacement	£5110	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Ankle surgery	£2667	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Hip replacement	£5877	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Knee replacement	£5745	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Cataract	£917	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Hernia repair	£1726	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Pacemaker	£2063	Not ulcer related	Reference costs 2015-16, Elective Inpatient(284)
Angiogram and stent	£1449	Ulcer related	Reference costs 2015-16, Daycase(284)

Follow-up outpatient visit

Resource	Unit Cost £	Assumption	Source
Without procedure	£140 / visit		Reference costs 2015-16: Vascular surgery(284)
Office-based sclerotherapy	£245 / visit		Brittenden 2015(259)
Primary care			
Visit to district nurse / GP practice nurse /vein clinic	£38 / visit	Assume 15.5 minutes	Reference costs 2015-16(284)
District nurse home visit	£72 /visit	Includes travel time	Reference costs 2015-16(284)
Visit to GP	£36 / visit		PSSRU 2016(285)
GP home visit	£88 / visit	Includes travel time	Personal Social Services: Expenditure and Unit Costs (PSSRU) 2015(286)
Other healthcare			
Occupational therapist	£79 / visit		Reference costs 2015-16(284)
Physiotherapist	£49/ visit		Reference costs 2015-16(284)
Home carer visit	£38 / visit	Nursing care	Assume same as district nurse
Home help visit	£29 / visit	Personal care	Personal Social Services: Expenditure and Unit Costs, England, 2014-15(287)
Medicines British National Formulary(282)			
Apixiban 2.5mg	£4.40 / day		5mg BD every day
Aspirin 75mg	£0.03 / day		75 mg OD every day
Clopidogrel 75mg	£0.06 / day		75 mg OD every day
Dalteparin 12,500 units/ml	£20.32 / day	Males	For average weight 96kg, 18000units / day
	£14.12 / day	Females	For average weight 80kg, 12500 units / day
Warfarin	£0.04 / day		
Rivaroxaban 10mg	£3.60 / day		20mg OD
Clexane (Enoxaparin):	£11.02 / day	Male	1.5mg/kg OD
	£7.84 / day	Female	
Dabigatran 150mg	£1.70 / day		150mg BD

h)   OD once daily; BD twice daily; EVLA Endovenous laser ablation; RFA Radiofrequency ablation; UGFS ultrasound-guided foam sclerotherapy; MOCA Mechanochemical endovenous ablation; GP general practitioner; NA dressing: non-adherent

Table S 3 - Resource use items collected in the study and assumptions made in the 3.5-year outcome analysis. Adapted from (218) with permission.

Resource use	Description
Procedures	Primary vein ablation procedures (early or deferred).
Hospital and community services	Episodes of contact with healthcare professionals related to the index ulcer (hospital inpatient admissions, outpatient clinics, General Practitioner, Community nurse, Physiotherapy, Occupational therapy)
Dressings and compression	Wound dressings, bandaging and compression consumables. It was assumed that dressings were changed twice a week while the primary ulcer or recurrent ulcer remained unhealed, and that compression bandages or stockings worn after healing were replaced every 3 months.
Medicines	Medications - antiplatelets or anticoagulants. Post 12 months, it was not known when medication was started or stopped. If the participant indicated at the extension follow-up that they were using aspirin, clopidogrel or warfarin, it was assumed that the participant used the same medication continuously from the 12-month follow-up to the end of the trial, at recommended daily doses. The trial recorded use of enoxaparin and new oral anticoagulants (apixaban, rivaroxaban, enoxaparin and dabigatran) at the extension follow-up. The costs of these medicines could not be included beyond this time as it could not be assumed that use was continuous over the whole follow-up.

Table S 4 - Unit costs for the 3.5-year outcomes. Adapted from (218) with permission,

Resource	Unit Cost £	Source
Index procedure		
Staff procedure costs		
EVLA	£5.49 / minute	Brittenden 2015, updated for inflation (Assumed same cost/minute for RFA)
UGFS	£4.67 / minute	Brittenden 2015, updated for inflation (Assumed same cost/minute for MOCA)
Disposable kit or catheter prices		
EVLA	£238.60	Angiodynamics list price (personal communication Caley Kitchen, Territory Manager – Vascular; 14/02/2018). List price catheter £200. Generator £22000- Assuming 2-year life, 600 procedures in total, cost of capital 3.5% per year. This gives an annuity cost per procedure of £38.60
RFA	£543	Medtronic list price. Personal communication (Harriet Ellis, vascular nurse specialist, 16/11/2017). Includes generator rental
MOCA	£375	Vascular Insights list price. Personal communication (Harriet Ellis, vascular nurse specialist, 16/11/2017)
Other theatre consumables and anaesthetic		
EVLA	£66	Brittenden 2015, adjusted for inflation
RFA	£66	Assumed same cost as EVLA
UGFS	£50	Brittenden 2015, adjusted for inflation
MOCA	£50	Assumed same cost as UGFS
Other costs of vein ablations(pre-procedure and recovery)		
EVLA	£72	Brittenden 2015, adjusted for inflation
RFA	£72	Assumed same cost as EVLA
UGFS	£42	Brittenden 2015, adjusted for inflation
MOCA	£42	Assumed same cost as UGFS
Consumables ulcer healing		
Urgo KTwo compression bandages	£7.84	NHS supply chain (Assumed changed 2 times per week until healing)
Ulcertec compression stockings	£27.10	NHS supply chain (Assumed two pairs changed every 3 months until healing)
Ulcer dressing		Assumed changed 2 times per week until healing

Resource	Unit Cost £	Source
NA dressing	£11.20 for 40	NHS supply chain
Inadine™ 9.5x9.5cm	£15 for 25	NHS supply chain
Atrauman® dressing	£10.89 for 30	NHS supply chain
Consumables after healing to prevent recurrence		
Class 2 compression stocking	£31.27	NHS supply chain (Assumed changed every 3 months)
Admissions to hospital for vein related procedures		
Overnight stay without procedure	£376 / night	Reference cost 2017-18
Ablation procedure day case	£1191	Reference cost 2017-18
Angiogram and stent	£1265	Reference cost 2017-18
Admissions to hospital (other than vein procedures)		
Spinal surgery	£4231	Reference cost 2017-18
Shoulder replacement	£5675	Reference cost 2017-18
Ankle surgery	£2778	Reference cost 2017-18
Hip replacement	£6061	Reference cost 2017-18
Knee replacement	£5793	Reference cost 2017-18
Cataract	£924	Reference cost 2017-18
Hernia repair	£1858	Reference cost 2017-18
Pacemaker	£1631	Reference cost 2017-18
Follow-up outpatient visit		
Without procedure	£ 138 / visit	Reference cost 2017-18
Office-based sclerotherapy	£245 / visit	Brittenden 2015, updated for inflation
Primary care		
Visit to district nurse	£ 38/ visit	Reference cost 2017-18
District nurse home visit	£ 76/visit	Reference cost 2017-18 plus 15mins travel time
Visit to GP	£ 37/ visit	PSSRU 2018
GP home visit	£ 88/ visit	PSSRU 2018 (includes travel time)
Other healthcare		
Occupational therapist	£ 81/ visit	Reference costs 2017-18
Physiotherapist	£57 / visit	Reference costs 2017-18

Resource	Unit Cost £	Source
Home carer visit (nursing care)	£76/ visit	Assume same as district nurse
Home help visit (personal care)	£29 / visit	Personal Social Services: Expenditure and Unit Costs, England, 2014-15 (updated for inflation)

Medicines British National Formulary

Resource	Unit Cost £	Source
Apixiban 2.5mg	£4.40 / day	5mg BD every day
Aspirin 75mg	£0.03 / day	75 mg OD every day
Clopidogrel 75mg	£0.06 / day	75 mg OD every day
Dalteparin 12,500units/ml	£20.32 / day	For average weight 96kg, 18000units / day (male)
	£14.12 / day	For average weight 80kg, 12500 units / day (female)
Warfarin	£0.04 / day	
Rivaroxaban 10mg	£3.60 / day	20mg OD
Clexane (Enoxaparin):	£11.02 / day	1.5mg/kg OD (male 96kg)
	£7.84 / day	1.5mg/kg OD (female 80kg)
Dabigatran 150mg	£1.70 / day	150mg BD

Resource use and unit costs (Curtis & Burns(288, 289), Brittenden 2015(259), British National Formulary 2017(290), NHS reference costs (291), NHS Supply Chain(292))

Table S 5 - Summary of quality of life (AVVQ, EQ-5D, SF36) at baseline, six weeks, six months and 12 months after randomisation. Adapted from (205) wither permission.

	Baseline	6 weeks	6 months	12 months	
	N_s=226	N_s=213	N_s=204	N_s=199	p-value[c]
	N_e=224	N_e=219	N_e=208	N_e=203	
AVVQ					
Deferred	44.3 (8.7) [n=192]	41.2 (9.3) [n=170]	39.5 (10.3) [n=140]	34.3 (10.4) [n=130]	
Early	44.1 (9.0) [n=200]	39.4 (10.2) [n=176]	34.6 (9.4) [n=139]	32.4 (8.3) [n=127]	
Difference[a]	-0.2 (-2.0, 1.6)	-2.1 (-4.0, -0.2)	-4.8 (-6.9, -2.7)	-1.8 (-4.0, 0.3)	0.0008
EQ-5D Health Score					
Deferred	70.1 (17.1) [n=225]	71.1 (18.7) [n=205]	71.4 (19.6) [n=193]	73.7 (17.4) [n=184]	
Early	70.2 (17.7) [n=222]	72.7 (18.6) [n=212]	74.1 (15.8) [n=185]	74.8 (16.9) [n=183]	
Difference[a]	0.1 (-3.1, 3.4)	1.7 (-1.6, 5.1)	1.8 (-1.6, 5.2)	1.3 (-2.1, 4.8)	0.72
EQ-5D Index Value[b]					
Deferred	0.73 (0.2) [n=226]	0.75 (0.2) [n=208]	0.76 (0.2) [n=192]	0.80 (0.2) [n=182]	
Early	0.73 (0.2) [n=222]	0.79 (0.2) [n=211]	0.81 (0.2) [n=186]	0.83 (0.2) [n=184]	
Difference[a]	-0.01 (-0.04, 0.03)	0.04 (0.00, 0.08)	0.04 (0.00, 0.08)	0.03 (-0.01, 0.07)	0.03
SF-36 Physical Function					
Deferred	37.5 (12.5) [n=225]	37.4 (13.0) [n=207]	37.4 (13.7) [n=193]	38.7 (13.4) [n=180]	
Early	37.3 (12.0) [n=223]	39.1 (12.7) [n=212]	39.1 (12.8) [n=187]	39.4 (12.9) [n=182]	
Difference[a]	-1.0 (-3.1, 1.1)	1.0 (-1.2, 3.1)	0.7 (-1.5, 2.8)	0.3 (-1.9, 2.6)	0.09
SF-36 Role-Physical					
Deferred	39.7 (12.1) [n=224]	41.4 (12.7) [n=207]	42.4 (12.7) [n=192]	44.3 (12.9) [n=180]	
Early	39.0 (12.2) [n=223]	40.3 (12.5) [n=211]	43.6 (12.6) [n=187]	43.0 (12.7) [n=181]	
Difference[a]	-1.3 (-3.5, 0.9)	-1.7 (-4.0, 0.6)	0.4 (-2.0, 2.7)	-1.7 (-4.1, 0.7)	0.28
SF-36 Body Pain					

Deferred	41.6 (11.9) [n=224]	44.3 (12.3) [n=207]	45.9 (12.2) [n=193]	47.8 (11.2) [n=180]	
Early	41.3 (11.1) [n=223]	46.6 (10.6) [n=212]	48.2 (11.0) [n=187]	49.3 (11.0) [n=182]	
Difference[a]	-0.5 (-2.6, 1.6)	2.2 (0.1, 4.4)	2.1 (-0.2, 4.3)	1.1 (-1.1, 3.3)	0.05
SF-36 General Health					
Deferred	46.0 (9.8) [n=225]	45.6 (9.2) [n=207]	44.5 (10.1) [n=193]	45.1 (10) [n=181]	
Early	45.8 (9.2) [n=223]	45.7 (9.1) [n=212]	44.9 (9.8) [n=187]	45.3 (10) [n=183]	
Difference[a]	-0.3 (-2.0, 1.5)	0.0 (-1.8, 1.8)	0.0 (-1.9, 1.8)	0.4 (-1.5, 2.3)	0.86
SF-36 Vitality					
Deferred	47.8 (10.6) [n=224]	47.5 (11.3) [n=207]	48.8 (10.8) [n=193]	49.6 (9.8) [n=179]	
Early	48.2 (10.2) [n=222]	49.1 (10.0) [n=212]	49.4 (9.5) [n=187]	50.5 (9.4) [n=182]	
Difference[a]	0.1 (-1.7, 2.0)	1.4 (-0.5, 3.3)	0.0 (-1.9, 2.0)	0.9 (-1.0, 2.9)	0.31
SF-36 Social Functioning					
Deferred	42.4 (13.5) [n=224]	44.0 (12.1) [n=207]	44.7 (12.5) [n=193]	47.3 (11.4) [n=181]	
Early	42.6 (12.4) [n=223]	44.9 (11.6) [n=212]	47.0 (10.5) [n=186]	47.4 (10.7) [n=182]	
Difference[a]	-0.1 (-2.3, 2.0)	0.6 (-1.6, 2.8)	1.5 (-0.8, 3.7)	-0.4 (-2.7, 2.0)	0.40
SF-36 Role-Emotional					
Deferred	43.7 (13.6) [n=224]	45.9 (13.3) [n=207]	45.1 (13.2) [n=193]	47.5 (12.2) [n=179]	
Early	42.7 (13.8) [n=222]	46.1 (12.8) [n=212]	47.2 (12.2) [n=187]	45.9 (13.0) [n=182]	
Difference[a]	-1.4 (-3.8, 1.0)	0.0 (-2.5, 2.5)	1.7 (-0.9, 4.2)	-1.7 (-4.3, 0.9)	0.08
SF-36 Mental Health					
Deferred	49.3 (10.7) [n=224]	49.2 (10.8) [n=207]	49.5 (10.4) [n=193]	50.7 (10.1) [n=179]	
Early	49.2 (10.3) [n=222]	50.6 (10.4) [n=212]	51.7 (9.7) [n=187]	51.0 (9.3) [n=182]	
Difference[a]	-0.2 (-2.1, 1.7)	1.3 (-0.7, 3.2)	1.7 (-0.3, 3.7)	-0.2 (-2.2, 1.8)	0.07
SF-36 Physical Component Summary					
Deferred	38.8 (10.8) [n=223]	39.6 (11.6) [n=207]	40.4 (12.1) [n=193]	41.8 (12.0) [n=178]	

Early	38.5 (9.9) [n=222]	40.4 (10.2) [n=212]	41.5 (11.5) [n=187]	42.1 (11.6) [n=181]	
Difference[a]	-0.8 (-2.8, 1.1)	0.3 (-1.7, 2.2)	0.3 (-1.7, 2.3)	0.3 (-1.7, 2.3)	0.41

SF-36 Mental Component Summary

Deferred	49.4 (11.6) [n=223]	50.2 (11.0) [n=207]	50.2 (10.4) [n=193]	52.0 (10.0) [n=178]	
Early	49.2 (10.9) [n=222]	51.1 (10.4) [n=212]	52.2 (9.8) [n=187]	51.6 (9.5) [n=181]	
Difference[a]	-0.3 (-2.2, 1.7)	0.9 (-1.1, 2.9)	1.5 (-0.5, 3.6)	-0.7 (-2.7, 1.4)	0.09

Data presented as mean (SD)

[a]*Difference between two groups estimated using a mixed model with adjustment for time, age, ulcer duration and size as fixed-effects, and study centre and participant as random-effects; deferred ablation group used as reference*

[b]*EQ-5D index calculated using the value set for England(206)*

[c]*p-value for the overall difference between the two groups over the whole study period*

Adapted from *N Engl J Med* Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N*, et al.* A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. 2018; 10.1056/NEJMoa1801214. http://dx.doi.org/10.1056/NEJMoa1801214. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.

Table S 6 - Summary of quality of life (AVVQ, EQ-5D, SF36) at baseline, six weeks, six months and 12 months after randomisation quality of life outcomes with multiple imputation of missing values. Adapted from (205) with permission.

	Baseline	6 weeks	6 months	12 months
AVVQ				
Early ablation	44.0 (9.0)	39.1 (10.2)	34.9 (10.1)	33.0 (9.7)
Deferred ablation	44.2 (8.9)	41.2 (9.7)	39.4 (10.3)	34.8 (10.8)
Difference[a]	-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 ablation	70.2 (17.7)	72.6 (18.7)	73.6 (16.3)	74.8 (17.5)
Deferred ablation	70.0 (17.1)	70.7 (19.1)	71.5 (19.4)	73.0 (17.8)
Difference[a]	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[b]				
Early ablation	0.73 (0.2)	0.79 (0.2)	0.81 (0.2)	0.83 (0.2)
Deferred ablation	0.73 (0.2)	0.74 (0.2)	0.77 (0.2)	0.80 (0.2)
Difference[a]	-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 ablation	37.4 (12.0)	39.1 (12.9)	39.4 (12.9)	39.7 (13.3)
Deferred ablation	37.5 (12.5)	37.4 (13.0)	37.9 (13.6)	38.3 (13.7)
Difference[a]	-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 ablation	39.1 (12.2)	40.3 (12.6)	43.6 (12.6)	43.3 (12.9)
Deferred ablation	39.7 (12.1)	41.5 (12.6)	42.6 (12.8)	43.8 (13.1)
Difference[a]	-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 ablation	41.3 (11.1)	46.6 (10.6)	48.3 (11)	49.4 (11.1)
Deferred ablation	41.6 (11.9)	44.0 (12.2)	46.1 (12)	47.5 (11.5)
Difference [a]	-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 ablation	45.8 (9.2)	45.5 (9.1)	44.8 (9.8)	45.1 (10.0)
Deferred ablation	46.0 (9.8)	45.5 (9.3)	44.7 (10.2)	44.6 (10.2)
Difference [a]	-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 ablation	48.2 (10.2)	49.0 (10.2)	49.1 (9.6)	50.2 (9.7)
Deferred ablation	47.9 (10.5)	47.4 (11.2)	48.7 (10.7)	49.0 (10.0)
Difference [a]	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 ablation	42.6 (12.4)	44.8 (11.6)	46.9 (10.7)	47.1 (11.0)
Deferred ablation	42.4 (13.5)	43.8 (12.1)	44.9 (12.4)	46.7 (11.7)
Difference [a]	-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 ablation	42.7 (13.7)	46.1 (12.8)	47.0 (12.5)	45.6 (13.4)
Deferred ablation	43.7 (13.6)	45.8 (13.3)	45.1 (13.1)	47.1 (12.7)
Difference [a]	-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 ablation	49.2 (10.3)	50.4 (10.5)	51.2 (10.1)	50.5 (10.2)
Deferred ablation	49.3 (10.7)	49.0 (10.8)	49.4 (10.5)	50.2 (10.6)
Difference [a]	-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 ablation	38.5 (10.0)	40.4 (10.4)	41.8 (11.4)	42.6 (11.8)
Deferred ablation	38.8 (10.7)	39.6 (11.5)	40.8 (12.1)	41.2 (12.2)
Difference [a]	-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 ablation	49.2 (10.8)	51 (10.4)	51.7 (10.2)	50.9 (10.2)
Deferred ablation	49.4 (11.5)	50 (11.1)	50.1 (10.4)	51.5 (10.4)
Difference [a]	-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

[a] Difference between two groups estimated by mixed model adjusting for time, age, ulcer size and duration as fixed-effect, and study centre and participant as random-effect; deferred ablation group as reference; the 95% confidence intervals have not been adjusted for multiplicity

[b]EQ-5D index calculated using the value set for England(206)
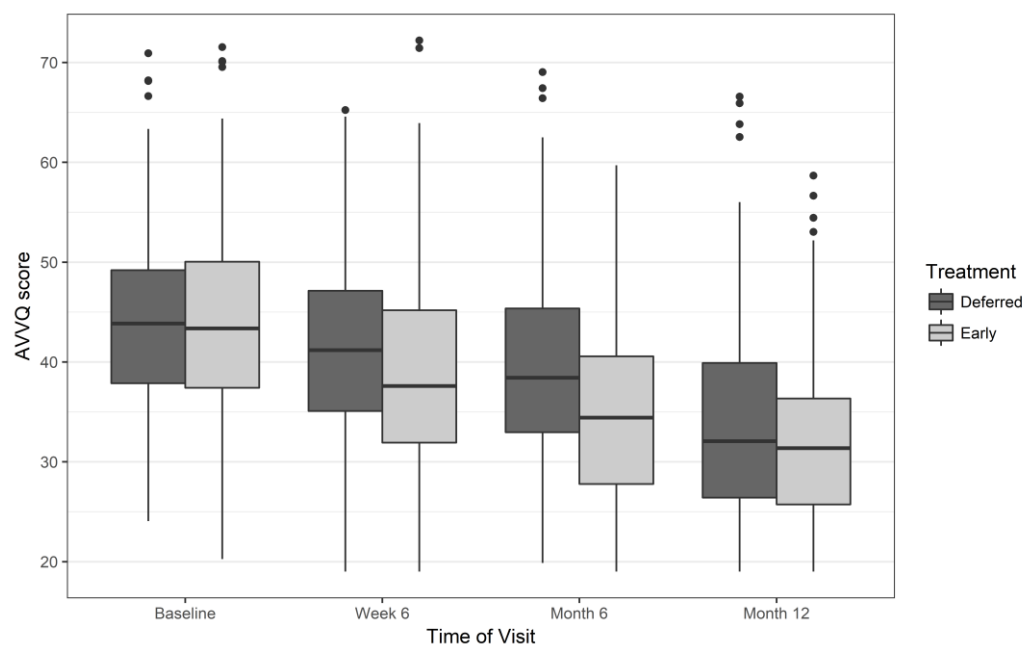
Figure S 1 - The changes in AVVQ score over time in the early and deferred ablation groups.

a)

b)
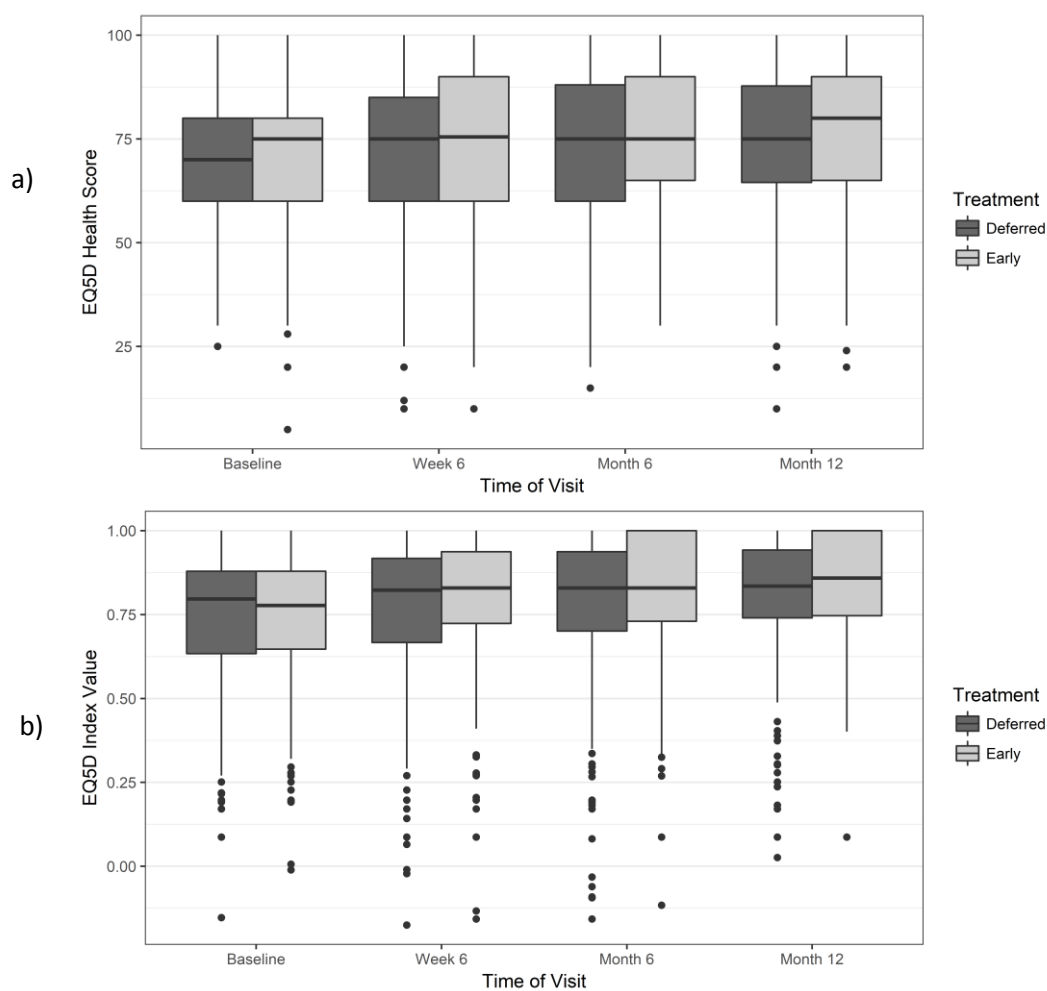
Figure S 2 - The changes in EQ5D: a) health Score; b) index value over time in the early and deferred ablation groups
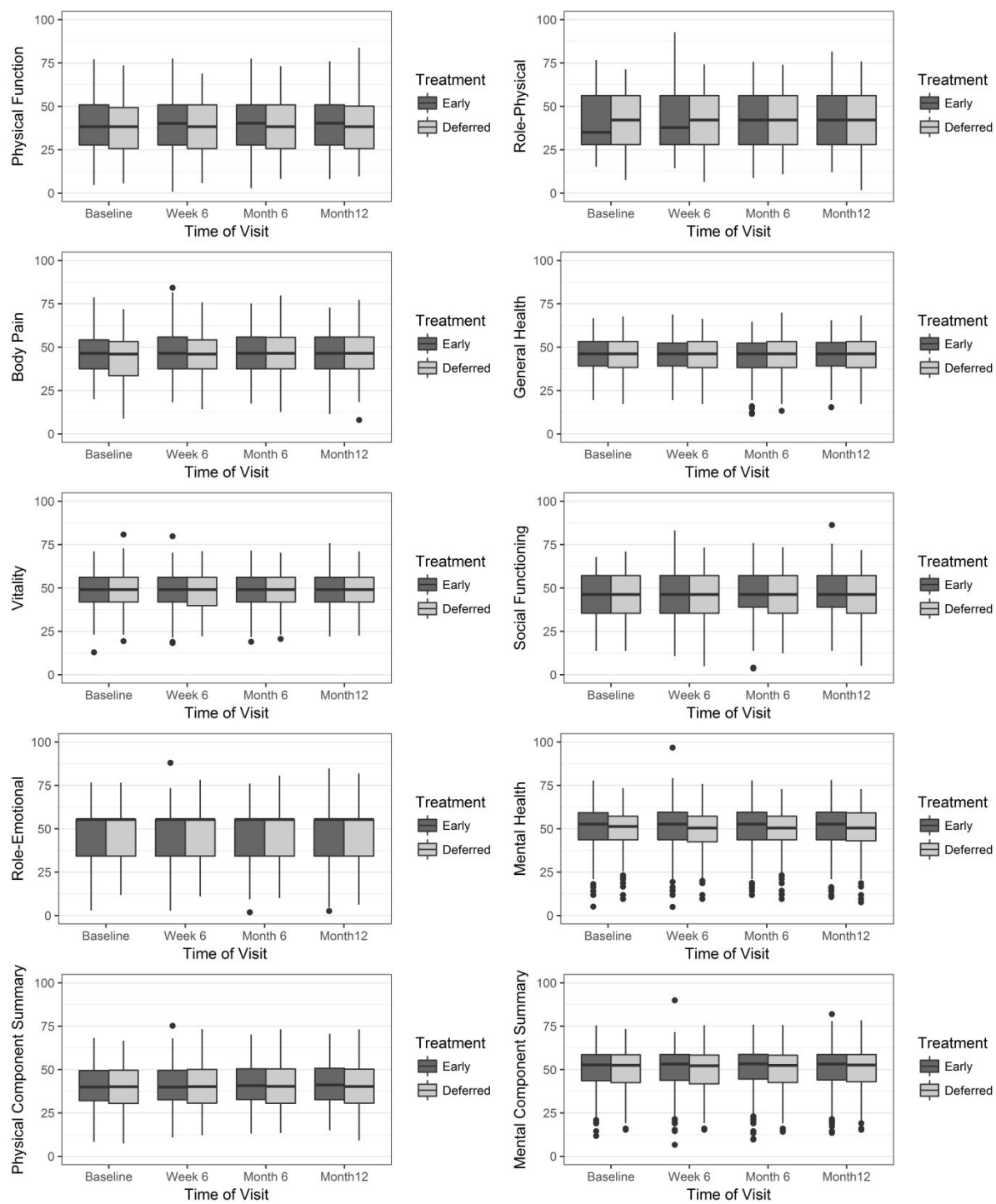
Figure S 3 - The changes in SF-36 scores over time in the early and deferred ablation groups

Table S 7 - Total resource use reported during the trial (n=450), and mean (SD) cost per participant with 12 months of follow up (n=419). Analyses performed without imputation. Adapted from (217) with permission

Resource Type	Unit of activity	Early (n=224) Resource use (total)	Deferred (n= 226) Resource use (total)	Early (n=208) Mean cost £	SD £	Deferred (n=211) Mean cost £	SD £
Treatment visits in the trial leg				523	368	370	369
No procedure		7	55				
At least 1 procedure		217	171				
At least 2 procedures		45	24				
At least 3 procedures		6	7				
At least 4 procedures		0	1				
Compression and dressings until healing (cost)				229	230	255	242
Compression stockings after healing (cost)				87	33	77	39
Hospital inpatient and day case admissions, not recorded as trial procedures	Admissions	27	16	227	693	207	1526
(Of which further ablation procedures, not recorded as trial procedures)		(12)	(5)				
Visits to DN	Visits	1947	2196	102	148	112	169
Visits from DN	Visits	624	1025	220	804	366	1263
Visits to GP	Visits	528	546	89	84	91	92
Visits from GP	Visits	23	49	9	28	20	56
Outpatient consultations and procedures, not recorded as trial procedures	Visits	807	731	588	851	527	952
(Of which further ablation procedures, not recorded as trial procedures)		(73)	(69)				
Occupational therapy	Visits	6	14	2	17	5	24
Costs of medicines							
Warfarin				1	4	2	4
Rivarox				16	106	24	159
Apixaban				13	114	1	9
Dalteparin				2	29	10	65

Item	Unit						
Dabigatran				0	4	2	36
Enoxaparin				0	0	2	23
Clopidogrel				1	3	1	3
Aspirin				2	4	2	4
Physiotherapy	Visits	106	247	25	109	57	285
Home care	Visits	1413	1573	257	1593	262	1207
Home help	Visits	875	882	121	799	121	646
Total cost				**2514**	**2770**	**2516**	**3242**
Hospital admissions unrelated to venous leg ulcer	Admissions	59	31	£342	1435	£192	1340
Outpatient visits unrelated to venous leg ulcer	Visits	151	156	£98	207	£103	414
Out of pocket expenses (OOP)	Patients with any OOP expense	87	122				
Unpaid carer	Days	4673	5132				
Off work days	Days	921	1458				
Normal days lost	Days	4068	4947				

Table S 8 - Unadjusted time to first ulcer recurrence (from date of healing) cox model

_t Treat	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Evra	0.786	0.143	-1.32	0.187	0.550	1.124

Table S 9 - Adjusted time to first ulcer recurrence (from date of healing) cox model (adjusted for patient age, ulcer duration and ulcer size)

_t Treat	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Evra	0.820	0.150	-1.09	0.278	0.572	1.174
Age	1.014	0.007	2.01	0.045	1.000	1.028
Ulcer_Size	1.005	0.003	1.86	0.063	1.000	1.010
ulcer_age	1.002	0.002	.688	0.491	0.997	1.006

Table S 10 - Unadjusted time to first ulcer recurrence (from date of randomisation) cox model (centre as random effect)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	0.836	0.153	-.982	0.326	0.585	1.195

Table S 11 - Adjusted time to first ulcer recurrence (from date of randomisation) cox model (adjusted for patient age, ulcer duration and ulcer size; centre as random effect)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	0.864	0.158	-.796	0.426	0.604	1.237
Age	1.014	0.007	1.99	0.047	1.000	1.028
Ulcer_Size	1.003	0.003	1	0.317	0.997	1.009
ulcer_age	1.001	0.002	.566	0.572	0.997	1.006

Table S 12 - Unadjusted time to ulcer healing (from date of randomisation) cox model (centre as random effect)

_t	Haz. Ratio	Std. Err.	Z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	1.355	0.132	3.11	0.002	1.119	1.641

Table S 13 - Adjusted time to ulcer healing (from date of randomisation) cox model (adjusted for, patient age, ulcer duration and ulcer size; centre as random effect)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	1.356	0.133	3.1	0.002	1.119	1.643
Age	0.999	0.003	-.411	0.681	0.992	1.005
Ulcer_Size	0.985	0.003	-4.84	0.000	0.979	0.991
ulcer_age	0.998	0.001	-1.71	0.086	0.995	1.000
site_group	0.962	0.037	-1	0.317	0.891	1.038

Table S 14 - Unadjusted healing time of first recurrence cox model (centre as random effect)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	0.911	0.183	-.464	0.643	0.615	1.350

Table S 15 - Adjusted healing time of first recurrence cox model (adjusted for Age, Ulcer Age and Ulcer size (Centre as random effect)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	0.911	0.183	-.463	0.644	0.615	1.351
Age	0.992	0.008	-1.03	0.301	0.977	1.007
Ulcer_Size	0.999	0.004	-.155	0.877	0.992	1.007
ulcer_age	0.996	0.003	-1.51	0.131	0.991	1.001

Table S 16 - Two-level, adjusted Cox model for time to healing of all recurrent ulcers (adjusted for age, ulcer duration and size, centre as random effect) Adapted from

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	1.101	0.188	.56	0.576	0.787	1.539
Age	0.993	0.006	-1.16	0.245	0.981	1.005
Ulcer_Size	1.001	0.003	.502	0.616	0.996	1.007
ulcer_age	0.996	0.002	-1.5	0.133	0.992	1.001

Table S 17 - Ulcer free time unadjusted cox model

Variable	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
EVRA	0.878	0.083	-1.37	0.170	0.729	1.057

Table S 18 - Ulcer free time adjusted cox model (centre as a covariate, rather than a random effect as would not converge)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Treat						
Evra	0.839	0.082	-1.8	0.072	0.692	1.016
Age	1.004	0.003	1.07	0.283	0.997	1.010
Ulcer_Size	1.006	0.002	3.95	0.000	1.003	1.010
ulcer_age	1.002	0.001	1.53	0.125	0.999	1.004
length_followup	0.993	0.000	-19.8	0.000	0.993	0.994
site_group						
2	1.105	0.180	.611	0.541	0.803	1.520
3	1.105	0.204	.54	0.589	0.770	1.586
4	1.131	0.192	.724	0.469	0.811	1.578
5	1.050	0.194	.265	0.791	0.731	1.508

Table S 19 - Summary of quality of life outcomes for extended follow-up

	Baseline	6 weeks	6 months	12 months	Extended follow-up
AVVQ					
Early intervention	28.8 (11.3)	22.9 (11.8)	16.9 (10.9)	14.6 (9.6)	12.8 (10.2)
Deferred intervention	28.8 (10.7)	25.2 (11.0)	22.6 (12.2)	17.1 (12.1)	15.3 (12.8)
Difference[†]	0.0 (-2.2, 2.2)	-2.6 (-4.9, -0.3)	-5.0 (-7.5, -2.5)	-2.1 (-4.7, 0.5)	-2.4 (-4.9, 0.0)
EQ-5D Health Score					
Early intervention	70.2 (17.7)	72.7 (18.6)	74.1 (15.8)	74.8 (16.9)	70.3 (18.7)
Deferred intervention	70.1 (17.1)	71.1 (18.7)	71.4 (19.6)	73.7 (17.4)	68.4 (19.3)
Difference[†]	0.1 (-3.1, 3.4)	1.7 (-1.6, 5.1)	1.8 (-1.6, 5.2)	1.3 (-2.1, 4.8)	1.3 (-2.4, 4.9)
EQ-5D Index Value[‡]					
Early intervention	0.73 (0.2)	0.79 (0.2)	0.81 (0.2)	0.83 (0.2)	0.5 (0.3)
Deferred intervention	0.73 (0.2)	0.75 (0.2)	0.76 (0.2)	0.80 (0.2)	0.5 (0.3)
Difference[†]	-0.01 (-0.04, 0.03)	0.04 (0.00, 0.08)	0.04 (0.00, 0.08)	0.03 (-0.01, 0.07)	-0.02 (-0.08, 0.04)
SF-36 Physical Function					
Early intervention	37.3 (12.0)	39.1 (12.7)	39.1 (12.8)	39.4 (12.9)	37.8 (13.8)
Deferred intervention	37.5 (12.5)	37.4 (13.0)	37.4 (13.7)	38.7 (13.4)	37.6 (13.4)
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)	0.0 (-2.4, 2.4)
SF-36 Role-Physical					

Early intervention	39.0 (12.2)	40.3 (12.5)	43.6 (12.6)	43.0 (12.7)	42.0 (12.7)
Deferred intervention	39.7 (12.1)	41.4 (12.7)	42.4 (12.7)	44.3 (12.9)	43.3 (12.5)
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)	-1.5 (-4.1, 1.0)
SF-36 Body Pain					
Early intervention	41.3 (11.1)	46.6 (10.6)	48.2 (11.0)	49.3 (11.0)	47.3 (12.2)
Deferred intervention	41.6 (11.9)	44.3 (12.3)	45.9 (12.2)	47.8 (11.2)	48.1 (12.7)
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)	-1.2 (-3.6, 1.2)
SF-36 General Health					
Early intervention	45.8 (9.2)	45.7 (9.1)	44.9 (9.8)	45.3 (10.0)	44.1 (10.8)
Deferred intervention	46.0 (9.8)	45.6 (9.2)	44.5 (10.1)	45.1 (10.0)	44.4 (11.0)
Difference[†]	-0.3 (-2.0, 1.5)	-0.0 (-1.8, 1.8)	0.0 (-1.9, 1.8)	0.4 (-1.5, 2.3)	-0.5 (-2.5, 1.5)
SF-36 Vitality					
Early intervention	48.2 (10.2)	49.1 (10.0)	49.4 (9.5)	50.5 (9.4)	48.9 (10.8)
Deferred intervention	47.8 (10.6)	47.5 (11.3)	48.8 (10.8)	49.6 (9.8)	49.8 (10.3)
Difference[†]	0.1 (-1.7, 2.0)	1.4 (-0.5, 3.3)	0.0 (-1.9, 2.0)	0.9 (-1.0, 2.9)	-1.5 (-3.5, 0.6)
SF-36 Social Functioning					
Early intervention	42.6 (12.4)	44.9 (11.6)	47.0 (10.5)	47.4 (10.7)	46.7 (11.5)
Deferred intervention	42.4 (13.5)	44.0 (12.1)	44.7 (12.5)	47.3 (11.4)	46.2 (12.9)
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)	0.3 (-2.2, 2.8)

SF-36 Role-Emotional					
Early intervention	42.7 (13.8)	46.1 (12.8)	47.2 (13.2)	45.9 (13.0)	44.9 (13.6)
Deferred intervention	43.7 (13.6)	45.9 (13.3)	45.1 (13.2)	47.5 (12.2)	45.5 (13.4)
Difference[†]	-1.4 (-3.8, 1.0)	0.0 (-2.5, 2.5)	1.7 (-0.9, 4.2)	-1.7 (-4.3, 0.9)	-0.8 (-3.6, 1.9)
SF-36 Mental Health					
Early intervention	49.2 (10.3)	50.6 (10.4)	51.7 (9.7)	51.0 (9.3)	51.0 (10.2)
Deferred intervention	49.3 (10.7)	49.2 (10.8)	49.5 (10.4)	50.7 (10.1)	51.1 (10.0)
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)	-0.5 (-2.6, 1.6)
SF-36 Physical Component Summary					
Early intervention	38.5 (9.9)	40.4 (10.2)	41.5 (11.5)	42.1 (12.0)	40.5 (11.9)
Deferred intervention	38.8 (10.8)	39.6 (11.6)	40.4 (11.5)	41.8 (12.0)	41.0 (12.8)
Difference[†]	-0.8 (-2.8, 1.1)	0.3 (-1.7, 2.2)	0.3 (-1.7, 2.3)	0.3 (-1.7, 2.3)	-0.9 (-3.0, 1.3)
SF-36 Mental Component Summary					
Early intervention	49.2 (10.9)	51 (10.4)	52.2 (9.8)	51.6 (9.5)	51.3 (10.5)
Deferred intervention	49.4 (11.6)	50 (11.0)	50.2 (10.4)	52.0 (10.0)	51.5 (10.6)
Difference[†]	-0.3 (-2.2, 1.7)	0.9 (-1.1, 2.9)	1.5 (-0.5, 3.6)	-0.7 (-2.7, 1.4)	-0.6 (-2.8, 1.6)

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 ‡EQ-5D index calculated using the value

Table S 20 - Time to first recurrence (from healing) per protocol – unadjusted cox model (centre as random effect)

_t Treat	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Evra	0.864	0.167	-.757	0.449	0.591	1.262

Table S 21 - Time to first recurrence (from healing) per protocol – adjusted cox model (adjusted for patient age, ulcer size and duration; centre as random effect)

_t Treat	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Evra	0.900	0.176	-.538	0.591	0.614	1.319
Age	1.015	0.007	1.95	0.051	1.000	1.029
Ulcer_Size	1.005	0.003	1.77	0.077	0.999	1.010
ulcer_age	1.002	0.002	.645	0.519	0.997	1.006

Table S 22 - Time to ulcer healing from randomisation per protocol – unadjusted cox model (no random effect)

_t Treat	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Evra	1.151	0.120	1.35	0.177	0.939	1.411

Table S 23 - Time to ulcer healing from randomisation per protocol – adjusted cox model (model (adjusted for patient age, ulcer size and duration; centre as random effect)

_t Treat	Haz. Ratio	Std. Err.	[95% Conf. Interval]	
Evra	1.169	0.122	0.954	1.434
Age	0.996	0.004	0.989	1.003
Ulcer_Size	0.986	0.003	0.979	0.992
ulcer_age	0.998	0.001	0.995	1.001

Table S 24 - NHS hospital and community health services use and non-NHS expenses. Adapted from (218) with permission.

	EVRA (n=186)	Deferred (n=193)
NHS resource use (number of episodes or visits)		
Hospital admission	0.06 (0.34)	0.07 (0.31)
Outpatient visit	1.91 (4.03)	2.46 (5.67)
GP clinic visits	0.63 (4.80)	0.23 (0.94)
GP home visits	0 (0)	0.02 (0.23)
DN clinic visits	10.99(46.12)	8.74(24.16)
DN home visits	2.18 (14.09)	6.31(34.38)
Occupational therapy sessions	0 (0)	0.05 (0.59)
Physiotherapy sessions	0.04 (0.59)	0 (0)
Other expenses for patients and family		
Out of pocket expenses (Pounds)	£7.58(46.67)	£7.16(38.24)
Paid carer (days)	6.24 (53.82)	4.03 (52.63)
Unpaid carer (days)	20.17(120.08)	10.08 (75.82)
Days lost from paid work	0.73 (7.21)	2.07 (19.07)
Days lost from usual activities	7.97(57.57)	22.66 (129.98)
Use of compression to prevent recurrence at extension follow up		
None	80	67
Bandage	9	15
Stocking	104	113
Use of medicines at extension follow-up		
Antiplatelets		
Aspirin	33	34
Clopidogrel	6	10
Anticoagulants		
Warfarin	16	18
New oral anticoagulants	13	14
Other	2	2

Data presented as mean (SD).

Table S 25 - Difference in discounted total mean costs and discounted QALY (early-intervention group – deferred-intervention group) at different time horizons (estimated using mixed model) Adapted from (218) wither permission.

Time horizon	Difference in cost, £	95% CI		Difference in QALY (a)	95% CI		Difference in QALY (b)	95% CI	
1 year	-67	-1011	788	0.053	0.022	0.084	0.041	0.013	0.069
3 year	-155	-1262	953	0.073	-0.057	0.204	0.024	-0.094	0.141
4 year	-132	-1322	1058	0.044	-0.139	0.226	-0.018	-0.183	0.147
5 year	-88	-1365	1188	0.051	-0.156	0.259	-0.029	-0.207	0.167

(a)QALY calculated using crosswalk tariff recommended by the National Institute for Care Excellence(209)
(b)QALY calculated using alternative tariff (206)
The incremental cost-effectiveness ratio is not calculable, as EVRA provides greater QALY benefit at lower cost

Table S 26 - Difference in discounted total mean costs and discounted QALY (early-intervention group – deferred-intervention group) at different time horizons (estimated using mixed model): per protocol (a). Adapted from (218) with permission.

Time horizon	Difference in cost, £	95% CI		Difference in QALY (b)	95% CI		Incremental cost-effectiveness ratio (c)
1 year	224	-617	1066	0.057	0.023	0.090	£3929 /QALY
3 year	222	-764	1209	0.098	-0.042	0.237	£2265/QALY
4 year	270	-791	1331	0.093	-0.102	0.288	£2903/QALY
5 year	309	-829	1447	0.120	-0.102	0.342	£2575/QALY

(a) The per-protocol analysis excludes patients with treatment-related protocol deviations (33 deferred intervention, 24 early intervention)
(b) QALY calculated using the crosswalk tariff recommended by the National Institute for Care Excellence (van Hout et al. 2012)
(c) The incremental cost- effectiveness ratio (ICER) is calculated as the difference in mean cost divided by the difference in mean QALY between the treatments, when the intervention costs more than the comparator and provides greater health benefit.

Appendix 7 – Clinician Questionnaire Global management of leg ulcers – Pre EVRA Results

Leg ulcers are very common and account for 2-3% of all healthcare budgets. The American venous forum has the Grade 2, Level C recommendation (weak recommendations based on observational studies or expert opinion) in favour of early intervention in active ulceration despite evidence from randomised trials indicating that there is no benefit.

The recent UK National Institute of Health (NIHR) funded **E**arly **V**enous **R**eflux **A**blation (EVRA) randomised controlled trial was designed to clarify whether early endovenous intervention (e.g. endothermal ablation and foam sclerotherapy prior to ulcer healing) of superficial venous reflux improves healing in patients presenting with a leg ulcer of less than 6 months in duration. The results will be available in April 2018, with further information about the trial here: http://www.evrastudy.org

This questionnaire hopes to gather information on the current global management of chronic venous leg ulcers and how the management and referral of patients may be affected by the results of the trial. Any information you provide will be treated as confidential and will not be disclosed in an identifiable form outside the research team. If you have any questions relating to this survey please contact Francine Heatley at: f.heatley@imperial.ac.uk (Academic Vascular Surgery, Imperial College London)

<u>Consent</u>

By completing this questionnaire I agree that:

- I am voluntarily offering my views, I understand that I do not have to take part, and I can stop at any time
- My comments may be anonymously quoted
- The research team will have access to my email if I provide this at the end so that I can be contacted once the results of the trial are available

Q1

What type of clinician are you?

- ○ Vascular surgeon
- ○ Phlebologist
- ○ General surgeon
- ○ Dermatologist
- ○ Family medical practitioner
- ○ Consultant vascular nurse
- ○ Vascular nurse specialist
- ○ Other

Q2

Age

- ☐ Under 30
- ☐ 30 to 39
- ☐ 40 to 49
- ☐ 50 to 59
- ☐ Over 60

Q3

Gender

- ◉ Male
- ☐ Female
- ☐ Prefer not to say

Q4

In which country do you practice?

- ☐ United Kingdom (specify):

  [_____]

- ☐ Europe (specify):

  [_____]

- ☐ North America (specify):

  [_____]

- ☐ South America (specify):

  [_____]

- ☐ Australasia (specify):

  [_____]

- ☐ Africa (specify):

  [_____]

- ☐ Asia (specify):

  [_____]

- ☐ Other (specify):

  [_____]

Q5

Which area of care is your centre?

- ☐ Primary / Community
- ☐ Secondary / District general hospital / District county hospital
- ☐ Academic / teaching
- ☐ Other (specify)

  [_____]

How many patients with open leg ulceration do you see each month?

[ ]

What is the average wait time for patients with chronic venous leg ulceration to be referred from primary care / GP to a specialised vascular centre in your area?

○ Weeks (how many?):

[ ]

○ Months (how many?):

[ ]

○ Unsure

Do you perform or arrange an ABPI at the first visit?

○ Yes

○ Depends (on what?):

[ ]

○ No (why not?):

[ ]

Do you usually perform a venous duplex ultrasound on all patients presenting with a leg ulcer?

○ Yes

○ Depends (on what?):

[ ]

○ No (why not?):

[ ]

Do you prescribe compression therapy for patients with venous ulcers (if not contraindicated)?

○ Yes

○ Depends (on what?):

[ ]

○ No (why not?):

[ ]

Display This Question:
If Do you prescribe compression therapy for patients with venous ulcers (if not contraindicated)? Depends (on what?): Is Select
Or Do you prescribe compression therapy for patients with venous ulcers (if not contraindicated)? Yes Is Selected

If you prescribe compression therapy, which type?

○ Compression bandages

○ Compression stockings

○ Other (pls specify):

[ ]

Q12

Do you think the treatment of superficial truncal venous reflux by endovenous intervention or surgery **benefits ulcer healing** in patients with chronic venous ulceration?

○ Yes

○ Depends (on what?):
[ ]

○ No (why not?):
[ ]

Q13

Do you think the treatment of superficial truncal venous reflux by endovenous intervention or surgery **prevents recurrence** in patients with chronic venous ulceration?

○ Yes

○ Depends (on what?):
[ ]

○ No (why not?):
[ ]

Q14

If you perform endovenous intervention or surgery when do you usually intervene?

◉ Do not perform intervention

○ Prior to ulcer healing

○ After ulcer healing

○ Depends (on what?):
[ ]

Q15

If you perform intervention, which methods of intervention do you use to treat **truncal** superficial venous reflux in patients with active leg ulceration (please indicate usage for each option below)?

	Always	Mostly	Sometimes	Never
Foam alone	○	○	○	○
Endothermal ablation alone	○	○	○	○
Mechanochemical Endovenous Ablation alone	○	○	○	○

	Always	Mostly	Sometimes	Never
Glue alone	○	○	○	○
Open surgery alone	○	○	○	○
Foam and Endothermal ablation combination	○	○	○	○
Foam and Mechanochemical Endovenous Ablation combination	○	○	○	○
Foam and Glue combination	○	○	○	○
Open surgery and foam	○	○	○	○
Other method not stated:	○	○	○	○

Q16

What is/are the main reason/s for the method/s you utilise to treat **truncal** superficial venous reflux in patients with active leg ulceration (tick all that apply)?

	Cost	Guidelines (evidence)	Clinician preference	Patient preference	Availability of equipment	Other
Foam alone	☐	☐	☐	☐	☐	☐
Endothermal ablation alone	☐	☐	☐	☐	☐	☐
Mechanochemical Endovenous Ablation alone	☐	☐	☐	☐	☐	☐

	Cost	Guidelines (evidence)	Clinician preference	Patient preference	Availability of equipment	Other
Glue alone	☐	☐	☐	☐	☐	☐
Open surgery alone	☐	☐	☐	☐	☐	☐
Foam and Endothermal ablation combination	☐	☐	☐	☐	☐	☐
Foam and Mechanochemical Endovenous Ablation combination	☐	☐	☐	☐	☐	☐
Foam and Glue combination	☐	☐	☐	☐	☐	☐
Open surgery and foam	☐	☐	☐	☐	☐	☐
Other method not listed:	☐	☐	☐	☐	☐	☐

Please state any other reasons you choose the method you use

Q17
Do you usually perform a duplex ultrasound post intervention to assess technical success?

○ Yes (at which time point/s?):

○ Depends (on what?):

○ No (Why not?):

Q18

Please rank the following measures of success of the treatment in order of importance to you as a clinician? (1 most important, 6 least important). Click and hold the option to move it up or down the list.

1 Ulcer healing
2 Ulcer recurrence
3 Quality of life
4 Cost
5 Number of reinterventions
6 Other (specify)

Q22

As detailed in the introduction, the Early Venous Reflux Ablation trial was designed to clarify whether early intervention (prior to ulcer healing) of superficial venous reflux improves healing. If the trial shows that early endovenous ablation **improves** ulcer healing would it change your practice?

○ Yes (in what way/s?):

○ Depends (on what and how:)?

○ No (why not?):

Q19

As detailed in the introduction, the Early Venous Reflux Ablation trial was designed to clarify whether early intervention (prior to ulcer healing) of superficial venous reflux improves healing. If the trial shows that early endovenous ablation **does not improve** ulcer healing would it change your practice?

○ Yes (in what way/s?):

○ Depends (on what and how?):

○ No (why not?):

Q20

Please let us know any barriers that would prevent you from changing your practice if you wanted to:

Q21

Please indicate anything else you would like us to know about how you manage patients with chronic leg ulcers:

Q22

Thank you for taking the time to respond to these questions. Your answers are important in helping us gain insight to the current management of patients with chronic venous ulceration.

We would like to contact you once the results of the EVRA trial are available to ask you further questions about practice.

If you are happy to answer further questions please leave your email address below. We will not share your contact details with anyone outside our research team.

[   ]

Appendix 8 – Management of Leg Ulcers in Primary Care in the UK: Pre EVRA results

Leg ulcers are very common and account for 2-3% of all healthcare budgets. The current NICE guidelines for varicose veins CG168 (published in July 2013) recommends that patients presenting with a leg ulcer over 2 weeks in duration are referred to a vascular service (a team of healthcare professionals who have the skills to undertake a full clinical and duplex ultrasound assessment and provide a full range of treatment). The guidelines also recommend referring patients with healed leg ulcers for further assessment, however we know that many patients are not referred for formal vascular assessment let alone interventional therapy. Those referred are often only done so once the ulcer has become chronic and hard to heal.

The recent UK National Institute of Health (NIHR) funded **E**arly **V**enous **R**eflux **A**blation (EVRA) randomised controlled trial was designed to clarify whether early endovenous intervention (e.g. endothermal ablation and foam sclerotherapy prior to ulcer healing) of superficial venous reflux improves healing, in patients presenting with a leg ulcer of less than 6 months in duration. The results will be available in April 2018, with further information about the trial here: http://www.evrastudy.org

This questionnaire hopes to gather information on the management of chronic venous leg ulcers in primary care and how the management and referral of patients may be affected by the results of the trial. Any information you provide will be treated as confidential and will not be disclosed in an identifiable form outside the research team. If you have any questions relating to this survey please contact Francine Heatley at: f.heatley@imperial.ac.uk (Academic Vascular Surgery, Imperial College London)

<u>**Consent**</u>

By completing this questionnaire I agree that:
- I am voluntarily offering my views, I understand that I do not have to take part, and I can stop at any time
- My comments may be anonymously quoted
- The research team will have access to my email if I provide this at the end so that I can be contacted once the results of the trial are available

Q1
What type of care giver are you?

◻ GP

○ Practice nurse

○ Community nurse

○ District nurse

○ Tissue viability nurse

○ Other

[   ]

Q2
How many patients with leg ulcers do you see each month?

[   ]

Q3
Who manages leg ulcers in your centre the majority of the time?

○ GP

○ Practice nurse

○ Community nurse

● District nurse

○ Tissue viability nurse

○ Other

[   ]

Q4
Do you perform or arrange an ABPI at the first visit?

○ Yes

○ Depends (on what?):

[   ]

○ No (why not?):

[   ]

Q5
Do you usually perform or arrange a venous duplex ultrasound on all patients presenting with a leg ulcer?

○ Yes

○ Depends (on what?):

[   ]

○ No (why not?):

[   ]

Display This Question:
If Do you usually perform or arrange a venous duplex ultrasound on all patients presenting with a le... Depends (on what?): Is S
Or Do you usually perform or arrange a venous duplex ultrasound on all patients presenting with a le... Yes Is Selected

Q6

What is the process for performing or arranging a duplex?

○ Refer to a provider to perform a duplex which you interpret and use to manage the patient

○ Refer to a provider who performs and interprets the duplex for you to manage the patient

○ Perform and interpret the duplex yourself which you use to manage the patient

○ Refer the patient to a provider who performs duplex which you use to refer the patient for management

○ Other

[ ]

Q7

Do you usually offer compression therapy to patients with venous ulcers?

○ Yes

○ Depends (on what?):

[ ]

○ No (why not?):

[ ]

Q8

Which type of compression do you use as an initial treatment?

○ Compression bandages

○ Compression stockings

○ Other

[ ]

Q9

Do you refer patients with an open venous ulcer to a vascular surgeon/secondary care?

○ Yes

○ Depends (on what?):

[ ]

○ No, always treated in the community (why?):

[ ]

Q10

If you refer patients with an active chronic venous ulceration to a vascular surgeon/secondary care, after what period of time do you refer (in months)?

[ ]

Q11

As detailed in the introduction, the Early Venous Reflux Ablation trial was designed to clarify whether early endovenous intervention (e.g. endothermal ablation and foam sclerotherapy prior to ulcer healing) of superficial venous reflux improves healing in patients presenting with a leg ulcer of less than 6 months in duration.
If the trial shows that early endovenous ablation **improves** ulcer healing would it change your practice?

⬭ Yes (please detail how):

[   ]

⬭ Maybe (please give more detail):

[   ]

⬭ No (please detail why not):

[   ]

Q12

As detailed in the introduction, the Early Venous Reflux Ablation trial was designed to clarify whether early endovenous intervention (e.g. endothermal ablation or foam sclerotherapy prior to ulcer healing) of superficial venous reflux improves healing in patients presenting with a leg ulcer of less than 6 months in duration.
If the trial shows that early endovenous ablation **does not improve** ulcer healing would it change your practice?

⬭ Yes (please detail how):

[   ]

⬭ Maybe (please give more detail):

[   ]

⬭ No (please detail why not):

[   ]

Q13

Please note any comment that you would like us to know about the management of chronic venous leg ulceration e.g. how the referral process could be made simpler or if there is any specific criteria by which you refer

[   ]

Q14

Thank you for taking the time to respond to these questions. Your answers are important in helping us gain insight to the current management of patients with chronic venous ulceration.

We would like to contact you once the results of the EVRA trial are available to ask you further questions about practice.

If you are happy to answer further questions please leave your email address below. We will not share your contact details with anyone outside our research team.

[   ]

Appendix 9 – Clinician Questionnaire on Global Management of Leg Ulcers: Post EVRA results

The recent UK National Institute of Health (NIHR) funded **E**arly **V**enous **R**eflux **A**blation (EVRA) randomised controlled trial was designed to clarify whether early intervention (prior to ulcer healing) of superficial venous reflux improves healing. It was published in April 2018 in the New England Journal of Medicine: https://www.nejm.org/doi/full/10.1056/NEJMoa1801214 with a quick take video here: https://www.nejm.org/do/10.1056/NEJMdo005294/full/ . The abstract is summarised below.

Abstract
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.

In a trial conducted at 20 centres 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 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 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 enrolment 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).

 This questionnaire hopes to gather information about how the management and referral of patients may be affected by the results of the trial. Any information you provide will be treated as confidential and will not be disclosed in an identifiable form outside the research team. If you have any questions relating to this survey, please contact Francine Heatley at: f.heatley@imperial.ac.uk (Academic Vascular Surgery, Imperial College London)

Consent
By completing this questionnaire I agree that:
1. I am voluntarily offering my views, I understand that I do not have to take part, and I can stop at any time
2. My comments may be anonymously quoted
3. The data I provide will be stored at Imperial College London

Q1
What type of clinician are you?

- ☐ Aesthetic Practitioner
- ☐ Consultant Vascular Nurse
- ☐ Dermatologist
- ☐ Family Medical Practitioner
- ☐ General Surgeon
- ☐ Interventional Cardiologist
- ☐ Interventional Radiologist

- ☐ Phlebologist
- ☐ Plastic Surgeon
- ☐ Tissue Viability Nurse
- ☐ Vascular Nurse Specialist
- ☐ Vascular Surgeon
- ☐ Other (specify)

Q2
In which country do you practice?

- ☐ United Kingdom (specify country)

- ☐ Europe (specify country)

- ☐ North America (specify country)

- ☐ South America (specify country)

- ☐ Australasia (specify country)

- ☐ Africa (specify country)

- ☐ Asia (specify country)

- ☐ Other (specify country)

Q3
What is your area of practice?

- ☐ Primary / Community
- ☐ Secondary / District General Hospital / District County Hospital
- ☐ Academic centre / Teaching hospital / Specialist hospital
- ☐ Other (please specify)

> **Q4**

What is the average time in weeks for patients with leg ulceration to be referred from primary care to your clinic / service?

- ☐ 0 weeks

> **Q5**

What is the average waiting time in weeks for patients to be seen in your clinic / service once they have been referred to you from primary care?

- ☐ 0 ☐ 0 weeks

> **Q6**

Had you heard of the EVRA leg ulcer study prior to seeing this questionnaire?

- ⭕ Yes
- ⭕ No

> **Q7**

Were you familiar with the results of the EVRA study prior to seeing this questionnaire?

- ⭕ Yes
- ⭕ No

> **Q8**

Prior to the EVRA results, did you usually perform endovenous ablation or surgery to correct superficial venous reflux prior to venous ulcer healing?

- ⭕ Yes, prior to ulcer healing
- ⭕ No, after ulcer healing
- ⭕ N/A, do not perform endovenous ablation or surgery

> **Display This Question:**
> If Prior to the EVRA results, did you usually perform endovenous ablation or surgery to correct supe... Yes, prior to ulcer heali

Q8a

If you perform intervention prior to ulcer healing, how many weeks after the diagnosis of venous leg ulceration would you *aim* to perform superficial venous intervention?

- ⭕ Immediately (less than one week)
- ⭕ Number of weeks (please write in the box)
  - ☐

> **Display This Question:**
> If Prior to the EVRA results, did you usually perform endovenous ablation or surgery to correct supe... Yes, prior to ulcer heali

Q8b

If you perform intervention prior to ulcer healing, how many weeks after the diagnosis of venous leg ulceration would you *actually* perform superficial venous intervention?

- ⭕ Immediately (less than one week)
- ⭕ Number of weeks (please write in the box)
  - ☐

Q8a

If you perform intervention after ulcer healing, how many weeks after healing of venous leg ulceration would you *aim* to perform superficial venous intervention?

- ⊙ Immediately (less than one week)
- ⊙ Number of weeks (please write in the box)

[   ]

Q8b

If you perform intervention after ulcer healing, how many weeks after healing of venous leg ulceration would you *actually* perform superficial venous intervention?

- ⊙ Immediately (less than one week)
- ⊙ Number of weeks (please write in the box)

[   ]

Q9

Have you changed your practice with respect to the timing of intervention based on the results of the EVRA trial?

- ⊙ Yes
- ⊙ No

Q9b

If **yes**, which factors were barriers to your practice changing? (select all that are applicable)

- ☐ I had no barriers changing practice
- ☐ The decision to change practice was made by somebody else (please state their role)

[   ]

- ☐ Resistance from colleagues
- ☐ Lack of trained staff
- ☐ Theatre capacity
- ☐ Duplex scanning capacity
- ☐ Lack of operating space or time
- ☐ Cost of changing the service model
- ☐ Reimbursement by health service or insurance companies
- ☐ Other costs (please specify)

[   ]

- ☐ Local / Clinical Commissioning Group Guidelines
- ☐ National guidelines
- ☐ Primary / secondary care integration / referral
- ☐ Other (please specify)

[   ]

Q9a

If you have not changed your practice with respect to the timing of intervention based on the results of the EVRA trial, would you like to?

- ○ Yes
- ○ No

Q9a1

If **yes**, which factors are barriers to your practice changing? (select all that are applicable)

- ☐ I have no barriers changing practice
- ☐ The decision to change practice is made by somebody else (please state their role)

[   ]

- ☐ Resistance from colleagues
- ☐ Lack of trained staff
- ☐ Theatre capacity
- ☐ Duplex scanning capacity
- ☐ Lack of operating space or time
- ☐ Cost of changing the service model
- ☐ Reimbursement by health service or insurance companies
- ☐ Other costs (please specify)

[   ]

- ☐ Local / Clinical Commissioning Group Guidelines
- ☐ National guidelines
- ☐ Primary / secondary care integration / referral
- ☐ Other (please specify)

[   ]

Q9b

If **no**, please select the appropriate statement below (select all that are applicable)

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- ☐ I already treat early / prior to ulcer healing
- ☐ The trial did not convince me (please specify why)

  [   ]

- ☐ Other (please specify)

  [   ]

Q10

Would the cost effectiveness results of early endovenous ablation alter how you make clinical decisions?

- ☐ Yes
- ☐ No
- ☐ Depends (please elaborate)

  [   ]

- ☐ The decisions are made by someone else (please state their role)

  [   ]

Q11

How do you think that early endovenous ablation (i.e. prior to venous ulcer healing) will affect long term venous ulcer recurrence rates?

- ☐ Reduces recurrence rates
- ☐ Increases recurrence rates
- ☐ No effect on recurrence rates
- ☐ Depends (please specify)

  [   ]

Thank you for taking the time to respond to these questions.

Please click the right arrow to complete the questionnaire.

Appendix 10 – Management of Leg Ulcers in Primary Care in the UK: Post EVRA

The recent UK National Institute of Health (NIHR) funded **E**arly **V**enous **R**eflux **A**blation (EVRA) randomised controlled trial was designed to clarify whether early intervention (prior to ulcer healing) of superficial venous reflux improves healing. It was published in April 2018 in the New England Journal of Medicine: https://www.nejm.org/doi/full/10.1056/NEJMoa1801214 with a quick take video here: https://www.nejm.org/do/10.1056/NEJMdo005294/full/ . The abstract is summarised below.

Abstract

Venous leg ulcers are open wounds occurring in patients with venous disease. They are common, painful, distressing and reduce patient quality of life. Leg ulcers often result from valves in the leg veins not working properly. The valves normally force blood back up towards the heart but blood can flow backwards (reflux) when they are damaged which can cause swelling and ulceration. Compression therapy (wrapping bandages around the legs) has been shown to help ulcers heal but it does not treat the underlying reflux problem with the veins. Treatment of superficial venous reflux by surgery has been shown to reduce ulcer recurrence. Newer, less invasive techniques (known as endovenous ablation) have taken over from surgery to correct venous reflux and are more acceptable to patients, as they can be performed quickly under local anaesthetic.

The aim of the study was to find out if treating patients with leg ulcers by early endovenous ablation (within two weeks) and standard compression therapy could increase ulcer healing, compared to standard compression therapy and deferred endovenous ablation once the ulcer had healed.
In total, 450 people agreed to take part in this study and were treated in 20 hospitals across England. Patients were randomly allocated to either early or deferred endovenous ablation and followed up for 12 months.

The study found that treating the veins early resulted in quicker ulcer healing than performing delaying treatment once the ulcer has healed (85.6% ulcers in the early group had healed by 24 weeks compared to 76.3% in the deferred group). The study also showed that participants had more time without an ulcer if the treatment was performed early rather than after ulcer healing.

This questionnaire hopes to gather information about how the management and referral of patients may be affected by the results of the trial. Any information you provide will be treated as confidential and will not be disclosed in an identifiable form outside the research team. If you have any questions relating to this survey please contact Francine Heatley at: f.heatley@imperial.ac.uk (Academic vascular surgery, Imperial College London)

Consent
By completing this questionnaire I agree that:
1. I am voluntarily offering my views, I understand that I do not have to take part, and I can stop at any time
2. My comments may be anonymously quoted

3. The data I provide will be stored at Imperial College London

Q1
What type of health care provider are you?

☐   GP   ☐   District nurse

☐   Practice nurse   ☐   Tissue viability nurse

☐   Community nurse   ☐   Other (please specify)
                                                 [   ]

Q2
Had you heard of the EVRA leg ulcer study prior to seeing this questionnaire?

- ☐ Yes
- ☐ No

Q3
Were you familiar with the results of the EVRA study prior to seeing this questionnaire?

- ☐ Yes
- ☐ No

Q4
If you are an Allied health professional are you able to refer patients directly to a vascular service?

- ☐ Yes, I can refer patients directly
- ☐ No, referrals must be made by the GP
- ☐ No, referrals are made by someone else in my practice / centre (please specify who)
  [   ]
- ☐ N/A, I am a GP

Q5
Prior to the EVRA results, how often were your patients with an **open** chronic venous leg ulcer referred to a vascular service?

- ☐ Never (0%)
- ☐ Rarely (25%)
- ☐ Sometimes (50%)
- ☐ Frequently (75%)
- ☐ Always (100%)

Q6

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Prior to the EVRA results, how often were your patients with a **healed** chronic venous leg ulcer referred to a vascular service?

- ☐ Never (0%)
- ☐ Rarely (25%)
- ☐ Sometimes (50%)
- ☐ Frequently (75%)
- ☐ Always (100%)

If your patients are referred to a vascular service, how long do you estimate it takes the patient to be seen by a vascular specialist due to hospital / clinic waiting lists, in weeks?

- [0] Number of weeks

Q7

Would you like to change your practice (with respect to referral) based on the results of the trial?

- ☐ Yes, I will refer to a vascular service earlier and have no barriers to this
- ☐ Yes, I would like to refer earlier but the decision is made by someone else (please state who)
  [   ]
- ☐ Yes, I would like to refer earlier but barriers prevent me (please state what)
  [   ]
- ☐ No, I already refer promptly
- ☐ No, (please state why not)
  [   ]
- ☐ Depends (please state on what)
  [   ]

Q8

Have you heard of the NICE Varicose veins: diagnosis and management clinical guideline [CG168]?

- ☐ Yes
- ☐ No

Q9

If yes, are you aware of what the guideline says with respect to referral to a vascular centre?

- ☐ Yes
- ☐ No
- ☐ × Not applicable

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What do you think of the recommendation that all leg ulcers should be referred to a vascular service for assessment and treatment? Please indicate on a scale of 0 to 10, where 0 is strongly disagree and 10 is strongly agree.

.

01		2	3	4	5	6	7	8	9	10

Please tell us why you gave the score you did above.

Thank you for taking the time to answer our questions.

Please click the right arrow to complete the questionnaire.

Appendix 11 –Thesis related publications

11.1 Journal publications

Francine Heatley, Layla Bolton Saghdaoui, Safa Salim, Sarah Onida, Alun Huw Davies: Primary care survey of venous leg ulceration management and referral pre-EVRA trial. British Journal of Community NursingVol. 25, No. Sup12. 10 Dec 2020 https://doi.org/10.12968/bjcn.2020.25.Sup12.S6

Salim S, Heatley F, Bolton L, Khatri A, Onida S, Davies AH. The management of venous leg ulceration post the EVRA (early venous reflux ablation) ulcer trial: Management of venous ulceration post EVRA. Phlebology. October 2020. doi: https://doi.org/10.1177/0268355520966893

Manjit S. Gohel, MD,1,2 Jocelyn Mora, MSc,2 Matyas Szigeti, MSc,3 David M. Epstein, PhD,4 Francine Heatley, BSc,2 Andrew Bradbury, MD,5 Richard Bulbulia, MD,6,7,8 Nicky Cullum, PhD,9 Isaac Nyamekye, MD,10 Keith R. Poskitt, MD,6 Sophie Renton, MS,11 Jane Warwick, PhD,3,12 and Alun H. Davies, for the Early Venous Reflux Ablation Trial Group: Long-term Clinical and Cost-effectiveness of Early Endovenous Ablation in Venous Ulceration: A Randomized Clinical Trial. JAMA Surg. 2020 Sep 23: e203845. doi: http://dx.doi.org/10.1001/jamasurg.2020.3845

Heatley F, Saghdaoui LB, Salim S, Onida S, Gohel MS, Davies AH. UK primary care survey of venous leg ulceration management and referral – Post-EVRA trial. Phlebology. July 2020. doi: https://doi.org/10.1177/0268355520944102

Heatley, Francine; Onida, Sarah, Davies, Alun H; The global management of leg ulceration: Pre early venous reflux ablation trial. Phebology Vol 35, Issue 8, 2020. https://doi.org/10.1177/0268355520917847

Manjit S. Gohel, Jocelyn Mora, Francine Heatley, Karen Dhillon and Alun H. Davies. Early referral of venous leg ulcers: lessons from the EVRA trial. Nursing & Residential Care. Vol 22, No.1 pg 30-36 https://doi.org/10.12968/nrec.2020.22.1.31

Gohel MS, Heatley F, Liu X, et al., 2019, Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT, Health Technology Assessment, Vol:23, ISSN:1366-5278, Pages:1-+: http://dx.doi.org/10.3310/hta23240

Manjit S. Gohel, M.D., David M. Epstein, Ph.D., Francine Heatley, B.Sc., Xinxue Liu, Ph.D., Andrew Bradbury, M.D., Richard Bulbulia, M.D., Nicky Cullum, 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. Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. *British Journal of Surgery* .Volume 106, Issue 5 https://doi.org/10.1002/bjs.11082

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 A Randomized Trial of Early Endovenous Ablation in Venous Ulceration, *New England Journal of Medicine* April 24, 2018 http://dx.doi.org/10.1056/NEJMoa1801214

David Epstein, Manjit Gohel, Francine Heatley, Alun H Davies. Cost-effectiveness of treatments for superficial venous reflux in patients with chronic venous ulceration. *British Journal of Surgery Open 10 May 2018* *https://doi.org/10.1002/bjs5.56*

11.2 Letters

Manjit S. Gohel, M.D., Francine Heatley, B.Sc. and Alun H. Davies, D.Sc. CORRESPONDENCE for the EVRA Trial Investigators A Randomized Trial of Early Endovenous Ablation in Venous Ulceration, *New England Journal of Medicine* April 24, 2018 http://dx.doi.org/10.1056/NEJMoa1801214

11.3 Abstracts

Heatley, F. et al. Global Management of Venous Leg Ulceration: Pre-EVRA Publication. Journal of Vascular Surgery: Venous and Lymphatic Disorders, Volume 7, Issue 2, 295: https://doi.org/10.1016/j.jvsv.2019.01.023

11.4 Posters

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies EVRA (Early Venous Reflux Ablation) ulcer trial: The issues of recruiting to a multicentre trial in patients with venous ulceration. April 2016. (Presented as a poster at the Wound Research network annual scientific meeting 2016)

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies. EVRA (Early Venous Reflux Ablation) ulcer trial: A randomised clinical trial to compare early versus delayed endovenous treatment of superficial venous reflux in patients with chronic venous ulceration. July 2015. (Presented as electronic poster at the European Venous Forum 2015)

11.5 Oral Presentations

F.Heatley, A.H.Davies, Global management of venous leg ulceration: pre EVRA publication. 25th June 2018 (Prize session *at the Venous forum annual meeting, London 2018)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies, EVRA (Early Venous Reflux Ablation) ulcer trial: The EVRA Trial – Methodology. 25th June 2018 (Invited presentation *at the Venous forum annual meeting, London 2018)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies, EVRA (Early Venous Reflux Ablation) ulcer trial: The results 26th April 2018 (Invited presentation *at the Tissue Viability Society, Newcastle 2018)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies, EVRA (Early Venous Reflux Ablation) ulcer trial: The results 24th April 2018 (Invited presentation *at the International Charing Cross Symposium, London 2018)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies, EVRA (Early Venous Reflux Ablation) ulcer trial: Baseline Characteristics & Event rates. February 2018 (*Presented at the XVIII International Union of Phlebology (UIP) World Congress, Melbourne 2018)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies, EVRA (Early Venous Reflux Ablation) ulcer trial: Baseline Characteristics & Event rates. February 2017 (*Presented at the 29th Annual Meeting of the American Venous Forum (AVF), New Orleans 2017)*

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies. (Early Venous Reflux Ablation) ulcer trial. October 2016. (*Invited Presentation at 17th Congress of the Asian Society for Vascular Surgery, Singapore 2016*)

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick, A.H.Davies. (Early Venous Reflux Ablation) ulcer trial: The issues of recruiting to a multicentre trial in patients with venous ulceration. February 2016. (*Presented at the 28th Annual Meeting of the American Venous Forum (AVF), Orlando 2016*)

F.Heatley, A.W.Bradbury, R.A.Bulbulia, N.Cullum, A.H.Davies, D.Epstein, M.Gohel, K.R.Poskitt, J.Warwick. EVRA (Early Venous Reflux Ablation) ulcer trial: A randomised clinical trial to compare early versus delayed endovenous treatment of superficial venous reflux in patients with chronic venous ulceration. August 2015. (*Presented at the Union Internationale de Phlebologie (UIP) Chapter Meeting 2015 Prize: In recognition of an exceptionally outstanding presentation at Seoul UIP 2015*)

Appendix 12 – Permissions

12.1 Figures 1&2

12.2 Any figures and tables from: Gohel MS, Heatley F, Liu X, et al., 2019, Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT, Health Technology Assessment, Vol:23, ISSN:1366-5278, Pages:1-+: http://dx.doi.org/10.3310/hta23240

12.3 Figures 4&5

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Description of figure/table/extracts	Fig 2	Kaplan-Meier survival analysis showing ulcer healing at three years Fig 3	Kaplan-Meier survival analysis showing ulcer recurrence at four years
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12.4 Figure 7

12.5 Any figures and tables from 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 A Randomized Trial of Early Endovenous Ablation in Venous Ulceration, New England Journal of Medicine April 24, 2018 http://dx.doi.org/10.1056/NEJMoa1801214

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12.6 Table 1

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Title of the article/chapter the portion is from	Primary care survey of venous leg ulceration management and referral pre-EVRA trial
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Heatley, Francine; Onida, Sarah, Davies, Alun H; The global management of leg ulceration: Pre early venous reflux ablation trial. Phlebology Vol 35, Issue 8, 2020. https://doi.org/10.1177/0268355520917847

Salim S, Heatley F, Bolton L, Khatri A, Onida S, Davies AH. The management of venous leg ulceration post the EVRA (early venous reflux ablation) ulcer trial: Management of venous ulceration post EVRA. Phlebology. October 2020. doi: https://doi.org/10.1177/0268355520966893

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Manjit S. Gohel, MD,1,2 Jocelyn Mora, MSc,2 Matyas Szigeti, MSc,3 David M. Epstein, PhD,4 Francine Heatley, BSc,2 Andrew Bradbury, MD,5 Richard Bulbulia, MD,6,7,8 Nicky Cullum, PhD,9 Isaac Nyamekye, MD,10 Keith R. Poskitt, MD,6 Sophie Renton, MS,11 Jane Warwick, PhD,3,12 and Alun H. Davies, for the Early Venous Reflux Ablation Trial Group: Long-term Clinical and Cost-effectiveness of Early Endovenous Ablation in Venous Ulceration: A Randomized Clinical Trial. JAMA Surg. 2020 Sep 23 : e203845. doi: http://dx.doi.org/10.1001/jamasurg.2020.3845

Appendix 13 – Publication full texts

Phlebology

The global management of leg ulceration: Pre early venous reflux ablation trial

Francine Heatley, Sarah Onida and Alun H Davies ⓘ

Abstract

Background: Various guidelines exist worldwide for the diagnosis and management of venous leg ulcers; however, these are difficult to implement resulting in disparate treatment of patients globally.

Method: An online, 26-question survey was designed to evaluate the current global management of venous leg ulceration and was emailed globally to approximately 15,000 participants (November 2017–February 2018).

Results: Overall, 799 responses were received from 86 countries, with a 5% response rate. The respondent physicians saw a median of 10 (interquartile range 5–20) patients per month, with a median time to referral from primary to secondary care of six weeks. Of the respondents, 61% arranged an ankle brachial pressure index on first visit and 84% performed a venous duplex, with 95% prescribing compression for those in whom it was not contraindicated. Fifty-nine percent performed endovenous intervention or surgery prior to ulcer healing.

Conclusions: The survey showed a diversity of treatment pathways. The need to develop a robust, clear pathway for patients with leg ulceration is clearly required.

Keywords

Venous ulceration, leg ulcers, compression bandaging, chronic venous insufficiency, endovenous treatment

Introduction

Venous leg ulcers (VLUs) are common, accounting for an estimated 70% of all leg ulcers and affecting up to 2% of the adult population. The estimated annual UK health service cost burden is between £400 million and £1 billion,[1–5] with the USA estimating costs to be as high as $15 billion.[6,7] The condition can be extremely distressing for patients, greatly affecting their quality of life.[8,9] There is currently no standalone National Institute for Health and Care Excellence (NICE) guideline for the treatment and management of leg ulceration in the UK, and there is evidence of considerable variation between National Health Service trusts as to which patients qualify for referral or treatment of varicose veins and leg ulcers. A substantial proportion of patients are still managed in the community, without referral to a specialist service, with widespread acceptance that the modern management of patients with VLUs is suboptimal.[10–12]

The 2013 NICE clinical guideline (CG) 168 for the diagnosis and management of varicose veins[13] recommends that patients with current ulceration should be referred to a vascular service for assessment and treatment within two weeks and that a venous duplex is performed to confirm the presence of superficial or deep venous reflux. The guidelines state that the first line of treatment should be interventional, and compression therapy alone should only be used if this is not indicated. Endothermal ablation (including radiofrequency ablation and endovenous laser ablation) should be considered, followed by ultrasound-guided foam sclerotherapy if endothermal ablation is deemed unsuitable, and finally surgery if both the former are not deemed suitable options. Intervention in the UK is usually performed once an ulcer is healed to prevent recurrence based on the results of the ESCHAR

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study,[14] with the use of compression bandaing if interventional treatment is not suitable or post intervention.

Guidelines in the USA and Europe do not make recommendations regarding referral from the community to specialist centres, but recommend ablation of the incompetent superficial veins in addition to compression therapy to help ulcer healing and prevent recurrence.[6,15,16] Unfortunately, as guidelines can be difficult to implement[17] and embed in healthcare systems, patients in both the UK and USA often suffer from delays in referral resulting in disparate care and harder to heal ulcers. A recent UK study looked at the number of leg ulcer referrals before and after implementation of the NICE CG 168 and found that, despite noting an increase in overall referrals since implementation, this did not impact on early referral, and it is likely that many patients are not referred at all.[4,18]

A National Institute of Health Research funded randomised controlled trial, Early Venous Reflux Ablation (EVRA), investigated the clinical and cost effectiveness of treating patients with early superficial venous ablation. Published in April 2018,[19] this study has the potential to influence chronic venous disease guidelines worldwide. The aim of this study was to determine the standards of global management of VLUs prior to publication of the 12-month outcome results of the EVRA study.

Methods

An online, 26-question survey, with an introduction detailing the EVRA trial, was designed using the Qualtrics management platform (Qualtrics, UT, USA) to assess various aspects of the global management of venous leg ulceration. A focus group of clinicians was asked to identify important and appropriate questions to include. The survey aimed to collect the number of patients with leg ulceration seen and referral times from primary to secondary care, whether ankle brachial pressure index (ABPI) and duplex ultrasound (DUS) assessments were performed, whether compression therapy was utilized, whether endovenous interventions or surgery were performed and, if so, the methods and timing of these. Clinicians were also asked their opinion on whether intervention affects healing and recurrence and whether the results of the EVRA study would influence their practice. The survey is detailed in supplementary Appendix 1 and was classed as a service evaluation exercise according to the Health Research Assessment (HRA) decision tool and therefore did not require ethical approval.[20] The survey underwent internal and external testing and was piloted externally to confirm appropriate content and face validity.[21]

An invitation email to complete the survey was circulated by various societies to approximately 15,000 participants using local, national and international mailing lists.

Reponses were collected within Qualtrics over a four-month period (November 2017–February 2018) prior to the publication of the EVRA trial. Continuous variables that follow a normal distribution were summarised using means and standard deviations. Skewed continuous variables were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages.

Results

There were 799 responses received from 86 countries, with a 5% response rate; Table 1 details the baseline characteristics of the respondents and global responses by country. As some respondents did not answer all questions, the total number of responses is stated in each section.

Number of patients seen each month with open leg ulceration

The median number of patients seen with open leg ulceration each month globally (and also in the UK) was 10 (IQR 5–20), as described by 797 respondents.

Average referral time from primary care

Of 797 respondents, the overall median referral time from primary care to a specialised vascular service was six weeks (IQR 2–12), whereas the median referral time in the UK was eight weeks (IQR 6–12).

ABPI performed or arranged

Of the respondents ($n = 786$), 61% performed or arranged an ABPI at the first visit. Those who did not, reported that they relied on a physical exam (palpable pulses), review of symptoms or results of a DUS.

Venous duplex performed or arranged

A venous DUS was performed on or arranged for patients presenting with a leg ulcer by 84% of the respondents ($n = 793$). Those who did not, stated that they mostly relied on a clinical arterial assessment or physical exam.

Compression prescribed

With respect to compression, 95% of the 793 respondents prescribed compression if not contraindicated, with 51% prescribing compression bandages, 31%

Table 1. Respondent baseline characteristics.

Characteristic	Respondents (n = 799)
Age (years)	n = 798
Under 30	10 (1.3%)
30–39	113 (14.2%)
40–49	222 (27.8)
50–59	280 (35.1)
Over 60	173 (21.7%)
Clinician type	n = 799
Vascular surgeon	552 (69.1%)
Phlebologist	115 (14.4%)
General surgeon	51 (6.4%)
Dermatologist	10 (1.3%)
Family medical practitioner	3 (0.4%)
Vascular nurse specialist	15 (1.9%)
Other	53 (6.6%)
Gender	n = 798
Female	112 (14.0%)
Male	681 (85.3%)
Prefer not to say	5 (0.7%)
Region of practice[a]	n = 799
United Kingdom	128 (16.0%)
Europe (excluding UK)	331 (41.4%)
North America	172 (21.5%)
Central America	16 (2.0%)
South America	48 (6.0%)
Australasia	19 (2.4%)
Africa	12 (1.5%)
Asia	59 (7.4%)
Middle East	14 (1.8%)
Area of care	n = 798
Primary/community	147 (18.4%)
Secondary/district general/county hospital	232 (29.1%)
Academic/teaching	316 (39.7%)
Other	102 (12.8%)

[a]Albania (n = 3), Argentina (n = 11), Australia (n = 15), Austria (n = 6), Bangladesh (n = 1), Belarus (n = 4), Belgium (n = 9), Bosnia (n = 1), Brazil (n = 26), Bulgaria (n = 5), Canada (n = 5), Caribbean (n = 3), Central America (n = 6), Chile (n = 3), Colombia (n = 3), Costa Rica (n = 1), Croatia (n = 1), Cyprus (n = 1), Czech Republic (n = 4), Denmark (n = 5), Ecuador (n = 2), Egypt (n = 3), El Salvador (n = 1), Estonia (n = 1), Finland (n = 1), France (n = 11), Georgia (n = 2), Germany (n = 21), Greece (n = 12), Honduras (n = 2), Hong Kong (n = 1), Hungary (n = 1), Iceland (n = 1), India (n = 27), Indonesia (n = 1), Iran (n = 1), Ireland (n = 8), Israel (n = 4), Italy (n = 49), Japan (n = 5), Jordan (n = 2), Kenya (n = 1), Kosovo (n = 1), Kuwait (n = 1), Latvia (n = 7), Lebanon (n = 3), Lithuania (n = 10), Luxembourg (n = 1), Mexico (n = 14), Moldova (n = 2), Morocco (n = 1), Nepal (n = 1), Netherlands (n = 15), New Zealand (n = 4), Nicaragua (n = 2), Norway (n = 7), Pakistan (n = 2), Panama (n = 1), Paraguay (n = 1), Peru (n = 2), Poland (n = 15), Portugal (n = 18), Romania (n = 2), Russia (n = 22), Saudi Arabia (n = 1), Senegal (n = 1), Serbia (n = 4), Slovakia (n = 4), Slovenia (n = 4), South Africa (n = 3), South Korea (n = 11), Spain (n = 23), Sri Lanka (n = 1), Sweden (n = 20), Switzerland (n = 6), Taiwan (n = 3), Thailand (n = 4), Tunisia (n = 1), Turkey (n = 9), United Arab Emirates (n = 2), Uganda (n = 1), Ukraine (n = 9), United Kingdom (n = 128), USA (n = 153), and Missing (n = 19).

prescribing stockings and 18% cited using other types of compression (n = 776).

Does treatment of superficial truncal venous reflux by endovenous intervention or surgery improve ulcer healing/reduce ulcer recurrence in patients with chronic venous ulceration?

Of the respondents (n = 787), 78% thought that the treatment of superficial truncal venous reflux by endovenous intervention or surgery improves ulcer healing in patients with chronic venous ulceration. Similarly, 80% of the respondents thought that the treatment of superficial truncal venous reflux by endovenous intervention or surgery reduces recurrence rates in patients with chronic venous ulceration.

Timing of intervention

Figure 1 shows the timing of endovenous intervention or surgery; 59% of respondents usually performed endovenous intervention or surgery prior to ulcer healing, with 19% after and 19% depending on the individual circumstances.

Intervention strategy preferences

Endothermal ablation alone was the most utilized method, followed by a combination of foam and endothermal, followed by foam alone and open surgery. Mechanochemical ablation, glue and combinations of those were the least utilized (Table 2).

Cost appeared to be the driver to use foam alone and open surgery, whereas guidelines were the driver for utilizing endothermal ablation alone, foam alone or a combination of the two. Clinician preference drove those using endothermal ablation alone and endothermal ablation and foam combination, whereas patient
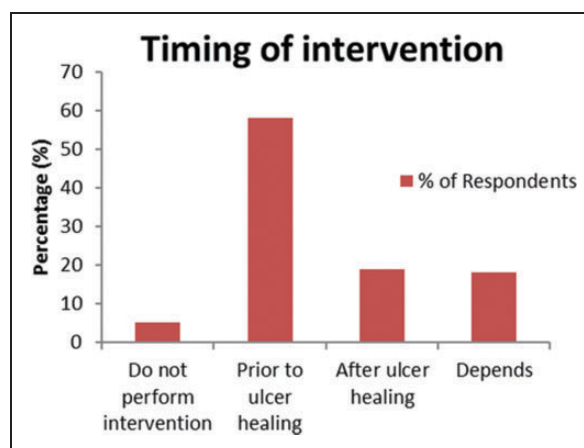

Figure 1. Timing of endovenous or surgical interventions (n = 785).

Table 2 Interventional strategies employed to treat truncal superficial venous reflux in patients with active leg ulceration.

Interventional strategy	Always (%)	Mostly (%)	Sometimes (%)	Never (%)	Total (n)
Endothermal ablation alone	14.6	38.3	34.7	12.5	583
Foam and endothermal ablation combination	9.7	22.3	40.6	27.4	547
Open surgery alone	4.2	17.0	43.4	35.4	553
Foam alone	3.5	8.4	51.2	36.9	549
Open surgery and foam	1.5	6.7	33.5	58.3	537
Mechanochemical endovenous ablation alone	1.2	5.0	22.2	71.6	514
Foam and mechanochemical endovenous ablation combination	0.9	2.6	16.9	79.5	508
Glue alone	0.2	1.2	15.9	82.7	504
Foam and Glue combination	0.00	1.2	10.9	87.9	506
Other method not stated	2.1	3.2	5.8	88.9	380

preference drove those using endothermal ablation alone and foam alone.

Assessing technical success

Of 647 respondents, 73% stated that they always perform a DUS post intervention to assess technical success. Those who did not usually cited lack of resources or that they had confidence in the effectiveness of their treatment. Some reported that performing a post interventional duplex was dependent on whether symptoms had resolved, whether the ulcer had healed or not, or if any complications were apparent.

Of those who perform a post interventional duplex ($n = 473$), 48% usually perform one, 16% perform two, 9% three and 3% four. Six percent of respondents perform more than four and 18% did not state the number. With respect to timings ($n = 473$), 42% performed the first post intervention duplex at one-week, 32% between one and six weeks and 9% post six weeks.

Healthcare perceptions of important outcome measures

Outcome measures of endovenous or surgical intervention were ranked in importance (1 most important; 6 least important) to the clinician. Ulcer healing was reported as being the most important outcome measure to the respondents (66.5%), followed by quality of life (22.2%) and ulcer recurrence (8.9%), whereas cost (1%) and number of reinterventions (0.7%) were considered much less important.

Changing practice

Of 681 global respondents, 46% stated that they would amend their practice to treat prior to ulcer healing if the EVRA study were to show that early intervention improves ulcer healing; 37% stated that they would not change practice but already treated prior to ulcer

healing, 6% would not change practice and currently treat after ulcer healing and 11% said it would depend on other factors not collected. If the EVRA trial were to show that early endovenous ablation did not improve ulcer healing, 46% of respondents ($n = 676$) stated that they would not change their practice. Reasons cited were that they were confident early ablation did improve ulcer healing, and it was already proven to reduce recurrence. A change in practice would be considered by 28% of respondents; reasons stated included insurance companies no longer covering early intervention or clinicians adopting less aggressive strategies.

Discussion

The survey results show that the referral and management of venous ulceration is disparate globally despite Level 1 evidence that surgical correction of truncal superficial venous reflux can reduce the risk of ulcer recurrence and Level 2 evidence that endovenous ablation may improve ulcer healing.[14] The results echo the findings of van der Velden et al.[22] who also demonstrated global variation in the management of patients with superficial venous disease and is likely a result of the difficulty of implementing guidelines, coupled with variation in the uptake of guidelines.[23,24]

If we look at the UK data as an example, the median number of patients seen by specialist vascular centres per month was reported to be 10 (IQR 5–20), which would indicate that only a small proportion of patients with leg ulceration (currently estimated at 278,000[4]) are actually referred to secondary care, assuming that each vascular surgeon in the UK sees 120 patients each year, which in itself may be an overestimation by the respondents.[4] It should be noted that there was no discrimination between new and recurrent ulcers in the survey responses.

The reported referral times were longer than the two weeks recommended by NICE.[13] These appear to

be unjustified treatment delays which may impact on ulcer healing times[25] and, indirectly, on the important clinical, quality of life and financial burden of venous leg ulceration. It is likely that the reasons for this are multifactorial; economic constraints, training and education of primary care providers, lack of patient awareness of available treatments and the absence of an evidence base underpinning the guidelines to encourage early diagnosis, referral and intervention at the time of survey completion.[26]

Investigations

The survey revealed that there was poor compliance with the recommendations for ABPI and venous duplex despite USA and UK guidelines advocating these.[6,16,27] Perhaps surprisingly, 73% of the respondents reported performing a DUS post intervention to assess technical success. Although not examined in detail by this survey, it is likely that this practice is related to the availability of funding to perform these assessments in different healthcare systems (e.g. nationalised versus private).

Interventions

The interventional strategies varied greatly, with the most utilized method reported as endothermal alone, which highlights potential under treatment by not targeting the incompetent tributaries or the veins in the sub-ulcer plexus. The UK recommends endothermal ablation as the first-line treatment, but kit availability varies amongst Trusts, with foam widely utilized due to its low cost. Globally, health systems have different methods and rules of reimbursement which may affect intervention timing and modality. Indeed, cost appears to be the driver to use foam alone, whereas guidelines were the driver for utilising endothermal ablation alone, foam alone or a combination of the two.

It is possible that the proportion of patients treated prior to ulcer healing will increase with Level 1 evidence now available from the EVRA trial that early intervention improves ulcer healing.[19] Indeed, nearly half of the respondents stated that they would change practice with respect to intervention timing if the EVRA study results show that early intervention improves ulcer healing, with surprisingly only a small number of clinicians reporting barriers to changing practice. There is no doubt that issues still exist with respect to referrals from primary to secondary care, resulting in a number of patients not receiving interventional treatment despite the evidence that this can prevent ulcer recurrence.[14,18,24,28] It will be interesting to see if the results of the EVRA trial influence practice in reality, and it would be helpful to resurvey the

participants to gain an understanding of the impact of the publication and gain a better insight into the challenges of changing leg ulcer pathways globally.

Limitations

The study is limited by the response rate which was estimated to be at least 5%, although it was impossible to determine the exact rate as some surgeons were listed multiple times, so it is likely the rate was higher than this; overall, 799 responses were received from 86 countries. In UK, 128 vascular surgeons responded to the survey; as there are approximately 450 consultant vascular surgeons registered with the Vascular Society of Great Britain and Ireland, nearly a third of the total vascular surgeons responded. As not all the surgeons will treat patients with venous ulceration, it is likely the representation is higher than anticipated.[29] It is also possible that the respondents may have overestimated the number of patients seen or treated, and therefore, the real-world scenario may be worse than demonstrated by these results.

Other potential limitations include selection bias for only targeting society members, although it would be almost impossible to contact clinicians who were not members of these societies for data protection reasons. The reimbursement mechanism (private versus state funded) of the targeted healthcare system was not collected which would have influenced some of the responses.

Conclusion

This survey highlights that global leg ulcer care is inconsistent, with a clear need to develop a robust pathway for patients with leg ulceration. The reasons for the variation are multifactorial, including local funding availability, access to healthcare, differences in training and education and inconsistent referral pathways coupled with a lack of Level 1 evidence that early intervention improves ulcer healing.

What does this study/review add to the existing literature and how will it influence future clinical practice?

This study highlights the disparity between current global venous leg ulceration practices with respect to the referral, assessment and management; it is likely that the recent randomised controlled EVRA trial will impact the management of these patients.

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Supplemental material

Supplemental material for this article is available online.

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Primary care survey of venous leg ulceration management and referral pre-EVRA trial

Abstract

Venous leg ulceration (VLU) is a public health concern that is largely managed in community settings. The present study aimed to survey current VLU management in the community. A 14-question survey was distributed to primary care professionals, and 90 responses were received. Some 54% of respondents stated that they would assess ankle brachial pressure indices (ABPI) for those with VLU, while 25% reported that they would not. Additionally, 62% reported not organising duplex ultrasound scanning. Compression therapy was offered by 82% of respondents. When asked whether VLU patients were referred to specialist services in secondary or tertiary care, some 32% reported that they would. However, 57% reported that, if a study suggested that referral to specialist services was beneficial, they would change their practice. On the basis of the findings, the authors concluded that there is diversity in VLU diagnostic and treatment pathways. New, high-quality evidence may improve practice, but care delivery is influenced by local factors including time and resource distribution.

■ Venous leg ulceration ■ Ankle brachial pressure index ■ Compression therapy ■ Duplex ultrasound
■ Evidence-based practice

A venous leg ulcer (VLU) is defined by the National Institute for Heath and Care Excellence (NICE) as loss of skin that takes more than 2 weeks to heal and is caused by sustained venous hypertension (NICE, 2019).

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VLU is the most common type of leg ulcer, accounting for 60–80% of all cases and affecting up to 3% of the population worldwide (Chamanga et al, 2014; Guest et al, 2018). Most common in older adults, it is a societal burden that continues to increase due to an ageing population, consuming a significant proportion of the NHS budget, equating to over £2.7 billion per year (Rabe and Pannier, 2010). VLU management is important as this condition is known to have a prolonged negative impact on patients' quality of life, due to chronic pain, immobility, reduced self-esteem and social isolation (Isaac and Watson, 2015).

At present, there is no standalone NICE guidance for leg ulcers in the UK. However, NICE guidance for the diagnosis and management of varicose veins recommends that patients with open ulceration should be referred within 2 weeks for assessment by a vascular specialist and receive appropriate wound care and compression treatment (NICE, 2019).

Most patients with VLU are treated in primary care by community, district and practice nurses, with GPs being the first point of contact (NHS, 2019). Although it is known that district nurses can spend as much as 50% of their time caring for chronic wounds, of which the vast majority will be VLU, there is a lack of centralised data regarding the number of patients treated and exactly who is providing care, making it difficult to ascertain the standards of leg ulcer management (Chamanga et al, 2014).

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Background

Referral pathways for patients with VLU have changed with difficulty over the years. While a 1985 postal survey determined that 83% of patients were managed entirely in the community, several studies that followed demonstrated that a systematic, multidisciplinary approach could optimise the effectiveness of VLU services (Callam et al, 1985). An example is the London Riverside project which, by trialing the consolidation of different care providers, achieved a 47% improvement in 12-week healing rates, highlighting that research-based interventions can lead to rapid clinical improvements (Moffatt et al, 1992; Moffatt and Oldroyd, 1994). This has culminated in NICE guidance, which is evidence-based, providing clear recommendations for patients with VLU to be referred to secondary care, to optimise patient assessment and management (NICE, 2013). In addition, the NICE clinical knowledge summary (NICE, 2015) specific to VLU and the Royal Society of Medicine's Venous Forum guideline (Venous Forum, 2018) provide clear frameworks and pathways to support referral from primary to secondary care. Despite these efforts, there has been little improvement in referral rates, and there is evidence that patients often still experience poorly integrated services (Davies et al, 2018; 2019).

One of the reasons for this ongoing issue is variability in local clinical commissioning group guidance (CCG) with respect to the conditions that should be funded via NHS pathways. CCGs have individual leg ulcer referral pathways, leading to great geographic variation in terms of when and where to refer patients (e.g. vascular service, leg ulcer service, tissue viability). The majority require a GP consultation for referral, and some CCGs may not recommend referral to a vascular service despite the evidence-based guidance, with patients largely treated in the community with disparate care.

Data on referral patterns to secondary care for patients with VLU is limited. With respect to referrals to vascular services, data from the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) suggest that rates are less than 3%, suggesting there is significant work required to increase this proportion (Petherick, 2010).

With there being limited up-to-date evidence outlining the management and referral pathway for patients with VLU in the UK, a service evaluation exercise was designed to survey health professionals. The survey was undertaken alongside a multi-centre randomised controlled trial conducted across the UK. The study (EVRA trial) aimed to investigate whether treatment with superficial venous reflux within 2 weeks of VLU presentation plus compression, as opposed to compression therapy alone, would reduce time to healing (Gohel et al, 2018). The aim of this survey was to gain an understanding of current practice with regard to VLU and understand how up-to-date evidence such as that from the EVRA trial might impact practice.

Survey design
To evaluate the current management of VLU in primary care in the UK, an 14-question online survey was created. Prior to

its dissemination, the survey was reviewed by a community/public health nursing lecturer involved in the National Wound Care Strategy programme. The appropriateness of the questions was reviewed by two independent district nurses and one vascular nurse specialist with expert knowledge of VLU and an understanding of research methodology. A short, simple design was used, with a voluntary, opt-in consent by completion of the questionnaire (Sawaya et al, 2018). To facilitate an open survey that allowed responses to be anonymous, the Qualtrics Survey platform was used. Questions were developed after a review of the literature to address the gaps in knowledge. They aimed to explore topics of relevance to local VLU management and the patient pathway, including: number of VLU patients seen per month; personnel responsible for VLU management; whether ankle brachial pressure index (ABPI) and/or duplex ultrasound were performed; the process for arranging the latter; whether compression bandaging was prescribed (if not contraindicated); details about the referral process for patients with active VLU; referral timelines. The survey was undertaken while the EVRA trial was being performed; thus, additional questions were included, enquiring as to whether the results of this study would influence the existing referral practice.

The survey allowed respondents to review and change their answers via the 'back' button and was equipped with a completeness check highlighting incomplete answers before the questionnaire could be submitted; this could, however, be overruled, and it was possible to submit an incomplete answer. Cookies were used to assign a unique user identifier to each respondent computer and set on each page.

Methods/survey distribution

Participation in the survey was voluntary, and it was circulated to primary care professionals, including GPs, community nurses and district nurses via local and national networks, such as Wounds Research Network (WREN) and the Tissue Viability Network (TVN). WREN and TVN have approximately 300 and 500 subscribers respectively on their mailing lists; the survey therefore was distributed via approximately 800 emails. In addition, WREN shared a post on its social media platform, reaching approximately 100 followers. Responses were collected over a 4-month period (November 2017 to February 2018).

Survey analysis
Continuous variables following a normal distribution were summarised using means and standard deviations (SDs). Skewed continuous variables were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text was categorised by common themes for ease of interpretation.

Ethics/research reporting checklist
Using the Health Research Authority's (HRA) development tool (www.hra-decisiontools.org.uk/research/), the survey was classed as a service evaluation and, therefore, did not require HRA/ethics approval (HRA, 2017).

This study has been reported in accordance with the EQUATOR guidelines. The CHERRIES checklist was used, as it was the most appropriate for a survey type service evaluation (Eysenbach, 2004).

Results

The survey received 90 complete responses out of approximately 900 survey distribution events (email, social media), indicating a response rate of 10%. Responses were variable, both in terms of professionals primarily responsible for VLU care (*Table 1*) and in terms of the number of patients seen with VLU every month (*Table 2*).

Assessment/treatment

ABPI assessment would be performed or arranged at a patient's first visit by 54% of respondents; 21% reported that performing ABPI depended on factors such as time and capacity or the patient history. Respondents did not expand on how the patient's history would influence their decision. A further 25% reported they do not perform ABPI assessment, as they lack time and resources, such as access to a Doppler machine. When asked about further baseline assessments, only 13% of respondents stated they would organise/perform a venous duplex on those presenting with a VLU, with 62% stating they would not do so. For 25% of respondents, the decision depended on other factors such as time and capacity, reflecting the response for ABPI.

Of those who would performed/would consider performing a duplex ('yes' or 'depends'), 24% referred patients to a provider for the scan, which they interpreted and used to manage the patient; 48% referred to a provider who performed and interpreted the duplex; 15% performed and interpreted the duplex themselves, which they used to manage the patient; 12% referred to a provider to perform a duplex, which they used to refer the patient for further management. Respondents were asked if they offered any type of compression therapy; 82% stated they offered compression; the 10% stating 'depends' added that it would depend on the ABPI or patient choice. Additionally, 7% stated that they did not offer compression

therapy due to lack of training and capacity. With respect to the type of compression therapy used, 72% reported the use of compression bandages, 4% compression stockings and 24% mentioned any other type of hosiery/compression.

Referral/treatment pathway

Respondents were asked if they referred patients with VLU to a vascular surgeon. Some 32% reported that they routinely referred patients with active VLU, while 53% stated that referral depended on other factors, such as patient response to compression or GP agreement. Interestingly, 14% of respondents reported that they never refer. For those referring to a vascular service, the median time for referral was 4 weeks (interquartile range, 2–8), with the breakdown as illustrated in *Table 3*. Reasons for delaying or not referring included issues with accessing vascular services, limitations with time and resources, in addition to cost and the interpretation of local CCG guidance.

Respondents were asked if they would change their practice should high-quality evidence find that early ablation improved ulcer healing. Over half (57%) stated that they would change their referral practice, 8% stated they would not and 35% stated that it would depend on other factors such a vascular service capacity and CCG approval. Additional questioning found that, should the EVRA trial not find that early intervention improved ulcer healing, 14% would change their practice, 26% would change their practice depending on other factors (e.g. whether they thought it would help recurrence) and 60% would not change their referral practice.

Table 1. Respondent primary caregiver type

Caregiver type	Respondents (n=88)
GP	2 (2.3%)
Practice nurse	19 (21.6%)
Community nurse	10 (11.4%)
District nurse	4 (4.6%)
Tissue viability nurse	37 (42.0%)
Other	16 (18.2%)
*two respondents did not answer this question	

Table 2. Number of patients seen with open leg ulceration each month

Patients with ulceration seen per month	n=90
Less than 10	27 (30.0%)
10 to 30	26 (28.9%)
More than 30	26 (28.9%)
Not known	11 (12.2%)
The median number of patients seen was 20 (IQR=5–30)	

Table 3. Average perceived wait time for patients with chronic venous leg ulceration to be referred from primary care/GP to a specialised vascular centre

Average referral wait time/weeks	n=68
Less than 6 weeks	25 (36.78%)
6 weeks to 6 months	23 (33.82%)
More than 6 months	8 (11.76%)
Not known	12 (17.65%)

Free-text comments

At the end of the survey, respondents were asked to provide further comments regarding the management of VLU. Comments were reviewed for recurrent themes. Lack of training was frequently highlighted, especially relating to the cause of leg ulcers, as these are often treated as a simple wound (with dressings) or as a lymphatic problem that cannot be addressed by venous surgery. Respondents also highlighted that it was sometimes difficult to access Doppler machines in a timely manner, and they were unaware of where to refer for a duplex ultrasound, leading to delays in assessment. A high variation in skill level, usually resulting from lack of funds and resources in certain clinics, was also highlighted, as was a need for clarity regarding referral and treatment pathways. Most often, direct referrals to vascular centres can only be made by the GP and not by district or tissue viability nurses; there was also a belief that waiting times for clinic appointments were considerable once patients were referred to vascular centres.

Some respondents raised conflicting issues, such as secondary care consultants encouraging conservative over interventional treatment once referred, or surgeons only accepting referrals for ulcers with an underlying arterial cause. Interestingly, some respondents highlighted that the recently published wound assessment guidance that aimed to assist in meeting the Commissioning for Quality and Innovation (CQUIN) targets had led to community and district teams not being able to cope with the increased demands for secondary care referrals (NHS England, 2016).

Discussion

The results of this survey demonstrate disparity in the management of patients with VLU and highlight a lack of understanding and awareness of current guidelines. Since various professionals contribute to the care of patients with VLU, it is unsurprising that levels of training and understanding of guidelines will differ.

An example of the disparity in care can be seen in the initial assessment of VLU. The completion of essential baseline assessments such as ABPI can depend on other factors such as time and resource availability. With compression therapy being the gold-standard wound management technique for VLU, it is encouraging that over half of the respondents would complete or arrange an ABPI at the first visit. However, 62% of practitioners do not routinely request a duplex ultrasound, an investigation that is key to diagnose venous insufficiency and highlight veins that may require treatment.

Despite NICE guidance (2013) outlining the need for referral to a vascular specialist, approximately a third of respondents (32%) said they would routinely refer and over half (53%) stated the decision would depend on different factors, such as the length of current treatment and the condition of the ulcer; this is not in keeping with national guidance. Reasons for this include lack of awareness or understanding of guidelines or the existence of barriers to guideline implementation, such as low clinician engagement and financial pressures (Davies et al, 2019). Free-text comments

KEY POINTS

- Patients with suspected venous leg ulceration (VLU) require prompt referral to vascular services
- A wide range of health professionals care for people with VLU, including tissue viability nurses and community and district nurses
- Assessment of VLU requires assessment of ankle brachial pressure index and duplex ultrasound
- Compression therapy is the gold-standard treatment for VLU
- To improve the patient care pathway, it is important to know how health professionals process patients with VLU

supported this finding, detailing a need for clarity regarding the referral pathway, in addition to addressing the issues of who can and cannot refer patients. With nurses predominantly managing care, it is interesting that the responses highlighted the need for a GP to send the referral. Answers to a number of questions revealed a belief that referral to a vascular specialist may not always be helpful due to an expectation of conservative treatment plans and lengthy waiting times for clinic appointments. Looking at the responses, it is clear to see where delays can happen, resulting in the 2-week referral timeline outlined by NICE not being met. In order to achieve this referral time, it is important to establish clear, national, standardised referral frameworks and pathways of care similar to the 2-week referral pathway in cancer care. This is something that may reduce care inequalities and help improve adherence to NICE guidance, improving the quality of care. Supporting published evidence, the CQUIN CCG indicator specifications for 2020–2021 have now been published and include the need for referral to vascular services for surgical interventions (NHS England, 2020).

The EVRA trial has been published, providing evidence that early treatment for venous reflux results in improved ulcer healing, in addition to a significant increases in ulcer-free time (Gohel et al, 2018). Now that clinicians are equipped with robust 'level 1' evidence to support treatment of venous incompetence, there is an expectation that the number of VLU referrals to vascular specialists will increase. Encouragingly, over half of the survey respondents (57%) stated that a positive outcome in the EVRA trial would result in a change in practice with respect to referral, but 35% stated that this would depend on other factors such as the capacity of local vascular services. Now that the evidence has been available for a considerable length of time, it would be helpful to re-survey a larger number of primary care practitioners to gain an understanding of the impact of the trial.

Limitations

Although this survey was useful to document the views of primary care professionals, a limitation is the low response rate. However, it is important to note that the response rate does not account for overlap between subjects who are subscribed

to mailing lists and also follow that organisation's social media platform. Additionally, there is likely to be some responder bias, as those who responded are likely to have a special interest in VLU, meaning the finding may not be representative of the wider community of primary care professionals. **CWC**

Conflict of interest: none

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CPD REFLECTIVE QUESTIONS

- What is the 'gold standard' treatment venous leg ulceration?
- What is the 'gold standard' assessment for the diagnosis of venous ulceration?
- What is your understanding of the NICE Clinical Knowledge Summary for venous leg ulceration?

ORIGINAL ARTICLE

A Randomized Trial of Early Endovenous Ablation in Venous Ulceration

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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.

A Quick Take is available at NEJM.org

V ENOUS 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. Multilayer 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 nonthermal, 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.
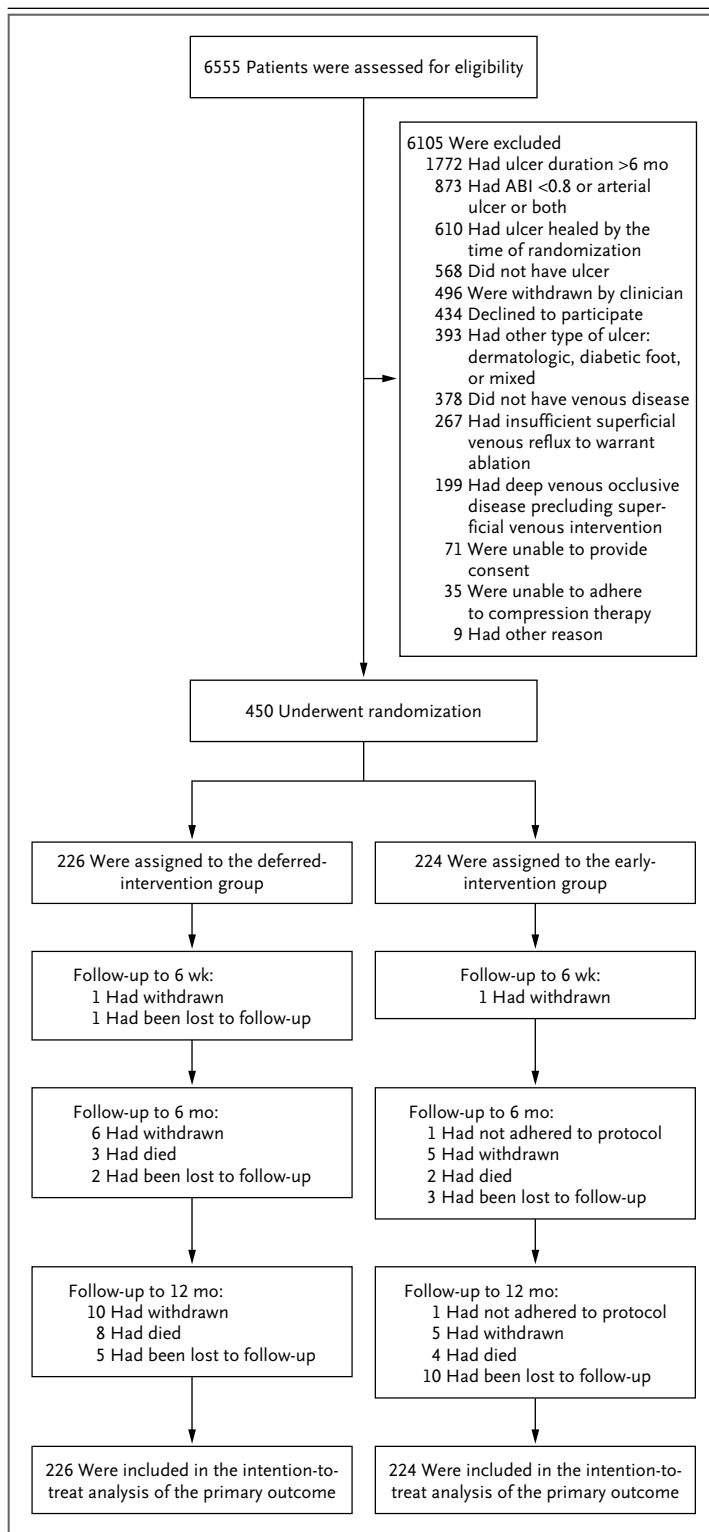
The secondary outcome measures were the rate of ulcer healing at 24 weeks, the rate of ulcer recurrence, the length of time free from ulcers (ulcer-free time) during the first year after randomization, and patient-reported health-related quality of life. Ulcer-free time was assessed only in patients 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

Figure 1. Enrollment, Randomization, and Follow-up.

Shown are the cumulative numbers of patients who had withdrawn, had died, had not adhered to the protocol, or had been lost to follow-up by each follow-up time point. 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. Treatment protocol violations occurred in 32 patients in the early-intervention group and in 31 patients in the deferred-intervention group.

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 Supplementary Appendix). Factors that are thought to affect the healing of venous leg ulcers, including 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.
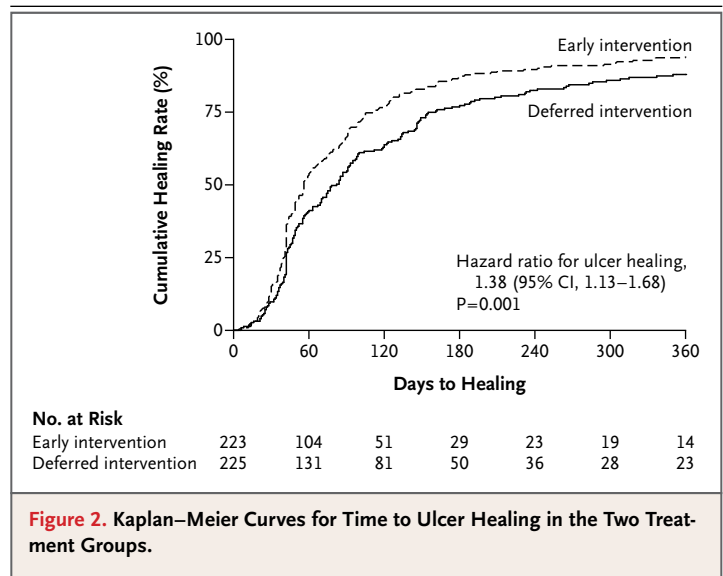
P=0.02). Mean (±SD) scores on the Venous Clinical Severity Score assessment tool did not differ significantly between the two treatment groups at randomization (15.8±3.3 in the early-intervention group and 15.7±3.1 in the deferred-intervention group). At 6 weeks, scores on the Venous Clinical Severity 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-

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.

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EUROPEAN COLORECTAL CONGRESS
Spotlight on the colon
1 – 5 December 2019, St.Gallen, Switzerland

Sunday, 1 Dec. 2019

MASTERCLASS

09.00
When the appendix plays nasty: intraoperative surprises, immediate solutions, and long-term treatment options
Justin Davies, Cambridge, UK

09.40
All the secrets of the pelvic floor - common disorders and proven solutions
Julie Cornish, Cardiff, UK

10.20
taTME in 2020 – when the dust settles: current and innovative indications, implementation, and practical advices
Roel Hompes, Amsterdam, NL

11.30
Complete mesocolic excision: indications, surgical approaches, and pitfalls
Paris Tekkis, London, UK

12.10
The views of an Editor and the wisdom of an Expert: contemporary publications with the potential to change and improve practice
Neil Mortensen, Oxford, UK

14.00
To ostomize or not and when? The value and downside of a diverting stoma versus virtual ileostomy versus no stoma
Gabriela Möslein, Wuppertal, DE

14.40
Extended lymph node dissection: indications, surgical anatomy, and technical approaches
Peter Sagar, Leeds, UK

15.20
Is the longer the new better - how to safely extend the interval after neoadjuvant chemoradiotherapy prior to surgery for rectal cancer
Ronan O'Connell, Dublin, IE

16:30
The colorectal anastomosis: time-proven wisdom, innovative configurations, and salvage techniques
André d'Hoore, Leuven BE

17.10
All you need to know about stomas but never dared to ask
Willem Bemelman, Amsterdam, NL

17.50
The EBSQ Coloproctology Examination
Michel Adamina, Winterthur, CH

18.00
Wrap-up
Michel Adamina, Winterthur, CH

Monday, 2 Dec. 2019

SCIENTIFIC PROGRAMME

09.45
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
Pathophysiology and non-operative management of symptomatic uncomplicated diverticular disease
Robin Spiller, Nottingham, UK

10.30
Surgery of acute diverticulitis – evidence, eminence and real life
Willem Bemelman, Amsterdam, NL

11.00
Management of atypical diverticulitis
Dieter Hahnloser, Lausanne, CH

11.30
Hartmann reversal: open, laparoscopic or transanal?
Roel Hompes, Amsterdam, NL

13.30
The surgeon personality – influence on decision making, risk-taking and outcomes
Desmond Winter, Dublin, IE

14.00
SATELLITE SYMPOSIUM
Medtronic

15.00
Clinical applications of image-guided cancer surgery
Cornelis van de Velde, Leiden, NL

16.00
Volvulus of the colon – a treatment algorithm
Peter Sagar, Leeds, UK

16.30
Hereditary colorectal cancer syndromes: tailored surgical treatment
Gabriela Möslein, Wuppertal, DE

17.00
Lars Pahlman and Herand Abcarian (2015)
Herand Abcarian, Chicago, US

17.20
Lars Påhlman Lecture
Steven Wexner, Weston, US

Tuesday, 3 Dec. 2019

09.00
Robotic-assisted versus conventional laparoscopic surgery for rectal cancer
Amjad Parvaiz, Poole, UK

09.30
Robotic multivisceral resection
Paris Tekkis, London, UK

10.00
SATELLITE SYMPOSIUM
Karl Storz

11.30
Neoadjuvant chemotherapy for advanced colon cancer: clinical and pathological Results
Dion Morton, Birmingham, UK
Philip Quirke, Leeds, UK

12.30
Cytoreductive surgery and hyperthermic intraoperative chemotherapy for intestinal and ovarial cancers: lessons learned from 2 decades of clinical trials
Vic Verwaal, Aarhus, DK

14.30
Mechanical bowel obstruction: rush to the OR or stent and dine
Neil Mortensen, Oxford, UK

15.00
Controversies in IBD surgery
André d'Hoore, Leuven, BE

16.00
How to deal with IBD and dysplasia
Janindra Warusavitarne, London, UK

16.30
Perianal Crohn – avoiding delay and best surgical practice
Justin Davies, Cambridge, UK

17.00
Perianal Crohn – stem cells therapy and current medical approach
Gerhard Rogler, Zürich, CH

Wednesday, 4 Dec. 2019

09.00
Is anastomotic leak an infectious disease
Ronan O'Connell, Dublin, IE

09.30
Is it time to invest in robotic surgery?
Antonino Spinelli, Milan, IT

10.00
SATELLITE SYMPOSIUM
Intuitive

11.00
New developments in robotic systems
Alberto Arezzo, Torino, IT

12.00
Posterior component separation for abdominal wall reconstruction: evolution from open to minimal invasive using the robotic platform
Filip Muysoms, Gent, BE

14.00
Coloproctology 4.0 – the networked surgeon
Richard Brady, Newcastle upon Tyne, UK

14.30
SATELLITE SYMPOSIUM
Olympus

15.30
The elderly colorectal patient – functional outcomes and patient reported outcomes
Isacco Montroni, Faenza, IT

16.30
The microbiome and colorectal cancer
Philip Quirke, Leeds, UK

17.00
Surgical management of rectal endometriosis
Eric Rullier, Bordeaux, FR

17.30
EAES Presidential Lecture 3D printing for the general surgeon
Andrea Pietrabissa, Pavia, IT

Thursday, 5 Dec. 2019

09.00
Management of locoregionally advanced colon cancer
Torbjörn Holm, Stockholm, SE

09.30
ROUNDTABLE
Herand Abcarian, Chicago, US
Bill Heald, Basingstoke, UK

10.30
Artificial intelligence in colorectal surgery
Michele Diana, Strasbourg, FR

11.30
The mesentery in colonic diseases
Calvin Coffey, Luimneach, IE

12.00
Technical pearls and typical mistakes in minimal invasive colectomy
Antonio Lacy, Barcelona, ES

12.30
Choosing the right anastomotic technique in colon surgery
Roberto Persiani, Rom, IT

13.00
Precision surgery: past, present and future
Brendan Moran, Basingstoke, UK

13.30
Poster award
Michel Adamina, Winterthur, CH

Information & Registration

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Cost-effectiveness analysis of a randomized clinical trial of early *versus* deferred endovenous ablation of superficial venous reflux in patients with venous ulceration

D. M. Epstein[1] , **M. S. Gohel[2,3]**, **F. Heatley[3]**, **X. Liu[4]**, **A. Bradbury[6]**, **R. Bulbulia[7,8,9]**, **N. Cullum[10]**, **I. Nyamekye[11]**, **K. R. Poskitt[7]**, **S. Renton[5]**, **J. Warwick[3,12]** and **A. H. Davies[3]** on behalf of the EVRA trial investigators[*]

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Correspondence to: Professor A. H. Davies, Academic Section of Vascular Surgery, 4 East, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK (e-mail: a.h.davies@imperial.ac.uk; 🐦 @EVRAtrial)

Background: Treatment of superficial venous reflux in addition to compression therapy accelerates venous leg ulcer healing and reduces ulcer recurrence. The aim of this study was to evaluate the costs and cost-effectiveness of early *versus* delayed endovenous treatment of patients with venous leg ulcers.

Methods: This was a within-trial cost-utility analysis with a 1-year time horizon using data from the EVRA (Early Venous Reflux Ablation) trial. The study compared early *versus* deferred endovenous ablation for superficial venous truncal reflux in patients with a venous leg ulcer. The outcome measure was the cost per quality-adjusted life-year (QALY) over 1 year. Sensitivity analyses were conducted with alternative methods of handling missing data, alternative preference weights for health-related quality of life, and per protocol.

Results: After early intervention, the mean(s.e.m.) cost was higher (difference in cost per patient £163(318) (€184(358))) and early intervention was associated with more QALYs at 1 year (mean(s.e.m.) difference 0·041(0·017)). The incremental cost-effectiveness ratio (ICER) was £3976 (€4482) per QALY. There was an 89 per cent probability that early venous intervention is cost-effective at a threshold of £20 000 (€22 546)/QALY. Sensitivity analyses produced similar results, confirming that early treatment of superficial reflux is highly likely to be cost-effective.

Conclusion: Early treatment of superficial reflux is highly likely to be cost-effective in patients with venous leg ulcers over 1 year. Registration number: ISRCTN02335796 (http://www.isrctn.com).

Introduction

Leg ulcers are a major burden to healthcare providers and represent a source of discomfort and social isolation to patients. In 70 per cent of cases, the underlying cause of leg ulceration is venous disease, sometimes evident as varicose veins but often undetectable by visual examination alone. One UK study[1] found a point prevalence of 1·5 cases of complex wounds per 1000 population, of which 28 per cent were leg ulcers. It should also be noted that, with an ageing and increasingly obese population, the incidence and prevalence of venous ulceration are both likely to increase. Treatment of venous leg ulcers has been estimated to cost £941 (€1061) million per annum in the UK[2].

Venous leg ulcers are characterized by protracted healing. Some ulcers may never heal, and those that do are at high risk of recurrence[3]. The mainstay of therapy for venous ulceration is compression therapy using bandages or stockings[3]. Current guidelines[4] recommend treatment of superficial venous reflux using endovenous ablation techniques (ultrasound-guided foam sclerotherapy (UGFS), endovenous laser or radiofrequency ablation), but many practitioners delay intervention until the ulcer has healed. More recently, the EVRA (Early Venous Reflux Ablation) trial[5] found that early endovenous ablation significantly reduced time to ulcer healing. This study presents an analysis of the cost-effectiveness of early *versus* delayed endovenous treatment, based on the EVRA trial data to 1 year. The protocol is available at http://www.imperial.ac.uk/media/imperial-college/medicine/surgery-cancer/clinical-trials/EVRA-Protocol-06.04.2017.pdf.

Methods

This study was a within-trial cost-utility analysis comparing early *versus* deferred endovenous ablation for truncal superficial venous reflux in patients with venous ulceration, within a 1-year time horizon. The primary difference between the two strategies was the timing of endovenous ablation: patients in the early intervention arm were treated within 2 weeks of randomization, whereas those randomized to the deferred intervention arm underwent endovenous ablation once the ulcer had healed, or after 6 months. All patients were treated with compression therapy in accordance with local standard practice.

Patients in the EVRA trial were aged at least 18 years, presented with a venous leg ulcer of between 6 weeks' and 6 months' duration, ankle : brachial pressure index 0·8 or above, able to tolerate compression therapy, and had superficial venous reflux requiring endovenous ablation. Patients were recruited from 20 vascular centres in the UK, and endovenous interventions were performed in outpatient clinic, operating room or treatment room settings (as per local practice). Most leg ulcer management takes place in a community care setting (community clinics or patient's home) or in primary care clinics.

Outcome assessment

The cost analyses were performed from the perspective of the UK National Health Service and Personal Social Services in accordance with UK methods guidance[6]. The price year was 2015–2016, and currency conversion was calculated at 2016 purchasing power parity[7]. No discounting was applied as the follow-up was 1 year. The study was reported according to guidelines for economic evaluation[8].

The primary health outcome in the cost-effectiveness analysis was quality-adjusted life-years (QALYs) at 1 year. Participants in the EVRA study were asked to complete the EQ-5D-5L™ (EuroQol Group, Rotterdam, the Netherlands) questionnaire at baseline, 6 weeks, 6 months and 1 year after randomization. EQ-5D™ is an instrument to measure generic health-related quality of life and has been validated in patients with leg ulcers, the EVRA population[9]. To convert patient responses into a health utility scale (where 1 represents perfect health and 0 a state equivalent to death), the base-case economic analysis used the crosswalk tariff[10], as recommended by the UK National Institute for Health and Care Excellence (NICE) in August 2017. This algorithm maps the EQ-5D™ five-level responses to three-level responses, and then values those health states using the original EQ-5D™ three-level tariff developed by Dolan[11]. As a sensitivity analysis, an alternative health utility tariff developed by Devlin and colleagues[12] for the EQ-5D-5L™ was used. Quality-adjusted life-years (QALYs) were estimated for each participant to 1 year as the area under the curve of EQ-5D-5L™ index values.

Resource use items were recorded for each participant at monthly follow-up telephone calls. The total cost per patient included the following resource items for vein or ulcer-related reasons: trial endovenous ablation procedures, dressings and bandaging consumables for wound healing, compression therapy to prevent recurrence after wound healing, visits to or from a district nurse, visits to or from a general practitioner, visits to a primary care practice nurse, inpatient and day-case hospital admissions, outpatient visits, use of antiplatelet and anticoagulant medicines, physiotherapy and occupational therapy, auxiliary nursing (home care) and personal care (home help).

To obtain a precise estimate of the effect of the intervention on healthcare use, and avoid statistical noise, the study aimed to include only resource use related to the ulcer. Researchers recorded the reason for the use of each item of healthcare as free text. Ulcer-related activity was considered to include: ulcer care, skin care, leg care, venous procedures, angiography, infection, rehabilitation, deep vein thrombosis and related keywords. Non-ulcer-related healthcare, as well as out-of-pocket expenses and time lost from usual activities, were tabulated but not included in total cost per patient. Costs were estimated by multiplying resource use by unit costs obtained from published literature[13], national unit cost databases for the UK[14–18], and manufacturers' list prices for catheters and other disposable items (*Table S1*, supporting information). Currency conversions from GBP (£) to euros (€) were calculated to

Table 1 Baseline characteristics of trial participants			
	Early intervention (*n* = 224)	Deferred intervention (*n* = 226)	Total (*n* = 450)
Age (years)*	67·0(15·5)	68·9(14·0)	68·0(14·8)
Height (cm)*	171·9(11·1)	170·5(10·8)	171·2(11·0)
Weight (kg)*	89·5(25·6)	88·8(24·1)	89·1(24·9)
BMI (kg/m²)*	30·1(7·8)	30·4(7·4)	30·3(7·6)
Sex			
F	97 (43·3)	106 (46·9)	203 (45·1)
M	127 (56·7)	120 (53·1)	247 (54·9)
Smoking			
Current	23 (10·3)	19 (8·4)	42 (9·3)
Former	86 (38·4)	101 (44·7)	187 (41·6)
Never	115 (51·3)	106 (46·9)	221 (49·1)
Ethnicity			
White	206 (92·0)	208 (92·0)	414 (92·0)
Mixed	1 (0·4)	0 (0)	1 (0·2)
Asian	11 (4·9)	12 (5·3)	23 (5·1)
Black	3 (1·3)	5 (2·2)	8 (1·8)
Other	3 (1·3)	1 (0·4)	4 (0·9)
EQ-5D™			
Health state score	70·2(17·7)	70·1(17·1)	70·2(17·4)
Index value	0·7(0·2)	0·7(0·2)	0·7(0·2)
SF-36*			
Physical function	37·3(12·0)	37·5(12·5)	37·4(12·2)
Role physical	39·0(12·2)	39·7(12·1)	39·4(12·2)
Body pain	41·3(11·1)	41·6(11·9)	41·4(11·5)
General health	45·8(9·2)	46·0(9·8)	45·8(9·5)
Vitality	48·2(10·2)	47·8(10·6)	48·0(10·4)
Social functioning	42·6(12·4)	42·4(13·5)	42·5(13·0)
Role emotional	42·7(13·8)	43·7(13·6)	43·2(13·7)
Mental health	49·2(10·3)	49·3(10·7)	49·2(10·5)
Physical component summary	38·5(9·9)	38·8(10·8)	38·6(10·4)
Mental component summary	49·2(10·9)	49·4(11·6)	49·3(11·2)
Total AVVQ*	44·1(9·0)	44·3(8·7)	44·2(8·8)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data for up to seven patients were missing for some continuous variables. SF-36, Short Form 36 (standard UK version 1.0; QualityMetric, Lincoln, Rhode Island, USA); AVVQ, Aberdeen Varicose Vein Questionnaire. Adapted from Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N *et al.*; EVRA Trial Investigators. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med* 2018; **378**: 2015–2114. Copyright © (2018) Massachusetts Medical Society.

the rate applicable at the time of conversion (£1 = €1·1273; exchange rate 20 September 2018).

Handling of missing data

There was a small amount of missing data in the trial owing to patient withdrawal and other reasons. Costs and EQ-5D-5L™ index were set to zero after the date of death. The base-case cost-effectiveness analysis used complete cases in an intention-to-treat analysis. A participant was considered a complete case if they completed all the EQ-5D™ questions at baseline, 6 weeks, 6 months and 1 year, and did not withdraw from the study before 12 months.

As a sensitivity analysis, multiple imputation using chained equations was employed to impute the remaining missing data by regression under the assumption of 'missingness at random'[19]. Missing costs in each treatment group were considered predictable from observed data, plus or minus a random error. For those lost to follow-up, costs for each participant were imputed at each month after the time of withdrawal, and the EQ-5D-5L™ index was imputed at 6 weeks, 6 months and 1 year if these data were missing. Ten imputed data sets were created and analysed using Rubin's rules (this was sufficient to give stable results allowing for Monte Carlo error)[19].

Fig. 1 Costs of early and deferred strategies for treatment of venous leg ulcers over 1 year
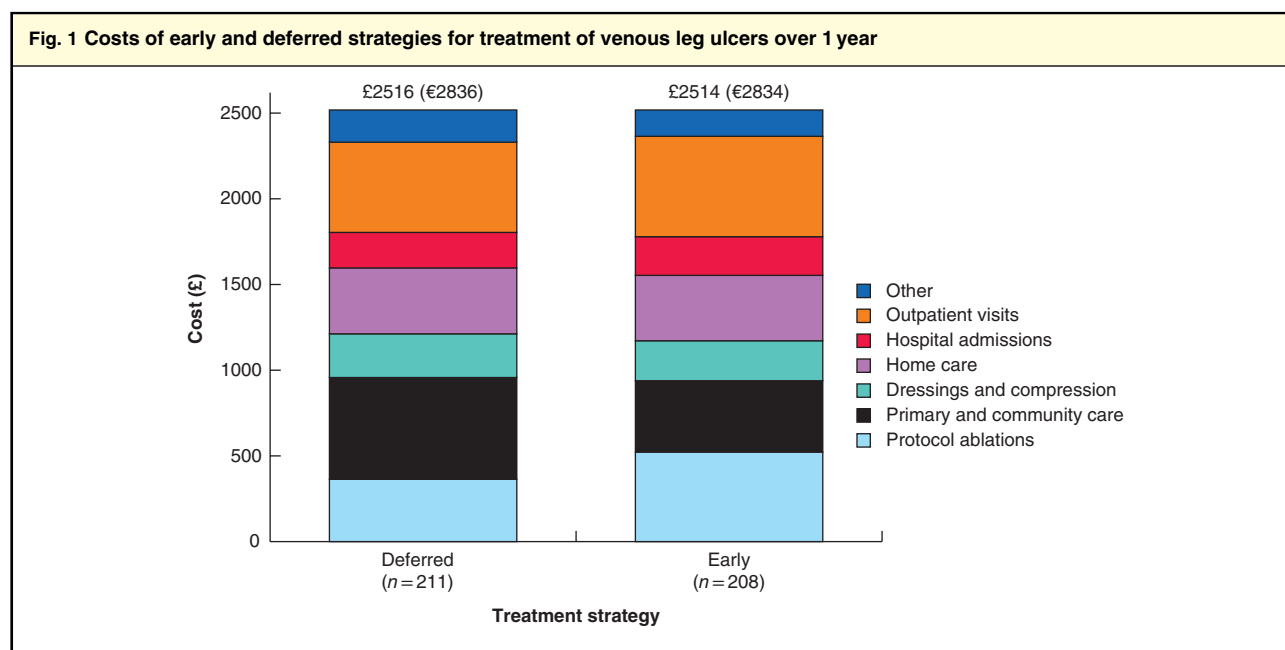
Mean National Health Service and Personal Social Services costs for early *versus* deferred strategies for patients with complete data on costs.

Handling of protocol deviations

In the clinical study, protocol deviations were seen in 117 patients (59 and 58 in the early and deferred groups respectively), the majority of which were late or missed follow-up appointments (40 of 59 patients in the early intervention group and 34 of 58 in the deferred intervention group)[5]. A sensitivity analysis was carried out excluding these patients.

Cost-effectiveness analysis

The difference in mean total cost and mean total QALY per participant between the treatment groups was estimated using regression methods, including baseline EQ-5D-5L™ in the QALY regression Monte Carlo resamples[20].

The incremental cost-effectiveness ratio (ICER) was calculated. An intervention may be considered cost-effective when its ICER is less than the threshold set by health policy decision-makers[21]. In the UK, the cost-effectiveness threshold is in the range £20 000–30 000 (€22 546–33 819) per QALY[6].

The probability that early ablation was more cost-effective than deferred ablation was estimated at different cost-effectiveness thresholds. The base-case analysis used bootstrapping, with 1000 Monte Carlo resamples with replacement. The bootstrap was used only for the analysis of complete cases, as bootstrap combined with multiple imputation can be very complex[22]. As an alternative method in sensitivity analyses, standard errors

and correlation between total costs and QALYs were estimated assuming bivariable normality (*Appendix S1*, supporting information).

Sensitivity analyses

Five models were estimated: model 1, the base case – complete cases with bootstrap standard errors and crosswalk EQ-5D-5L™ tariff; model 2, complete case with bivariable normal standard errors and crosswalk EQ-5D-5L™ tariff; model 3, multiple imputation with bivariable normal standard errors and crosswalk EQ-5D-5L™ tariff; model 4, complete case with bootstrap standard errors and EQ-5D-5L™ tariff estimated according to Devlin *et al.*[12]; model 5, per-protocol analysis (this was the same as model 1, but excluded patients with a protocol deviation).

Results

Baseline characteristics for the study groups, described in full elsewhere[5], were evenly matched across the arms of the EVRA trial (*Table 1*).

Resource use and total cost analysis

The total mean cost per patient over 1 year, excluding patients who did not complete follow-up to 12 months is shown in *Table S2* (supporting information). Participants

Table 2 Results of regression for cost-effectiveness analysis					
	Model 1*	**Model 2†**	**Model 3†**	**Model 4**	**Model 5**
Coefficient	Complete case (*n* = 344), with bootstrap standard errors (1000 samples) and crosswalk EQ-5D™ tariff	Complete case (*n* = 344), with bivariable normal standard errors and crosswalk EQ-5D™ tariff	10 multiple imputations (*n* = 450), with bivariable normal standard errors and crosswalk EQ-5D™ tariff	Complete case (*n* = 344) with bootstrap standard errors and Devlin EQ-5D-5L™ tariff	Per-protocol compliers (*n* = 273) with bootstrap standard errors
Difference in cost					
Mean(s.e.m.)					
£	163(318)	163(322)	−72(290)	163(322)	486(326)
€	184(358)	184(363)	−81(327)	184(363)	548(367)
P	0·607	0·612	0·803	0·612	0·137
Difference in QALYs					
Mean(s.e.m.)	0·041(0·017)	0·041(0·018)	0·058(0·018)	0·033(0·016)	0·056(0·019)
P	0·017	0·024	0·002	0·039	0·003
ICER					
£/QALY	3976	3976	n.c.	4939	8679
€/QALY	4482	4482	n.c.	5568	9784

*Base-case or primary analysis. †Estimated correlation of residuals between cost and quality-adjusted life-years (QALYs) in the bivariable normal model: −0·294 (*P* < 0·001). n.c., Incremental cost-effectiveness ratio (ICER) not calculable because early ablation dominates (both cost-saving and more effective).

who died during the year were included in these data, with costs set to zero after the date of death. For the purposes of this analysis, 419 patients completed 12 months of the study or died, 211 in the deferred ablation group (226 randomized, less 15 withdrawals or lost to follow-up) *versus* 208 in the early group (224 randomized, less 16 withdrawals or lost to follow-up).

The total mean(s.d.) cost per patient over 1 year was similar in the two study groups: £2514(2770) (€2834(3123)) for 208 patients randomized to early ablation *versus* £2516(3242) (€2836(3655)) for 211 patients in the deferred group (*Fig. 1*).

The early ablation group incurred a greater initial cost due to the allocated endovenous ablation procedure. Although the study protocol recommended that participants in the deferred group should have an ablation procedure once the ulcer had healed, many did not receive this treatment. At 1 year, 55 of the 226 patients in the deferred arm had received no intervention, compared with seven of 224 in the early arm (*Table S2*, supporting information). Of the 55 with no intervention in the deferred arm, 35 subjects completed the study, of whom 26 had a healed ulcer after 1 year. Reasons for not performing ablation procedures in participants randomized to deferred ablation were unclear, but both participant and clinician preferences are likely to have played a role. The greater initial costs in the early ablation group were compensated by lower costs of district nurse home visits due to quicker wound healing (*Table S2*, supporting information). Other resource use was similar in the two groups.

Cost-effectiveness analysis

Table 2 shows the results of the cost and QALY regressions for the cost-effectiveness analyses. In the complete-case analysis (model 1 or base case), 106 of 450 patients (23·6 per cent) had incomplete EQ-5D™ or cost data over the year, and thus 344 (76·4 per cent) were included in this analysis. The proportion of missing data was similar in the early (22·8 per cent) and deferred (24·3 per cent) intervention arms. Greater costs and QALYs were recorded for patients in the early intervention group, with a mean(s.e.m.) difference in cost per patient of £163(318) (€184(358)), a difference in QALYs at 1 year of 0·041(0·017). The ICER was £3976 (€4482)/QALY. There was an 89 per cent probability that early endovenous intervention is cost-effective at a threshold of £20 000 (€22 546)/QALY (*Fig. 2*). When bivariable normality was assumed to estimate standard errors, the results were similar (model 2). There was a significant negative correlation between costs and QALYs, indicating that participants with a worse quality of life were also those who tended to incur greater healthcare costs (correlation −0·294, *P* < 0·001).

In model 3, missing data were imputed. All 450 randomized patients were included in this model. The mean(s.e.m.) difference in total cost was −£72(290) (−€81(327)) (early intervention was cost-saving) and the mean difference in QALYs over 1 year was 0·058(0·018) (greater in the early intervention group), with more than 99 per cent probability of being cost-effective at a threshold of £20 000 (€22 546)/QALY. The use of alternative tariff values for

Fig. 2 Cost-effectiveness acceptability curves for models 1–5
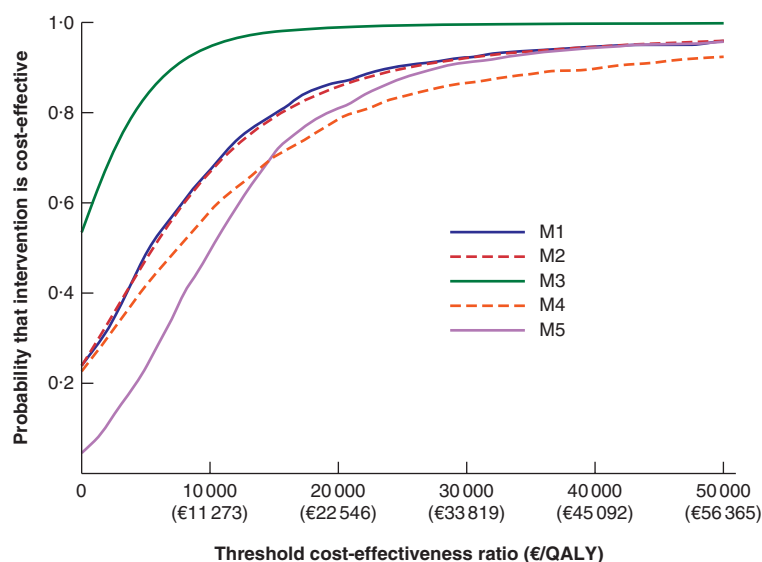
Model 1, complete case; model 2, complete case using bivariable normal model; model 3, multiple imputation; model 4, alternative EQ-5D-5L™ tariff; model 5, per-protocol. QALY, quality-adjusted life-year.

the EQ-5D-5L™ (model 4) resulted in a slightly smaller difference in QALYs between the treatment groups than for the base case, but the ICER was similar.

The per-protocol analysis was carried out using the same approach as model 1, but excluding patients with protocol deviations. Protocol deviations were seen in 117 patients (59 and 58 in early and deferred groups respectively), of whom 71 had complete data. This left 273 patients for analysis (344 with complete data at 12 months, less 71 protocol deviations). The ICER was £8679 (€9784)/QALY (model 5).

Discussion

This study has demonstrated that early endovenous intervention for superficial venous reflux is highly likely to be a cost-effective treatment for patients with a venous leg ulcer. The complete-case analysis showed little difference in total mean cost per patient over 1 year between the early and deferred ablation strategies (mean(s.e.m.) difference £163(318) (€184(358); $P = 0.607$). The greater initial mean cost of the early intervention strategy was mostly offset by the reduced cost of treating unhealed leg ulcers. There was, however, a substantial and statistically significant gain in QALYs over 1 year, with a mean difference of 0·041(0·017) in favour of early intervention ($P = 0.017$). The ICER for early intervention at 1 year is therefore £3976 (€4482)/QALY.

From the complete-case analysis, the probability of cost-effectiveness was 89 per cent using UK thresholds. Therefore, there is little chance that delayed ablation would offer greater net benefit at conventional thresholds of willingness-to-pay. Sensitivity analyses using alternative statistical models gave qualitatively similar results.

This economic analysis compared early *versus* delayed endovenous ablation for venous leg ulcers. Tricco and colleagues[23] reviewed studies that evaluated the costs and benefits of alternative medical therapeutic strategies. It was notable that the difference in QALYs between the strategies reported by these studies was generally small. For example, the largest QALY gain observed in any previous study was in VenUS I (difference of 0·02 QALYs for four-layer bandages *versus* short stretch bandages)[24]. The difference in QALYs between early and delayed ablation found in the present study was much larger: 0·041 over 1 year. This study did not consider whether cost-effectiveness might vary across subgroups. The EVRA trial[5] assessed the clinical benefit across several predefined subgroups and detected some interesting trends for potentially greater benefits for early intervention, such as in patients with longer ulcer duration. However, the clinical study was not powered to detect differences across subgroups, and furthermore patients with ulcer duration of more than 6 months were excluded. Thus, further studies are required to confirm these findings and assess whether there may be greater cost-effectiveness in these

populations, or with specific endovenous interventions such as UGFS.

The benefits of early endovenous ablation in the present study arose because of faster ulcer healing in the first 12 months after randomization. The long-term benefits and costs will also depend on whether the treatments can reduce ulcer recurrence rates. Evidence from other randomized trials suggests that surgical intervention for superficial reflux reduces recurrence, compared with compression therapy alone[25]. If early endovenous ablation can impact on both healing and recurrence, it could be even more cost-effective over the patient's lifetime[26]. In the EVRA study, there were insufficient recurrences over 1 year to permit meaningful comparison. Evaluation of ulcer recurrence in the EVRA population is ongoing.

This study showed that early endovenous ablation had a significant and substantial impact on a patient's quality of life, with no material increase in the burden of cost on payers. Hence this strategy is very likely to be cost-effective. The resources needed for implementation of an early intervention strategy will depend on the individual setting[3], but any effective wound management strategy would require close multidisciplinary teamwork between primary care and specialist vascular centres to conduct prompt assessment of patients with a venous leg ulcer, referral and treatment of superficial venous reflux.

Collaborators

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

Phlebology

The management of venous leg ulceration post the EVRA (early venous reflux ablation) ulcer trial: Management of venous ulceration post EVRA

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Abstract

Objectives: This survey study evaluates current management strategies for venous ulceration and the impacts of the EVRA trial results.
Methods: An online survey was disseminated to approximately 15000 clinicians, through 12 vascular societies in 2018. Survey themes included: referral times, treatment times and strategies, knowledge of the EVRA trial and service barriers to managing venous ulceration. Data analysis was performed using Microsoft Excel and SPSS.
Results: 664 responses were received from 78 countries. Respondents were predominantly European (55%) and North American (23%) vascular surgeons (74%). Responses varied between different countries. The median vascular clinic referral time was 6 weeks and time to be seen in clinic was 2 weeks. This was significantly higher in the UK (p ≤ 0.02). 77% of respondents performed surgical/endovenous interventions prior to ulcer healing, the median time to intervention was 4 weeks. 31% of participants changed their practice following EVRA. Frequently encountered barriers to implementing change were a lack of operating space/time (18%).
Conclusion: Venous ulcers are not managed as quickly as they should be. An evaluation of local resource requirements should be performed to improve service provision for venous ulceration. When interpreting the results of this survey consideration should be given to the response rate.

Keywords

Venous ulceration, EVRA, endovenous ablation, surgical ablation

Background

Venous leg ulceration (VLU) affects an estimated 1%[1] of the population internationally. It costs approximately 2% of healthcare budgets in western societies[2] and has a significant impact on patient morbidity.[3,4] There are no national guidelines for the treatment of VLU in England, however, the National Institute for Health and Care Excellence (NICE) guidance for varicose veins[5] suggest that patients with ulceration that persists for more than two weeks should be referred to a specialist vascular unit. Patients referred to vascular units often receive a duplex scan and, if indicated, surgical/endovenous ablation of superficial veins. The ESCHAR[6] study suggested that there was reduced ulcer recurrence in patients who received compression with surgery as opposed to compression alone. Consequently, surgery was frequently performed once ulcers had healed to prevent recurrence. This is further reflected in European and American guidelines.[7–9] The Early Venous Reflux Ablation (EVRA) ulcer trial[10] identified that patients who underwent early endovenous ablation had improved ulcer healing rates and ulcer free time. The implementation of both the NICE guidelines on referrals and the EVRA study results are likely to be challenging; indeed it has been shown that patients with ulcers are not referred to specialist care within the 2 week limit in the UK.[11,12]

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This survey study aims to determine the standards of the global management of patients with VLU, four to six months after the release of the EVRA trial results.

Methods

This descriptive, cross-sectional study utilised an online survey to collate VLU practices and perspectives. The initial survey was designed using the Qualtrics management platform (Qualtrics, Utah, USA) following discussion of important themes in a focus group with three vascular clinicians. Themes included: time from VLU development to secondary care referral and clinic visit, understanding of the NICE guidelines, knowledge of the EVRA study trial results and the impact these have had on practice. Additional information on clinician demographics was collected. The survey underwent five rounds of revision following review and feedback by a panel of vascular surgeons. The final online survey (Appendix, Supplementary material), consisting of 11 questions, was piloted on an additional five vascular surgeons prior to dissemination. The survey was circulated to approximately 15,000 participants through 12 national and international vascular societies. Reponses were collected over a four-month period between September 2018 and December 2018.

Outcomes of interest included referral time, time to vascular clinic review, aimed and actual time to surgical/endovenous intervention, whether interventions were performed before or after ulcer healing, whether EVRA trial results had changed practice, what the anticipated and actual barriers to implementing change were and views on the clinical and cost effectiveness of the EVRA trial findings.

Referral time was defined as the time between a patient's first presentation to primary care for a venous ulcer to the date that they were referred to a vascular service. Time to vascular clinic review was defined as the time between the vascular clinic referral and first being seen in vascular clinic. Surgical/endovenous interventions encompassed all methods of superficial venous ablation. Time to intervention was defined as the time from the clinical decision to proceed with intervention to the patient undergoing this.

Descriptive statistics and normality were calculated using Microsoft Excel to analyse the results. All evaluated outcomes were not normally distributed and summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Free text in survey responses were categorised by common themes for the ease of interpretation. A Mann-Whitney U test in SPSS was used to compare differences between the UK and global responses.

Results

664 responses were received from 78 countries giving an approximate response rate of 4.4%. Respondent characteristics are summarised in Table 1. Respondents were predominantly vascular surgeons (74.2%). Most clinicians worked in Europe (54.5%) or North America (23%). Of 659 respondents, 454 (69%) had heard of the EVRA trial and 415 (63%) were familiar with the results. Of 627 respondents, 82% believed early surgical/endovenous intervention would reduce recurrence rates, 0.3% thought it would increase them, 13% thought there would be no effect, 3.7% thought it would depend on other factors such as the age of the ulcer, or extent of deep disease.

Current intervention

Globally, the median referral time from primary care to a vascular service was six weeks (IQR 2-12 weeks); this was longer in the UK where the median time was 8 weeks (IQR 4-14 weeks), $p = 0.02$. The median time to outpatient clinic appointment once referred was 2 weeks (IQR 1-4 weeks); increasing to 4 weeks in the UK (IQR 2 - 6), $p < 0.01$.

Of 656 global respondents, 507 (77%) reportedly performed surgical/endovenous intervention prior to ulcer healing, 129 (20%) after ulcer healing and 20 (3%) did not perform surgical/endovenous intervention for ulceration. Of the 507 global respondents who treated prior to ulcer healing, 227 (45%) aimed to perform the intervention immediately, of these, 142 (63%) were able to do this. 280 (55%) of global respondents did not aim to immediately perform intervention and instead aimed-to-treat at a median time of 3 weeks (IQR 2 to 4). The median time to actually treating patients was 4 weeks (IQR 2 to 5).

Of the 129 global respondents who treated after ulcer healing, 50 (39%) of participants would aim to perform the intervention immediately after healing, 28 (56%) of these participants were able to. For those who did not aim-to-treat immediately, the median aim-to-treat time was 4 weeks (IQR 2 to 4) after ulcer healing. The median time from healing to actual intervention was 4 weeks (IQR 4 to 8).

Of 107 UK respondents, 70 (65%) usually performed surgical/endovenous intervention prior to ulcer healing, 32 (30%) after and 5 (5%) did not perform intervention. Of the 70 respondents who treated prior to ulcer healing, 23 (33%) would aim to perform intervention immediately. However, only 9 (39%) of these were able to do so. For those who did not aim to treat immediately, the median aim-to-treat-time was 4 weeks (IQR 2 to 6). The median time to treatment was 6 weeks (IQR 4 to 8).

Table 1. Baseline characteristics of respondents.

Clinician type (n = 662)	
Vascular surgeon	491 (74.2%)
Phlebologist	68 (10.3%)
General surgeon	38 (5.7%)
Interventional radiologist	16 (2.4%)
Vascular nurse specialist	12 (1.8%)
Dermatologist	5 (0.8%)
Interventional cardiologist	4 (0.6%)
Consultant vascular nurse	3 (0.5%)
Family medical practitioner	1 (0.2%)
Plastic surgeon	0 (0%)
Aesthetic practitioner	0 (0%)
Tissue viability nurse	0 (0%)
Other	24 (3.6%)
Region of practice* (n = 660)	
Europe (excluding UK)	252 (38.2%)
North America	152 (23.0%)
Central America	4 (0.6%)
United Kingdom	108 (16.4%)
South America	62 (9.4%)
Asia	39 (5.9%)
Australasia	24 (3.6%)
Africa	16 (2.4%)
Middle East	3 (0.5%)
Area of care (n = 657)	
Academic/teaching	369 (56.2%)
Secondary/district general/county hospital	127 (19.3%)
Primary/Community	94 (14.3%)
Other	67 (10.2%)

*Algeria (n = 1), Albania (n = 2), Argentina (n = 10), Australia (n = 19), Austria (n = 7), Bahrain (n = 1), Bangladesh (n = 1), Belarus (n = 1), Belgium (n = 12), Bolivia (n = 1), Bosnia (n = 1), Brazil(n = 40), Bulgaria (n = 7), Canada (n = 6), Chile (n = 1), China (n = 1), Colombia (n = 4), Costa Rica (n = 1), Croatia (n = 3), Cuba (n = 1), Czech Republic (n = 4), Denmark (n = 2), Ecuador (n = 2), Egypt (n = 5), El Salvador (n = 1), Finland (n = 4), France (n = 5), Georgia (n = 1), Germany (n = 22), Greece (n = 12), Honduras (n = 1), Hong Kong (n = 1), Hungary (n = 3), India (n = 11),Indonesia (n = 2), Iraq (n = 1), Ireland (n = 6), Israel (n = 4), Italy (n = 37), Japan (n = 2), Kenya (n = 1), Kosovo (n = 1),Kuwait (n = 1), Latvia (n = 2), Lithuania (n = 3), Malaysia (n = 1), Mexico (n = 19), Monaco (n = 1), Montenegro (n = 1), Netherlands (n = 8), New Zealand (n = 5), Norway (n = 4), Pakistan (n = 2), Palestine (n = 1), Paraguay (n = 1), Peru (n = 1), Poland (n = 8), Portugal (n = 23), Romania (n = 3), Russia (n = 9), Serbia (n = 3), Slovakia (n = 5), Slovenia (n = 6), South Africa (n = 8), South Korea (n = 1), Spain (n = 20), Sri Lanka (n = 2), Sweden (n = 10), Switzerland (n = 5), Taiwan (n = 1), Thailand (n = 9), Turkey (n = 6), Ukraine (n = 3), United Kingdom (n = 108), USA (n = 127),Uruguay (n = 1), Missing (n = 3)

Of the 32 UK respondents who treated after ulcer healing, only 5 (16%) would aim to treat immediately after ulcer healing. Only one respondent was able perform the intervention immediately. For those who did not aim-to-treat immediately, the median recorded aim-to-treat time was 4 weeks (IQR 3 to 5.25) after ulcer healing. The median time from healing to treatment was 8 weeks (IQR 4 to 10).

Changing practice

Clinical practice before and after EVRA are described in Table 2. 195 (30%) of global respondents (n = 637) reported they had changed practice with respect to the timing of intervention based on the results of the EVRA study, 418 (66%) did not change practice and 24 (4%) did not answer the question. Of the 418 global participants who did not change practice, 192 (46%) stated that they would like to, 206 (49%) stated that they already treat prior to ulcer healing and 20 (5%) participants did not wish to change.

In the UK, of 100 respondents, 48% stated that they changed their practice with respect to the timing of intervention based on the EVRA results, 50% did not and 2% did not answer. Of the 50 respondents who did not change following EVRA, 22 (44%) indicated that they would like to, 26 (52%) stated they already treat prior to ulcer healing and 2 (4%) participants did not wish to change.

Barriers to changing practice

195 (31%) global respondents stated they had changed practice with respect to the timing of intervention

Table 2. Current practices for surgical/endovenous interventions for venous ulcers.

Current interventions	Global participants	UK participants
Median referral time from primary care to a vascular service	6 weeks (IQR 2-12)	8 weeks (IQR 4-14)
Median time to outpatient clinic appointment once referred	2 weeks (IQR 1-4)	4 weeks (IQR 2-6)
Surgical/endovenous intervention **prior** to ulcer healing	507/656 (77%)	70/107 (65%)
• Aimed to perform immediately	227/507 (45%)	23/70 (33%)
• Number of participants who planned to perform procedure immediately and were able to	142/227 (63%)	9/23 (39%)
• If not immediate, median number of weeks clinicians aimed to perform procedure	3 weeks (IQR 2-4)	4 weeks (IQR 2-6)
• Time actually taken to perform procedure	4 weeks (IQR 2-5)	6 weeks (IQR 4-8)
Surgical/ endovenous intervention **after** ulcer healing	129/656 (20%)	32/107 (30%)
• Aimed to perform immediately	50/129 (39%)	5/32 (16%)
• Number of participants who planned to perform procedure immediately and were able to	28/50 (56%)	1/5 (20%)
• If not immediate, median number of weeks clinicians aimed to perform procedure	4 weeks (IQR 2-4)	4 weeks (IQR 3- 5.25)
Time actually taken to perform procedure	4 weeks (IQR 4-8)	8 weeks (IQR 4-10)
Practice change based on EVRA	Global participants	UK participants
Number of participants who changed practice based on EVRA	195/637 (30%)	48/100 (48%)
Reasons why participants had not changed practice		
• Would like to change practice	192/418 (46%)	22/50 (44%)
• Already treat patients according to EVRA	206/418 (49%)	26/50 (52%)
• Did not wish to change practice	20/418 (5%)	2/50 (4%)

Changes to practice based on EVRA.

based on the results of EVRA study. The barriers faced by the respondents in changing practice are summarised in Table 3. Respondents could select more than one barrier and therefore 347 barriers were recorded in total. The most frequently anticipated and encountered barriers to implementing EVRA were a lack of operating space/time (18%) and a lack of theatre space (15%). A fifth of participants felt there were no barriers to changing practice.

192 (43%) global respondents stated they had not changed practice with respect to the timing of intervention based on the results of the EVRA study but would like to. These respondents listed their anticipated barriers (Table 3).

62% of respondents stated that the cost effectiveness results would alter how they made clinical decisions and 30% said they would not have any impact. 4% stated that this would depend and 4% said the decisions are made by someone else such as Clinical Commissioning Groups (CCGs) in the UK.

Discussion

The survey responses generated from this study provide helpful insights into the global management of venous leg ulceration post the EVRA trial.[10]

Globally, the median time to referral was 6 weeks, increasing to 8 weeks in the UK. This is longer than the recommendations issued by NICE.[5] Reasons for this could include education in primary care,[13] ease of referral, access to secondary care services and patient preference. Recent evidence suggests that most CCGs commission this service in the UK[14] and measures are being taken to improve referral access from primary to secondary care.[15]

This survey has additionally shown that there are some perceived constraints in secondary care with approximately only 60% of participants feeling they are able to perform intervention in the time frame in which they hope to. This is reflected when evaluating perceived barriers to implementing EVRA as many respondents cited a lack of theatre space or time as barriers to care.

A minority of clinicians chose to perform surgical/ endovenous intervention after ulcer healing. Although evidence from randomised control trials indicates that surgical/endovenous intervention can help promote venous ulcer healing,[10] this is not reflected in the UK,[5] European[9] or American guidelines.[8] The results of this survey suggest that most clinicians would align their practice with the EVRA trial results. The EVRA trial results should be reflected in national and international guidelines to better guide clinical practice.

This survey suggests that the UK comparatively has significantly longer referral times, longer waiting times to secondary care and longer times to intervention.

Table 3. Clinician perspectives on the barriers of implementing EVRA in normal practice.

Barriers to changing practice	Actual (n = 347)	Anticipated (n = 347)
I had no barriers changing practice	70 (20.2%)	66 (19.0%)
Lack of operating space or time	63 (18.2%)	59 (17.0%)
Theatre capacity	52 (15.0%)	49 (14.1%)
Primary/secondary care integration/referral	26 (7.5%)	28 (8.1%)
Duplex scanning capacity	26 (7.5%)	21 (6.1%)
Reimbursement by health service or insurance companies	21 (6.1%)	38 (11.0%)
Resistance from colleagues	20 (5.8%)	18 (5.2%)
Cost of changing the service model	19 (5.5%)	18 (5.2%)
Other	15 (4.3%)	11 (3.2%)
Local/Clinical Commissioning Group Guidelines	12 (3.5%)	8 (2.3%)
Lack of trained staff	9 (2.6%)	10 (2.9%)
National guidelines	8 (2.3%)	9 (2.6%)
The decision to change practice was made by somebody else	5 (1.4%)	8 (2.3%)
Other costs	1 (0.3%)	4 (1.2%)

Clinicians who have already implemented EVRA listed the actual barriers they experienced doing this. Clinicians who have not yet implemented EVRA listed the barriers that they anticipated would arise.

This is supported elsewhere where it is suggested that the UK is possibly undertreating patients with chronic venous disease.[16] This may relate to relative constraints of the National Health Service compared to other privatised health care systems globally.

The survey was predominantly completed by vascular surgeons working in academic units in Europe; this selection bias could lead to inadequate representation of the care administered in other types of units. Although the number of respondents was high, there was a low overall response rate; this again could contribute to a selection bias. The survey was only performed 6 months after the EVRA trial results were published; the impact of the EVRA trial may become more pronounced with time. It is also important to note that this survey evaluates subjective clinician perspectives on how venous ulceration is currently managed; further work evaluating additional objective measures should be performed.

Conclusion

Evaluating clinician perspectives has provided helpful insights into the current management of venous ulceration and what impacts EVRA may have had on this. This survey has identified that although many clinicians are aware of EVRA, there may be a number of barriers in implementing its findings to clinical practice. The healthcare structures in each geographical region may vary significantly. Given the low response rate, a more in-depth evaluation of the barriers to achieving and delivering best practice care should be performed in each local region to advance service provision.

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Supplemental material

Supplemental material for this article is available online.

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Phlebology

UK primary care survey of venous leg ulceration management and referral – Post-EVRA trial

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Abstract

Objective: Determine standards of referral and management of patients with venous leg ulceration in primary care after the release of the EVRA (A Randomized Trial of Early Endovenous Ablation in Venous Ulceration) study results.
Methods: An online questionnaire was disseminated over four months to professionals working within primary care.
Results: The survey received 643 responses. Of respondents, 90 (14%) had heard of the EVRA trial and 51 (8%) were familiar with the results. Of those who answered the following questions, 410 (69.1%) stated that referral to a vascular specialist must be made by the General Practitioner and 13 (2.2%) reported that they would always refer patients for secondary care assessment before the publication of EVRA. Considering the EVRA results, 128 (29%) reported that they would change practice regarding referral and would experience no barriers and 198 (45%) reported that they would like to refer earlier but is not their decision. Barriers to changing practice included local referral policies, training and time restrictions, 266 (59%) had heard of the NICE guideline (CG168) and 194 (43%) were aware of the recommendations for referral to a vascular service within two weeks for patients with an open or healed ulcer.
Conclusion: There is a considerable variation in local referral pathways for venous leg ulceration, and despite clinicians wanting to refer promptly, many primary care professionals are unable to. Unfortunately, the EVRA study alone may not change the overall practice, and work is needed to overcome barriers faced by primary care professionals.

Keywords

Wound care, venous disease, leg ulcers

Background

Venous leg ulceration (VLU) affects up to 2% of the population worldwide and accounts for 60–80% of all cases of ulceration.[1] It is defined by the National Institute for Health and Care Excellence (NICE) as loss of skin taking more than two weeks to heal as a result of sustained venous hypertension.[2] Affecting mostly the older adult population, the wound care and treatment associated with VLU consume over £2.7 billion per year of the NHS budget.[3] In addition to the financial burden, VLU has a profound effect on a patient quality of life due to prolonged pain, immobility and social isolation.[4] District and community nursing teams are primarily responsible for the long-term management of VLU and spend 25–50% of their time caring for this patient population.[1]

VLU does not currently have a set of standalone NICE guidelines; however, it is outlined within the guidelines for the Diagnosis and Management of Varicose Veins (NICE CG168). Recommendations include referral to a vascular specialist within two weeks of ulcer presentation for assessment and management, in addition to compression bandaging.[2] In the absence of a specific NICE guideline, the Royal Society of Medicine's Venous Forum developed a guideline titled 'Management of Patients with Leg Ulcers' to guide clinicians in 2017 (Royal Society of Medicine

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Venous Forum, 2017)[5] (online Appendix 1). However, despite publication of the guidelines in 2013, there has been little improvement in how quickly patients are referred.[6] Unfortunately, delays in referral and barriers accessing specialist treatment are a global issue. A study from the Netherlands found that the median referral time to specialist services was 14.7 months, with patients experiencing an average of 2.73 ulcers before referral.[7] Additionally, a survey of US practitioners found disparities in the care pathway for patients presenting with venous ulceration. The study concluded that practitioners who are first to assess venous disease do not provide care in a uniform way.[8]

The landmark trial providing evidence to support early referral and treatment of venous reflux was the EVRA trial (A Randomized Trial of Early Endovenous Ablation in Venous Ulceration), which showed that early treatment of underlying venous incompetence leads to improved healing rate and greater ulcer-free time.[9] In addition to publication in medical journals and presentation at national and international conferences, the study was also disseminated via nursing periodicals such as *Wounds UK* and the *Nursing Times*. Following the publication, initiatives were outlined for the development of a national wound care strategy and an increase in the workforce of an additional 5000 district nurses.[10]

Aims

This survey aimed to determine the standards of referral and management of patients with venous leg ulceration in primary care after the release of the EVRA results.

Methods

To explore standards of referral and the management for patients with venous leg ulceration, an online 11-question survey was created. A short, simple design was utilized, and through the use of the online platform 'Qualtrics Survey', a voluntary, opt-in consent by completion approach was taken, allowing all responses to be anonymous. The platform enabled respondents to review and change their answers via the 'back' button in addition to being equipped with a completeness check highlighting incomplete answers to before the questionnaire could be submitted, this could however be overruled. Cookies were used to assign a

Table 1. Respondent primary caregiver type.

Care giver type	Respondents (n = 642)
GP	7 (1.1%)
District nurse	311 (48.4%)
Community nurse	246 (38.3%)
Tissue viability nurse	35 (5.5%)
Practice nurse	19 (2.9%)
Specialist nurse	13 (2.0%)
Other	11 (1.7%)

Table 2. Overall response to how leg ulcer referrals must be made to a specialised leg ulcer service.

Referrals	Respondents (n = 593)
Can refer patients directly	149 (25.1%)
Referrals must be made by GP	410 (69.1%)
Referrals must be made by someone else	25 (4.2%)
N/A – GP and can refer	9 (1.5%)
	0

Table 3. Professionals stating referral to a specialised leg ulcer service must be made be a GP.

Profession	Respondents (n = 410)
Community nurse	169 (41%)
District nurse	201 (49%)
Practice nurses	5 (1%)
Tissue viability nurse	17 (4%)
Other	17 (4%)

Table 4. Professions of respondents who can refer directly to a specialist leg ulcer service.

Profession	Respondents (n = 149)
Community nurse	51 (34%)
District nurse	65 (43%)
Tissue viability nurse	13 (9%)
Practice nurse	10 (7%)
Other	10 (7%)

Table 5. Professions of respondents stating referral must be made by another member of staff.

Profession	Respondents (n = 25)
District nurse	16 (68%)
Community nurse	8 (28%)
Tissue viability nurse	1 (4%)
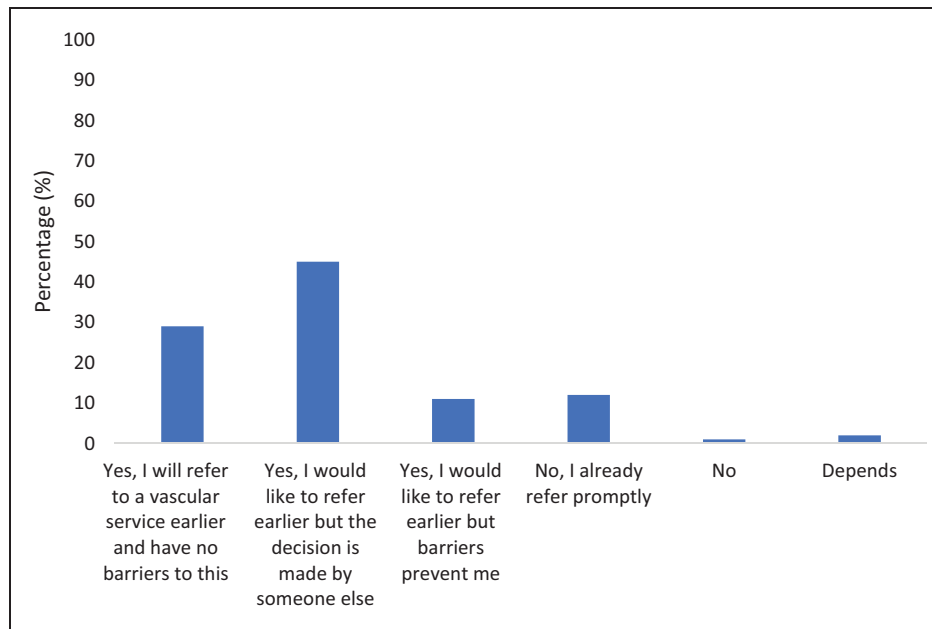
Figure 1. Practice change with respect to referral timing based on the EVRA results.

unique-user identifier to each respondent computer and set on each page.

To ensure the appropriateness of questions, the survey was reviewed by several experts in the field of venous leg ulceration, who also have expertise in research methodology. Using the Health Research Authority (HRA) development tool, the survey was classed as a service evaluation and therefore was deemed not to require HRA/ethical approval.

The questions aimed to determine whether respondents were familiar with the EVRA trial, whether they could refer patients with venous leg ulceration directly to a vascular service and, if not, who was responsible for this. The questions also probed what proportion of patients with open and healed ulceration were referred to specialised vascular centres and their anticipated waiting times. Opinions were sought on the guideline recommendation that all patients with venous leg ulceration should be referred to a vascular service. The survey is detailed in online Appendix 2.

Survey distribution

Responses were collected over four months (September 2018–December 2018). The survey was circulated via local and national networks, such as the Tissue Viability Network and the Wounds Research Network (WREN) by attaching it to the monthly email bulletin forwarded to the regular mailing list. At the time, WREN had approximately UK 300

subscribers on their mailing list and 500 subscribed to the Tissue Viability Network mailing list. To increase awareness of the survey, it was also circulated via the RCN District and Community Nursing Facebook forum, which had approximately 5500 members that time. Therefore, the total distribution of the survey was to approximately 6000 health care professionals with an interest in wound care.

Data analysis

Continuous variables that followed a normal distribution were summarised using mean and standard deviation. Skewed continuous variables were summarised using median and interquartile range (IQR). The free text was categorised by common themes for the ease of interpretation.

Results

With a response rate of approximately 10% the survey received 643 responses in total, however, some participants did not answer all the questions. For clarity, the total number of responses are detailed for each question. The professions of respondents are outlined in Table 1, of all 643 respondents, only 90 (14%) had heard of the EVRA trial and 51 (8%) were familiar with the results.

Referring professional

The vast majority of participants stated that referrals to specialist care had to be made by the GP (69%). Only 25% could refer patients directly. Details regarding the referral pathways are presented in Tables 2 to 5.

Referral practices pre-EVRA publication

Respondents were questioned regarding how often they would refer patients with open venous leg ulceration to a specialist vascular centre before the EVRA results were published. Of the 589 respondents, 227 (47%) reported referring sometimes, 165 (28%) reported referring rarely, 119 (20.2%) reported referring frequently, 15 (2.6%) reported never referring and only 13 (2.2%) reported they would always refer.

When asked how often they would have referred patients with healed venous leg ulceration to specialist vascular centre before the EVRA publication, of 588 responses, we received the following responses: 278 (47.3%) would rarely refer (25% of the time), 225 (38.3%) would never refer, 67 (11.4%) would sometimes refer (50% of the time), 13 (2.2%) would frequently refer (75% of the time) and 5 (0.9%) would always refer.

Estimated waiting times

Respondents were asked how long they felt it would take for a patient to be seen by a vascular specialist after a referral had been made. The overall estimated median waiting time from community review to outpatient clinic assessment was eight weeks (IQR 4–12). Of 444 respondents, 304 (68.5%) assumed that patients waited six weeks to six months, 130 (29.3%) assumed that they waited less than six weeks and 10 (2.3%) assumed that they waited more than six months.

Change in practice post-EVRA publication

Respondents were asked if they will change their practice with respect to the referral of patients based on the EVRA study results. Of the 444 responses, only 53 (12%) reported that they already refer promptly. However, 128 (29%) reported that they will change their practice and face no barriers to do so; 198 (45%) reported that they would like to refer earlier but the decision is made by someone else. A further 48 (11%) reported that although they would like to change practice, they face certain barriers stopping them from doing so (Figure 1). Of respondents reporting that it was someone else's decision ($n = 198$), 169 (85%) recorded that it was the GP's decision, 10 (5%) the tissue viability nurse, 16 (8%) other and 4 (2%) not stated.

Using free text comments, the main barriers stated for changing practice were local referral pathway and policies, the capacity of vascular clinics and waiting times, training/confidence of the primary care professionals, availability of equipment such as Dopplers and time restrictions to perform the ABPI.

Guidelines

Of 450 respondents, 266 (59%) had heard of the NICE CG168 guideline, and 194 (43%) were aware of the guideline recommendation regarding referral to a vascular service. Respondents were then asked for their views on the recommendation that all venous leg ulcers should be referred to a vascular service for assessment and treatment. Of 449 respondents, 85 (19%) ranked the recommendation to refer all leg ulcer patients from zero to four (i.e. strongly disagree to disagree), 63 (14%) ranked the recommendation as five (neither agree nor disagree) and 301 (67%) gave a score of 6–10 (i.e. agree to strongly agree), including 60 (20%) of respondents who agreed strongly with the recommendation.

Discussion

Only a quarter of respondents reported that they could refer patients with a leg ulcer directly to a specialised vascular service with the remaining 75% requiring that referrals must be made by a GP, indicating a level of complexity in the referral pathway. It appears that some district, community and tissue viability nurses can refer directly, whereas some must refer via the GP, so the ability is not role-dependent and appears to be determined by local referral pathways. It is clear that GPs, therefore, act as the gatekeepers for the referral of patients into secondary care. GPs were not represented in this survey, and therefore their views and referral criteria have not been explored, which is a limitation of this survey.

Despite 43% of respondents reporting that they were aware of the NICE recommendations for referral, only 2% of respondents stated that patients with open leg ulceration were always referred to a vascular centre. A further 20% were frequently referred, and about half sometimes referred. Over one-third of patients were rarely and never referred which may be a reflection of the referral pathways. Additionally, despite evidence from the ESCHAR trial showing that surgical intervention can reduce the rate of ulcer recurrence, 85% reported that ulcer-healed patients were reported as rarely or never being referred.[11] Perhaps, another factor affecting referrals is the estimated waiting time for patients to be seen in clinic, which was a median of eight weeks.

Just under one-third of respondents reported that they would change practice with respect to referral timing and had no barriers to this, although 45% of respondents reported that they would like to change practice, but the decision was made by someone else, with 85% reporting that this was the GP's decision. To encourage changes in practice, the publication of NHS England's Commissioning for Quality and Innovation CCG indicator specifications for 2020–2021 now includes the need for a comprehensive wound assessment and referral to a vascular specialist.[12]

When detailing barriers, it was apparent that guideline awareness is a problem; this is evident considering 41% of respondents were not aware of the NICE guidance. Of the respondents who were aware of the guidance, less than half stated being aware of what the guideline recommends for referral. In spite of the gaps in knowledge, the majority of respondents thought that referring all patients with a leg ulcer to a specialist vascular service was a good policy, with less than one-fifth disagreeing.

Although this survey provides some insight into venous leg ulcer care, it only provides an overview of the barriers faced by a proportion of healthcare professionals. More detailed and in-depth work is needed to understand the experience of all staff involved in the pathway, such as general practitioners, in addition to patients and their careers.

Conclusion

It is evident that there is variation across the board when it comes to local referral pathways for patients with venous leg ulceration. There is evidence that in many cases, local referral pathways restrict the referral of these patients to secondary care. Additionally, it is also clear that the publication of the EVRA trial alone may not change overall practice, and work is needed to overcome the various barriers faced by primary care professionals to implement best practice.

Limitations

The numbers of community and district nurse respondents were 246 and 311, respectively, which is approximately 1% of the community nurse population and about 8% of the district nurse population. Although the overall number of responses to this survey ($n = 643$) was encouraging, with nurses being the primary caregiver for venous leg ulcer patients, it still only represents a small number of a large community of professionals.

General practitioners were underrepresented in the survey. The survey did, however, provide good evidence that, in most cases, the GP decides whether or not to make a referral. More work is needed to understand the reasons why GPs do not refer to a vascular service when a patient presents with venous leg ulceration.

CONSORT reporting guidelines

This study has been reported in accordance with the EQUATOR guidelines. The CHERRIES checklist was used as it was the most appropriate for a survey-type service evaluation.

Ethical approval

Using the HRA development tool, the survey was classed as a service evaluation and therefore was deemed not to require HRA/ethical approval.

Guarantor

AHD

Contributorship

FH – Principle investigator of research and made substantial contribution to concept and deign of work; LBS – Drafted article; SS – Drafted article; SO – Drafted article and approved version to be published; MSG – Approved version to be published; AHD– Concept, design, drafted article and approved version to be published.

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Supplemental Material

Supplemental material for this article is available online.

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JAMA Surgery | **Original Investigation**

Long-term Clinical and Cost-effectiveness of Early Endovenous Ablation in Venous Ulceration
A Randomized Clinical Trial

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+ Invited Commentary

+ Supplemental content

IMPORTANCE One-year outcomes from the Early Venous Reflux Ablation (EVRA) randomized trial showed accelerated venous leg ulcer healing and greater ulcer-free time for participants who are treated with early endovenous ablation of lower extremity superficial reflux.

OBJECTIVE To evaluate the clinical and cost-effectiveness of early endovenous ablation of superficial venous reflux in patients with venous leg ulceration.

DESIGN, SETTING, AND PARTICIPANTS Between October 24, 2013, and September 27, 2016, the EVRA randomized clinical trial enrolled 450 participants (450 legs) with venous leg ulceration of less than 6 months' duration and superficial venous reflux. Initially, 6555 patients were assessed for eligibility, and 6105 were excluded for reasons including ulcer duration greater than 6 months, healed ulcer by the time of randomization, deep venous occlusive disease, and insufficient superficial venous reflux to warrant ablation therapy, among others. A total of 426 of 450 participants (94.7%) from the vascular surgery departments of 20 hospitals in the United Kingdom were included in the analysis for ulcer recurrence. Surgeons, participants, and follow-up assessors were not blinded to the treatment group. Data were analyzed from August 11 to November 4, 2019.

INTERVENTIONS Patients were randomly assigned to receive compression therapy with early endovenous ablation within 2 weeks of randomization (early intervention, n = 224) or compression with deferred endovenous treatment of superficial venous reflux (deferred intervention, n = 226). Endovenous modality and strategy were left to the preference of the treating clinical team.

MAIN OUTCOMES AND MEASURES The primary outcome for the extended phase was time to first ulcer recurrence. Secondary outcomes included ulcer recurrence rate and cost-effectiveness.

RESULTS The early-intervention group consisted of 224 participants (mean [SD] age, 67.0 [15.5] years; 127 men [56.7%]; 206 White participants [92%]). The deferred-intervention group consisted of 226 participants (mean [SD] age, 68.9 [14.0] years; 120 men [53.1%]; 208 White participants [92%]). Of the 426 participants whose leg ulcer had healed, 121 (28.4%) experienced at least 1 recurrence during follow-up. There was no clear difference in time to first ulcer recurrence between the 2 groups (hazard ratio, 0.82; 95% CI, 0.57-1.17; P = .28). Ulcers recurred at a lower rate of 0.11 per person-year in the early-intervention group compared with 0.16 per person-year in the deferred-intervention group (incidence rate ratio, 0.658; 95% CI, 0.480-0.898; P = .003). Time to ulcer healing was shorter in the early-intervention group for primary ulcers (hazard ratio, 1.36; 95% CI, 1.12-1.64; P = .002). At 3 years, early intervention was 91.6% likely to be cost-effective at a willingness to pay of £20 000 ($26 283) per quality-adjusted life year and 90.8% likely at a threshold of £35 000 ($45 995) per quality-adjusted life year.

CONCLUSIONS AND RELEVANCE Early endovenous ablation of superficial venous reflux was highly likely to be cost-effective over a 3-year horizon compared with deferred intervention. Early intervention accelerated the healing of venous leg ulcers and reduced the overall incidence of ulcer recurrence.

TRIAL REGISTRATION ClinicalTrials.gov identifier: ISRCTN02335796

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Group Information: The members of the Early Venous Reflux Ablation Trial Group are listed at the end of the article.

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V enous leg ulceration is the most extreme manifestation of chronic venous disease, and worldwide prevalence is increasing.[1,2] Compression therapy has been shown to improve ulcer healing, and 1-year outcomes from the Early Venous Reflux Ablation (EVRA) trial revealed that early endovenous ablation of superficial venous reflux (varicose veins) accelerated healing of venous leg ulcers compared with deferred intervention.[3,4] Early intervention was also shown to be cost-effective in the short term.[5] In the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study, superficial venous surgery reduced venous ulcer recurrence at 4 years from 56% in participants treated with compression alone to 31% in the group treated with compression and varicose vein surgery.[6] Ulcer recurrence rates are likely to be higher than the 56% in the ESCHAR trial because compression is often not prescribed and compliance is poor, particularly outside clinical trials. Superficial venous surgery has largely been superseded by endovenous ablation procedures (ultrasound-guided foam sclerotherapy and thermal and nonthermal ablation), but long-term outcomes in patients with venous leg ulcers are unknown.

Extended follow-up was performed for participants in the EVRA trial to evaluate the influence of early endovenous ablation of superficial venous reflux on outcomes up to 5 years for participants with venous leg ulcers.

Methods

Study Design and Population
This parallel-group randomized controlled trial was conducted in 20 centers in the United Kingdom (trial protocol in Supplement 1 and eTable 1 in Supplement 2), where potential participants were screened from October 24, 2013, to September 27, 2016. Eligible participants had venous leg ulceration that had been present for 6 weeks to 6 months in addition to significant superficial venous reflux as assessed by the treating clinician. All trial centers had established leg ulcer referral and treatment pathways and were able to provide endovenous intervention within 2 weeks.

The study design and 1-year outcomes of the EVRA trial have been published previously.[3,4] Extended follow-up was approved by the South West-Central Bristol Research Ethics Committee on May 24, 2017. The independent trial steering committee and independent data and safety monitoring committees were retained to provide ongoing oversight for the study extension. All patients provided written informed consent for long-term follow-up at randomization, and this consent was reaffirmed for all participants contacted for long-term data collection. The EVRA trial was funded by the UK National Institute for Health Research Health Technology Assessment Programme, and the funder of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. During protocol development, a patient focus group was used to guide study design, and a patient was also included as a member of the trial steering com-

Key Points

Question In patients with venous leg ulceration and superficial reflux, what is the clinical and cost-effectiveness of early endovenous ablation of reflux?

Findings In this 450-patient, multicenter, randomized clinical trial, early endovenous ablation with compression accelerated venous ulcer healing, reduced the overall incidence of ulcer recurrence, and was highly cost-effective compared with compression with deferred intervention.

Meaning To deliver clinical and cost benefits, leg ulcer care pathways should be revised to include early assessment and treatment of superficial venous reflux.

mittee. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Randomization
Participants were assigned randomly in a 1:1 ratio to receive compression therapy and endovenous ablation within 2 weeks (early-intervention group) or to receive compression therapy alone with deferred endovenous ablation once the ulcer had healed, or after 6 months if the ulcer had not healed (deferred-intervention group). Randomization sequences were created in advance for each center by a trial statistician, and randomly permuted blocks were used with 2 block sizes. Surgeons, participants, and follow-up assessors were not blinded to the treatment group. Photographic verification for healing of primary ulceration was performed by clinical experts blinded to treatment allocation.

Procedures
Wound care and compression therapy were guided by local protocols, and multilayer elastic compression (2, 3, or 4 layers), short-stretch bandaging, and compression hosiery were all accepted. The endovenous treatment was left to the discretion of the responsible clinical teams, with endovenous thermal ablation modalities (laser or radiofrequency ablation), ultrasound-guided foam sclerotherapy, or nonthermal nontumescent endovenous interventions performed alone or in combination. Decisions regarding treatment of branch varicosities or perforators were left to physician choice. EVRA trial centers had extensive experience in performing endovenous ablation procedures. Participants in the early-intervention group underwent follow-up duplex ultrasound assessment 6 weeks after endovenous ablation, and additional interventions for superficial venous reflux in either group were performed at the discretion of the treating clinical teams. All participants were advised to use compression hosiery after ulcer healing, guided by local policy; additional duplex ultrasound assessment was not in the study protocol.

Telephone follow-up for all living participants was performed between October 2018 and March 2019 to obtain primary and secondary end point data. Where possible, participants in the EVRA trial were reminded at the 12-month visit to record any recurrent ulcers and health care visits in a participant diary to aid in subsequent recall. In the extended-phase follow-up, participants were asked on the telephone

(using a standardized questionnaire) about ulcer recurrences (defined as any wound on the study leg) and asked to recall dates of recurrence, subsequent healing, and details of additional treatments. Hospital and community clinical records were reviewed for further verification, and further calls were made to participants to clarify discrepancies.

A disease-specific quality-of-life assessment (Aberdeen Varicose Vein Questionnaire) and 2 generic quality-of-life assessments (the EuroQol Group 5-Dimension 5-Level questionnaire [EQ-5D-5L] and the Medical Outcomes Study 36-Item Short-Form Health Survey) (eTable 2 in Supplement 2) were performed between October 2018 and March 2019 (either on telephone or by mail). Adverse events were recorded in accordance with Good Clinical Practice guidelines.

Outcome Assessments

The primary outcome for the extended follow-up phase of the study was time to first ulcer recurrence from date of ulcer healing. The 1-year results, with time to ulcer healing as the primary outcome measure, were reported previously.[3,4] Healing of the primary venous leg ulcer was defined as complete re-epithelialization of all ulceration on the randomized (reference) leg with no scab or requirement for dressings, and a blinded verification process was used to confirm healing.[7]

The secondary outcome measures were time to first ulcer recurrence from date of randomization, the proportion of participants with recurrent ulceration at different time points (ulcer recurrence rate), time to healing of index and recurrent ulcers, length of time free from ulcers from randomization to final follow-up (ulcer-free time), recurrent ulcer incidence rate and incidence rate ratio, participant-reported health-related quality of life, and cost-effectiveness.

Statistical Analysis

Statistical analyses of the data were performed from August 11, 2019, to November 4, 2019. The trial was designed to detect a 15% absolute difference in ulcer-healing rates at 24 weeks (assuming a 60% rate of ulcer healing in participants randomized to compression alone) with 90% power and 2-sided alpha level of 5%. Assuming 90% of the participants in the EVRA trial would achieve ulcer healing and 15% losses to follow-up, death, or withdrawal from the study, we estimated that 344 participants would be available for analysis of ulcer recurrence. For extended follow-up analysis, we calculated that this was sufficient to detect a 15% difference in ulcer recurrence (30% in the early-intervention group vs 45% in the deferred-intervention group) with 82% power or a 20% difference in ulcer recurrence (30% in the early-intervention group and 50% in the deferred-intervention group) with 97% power.

The null hypothesis was that there is no difference in time to ulcer recurrence between the early-intervention group and the deferred-intervention group. This was tested using Cox regression with center as a random effect and participant age, ulcer size, and chronicity as fixed effects. We used Cox regression, adjusted as mentioned, to test for differences in time to healing of primary ulcer and recurrent ulcers. Ulcer recurrence rates (unadjusted) were calculated at annual time points up to 4 years with 95% CIs using the Kaplan-Meier method.[8]

Moreover, the incidence rate of recurrent ulcers (ulcers per person-years) and incidence rate ratios with 95% CIs were calculated. Ulcer-free time was defined as the total number of days that the reference leg remained healed during the entire follow-up period. We used a Cox regression model adjusted for center, patient age, ulcer size, and ulcer chronicity, as mentioned, as well as length of follow-up (as a fixed effect) to test the hypothesis that there was no difference in ulcer-free time between the early-intervention and deferred-intervention groups. Participants who did not consent to the extended follow-up are included to 12 months only. Adverse events were recorded.

Differences between study groups to 1 year for each quality-of-life measure have been published previously.[3] We used 3-level mixed models to assess differences in each quality-of-life measure between the 2 treatment groups. All analyses were performed on intention-to-treat. Participants whose primary ulcer did not heal were not eligible for analysis for ulcer recurrence, but were included in all other secondary analyses. There were no statistical adjustments for multiple testing. We performed per-protocol analyses for time to ulcer healing and time to first ulcer recurrence, and statistical significance was set at 5%.

Health Economic Analysis

We performed an in-trial health economic evaluation and estimated costs and quality-adjusted life years (QALYs) from the perspective of the UK National Health Service and Personal Social Services over a 3-year time horizon. Results to 1 year have been published previously.[5] The price year was the 2017 to 2018 period. Discounting was applied according to UK Government guidelines (3.5% per year for costs and health outcomes).[9] Study conduct and reporting complied with current guidelines for economic evaluation.[10] We collected details of resource use in hospital and community care related to venous leg ulcer treatment, adverse events, or complications of venous leg ulcers or treatments. We used case note review and questionnaires completed at baseline and monthly thereafter to 1 year, plus 1 further telephone follow-up between October 2018 and March 2019, with notes review for additional verification. Each item of resource use was multiplied by unit costs obtained from published literature,[11] national unit costs,[12,13] and manufacturers' list prices to calculate overall costs for each participant (eTable 3 in Supplement 2).

The EQ-5D-5L was completed at baseline, 6 weeks, 6 months, 12 months, and 1 further follow-up between October 2018 and March 2019. Utility indices for each individual at each follow-up time were calculated from the EQ-5D-5L questionnaire using the tariff recommended by the National Institute for Health and Care Excellence.[14] Cost and EQ-5D-5L data were analyzed using mixed models and total mean costs, and total mean QALYs were estimated for the 3-year time horizon. Sensitivity analyses used an alternative tariff for the EQ-5D-5L, per-protocol analysis and 4- and 5-year time horizons.[15] Uncertainty in mean costs and QALYs was quantified using bootstrapping and presented using cost-effectiveness acceptability curves (full description in eMethods and eTable 3 of Supplement 2).

Results

Patients

From October 24, 2013, through September 27, 2016, we randomly assigned 450 participants to undergo early intervention (224 participants) or deferred intervention (226 participants) in addition to compression therapy. The early-intervention group consisted of 224 participants (mean [SD] age, 67.0 [15.5] years; 127 men [56.7%] and 97 women [43.3%]; 206 White participants [92%]). The deferred-intervention group consisted of 226 participants (mean [SD] age, 68.9 [14.0] years; 120 men [53.1%] and 106 women [46.9%]; 208 White participants [92%]) (**Table 1**).[3,4] Of 224 participants randomized to early intervention, 203 (90.6%) underwent endovenous ablation within 2 weeks of randomization. Of 226 participants in the deferred-intervention group, 171 (75.6%) were treated with endovenous ablation within 12 months (Table 1). The final telephone follow-up was completed on March 28, 2019.

Data were collected over the telephone and from medical notes or from medical notes alone for 399 of 422 participants (94.5%) still participating at 1 year (**Figure 1**). Median follow-up period from randomization was 1286 days (interquartile range [IQR], 1038-1531 days) in the early-intervention group and 1287 days (IQR, 1063-1519 days) in the deferred-intervention group. Mortality was similar between the 2 groups, and no participants died as a result of intervention (eFigure 1 in Supplement 2).

Ulcer Recurrence

Of the 426 participants whose leg ulcer had healed, 121 (28.4%) experienced at least 1 recurrence. There were 175 episodes of recurrent ulceration during follow-up (72 in the early-intervention group [56 participants]; 103 in the deferred-intervention group [65 participants]).

Time to first recurrence from ulcer healing (adjusted for participant age, ulcer size, and ulcer chronicity) was similar in the early-intervention group and the deferred-intervention group (hazard ratio [HR] for ulcer recurrence, 0.82; 95% CI, 0.57-1.17; $P = .28$) (**Figure 2**A). Calculating time to ulcer recurrence from randomization rather than date of healing did not affect these findings (HR, 0.86; 95% CI, 0.60-1.24; $P = .43$) (eFigure 2 in Supplement 2). Ulcer recurrence rates (from ulcer healing) at 4 years were 34.6% (95% CI, 26.7%-44.0%) for the early-intervention group and 38.4% (95% CI, 30.8%-47.2%) for the deferred-intervention group (**Table 2**). In the early-intervention group, 72 recurrent ulcers occurred in 675.5 years of follow-up after healing of the primary ulcer compared with 103 ulcers in the deferred-intervention group during 636.0 years of follow-up. Therefore, ulcers recurred at a rate of 0.11 per person-year in the early-intervention group and 0.16 per person-year in the deferred-intervention group (incidence rate ratio, 0.658; 95% CI, 0.480-0.898, $P = .003$).

Secondary Outcomes

Time to ulcer healing of the primary ulcer was shorter in the early-intervention group compared with the deferred-

Table 1. Baseline Characteristics and Details of Interventions Performed

Characteristic	No. (%)[a]	
	Early intervention (n = 224)	Deferred intervention (n = 226)
Age, mean (SD), y	67.0 (15.5)	68.9 (14.0)
Sex		
Women	97 (43.3)	106 (46.9)
Men	127 (56.7)	120 (53.1)
Body mass index, mean (SD)[b]	30.1 (7.8) [n = 218]	30.4 (7.4) [n = 219]
Race/ethnicity		
White	206 (92.0)	208 (92.0)
Other[c]	18 (8.0)	18 (8.0)
History of DVT[d]	15 (6.7)	15 (6.6)
Diabetes	34 (15.2)	28 (12.4)
Previous leg ulceration[d]	118 (52.7)	117 (52.0) [n = 225]
Ulcer chronicity, median (IQR), mo[e]	3.2 (2.3-4.2)	3.0 (1.7-4.2)
Trial leg		
Right	107 (47.8)	115 (50.9)
Left	117 (52.2)	111 (49.1)
Ulcer size,[f] median (IQR), cm²	2.4 (1.0-7.1)	2.9 (1.1-8.2)
Presence of deep reflux[d,g]	74 (33.0)	69 (30.5)
Pattern of superficial reflux at baseline[d]		
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)
Timing of first endovenous treatment, from randomization		
Within 2 wk	203 (90.6)	1 (0.4)
Between 2 wk and 12 mo[h]	15 (6.7)	170 (75.2)
After 12 mo	0 (0.0)	8 (3.5)
No treatment[i]	6 (2.7)	47 (20.8)
Total No. of procedures	283	227
No. of procedures per participant		
1	164	144
2	43	23
3	11	11
4	0	1

Abbreviations: DVT, deep vein thrombosis; GSV, great saphenous vein; IQR, interquartile range; SSV, small saphenous vein.

[a] Values are presented as No. (%) for categorical variables and mean (SD) for continuous variables unless otherwise specified.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Early-intervention group: Asian, 11; Black, 3; and other, 4; deferred-intervention group: Asian, 12; Black, 5; and other, 1.

[d] In randomized leg.

[e] As reported by participant.

[f] Ulcer size evaluated using digital planimetry from standardized digital photographs by assessor blinded to intervention group.

[g] Defined as presence of retrograde flow in common femoral, femoral, or popliteal veins of >1-second duration after augmentation.

[h] Further details of timings of interventions have been published previously.[3,4]

[i] Reasons for no treatment in the deferred-intervention group were patient choice (16 of 47), patient died (7 of 47), withdrawal from study (7 of 47), lost to follow-up (5 of 47), clinician decision (3 of 47), and reason not recorded (9 of 47).

Figure 1. Consort Diagram Showing Enrollment, Allocation, 1-Year, and Extended Follow-Up
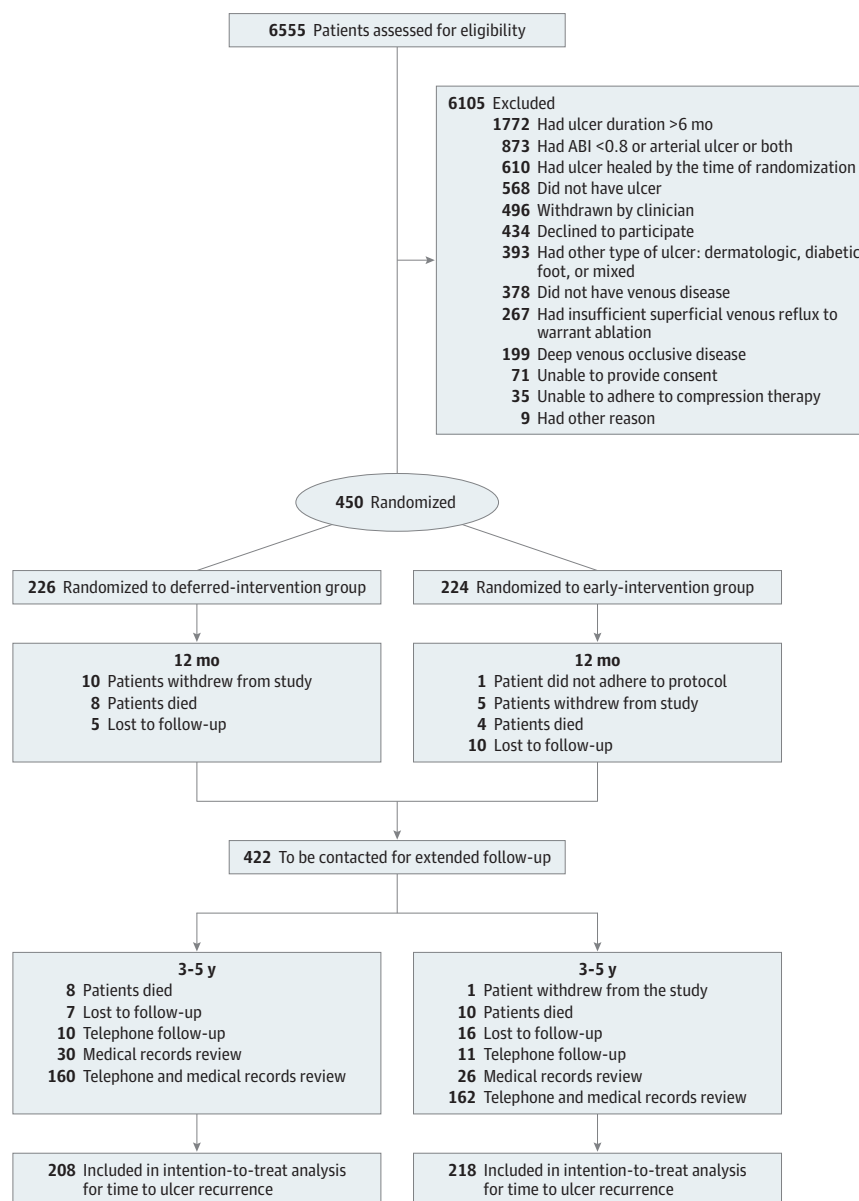
ABI indicates ankle-brachial index.

intervention group (HR, 1.36; 95% CI, 1.12-1.64, *P* = .002) (Figure 2B). Unlike the 1-year healing outcomes published previously,[3,4] this analysis also included primary ulcers that healed after 12 months. There was no clear difference in time to healing of recurrent ulcers between the early-intervention group and the deferred-intervention group (HR for healing including all ulcer recurrences, 1.10; 95% CI, 0.79-1.54; *P* = .58; eFigure 3 in Supplement 2) (HR for healing of first recurrence, 0.91; 95% CI, 0.62-1.35; *P* = .64).

The median ulcer-free time was 1137 days (IQR, 860-1411 days) in the early-intervention group and 1090 days (IQR, 625-1364 days) in the deferred-intervention group. Adjusting for follow-up period, participant age, ulcer size, and ulcer chronicity, there was no difference between the groups (HR for greater ulcer-free time, 0.84; 95% CI, 0.69-1.02; *P* = .07). Pre-

specified per-protocol analyses are presented in eFigures 4 and 5 in Supplement 2. During extended follow-up, the Aberdeen Varicose Vein Questionnaire, EQ-5D-5L, and the 36-Item Short-Form Health Survey domains were similar between the 2 groups (eTable 4 in Supplement 2).

Health Economic Analysis

Full details of resource use and costs for the 2 groups are presented in eTables 5 and 6 in Supplement 2. Discounted total mean cost of early intervention was –£155 (95% CI, –£1262 to £953) ($–213 [95% CI, –$1654 to $1249])compared with deferred intervention per participant over 3 years (Figure 3; and eTable 7 in Supplement 2), indicating that early intervention was, on average, the less costly strategy. Participants randomized to early intervention experienced, on average, greater QALYs after 3 years (mean

Figure 2. Kaplan-Meier Curves for Time to Primary Ulcer Recurrence and Ulcer Healing in Early-Intervention and Deferred-Intervention Groups

A Primary ulcer recurrence

Hazard ratio, 0.82; 95% CI, 0.57-1.17;
log-rank *P* = .28

No. at risk

Early	218	162	149	101	31
Deferred	208	153	131	92	31

B Ulcer healing

Hazard ratio, 1.36; 95% CI, 1.12-1.64;
log-rank *P* = .002

No. at risk

Early	223	13	6	4	0
Deferred	225	24	11	4	2
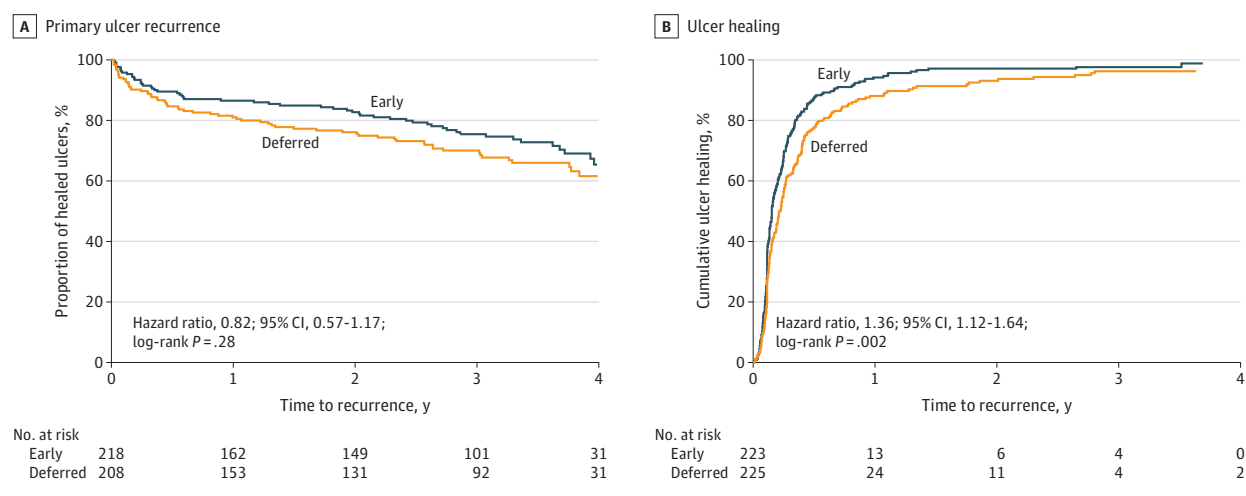
Table 2. Ulcer Recurrence Rates in Early-Intervention and Deferred-Intervention Groups

Study group	Follow-up, y	No.[a]	Recurrences	Cumulative recurrence rate, %	95% CI
Early-intervention group	1	162	28	13.48	9.51-18.94
	2	150	7	17.28	12.71-23.26
	3	102	12	24.56	18.99-31.41
	4	32	8	34.6	26.7-44.04
	5	1	1	NA	NA
Deferred-intervention group	1	154	38	18.98	14.18-25.13
	2	132	9	23.9	18.52-30.53
	3	93	10	29.95	23.92-37.1
	4	32	8	38.42	30.81-47.18
	5	1	0	NA	NA

Abbreviation: NA, not available.

[a] Number of participants successfully followed up for ulcer recurrence at each time period postrandomization.

Figure 3. Mean Cost Per Participant at 3 Years

3 years using an alternative tariff for EQ-5D-5L (eTable 7 in Supplement 2). Analysis using bootstrap simulations demonstrated that early intervention was 91.6% likely to be cost-effective at a willingness-to-pay threshold of £20 000 ($26 283) per QALY and 90.8% at a threshold of £35 000 ($45 995) (eFigures 6 and 7 in Supplement 2).

Discussion

One-year results from the EVRA trial showed that early ablation of superficial venous reflux accelerated healing of venous leg ulcers.[3,4] Longer-term follow-up in this study demonstrated that fewer recurrent ulcers per year of follow-up occurred in the early-intervention group, even though the time to first ulcer recurrence did not differ between the groups. The total mean costs were lower in the early-intervention group, and participants reported higher QALYs, indicating that early intervention is highly likely to be cost-effective irrespective of the willingness-to-pay threshold used by the health care system.

Ultrasound-guided foam sclerotherapy was the most common endovenous treatment in this trial, and some studies have reported high rates of technical failure compared with other endovenous modalities or open varicose vein surgery.[11,16] The 4-year

difference in QALY, 0.073; 95% CI, −0.06 to 0.20) using the EQ-5D-5L tariff recommended by National Institute for Health and Care Excellence. Early intervention was therefore a dominant strategy, with lower mean cost and greater mean QALY benefit. Findings were similar for 4-year and 5-year horizons (eTable 7 in Supplement 2) and with a per-protocol analysis (eTable 8 in Supplement 2), although the difference in QALY was smaller at

ulcer recurrence rates in this trial are comparable to those of previous studies evaluating ulcer recurrence after open varicose vein surgery, and outcomes in both groups of the EVRA trial are favorable compared with outcomes with compression alone.[6,17] These findings support the strategy adopted in this study, where the choice of endovenous modality was left to the discretion of the treating clinician. Ablating superficial venous reflux is likely to be more important than the choice of modality.

Strengths and Limitations

The health economic benefits of early intervention demonstrated in this trial are particularly compelling because the premise of a less costly treatment strategy that offers more QALYs is an important driver for change in behavior irrespective of the country or health care system. The method of follow-up is a limitation of this study, as only telephone follow-up at a single time point after 1 year was possible owing to funding limitations; photographic assessment was not deemed feasible. However, most participants in this trial were kept under regular surveillance by recruiting centers as part of normal clinical care, resulting in accurately recorded outcome data. One-fifth of the participants in the deferred-intervention group did not undergo endovenous intervention at all. It is difficult to predict whether clinical outcomes would have been better if all participants had been treated, but delaying intervention was associated with fewer participants undergoing endovenous ablation. The results of this study reinforce the conclusions from the 1-year EVRA results, that early endovenous ablation of superficial venous reflux is highly beneficial for both patients and health care professionals. These ob-

servations indicate that a policy of deferred or delayed endovenous intervention is illogical for patients with venous ulceration.

Long-term outcomes beyond 4 years remain unknown. Because chronic venous hypertension is multifactorial, ulcer recurrence is likely to be a common event in this population, despite endovenous ablation. Thirty percent of participants recruited to the EVRA trial suffered recurrent ulcers during follow-up. Aggressive investigation and treatment of venous outflow obstruction have been advocated, and the use of venous stents to correct nonthrombotic and post-thrombotic deep venous occlusive disease is increasing in popularity but requires robust evaluation.[18,19] Although there may be a role for deep vein stenting in some patients with venous ulceration, excellent healing outcomes were achieved in the EVRA trial cohort with combined good compression therapy and superficial venous ablation. It should also be noted that patients with concomitant arterial disease, foot ulceration, or those not compliant with compression were not included.

Conclusion

In this randomized clinical trial, early endovenous ablation of superficial venous reflux in addition to compression therapy reduced time to ulcer healing for primary ulcers. We found no statistical evidence that early endovenous ablation reduces time to first ulcer recurrence, but it was associated with a reduced incidence rate of recurrent ulcers and is highly likely to be cost-effective in the management of venous leg ulceration.

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