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An RCT of clinical and cost effectiveness of endovenous laser therapy in the treatment of varicose veins secondary to isolated sapheno-popliteal incompetence and small saphenous reflux.

Thesis submitted for the degree of MD at Hull York Medical School, University of Hull, United Kingdom

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ABSTRACT

BACKGROUND

Lower limb varicosities are common and cause significant impairment of quality of life to the sufferers. Patients with small saphenous incompetence form a small but significant part of this group who have traditionally been treated by surgical ligation with or without stripping of small saphenous vein (SSV). Within the last decade however, this has been challenged by endovenous thermal and chemical ablation interventions. No randomized clinical trial comparing treatment options for SSV incompetence exists, and there is no clear evidence that this axis behaves the same as the great saphenous vein (GSV) following treatment. This means that the existing literature base, centred on the treatment of GSV incompetence cannot simply be extrapolated to inform the management of SSV insufficiency.

OBJECTIVES

This trial aimed to compare the technical efficacy, safety and clinical effectiveness of minimally invasive endovenous laser ablation (EVLA) with the gold standard treatment of conventional surgery (CS) in the management of SSV incompetence.

Costs and utilities of EVLA and CS were compared to establish the most cost-effective treatment.

The risks and benefits of stripping SSV in the surgical treatment; and efficacy of EVLA in relation to the site of SSV access was also evaluated to establish best practice in both these interventions.

METHODS

Patients with unilateral, primary saphenopopliteal junction (SPJ) incompetence and SSV reflux were randomized equally into parallel groups receiving either Surgery or EVLA, with concomitant phlebectomies of tributary veins. Patients were assessed at baseline and weeks 1, 6, 12 & 52. Outcomes included: successful abolition of axial

reflux on duplex scan (Primary outcome); Visual analogue pain scores; recovery time; complication rates; Venous Clinical Severity Score (VCSS) and Quality of life (QoL) profiling.

For cost-effectiveness analysis, the hospital, general practice, patient costs incurred until full recovery and the indirect cost to society due to sickness leave after treatment, were calculated to indicate mean cost per patient under each treatment category. EQ-5D health utility index was calculated from EuroQol generic QoL questionnaire, and quality adjusted life years (QALYs) were generated by calculating the area under curve. Cost/QALY and incremental cost effective ratio (ICER) was calculated for both treatment groups to determine the more cost-effective treatment.

For patients undergoing surgical treatment, the aim was for SPJ ligation (SPL) and stripping of SSV in each case, but in a proportion this was not possible. Hence, patients were retrospectively sub grouped into SPL with short segment excision ≤ 5 cm and SPL with extended stripping > 5 cm. Clinical and QoL outcomes including recurrence and complications were compared between these surgical subgroups.

Patients undergoing EVLA (810 nm, 14 W diode laser) for small saphenous incompetence were retrospectively divided into two subgroups: access gained at or above mid-calf (AMC) and below mid-calf (BMC), based on the level of endovenous access gained at the lowest site of truncal reflux. Similar clinical and QoL outcomes including recanalization and sensory disturbance were compared between the EVLA subgroups.

RESULTS

106 patients were recruited and randomized to Surgery (n=53) or EVLA (n=53). The primary outcome of abolition of SSV reflux was significantly higher following EVLA 96.2% vs. Surgery 71.7% ($P<0.001$). Postoperative pain was significantly lower after EVLA ($P<0.05$), allowing an earlier return to work and normal function

(P<0.001). Minor sensory disturbance was significantly lower in the EVLA group 7.5% vs. Surgery 26.4% (P=0.009). Both groups demonstrated similar improvements in VCSS and quality of life measures.

The hospital costs for EVLA was less expensive compared to Surgery, mean (s.d.) £690.31 (121.66) vs £730.77 (304.82) per patient (P=0.390); and enabled patients to return to work 9.6 days (95% CI 4.9-14.3) earlier than after surgery. Based on the Annual Survey of Hours and Earnings 2012 for full time employees, the cost per working hour gained after EVLA was 13.96 pounds (95% CI 7.41 - 20.50). There was no significant difference in mean QALYs gained between the two treatments (P=0.101); however the mean (s.d.) Cost/QALY was significantly lower for EVLA £1652.58 (966.20) as compared to surgery £2123.48 (1084.54) (P=0.032).

Of the 53 surgical patients, inversion stripping was possible in 35 (66%) and in the rest 18 (34%), a short segment of SSV was excised following SPL. Recurrence rates were higher in the short excision subgroup at 44.4% versus 2.9% in the inversion stripping subgroup causing a decline in patient satisfaction with treatment and cosmetic outcomes at the end of follow-up period (P<0.05). There was no significant difference in sensory disturbance or complications between the two subgroups (P>0.05).

Of the 53 EVLA patients, access was gained above mid-calf in 30 (57%) and below mid-calf in 23 (43%). SSV occlusion was equally high in both subgroups with no significant difference in complications or recurrence rates (P>0.05). Patient satisfaction with overall treatment declined in the AMC subgroup (P=0.011). Both EVLA subgroups demonstrated significant improvement in venous severity and QoL measures over the follow-up period (P>0.05).

CONCLUSIONS

EVLA produced the same clinical benefits as conventional surgery, but was more effective in addressing the underlying pathophysiology and was associated with less peri-procedural morbidity, allowing a faster recovery for patients. Of the two interventions, EVLA is the more cost-effective option in the short-term, feasible in an outpatient setting under tumescent local anaesthesia. These findings support the adoption of EVLA with concomitant phlebectomy as the standard treatment for primary small saphenous insufficiency.

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Yorkshire Vascular Forum – Second Prize October 2011 (Co-author)

Royal Society of Medicine Venous Forum / Vascular Society of Great Britain and Ireland – First Prize November 2010 (Co-author)

Royal Society of Medicine Venous Forum – Third Prize April 2010 (Co-author)

Publications during research

Samuel N, Carradice D, Wallace T, Smith GE, Chetter IC. Endovenous thermal ablation for healing venous ulcers and preventing recurrence. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD009494. DOI:10.1002/14651858.CD009494.pub2

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Every blessing You pour out Lord, I'll turn back to praise….

Blessed be the name of the Lord, Blessed be your glorious name

Matt Redman

DECLARATION

I Nehemiah Samuel, confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources'.

Conflicts of interest:

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Sd/-

Nehemiah Samuel

Date: 31/03/2014

ABBREVIATIONS

AASV	Anterior Accessory Saphenous Vein
AMC	Above mid-calf
APG	Air-Plethysmography
ASHE	Annual Survey of Hours and Earnings
AUC	Area under the curve
AVF	American Venous Forum
AVP	Ambulatory Venous Pressure
AVVQ	Aberdeen Varicose Vein Questionnaire
BMC	Below mid-calf
Cm	Centimetre
CEAP	Clinical, Etiologic, Anatomic, Pathophysiologic
CFV	Common Femoral Vein
CI	Confidence Interval
CS	Conventional Surgery
CVI	Chronic Venous Insufficiency
DN	District Nurse
DUS	Duplex Ultrasound Scan
DVI	Deep Venous Insufficiency

DVT	Deep Vein Thrombosis
EQ-5D	EuroQol – 5D questionnaire
EVLA	Endovenous Laser Ablation
EVLT	Endovenous Laser Treatment
F-A	Friedman ANOVA - statistical test
FET	Fisher's Exact Test - statistical test
GP	General Practice
GSV	Greater saphenous vein
GV	Gastrocnemius Vein
HR-QoL	Health Related Quality of Life
HELP-2	Hull Endovenous Laser Project – 2
HRI	Hull Royal Infirmary
HYMS	Hull York Medical School
ICER	Incremental Cost Effective Ratio
i.q.r	inter quartile range
IUP	International Union of Phlebology
IVC	Inferior Vena Cava
JVRG	Joint Vascular Research Group
LED	Laser Energy Density

MMP	matrix metalloproteinase
mm	millimetre
mmHg	millimetre of mercury
MPFF	micronized purified flavonoid fraction
MWU	Mann Whitney U Test - statistical test
NHS	National Health Service
NICE	National Institute of Clinical Excellence
PPG	Photoplethysmography
PE	Pulmonary Embolism
PV	Popliteal Vein
PASV	Posterior Accessory Saphenous Vein
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RF	Radio Frequency
RFA	Radiofrequency Ablation
RR	Relative Risk
s.d.	standard deviation
SFJ	Saphenofemoral Junction
SPJ	Saphenopopliteal Junction

SPL	Saphenopopliteal junction ligation
SF-36	Short Form - 36
SSV	Small saphenous vein
STS	sodium tetradecyl sulphate
SPSS	Statistical Package for the Social Sciences
SFV	Superficial Femoral Vein
SVI	Superficial Venous Insufficiency
TIMP	tissue inhibitor of metalloproteinase
TLE	Total Laser Energy
UIP	Union Internationale de Phle´bologie
UK	United Kingdom
USA	United States of America
UGFS	Ultrasound Guided Foam Sclerotherapy
VV	Varicose vein
WSR	Wilcoxon Signed Rank - statistical test

CHAPTER 1

1.1 INTRODUCTION

Varicose veins (VVs) are generally a non-life threatening condition that commonly affects the adult population. With an estimated age-adjusted prevalence of 40% in men and 32% in women[1], lower limb varicosities are classed as a major health problem in the industrial west. They not only cause pain, disability and hundreds of millions of pounds in healthcare costs but also negatively impact upon quality of life (QoL) in the afflicted patients. Lower limb varicosities are disreputably the commonest vascular disorder affecting man, and hence is unsurprisingly one of the commonest referral diagnoses to the vascular or general surgical clinics. The management of this condition thus impacts significantly on the surgical workload, which is mirrored by the ever increasing surgical procedures undertaken within the National Health Services (NHS); an average 50,000 operations for VVs performed in England and Wales every year[2] at an estimated cost of £20-£25 million pounds, thus consuming significant healthcare resources. With a number of varicose vein sufferers still economically active, the physical impairment causing suboptimal productivity, including the working days lost during recovery from surgery, all contribute to significant socio-economic impact both at an individual level and to the society as a whole.

The majority of patients who are treated for lower limb varicosities have saphenofemoral junction (SFJ) incompetence with greater saphenous vein (GSV) insufficiency[3]; saphenopopliteal junction (SPJ) incompetence with small saphenous vein (SSV) insufficiency is found in approximately 15% of all such patients with primary varicosities[4-6] and may result in symptoms of equal severity[7]. The spectrum of symptoms and signs due to chronic venous insufficiency (CVI) may include pain, ache, heaviness, fatigue, cramps and cosmetic disfigurement, dermato- or liposclerosis, phlebitis or ulceration as the worst extreme complication. Symptomatic small saphenous varicosities have traditionally been managed surgically by saphenopopliteal junction ligation (SPL)[8 9], which is relatively more challenging,

with higher complications and recurrence rates as compared to GSV surgery[10]. The unpredictable and variable anatomy of SPJ often requiring deep and difficult dissection; proximity of SPJ/SSV to major neurovascular structures with its increased potential to nerve injury; and the lack of consensus on SSV stripping are some of the drawbacks associated with this treatment modality that has in recent times deterred surgeons from undertaking this procedure[11], more so with the availability of alternative minimally invasive endovenous interventions that circumvent the need for popliteal dissection and/or SSV stripping with their associated morbidity.

Over the last decade minimally invasive endovenous techniques have evolved as alternatives to conventional surgery in an attempt to reduce procedural morbidity and improve recovery times. Endovenous ablation achieved by laser or radiofrequency thermal energy or foam sclerotherapy, have been extensively evaluated in the treatment of GSV incompetence and the early results for anatomical success, reduced complications and patient satisfaction achieved with these techniques have been promising. However, much less is known about endovenous treatment of SSV insufficiency. Although it is suggested that these minimally invasive techniques are more effective than conventional surgery, no randomized clinical trials have been done to prove this. There is emerging evidence that SSV may behave differently to GSV incompetence following treatment, hence available evidence for GSV cannot be extrapolated to SSV management, rather it is only relevant to consider GSV and SSV as two distinct entities given the variation in the length and pressure columns of the two veins, the relation to neighbouring neurovascular structures and the intra-fascial course of SSV along its entire length.

Endovenous laser ablation (EVLA), one of the most promising of the endoablative techniques has been reported in literature as limited case-series in the treatment of SSV incompetence[12-21]; often as a subset population in the evaluation of this intervention for lower limb varicosities originating from GSV incompetence. It

involves percutaneous cannulation of saphenous vein under ultrasound guidance and thermal ablation of the vein wall using laser energy, delivered via endovenous laser fibre. By reporting early success rates ranging from 91% to 100% and improved patient satisfaction with EVLA treatment, these non-comparative studies have sought to establish the safety and efficacy of EVLA in SSV treatment, while also underscoring the potential advantages of not requiring popliteal exposure to ligate SPJ; lesser pain/ bruising by avoiding SSV stripping; faster recovery and earlier return to normal functioning; and the convenience of the procedure being performed under local/ tumescent anaesthesia, in comparison to conventional surgery. However there are also potential disadvantages of risk of paraesthesia and skin burns, non-suitability of the procedure for tortuous and abnormally dilated veins; risk of thrombosis in the proximal SSV extending into the popliteal vein; as yet unknown long term recurrence and the cost-effectiveness of the intervention. Whether these advantages and disadvantages outweigh outcomes from conventional surgery which is still considered "gold standard" treatment, cannot be established from these studies. There is thus a clear need to establish the role of EVLA in the treatment of SSV incompetence and evaluate its impact on early morbidity, complications, QoL changes and patient satisfaction. A robust and comprehensive comparative assessment between EVLA and conventional surgery can be achieved through a prospective randomized controlled trial. Such a trial has not been conducted to date in the UK and would help to accurately measure the above outcomes in the two groups and also provide a definitive estimate of the comparative costs. This evidence base can then be used to inform decision making in both clinical and commissioning context.

1.2 BACKGROUND

HISTORICAL ASPECTS

The origin of the word “varicose" comes from the Greek term "grapelike". It was probably first used as a medical description by Hippocrates of Cos (Greece) in 460 BC. Indeed, since the beginning of written history, mankind has suffered from - and continually devised treatment options for varicose veins. For more than 2000 years treatment methods have been developed; but not until the present era has there been an in-depth understanding of the pathophysiological basis of underlying chronic venous insufficiency and adoption of a physiological approach to the treatment of venous disease, aided by advances in technology.

Varicose veins were first described in the Ebers papyrus 3500 years ago. This ancient Egyptian work described 'serpentine windings' on the legs, and the author advised against operation for this condition because the patients would be 'head to the ground', implying ‘die of haemorrhage’. This is the first description of what must have been a failed attempt at surgery to treat varicose veins. Since then treatment for varicose veins has advanced many-fold and surgery when indicated can be offered with minimal risk to the affected patient. Hippocrates, the “father of medicine” wrote some of the earliest medical descriptions of varicose veins and leg ulcers. He associated ulcers on the legs with enlarged veins and in The Hippocratic Treatises (460 BC) wrote: ‘*In the case of an ulcer, it is not expedient to stand; more especially if the ulcer be situated in the leg*’. Whilst he did not recommend the surgical excision of varicose veins, he however prescribed compression following multiple punctures; also suggesting that the occurrence of the ulcers could be related to the incisions themselves.

In a medical treatise De Medicina, a Roman physician named Aulus Cornelius Celcus (25 BC - AD 14) described the ligation and excision surgery for varicose veins, as

well as possible complications. He made multiple incisions 4 fingerbreadths apart, then touched the vein with cautery, grasped it and extracted as much of the vein as possible, double clamping and dividing the vein between ligatures. Another description of varicose veins treatment was provided by Galen (AD 131 - 201), who promoted use of severing connections between arteries to veins in order to reduce pain and avoid spreading gangrene. He also described making 3-6 incisions with a hook and then bandaging the leg. Celsus and Galen were possibly the first to describe 'phlebectomies', a technique still used today. Although the current technique is slightly different, yet the principle remains the same. What has definitely changed is the pain experienced by the patient during the procedure. The Roman tyrant Caius Marius who died in 86 B.C. underwent varicose vein surgery and after treatment on one leg, declined surgery to the other leg declaring '*I see the cure is not worth the pain*'.

Hippocrates' theory of the liver being the "root" of all veins and that the veins alone contained blood for the body's nourishment and the arteries contained an elastic ethereal fluid, the "spirit of life"; wrongly based upon the Pythagorean doctrine of the four humors (blood, phlegm, yellow bile, and black bile), remained the basis for medical practice for the next 1500 years before the concept of blood circulation was born. The widely held belief that varicosities were filled with black bile and would be trapped by the healing ulcer (humoral theory of Galen), thereby making it too risky to cure leg ulcers, continued to be held even as late as the early part of the 19th century. Varicosities were also attributed to the 'weight' of the stagnant blood on the walls of the veins. A popular theory of the early days was that the 'gross' menstrual blood which was presumed to stagnate during pregnancy was believed to cause varicosities and subsequent ulceration which then allowed the 'trapped' blood to escape. It was the works of anatomists such as Hieronymus Fabricus who accurately described venous valves; and William Harvey, the Englishman who described the functions of such valves in context to the physiology of venous circulation in his classic work

Exercitatio Anatomica de Motu Cordis et Sanguini in Animalibus (1628), which were the basis for the concepts of unidirectional blood flow and the venous valves role in preventing blood to flow backwards. Harvey also realized the effect of muscular contraction in assisting venous blood flow towards the heart from the lower limbs. Wiseman (1676) pointed out venous dilatation as a cause of valvular incompetence and hypothesized circulatory defects as the cause of ulcers. For this, he also went on to advocate laced leather compression stockings which grew in popularity, as the degree of compression could be easily manipulated by fastening the lace. Despite these advances it was not until the beginning of the 19th century that the term 'varicose ulcer' became established and that varicose veins and venous thrombosis were believed to be important causative factors for ulceration. During the same time Friedrich Trendelenburg (1844-1924) popularized saphenous ligation without "blood-letting" – the latter hitherto practiced for hundreds of years with variable success. By the beginning of the 19th century, although compression bandaging, ligation, dissection, stripping and sclerosis were all practiced, the surgical techniques were however unpopular due to patients suffering pain and complications of infection. These trepidations did diminish with introduction of modern anaesthetic techniques and antiseptic methods pioneered by Lister.

In 1884 Madelung of Germany described complete excision of the greater saphenous vein through a long incision in the leg similar to that used in the present day for harvesting GSV for bypass procedures; varicectomy and ligation of tributary stumps. The Madelung procedure however carried several complications[22]. In 1897, the first varicose vein operation under anaesthetic was performed in Finland[23]. Subsequently Keller developed invagination stripping in 1905 by passing a twisted rigid wire with a terminal loop intraluminally and extracting the vein by inverting it into itself[24]. Babcock's modification of Keller's technique was the use of a flexible rod and acorn tip to prevent tearing of the vein[25]. Charles Mayo also described an extra-luminal ring stripper for axial varicectomy[26]. Thus the surgical treatment for varicose veins was

fairly established by the beginning and changed little until the end of the 20th Century.

Joseph Hodgson's (1815) observation of 'spontaneous cure of varicosities' as a consequence of venous thrombosis was the basis for subsequent efforts to achieve intraluminal thrombosis using sclerosing agents such as iron perchloride, iodotannin and iron chloride. Sclerotherapy described by Chassaignac in 1855 did not become popular, principally due to the high recurrence rates and side-effects of inflammation and suppuration before the antiseptic era. Genervrier's accidental observation of intimal damage and venous sclerosis following intravenous quinine administration for malarial crisis treatment, led to the development of sclerosants such as hypertonic saline and sodium morrhuate which induced thrombosis by intimal injury. The waning popularity of sclerotherapy found a revival with the development of foam sclerotherapy technique at the turn of the 21st century.

Towards the latter half of the 20th century advances in technology ensured better evaluation of venous disorders, which in turn significantly influenced understanding of the pathophysiologic basis for chronic venous insufficiency and its treatment. The development of diagnostic tools such as phlebography (Berberich and Hirsch, 1923) and air plethysmography (Van Rijn, 1987) followed by non-invasive techniques such as hand-held continuous wave Doppler (Stegall and Rushmer, 1961) and colour duplex ultrasound (Szendro et al., 1986) coupled with concurrent advances in medical technology saw the dawn of the modern endovascular era in the treatment of varicose veins. The early concepts of "electrofulguration" (Werner and McPheeters, 1964), "endovenous electrosurgical desiccation" by diathermy (Watts, 1972) and "freezing technique" (Milleret and Le-Pivert, 1981) for superficial venous insufficiency (SVI), were drastically revolutionized with the introduction of endovascular radiofrequency and laser therapy for the treatment of varicose trunks. The first radiofrequency Closure® system (1998) was abandoned due to disappointing failure rates; however the manufacturer subsequently improvised a more sophisticated indirect RFA system,

the VNUS® ClosureFast®. The use of endovenous laser was first proposed by Puglisi at the IUP World Congress (1989), Strasbourg. The refined technique reported by Boné (1999) for the treatment of SVI[27 28] generated a lot of interest worldwide. Since the publication of Boné's case series, the newer endovenous techniques have been rigorously scrutinised using randomised clinical trials and explicitly reported in the scientific literature in order to inform practitioners their specific role in the treatment of venous disease.

ANATOMY OF LOWER LIMB VENOUS SYSTEM

The veins of the lower extremity are anatomically subdivided into the superficial and deep subsets, depending on their relation to the deep fascia surrounding the calf and thigh muscles. The superficial veins that course subcutaneously between the two layers of the superficial fascia drain into the deep system at the junctions or via perforating veins; whereas the deep veins beneath the deep fascia are typically accompanied by major arteries and return blood from the peripheries to the heart. Both subsets including the perforators are provided with valves which are relatively more in number in the deep veins. Each of these components is considered below.

Superficial Venous System

The superficial venous system comprises of thin-walled venules which form an extensive plexus beneath the skin; a network of subcutaneous venous tributaries which arise from the plexus of venules and drain into the axial trunks; and the main trunks of great and small saphenous veins, which drain skin and subcutaneous tissue of lower limbs, lower abdominal wall and pudendal region into the deep system. Although the two named trunks are usually present, far more anatomical variations exist within the superficial system.

Venous drainage of foot

The toes are drained by two dorsal and two plantar *digital veins* each. The former receive *intercapitular veins* from the latter and join at the toe clefts to form short *common digital veins*. These unite across proximal parts of the metatarsal bones to form the *dorsal venous arch*. The medial and lateral ends of the dorsal arch in turn receive the *medial and lateral marginal veins* and continue proximally as the *great saphenous vein* and the *small saphenous vein* respectively. On the sole of the foot, the plantar digital veins form a plantar cutaneous venous arch which joins the medial and lateral marginal veins on either side of the foot. Proximal to and communicating with the cutaneous venous arch is the plantar cutaneous venous net-work which is chiefly drained by the medial and lateral marginal vessels. Since the weight-bearing function of the sole of the foot constantly places it under significant pressure, the majority of its venous drainage is into the subcutaneously placed dorsal venous arch.

Great Saphenous Vein (Syn. Long or Large or Internal Saphenous Vein or saphena magna)

The great saphenous vein (GSV) is the longest vein of the body and hence commonly predisposed to superficial venous insufficiency. Distally it commences as the continuation of the medial marginal vein of the foot, passing anterior to the tibial medial malleolus and ascending along the medial border of the tibia accompanied by the saphenous nerve in the subcutaneous tissues; prior to crossing the knee it loops posteriorly lying posteromedial to the medial condyles of the tibia and femur; and then ascends forwards to the medial thigh, proximally piercing the cribriform fascia covering the saphenous opening to terminate by emptying into the superficial femoral vein (SFV) at the saphenofemoral junction (SFJ). The surface marking of SFJ is approximately 3 cm below and 3 cm lateral to the pubic tubercle and a line traced from this point to the femoral adductor tubercle represents the GSV in the thigh. In the lower two-thirds of the leg and in the upper two-thirds of the thigh the GSV lies

on the deep fascia and is placed more superficially behind the knee. In a quarter of the population the GSV is duplicated distal to the knee. Duplication could lead to inadequate removal of incompetent vein during surgery, thereby leading to residual or recurrent varicosities.

Relations: The saphenous nerve lies anterior to the GSV in the foot and the leg; and is in close proximity to the vein in the lower two-thirds of the leg. The rationale for not stripping the vein beyond a few centimetres distal to the tibial tubercle during surgery is to avoid the potential risk of nerve injury during stripping or avulsions of veins. At the knee the saphenous branch of the descending genicular artery lies anterior to the vein. Branches of medial femoral cutaneous nerve accompany the vein in the thigh. Accessory saphenous veins which are frequently present lie parallel to GSV both in the thigh and leg, running either anterior or posterior or superficial to the main trunk.

Tributaries: at the ankle GSV receives branches from the sole of foot via the medial marginal vein; it communicates with the SSV, anterior and posterior tibial veins; also receiving numerous unnamed cutaneous veins. The posterior accessory saphenous vein of the leg (Leonardo's vein or posterior arch vein) is a common tributary which begins posterior to the medial malleolus, ascends on posteromedial aspect of calf and joins GSV distal to knee. In the thigh GSV communicates with the femoral vein and receives several superficial tributaries of which the larger two are the anterior accessory saphenous vein (AASV) and the posterior accessory saphenous vein of thigh (PASV). The AASV originates at the lateral border of the knee, sometimes originating as low as the lateral side of dorsal venous arch. It joins the GSV at a variable level, but commonly at or near the junction itself. The AASV can be mistaken for the GSV itself, more so when the latter is hypoplastic. The PASV connects distally with the SSV and occasionally enters the femoral vein independently below the SFJ. Occasionally it acts as the main channel for SSV drainage into the deep system when the SSV fails to communicate with the popliteal

vein as discussed below. Before piercing the cribriform fascia covering the saphenous opening in the groin, the GSV receives tributaries corresponding to the arterial branches of the common femoral artery- the superficial circumflex iliac, superficial epigastric, superficial and deep external pudendal veins. Other occasional tributaries of GSV in the groin are the anterior and posterior thigh circumflex veins.

Small Saphenous Vein (Syn. Short or Lesser or External Saphenous Vein or saphena parva)

The small saphenous vein (SSV) begins behind the lateral malleolus as a continuation of the lateral marginal vein. In the distal third of the leg it ascends along the lateral margin of achilles tendon lying on the deep fascia covered only by skin and superficial fascia. In the middle third, it ascend in the midline of the calf enclosed within a fascial compartment formed by the aponeurotic investment of the gastrocnemius muscle. In the upper third it pierces the deep fascia to run between the two heads of the gastrocnemius muscle and enters the popliteal fossa to drain into the popliteal vein at the saphenopopliteal junction (SPJ). This junction is usually 3-7.5 cm above the knee joint, however it is highly variable and the SSV may terminate above, below or at the level of the knee and may join the popliteal vein, GSV, deep posterior femoral veins or deep sural muscular veins.

Relations: The SSV is closely accompanied by the sural nerve on its lateral aspect in the lower third of the leg. Lymphatic trunks draining the lateral aspect of the foot also accompany the SSV to drain into the popliteal lymph nodes. At its termination in the popliteal fossa, the SSV is closely related to the medial popliteal nerve (Syn. Tibial nerve), a terminal branch of the sciatic nerve, which should be protected during popliteal fossa dissection for SPJ ligation.

Tributaries: The SSV communicates with the deep veins on the dorsum of the foot and receives several unnamed tributaries from the back of the leg; it also sends

several rami proximally and medially to join the GSV. Prior to piercing the deep fascia, the SSV may extend cranially beyond the SPJ, also known as the cranial extension of SSV which terminates by piercing the fascia in the posterior thigh to drain into the deep system or communicate with the GSV at or about the SFJ, the latter also known as the ascending superficial vein (Syn. Giacomini vein). This cranial extension of SSV may occasionally be coupled with absence of its junction with the popliteal vein in the popliteal fossa. The SSV is connected to the venous arches that connect the perforators along the medial aspect of ankle; thereby incompetence of SSV could manifest as varicosities both on the medial and lateral aspects of the ankle. The SSV communicates with the peroneal vein via a large lateral ankle perforating vein and with the soleus sinusoids via an inconstant mid-calf perforating vein.

Deep Venous System

The deep veins of the lower limb accompany the arteries and their branches. They possess numerous valves that ensure venous blood flow towards the heart, thereby emptying the deep system and reducing its pressure, usually to less than 30 mmHg.

Anterior Tibial Veins: are the upward continuations of the dorsalis pedis veins. They run up over the interosseous membrane between the tibia and fibula and unite with the posterior tibial vein to form the popliteal vein at the lower border of the popliteus.

Posterior Tibial Veins: accompany the posterior tibial artery and are formed by the union of the medial and lateral plantar veins behind the medial malleolus; they course upwards on the tibialis posterior muscle, receiving tributaries from the soleus venous plexus, perforators along the medial ankle and the peroneal veins.

Popliteal Vein: is formed at the lower border of the popliteus muscle by the union of the anterior and posterior tibial veins. It crosses the popliteal fossa and ascends as the

femoral vein beyond the hiatus of the adductor magnus. It is placed medial and superficial to the popliteal artery in its lower course, crossing to its lateral side above the knee joint in the popliteal fossa. It receives the SSV, veins corresponding to the branches of the popliteal artery and some muscular tributaries.

Femoral Vein: is the continuation of the popliteal vein beyond the adductor magnus aperture. It runs upwards in the femoral triangle crossing behind the femoral artery from the lateral to medial side and terminates behind the inguinal ligament as the external iliac vein. It receives numerous muscular tributaries, the profunda femoris vein, lateral and medial circumflex femoral veins and the GSV near its termination.

Deep Femoral Vein (Syn. Profunda Femoris Vein): accompanies the profunda femoris artery, receiving tributaries corresponding to the perforating branches of the same and through these communications connects the popliteal vein below and the inferior gluteal vein above. It drains into the femoral vein proximally.

Gastrocnemius Veins: are large veins that drain the venous sinuses of the gastrocnemius muscle bellies and terminate by joining the popliteal vein. These veins may become varicose following thrombotic destruction of functioning valves in the popliteal and femoral veins.

Soleus Venous arcade: the veins draining the soleus muscle forms arcades joining the posterior tibial and the peroneal veins. They have multiple valves to facilitate proximal blood flow. Soleal sinusoids are dilated segments of the venous arcade which act as the main collecting chambers of the ‘calf muscle pump’. Perforators communicate with the posterior tibial and peroneal veins close to the confluence of the soleal arcade veins, which may explain the extension of thrombosis from the soleal sinusoids into the perforating veins thereby causing destruction of valves in the latter, resulting in incompetence and ankle oedema.

Perforators and communicating veins

Perforating veins connect the deep veins to the superficial veins or their tributaries and are provided with valves such that blood flows in one direction from the superficial to the deep system. Significant variation exists in the location of individual perforators; however distribution of groups of perforators follows a predictable pattern. Clinically significant perforating veins include the anterior, medial and lateral ankle perforators, of which the medial veins draining the 'ulcer-bearing area' of the ankle are divided into posterior tibial and para-tibial perforators. Three groups (lower, middle, upper) of posterior tibial perforating veins also known as Cockett I-III perforators connect the PASV of the leg to the posterior tibial veins close to the junctions with the soleal arcade veins. Thus a thrombus originating from within the soleal muscle veins can simply spread distally down the perforators and posterior tibial veins; recanalization and destruction of valves within these veins leads to reflux from the deep to superficial veins subsequently causing venous hypertension and tissue destruction. The paratibial perforators also drain into posterior tibial veins. Other perforators that join the GSV or its tributaries are the upper calf (tibial tubercle or Boyd's perforators); the distal thigh (Dodd's perforators); and the mid-thigh (Hunterian) perforators. At the junction of lower and middle third of the calf, the lateral and external ankle perforators bridge the SSV to the peroneal vein and a mid-calf perforator may connect the former to the soleal sinusoids.

Venous valves

The valves found in healthy leg veins direct blood from the superficial to the deep veins and from distal to proximal segments, preventing retrograde flow and thus reducing venous pressure in both superficial and deep systems in the upright position. Their functions are complementary to the calf muscle pump which helps return venous blood to the heart against gravity. The valves are variable in number and position and are usually found along the course of GSV and SSV and at their junctions with the deep system. The number of valves in the deep veins becomes

progressively less from distal to proximal such that the common femoral vein (CFV) and external iliac veins have only one valve between them in two thirds of the population[29] and in a third, no valve exists between the CFV and the heart[30]. This is innate to withstand the greater hydrostatic pressures of the blood column in the veins of the lower leg than the more proximal ones. The valves of the perforators are also placed at their junction with the deep system and help prevent retrograde blood flow to the superficial system.

PHYSIOLOGY & PATHOPHYSIOLOGY OF VENOUS SYSTEM

In order to understand treatment of lower limb venous disorders, it is vital to know both the anatomy and physiology of the veins including mechanisms that causes derangements of its normal function, thereby causing chronic venous hypertension and its accompanying changes.

The systemic venous system contains approximately 60% of the total blood volume with an average pressure of around 5-10 mmHg. The pressures within the venous system are largely determined by gravity, and the physiology of venous return differs in the supine and upright positions. In the former position, blood flow and hence venous pressures are evenly distributed in the lower limbs, abdomen, chest and extended arms. However in the upright position the peripheral venous pressure is affected by gravity with an estimated increase of 0.77mmHg for every cm below the right atrium. In the standing position without skeletal activity venous pressure in the foot veins may reach up to 80-90 mmHg, determined by the hydrostatic pressure of the blood column from the heart down to the foot and the capillary blood flow[31]. The mechanical factors facilitating antegrade venous return towards the heart against gravity are the muscle and respiratory “pumps”.

Musculo-Venous Pump

Around 90% of venous return from the lower extremities is through the deep venous system aided by the action of the foot, calf and thigh muscle pumps[32]. The action of

these valved pumps is dependent on the deep fascia of the leg, which invests around its muscles as an unyielding cylindrical sleeve, thereby generating high pressures within the muscular compartments during muscle contraction. Raised pressures as high as 200-300 mmHg in the leg (calf pump) and 100-120 mmHg in the thigh (thigh pump) are generated during muscle contraction and exerted onto the relatively thin walled intra- and inter- muscular veins, thus propelling venous blood upwards against the intravenous hydrostatic pressure gradient. Similarly during walking, the foot pump aids the drainage of blood from the superficial plantar veins into the distal deep veins. The reduction of mean venous hydrostatic pressure in the emptied veins is complemented by the function of the venous valves which prevent retrograde flow, thus lowering the resting venous pressure. Pressures in the posterior tibial vein decreases from 80-100 mmHg to less than 30 mmHg[31]. A reduction in the deep venous pressure during the relaxation phase in turn favours the flow of venous blood from the superficial to the deep system via the perforating veins.

Additionally during respiration, the inspiratory expansion of the thorax decreases the intra-thoracic pressure which augments antegrade venous blood flow from the peripheries towards the heart. The success of this mechanism also relies on competent venous valves preventing retrograde flow.

Venous Insufficiency

Venous insufficiency also known as venous incompetence or reflux occurs when the veins become diseased with derangement of normal antegrade blood flow. This results from venous obstruction, venous reflux, calf muscle pump dysfunction or a combination of such factors. Failure of adequate venous return coupled with retrograde turbulent blood flow within the vessels results in venous hypertension, which is strongly implicated in the development of venous insufficiency. Cutaneous telangiectasia and subcutaneous varicose veins are usually classed as primary venous insufficiency and limbs with progressive skin changes of hyperpigmentation, oedema,

healed or active venous ulceration collectively referred to as chronic venous insufficiency (CVI). These clinical manifestations are associated with varying severity of symptoms which affect the patient's quality of life (QoL)[33-37].

Primary Venous Insufficiency

Venous system dysfunction occurs following injury to vein walls and its valves. The principal attribute for such occurrence is inflammation, rather than it being a secondary change as postulated by the classical 'descending theory' of proximal valve failure with propagation of increasing venous pressure down the venous axis that causes dilatation and degradation of vein walls and consecutive valves. The descending theory simplifies the most commonly seen patterns of SVI with junctional valve failure, supported by the pathological findings of absence, deformity, distortion of vein valves seen both macroscopically and angioscopically[38 39]; in addition to the structural changes and inflammatory infiltration seen at the cellular level[40 41]. However patterns of reflux seen in some varicose veins such as those with no incompetence in the trunks or at junctions or perforators, and incompetent distended trunks distal to competent valves, cannot simply be explained by the 'descending theory' of primary mechanical failure of junctional valves.

Recent research has alluded to the existence of a vicious cycle (Figure 1) of inflammation causing structural damage and weakening of valves and vein walls, which in turn causes progressive worsening of venous hypertension which then further aggravates inflammation. Though this cycle can be initiated at any point in the pathogenesis of venous insufficiency, it is often found to be multifocal with progression of the disease over time. Non-acquired factors such as heredity, obesity, female gender, pregnancy, standing occupation more so in women also contribute to such injury.

The earliest signs of venous insufficiency are elongated and dilated intradermal venules less than 1mm in diameter called *telengiectasias* (thread veins, spider veins, and hyphen webs). Slightly deeper and under the skin are small dilated, often tortuous "bluish" subdermal veins measuring between 1 and 2.9mm in diameter known as the *reticular veins.* Still deeper but superficial to the superficial fascia are the subcutaneous *varicose veins* which are dilated veins 3mm in diameter or larger, frequently elongated and tortuous, with intermittent "blowouts", but are truly defined by the presence of reflux and may be tubular in morphology[42].

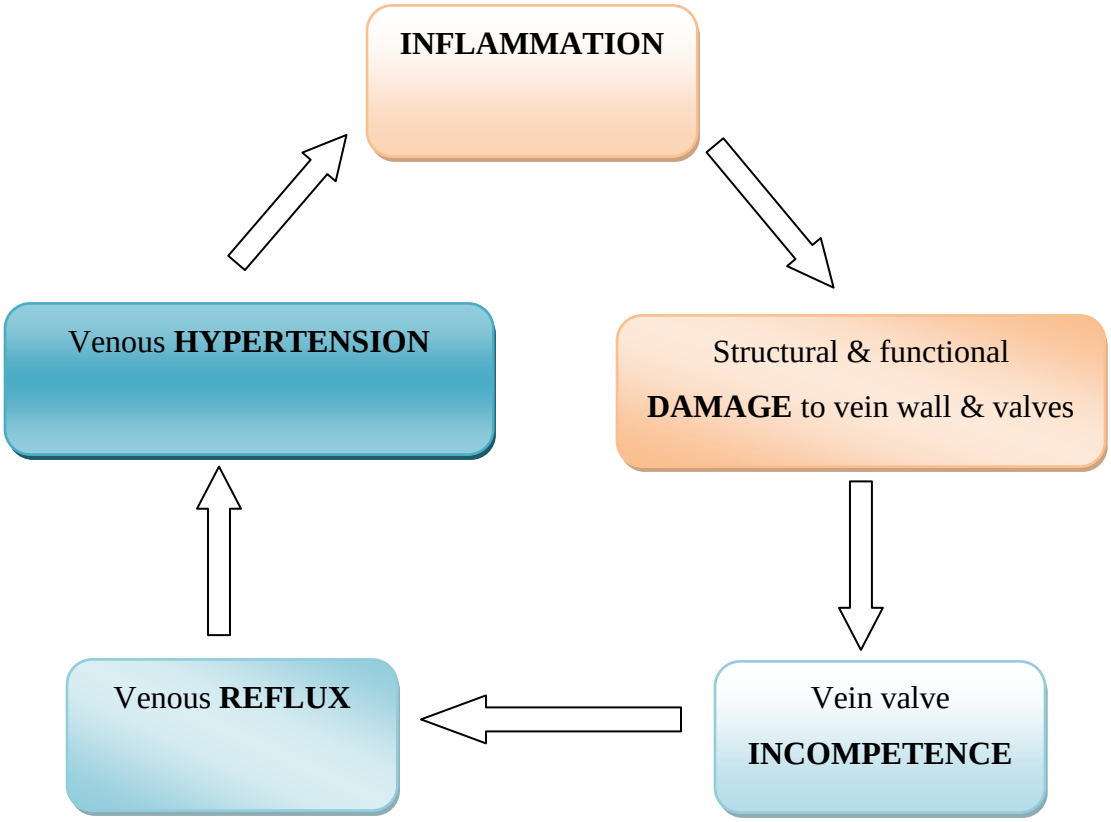


Figure 1: pathophysiologic cycle of primary venous insufficiency.

Inflammation and damage of venous structures

It is not clear as to what triggers the pathological cycle of venous insufficiency, but it is possible that venous stasis and hypertension causes a mechanical stress dependent change in shear stress and venous wall hypoxia[43 44]. Prolonged high pressure on the venous endothelium causes an imbalance in the endogenous humoral control of venous tone thereby causing venous wall relaxation. Over distension in turn causes release of inflammatory mediators and growth factors[43-46]. Leukocytes, mast cells and macrophages migrate to such areas of inflammation[47-52] and release superoxide anions and proteases which act by breaking down the extracellular matrix, in turn weakening the structural integrity of the vein wall[43 44]. The growth factors trigger remodelling of vein wall structures[43-45], which become less elastic and stiffer due to smooth muscle proliferation, collagen imbalance (increase in type I and decrease in type III)[53] and a reduction in the elastin content of the tunica media. The inelasticity is augmented by fragmentation of collagen and elastic lamina[32 54-58]. The proliferated smooth muscles are themselves dysfunctional due to dedifferentiation and structural disorganization causing impaired contractile function[59 60]. The overall consequence to the vein wall is a patchy distribution of stiffened inelastic media interspersed with structurally weakened media, prone to distension, which gives varicose veins their classical dilated, tortuous appearance. The macrophages also elaborate matrix metalloproteinases (MMPs) which cause further damage to the extracellular matrix by destroying elastin and possibly also collagen[61 62]. In health, the structural matrix of the vein is established by the competing action of MMPs and their tissue inhibitors (TIMPs). Normal homeostasis depends on the balance between MMPs and TIMPs actions[45 61-63]. Inflammation and vein wall tension[64-66] causes imbalance of this mechanism causing reduction in venous tone and resulting in varicose veins[47-49 64].

Chronic Venous Insufficiency

Venous incompetence precludes a fall in superficial venous pressure during exercise, resulting in ambulatory venous hypertension which is strongly implicated in the development of chronic venous insufficiency (CVI). Clinically apparent oedema, skin changes of hyperpigmentation, scarring from previous ulceration and active ulceration are grouped under CVI. Patients with an ambulatory venous pressure (AVP) of less than 30 mmHg have a negligible incidence of ulceration as compared to 100% incidence of venous ulceration in those with AVP of greater than 90 mmHg[67 68]. The AVP generated by the refluxing blood at the junction, is in the larger axial veins, which can distribute the pressure widely through its numerous tributaries; however at the ankles, the pressure transmitted outwards is through short wide perforators or veins that drain directly into the adjacent capillary bed and hence the effects of venous pressure leak here is likely to be more damaging than proximally in the leg. Similarly, incompetence of the deep veins has a more severe effect on the skin of 'gaiter areas' than that due to superficial incompetence only. Reflux in the popliteal and infrapopliteal veins are believed to be more pertinent than reflux in the proximal deep veins in the development of advanced CVI[69]. Although, the spectrum of skin changes of CVI can result from superficial incompetence alone with an intact deep venous system[70-74].

Venous hypertension causes an increase in capillary hydrostatic pressure thereby causing an imbalance in the net hydrostatic pressure across the capillary walls. This causes an increase in the movement of protein-free plasma into the interstitial space causing oedema. The process of trophic skin changes seen in CVI are explained by two main hypotheses: the 'fibrin cuff' and 'white blood cell trapping' theories.

The Fibrin Cuff Hypothesis[75] **–** postulates that the increase in AVP is transmitted to capillaries[48] resulting in elongation and convolution of capillaries with widening of pores between endothelial cells[76], allowing the exudation of fibrin, extracellular

matrix proteins, leucocytes, platelet activators and inflammatory cells[77]. This along with defective fibrinolysis[78] causes fibrin cuffs to form around the capillaries, which act as a barrier to oxygen and nutrient exchange resulting in tissue ischaemia and cell death[75 79]. Although a true pericapillary fibrin cuff has been identified histologically, perimalleolar tissue hypoxia has not been conclusively demonstrated.

White Blood Cell Trapping Hypothesis[80] **–** the more recent and accepted of the two theories is based upon the observation that the returning venous blood from the feet that have been passively dependent for up to an hour is depleted of leucocytes, especially in patients with CVI[80 81]. Venous hypertension causes sequestration of leucocytes in the microcirculation of the leg. This is likely due to leucocyte adhesion to capillary endothelium facilitated by decreased shear force[82] and increase in adhesion-molecules in response to venous hypertension[83-85]. Simultaneous increase in the plasma levels of soluble adhesion molecules demonstrates the shedding of these leucocyte surface molecules during leucocyte-endothelial adhesion[83 84]. Following trapping, these leucocytes migrate to the interstitium, become inappropriately activated and release lysosomal enzymes which cause tissue destruction, apparent as skin changes[86-89]. During inflammation, tissue injury is mediated by increased activity of MMPs (especially MMP-2) as observed in lipodermatosclerosis[90] and venous ulcers[91 92]. In contrast, the levels of TIMP-2 are lower in the above conditions[90 91], resulting in unrestrained activity of MMPs, breaking down extracellular matrix and promoting ulcer formation.

Clinical features of chronic venous hypertension vary from mild brown pigmentation of skin to active ulcers. The sustained high venous pressure at the ankle causes extravasation of red blood cells out of skin capillaries where the haemoglobin is broken down to haemosiderin giving rise to a brown discoloration of the skin. This is an early sign of skin injury and rather than being a cosmetic problem, this process may cause oxidative stress, MMP activation and creation of a microenvironment that

causes further tissue damage and delay healing. Eczematous patches may develop as dry, pigmented, scaly lesions over enlarged varices or over the perimalleolar region. This is followed by a more serious stage of lipodermatosclerosis, which can be considered the clinical precursor of venous ulcers.

EPIDEMIOLOGY & RISK FACTORS

Epidemiology

Venous disease of the lower limbs is a common condition in the western world; data from elsewhere is scarce and the true global magnitude of the problem is unknown. Even in the developed west, the chronic non-critical nature of the problem renders its magnitude to be inaccurately estimated. Published epidemiological literature on prevalence estimates vary because of differences in the methods of evaluation, definitions, and the geographic regions assessed, thus making comparison of available data difficult[93]. The prevalence of varicose veins reported in such studies ranges from 2%-56% in men and from 1%-60% in women[94] (Table 1). Prevalence estimates of CVI also vary, from < 1% to 17% in men and < 1% to 40% in women. Reported estimates of CVI are interdependent on the inclusion (or exclusion) of clinical features defining CVI; studies limiting classification to an active, visible or healed ulcer, report a relatively lower occurrence when compared to those that included the spectrum of hyperpigmentation, eczema, and varicose veins to its clinical definition[93] (Table 2).

Of the population based surveys conducted to date[1 95-100], only a few have measured the incidence of varicose veins and/or CVI. In the Framingham epidemiological study conducted in USA, participants were clinically examined for visible varicosities every second year over a period of 16 years; the incidence of varicose veins was estimated at 1.9% in men and 2.9% in women (aged between 40 and 89). The two year incidence of VVs was 39 per 1000 years in men and 52 per 1000 years in women[101]. In the Edinburgh Vein study, a cohort study of random samples of the general

population of Scotland, the 13-year follow-up examination results showed an annual incidence of varicose veins (C2) of 1.4% (incidence being similar in both men and women) and the age-adjusted incidence over the same period of 15.2% in men and 17.4% in women. The annual incidence of CVI was 0.7% (incidence being similar in men and women). The incidence of both VVs and CVI was found to consistently increase with age over the follow-up period.

Table 1: Summary of reported studies estimating prevalence of varicose veins[94]

Author et al.	Year	Country	Study Sample	Prevalence (%)	
				Men	Women
Lake	1942	United Sates	536	40.7	73.2
Arnoldi	1958	Denmark	1684	18.4	38
Bobek	1966	Bohemia	15060	6.6	14.1
Mekky	1969	England	504		32.1
Mekky	1969	Egypt	467		5.8
Prior	1970	New Zealand	232	25	42
Malhotra	1972	N. India	354	6.8	
	1972	S. India	323	25.1	
Coon	1973	United Sates	6,389	12.9	25.9
Guberan	1973	Switzerland	610		29
DaSilva	1974	Switzerland	4376	57	68
Stanhope	1975	New Guinea	728	5	0.1
Beaglehole	1975	Tokelau Island	786	2.9	0.8
		Cook Island	377	2.1	4.0
			417	15.6	14.9
		New Zealand	721	33.4	43.7
			356	19.6	37.8
Richardson	1977	Tanzania	1259	6.1	5.0
Widmer	1978	Switzerland	4529	56	55
Ducimetiere	1981	France	7425	26.2	
Stvrtinova	1981	Czechoslovakia	696		60.5
Abramson	1981	Israel	4802	10.4	29.5
Maffei	1986	Brazil	1755	37.9	50.9
Novo	1988	Sicily	1122	19.3	46.2
Leipnitz	1989	Germany	2821	14.5	29
Hirai	1990	Japan	541		45
Franks	1992	England	1338	17.4	31.6

Laurikka	1993	Finland	5568	18	42
Komsuoglu	1994	Turkey	856	34.5	38.3
Sisto	1995	Finland	8000	6.8	24.6
Canonico	1998	Italy	1319	17	35.2
Evans	1999	Scotland	1566	39.7	32.2
Kontosic	2000	Croatia	1324	18.9	34.6
Criqui	2003	United States	2211	15	27.7
Maurins	2008	Germany	3072		31.4

Table 2 Summary of studies estimating prevalence of clinical manifestations of CVI[93]

Author et al.	**Year**	**CVI manifestations**	**Prevalence (%)**	
			Men	**Women**
Arnoldi	1958	Active or healed ulcer	1.9	5.5
Bobek	1966	Active or healed ulcer	0.9	1.1
Mekky	1969	Hyperpigmentation, ulcer, edema, and eczema		10
Coon	1973	Stasis skin change	3	3.7
		Active or healed ulcer	0.1	0.3
DaSilva	1974	Dilated subcutaneous veins	10	15
		Hyperpigmentation	8.7	9.6
		Active or healed ulcer	1.1	1.4
Widmer	1978	Skin changes	6	5
		Active or healed ulcer	1	1
Maffei	1986	Oedema	17.1	20.3
		Hyperpigmentation	7.6	5.2
		Eczema	2.5	1.1
		Fibrosis	1.3	0.5
		Active or healed ulcer	2.5	4.1
Franks	1992	Active or healed ulcer	4.7	4
Komsuoglu	1994	Hyperpigmentation	0.3	2.8
		Eczema	0.5	1.8
		Active or healed ulcer	0.6	1.4
Evans	1999	Dilated subcutaneous veins	6.9	5.3
Ruckley	2002	Hyperpigmentation	1.3	1.1
		Active or healed ulcer	1	0.2
Criqui	2003	Trophic changes	7.8	5.3
		Oedema	7.4	4.9

Risk Factors and Associations

There are many hypothesis concerning the risk factors and/or associations for the development of varicose veins, mostly based on their pathophysiological plausibility. Much of the evidence ascertained from epidemiological data is old, involving highly selected groups that failed to control for potential confounding factors such as age[102-104], which has a strong association with venous insufficiency. Other important risk factors for primary varicose veins are female gender, pregnancy, family history of varicose veins, obesity (especially in women), taller in height, and lifestyle factors such as prolonged standing, heavy lifting as discussed below[98 102 104-106].

Age

There is consistent evidence that all levels of visible and functional venous disease in both sexes increase with age[1 96-101 103 104 107-111]. Studies such as the Edinburgh and Bonn vein studies established definitive correlation between the prevalence of SVI and increasing age. In the Tampere varicose vein study, a Finnish study, the highest incidence was in the cohort of 50-year olds compared to cohorts of 40 and 60-year olds, with statistically significant difference reached only in women. In contrast a Turkish study on population aged 60 or over found the increase in prevalence of varicose veins to rise with age, only in men and not in women; the prevalence was higher in the 70 to 79-year subgroup of women compared to the over 80 year olds. Despite such variation in reported population based studies, multiple logistic regression analyses to estimate the independent effect of risk factors upon clinical disease does confirm the significant association of age and clinical venous disease (Tables 3 – 5). Excluding congenital venous malformations, venous dysfunction has been shown to occur early in life, with the Bochum (I-III) study reporting saphenous incompetence on plethysmographic evaluation in 2.5% of a cohort of school children aged 10-12 years, increasing to 12.3% after 2 years and 19.8% by the age of 18-20 years. In the same group, visible varicose veins were seen in 2.5% of 14-16 year olds

increasing to 8.3% by the age of 18-20 years[112]. Age has also been reported to be a risk factor for progression from uncomplicated to complicated venous disease[103]; prevalence of venous ulcers, the worse extreme in the spectrum of CVI is less common below the age of 60 and hence its occurrence seems to exponentially increase after this age[100 113-115]. This association of worsening disease severity with age equates to overall clinical deterioration of patients with untreated venous disease with time.

Table 3: Independent odds ratios (95% CI) for proposed risk factors in 5326 eligible individuals in the Tampere varicose vein study[98]

Determinant of varicose veins	**Odds Ratio**	**95% confidence interval**
Sex:		
Male	1.0	
Female	2.3	(1.8-2.9)
Age (Years):		
40	1.0	
50	2.2	(1.9-2.6)
60	2.8	(2.4-3.3)
Weight (Kg):		
≤ 65 (W) or ≤ 80 (M)	1.0	
≥ 65 (W) or ≥ 80 (M)	1.2	(1.1-1.4)
Height (cm):		
≤ 165 (W) or ≤ 175 (M)	1.0	
≥ 165 (W) or ≥ 175 (M)	1.4	(1.2-1.6)
Posture at work:		
Sedentary	1.0	
Mainly standing	1.6	(1.4-1.8)
Varicose veins in parents or siblings:		
Negative	1.0	
Positive	4.9	(4.2-5.7)
Unknown	2.6	(2.2-3.2)

Parity:		
None	1.0	
1 birth	1.2	(1.0-1.6)
2 births	1.7	(1.3-2.1)
3 births	1.9	(1.4-2.5)
≥ 4 births	2.7	(1.9-3.9)

Table 4: Comparative proportions (%) by gender for etiologic risk factors for varicose veins in the Tampere study[98].

Risk Indicators	Men	Women
Age 50 years	23	12
Age 60 years	21	18
Varicose veins in parents or siblings	38	31
Weight > 65 kg (W) or > 80 kg (M)	12	12
Height > 165 cm (W) or > 175 cm (M)	14	4
Standing type of work	12	15
Births	NA	24

Table 5: Independent odds ratios (95% CI) for proposed risk factors for varicose veins in a population based study in France[116].

Risk Factors for varicose Veins	Men OR (95% CI)	Women OR (95% CI)
Age (Years)	1.05 (1.02-1.07)	1.04 (1.02-1.05)
Family History of varicose veins	3.53 (1.91-6.54)	3.47 (2.38-5.07)
History of thromboembolic disease	1.58 (0.22-5.29)	1.93 (0.66-5.72)
≥ 1 pregnancies	NA	1.98 (1.20-3.25)
Activity (prolonged sitting or standing)	1.48 (0.80-2.72)	1.16 (0.78-1.73)
Exercise less than once a week	1.97 (1.08-3.61)	0.87 (0.59-1.30)
Height >1.65 m	1.62 (0.67-2.46)	1.32 (1.08-1.62)
Body mass index >23 kg/m^2	0.73 (0.40-1.44)	0.93 (0.61-1.43)

Logistic regression adjusted for the geographic area, smoking status, alcohol use, education, occupation and oestrogen therapy (women only); not significant and not shown in table

Gender

A large number of population based studies have reported a higher overall prevalence of varicose veins in women than men[95 96 99 100 108 110 116-121], but in some studies the difference between genders was either not statistically significant[122 123] or conversely

the prevalence was found to be higher in men[1 124-126]. Such disagreement in the prevalence of varicose veins may be multifactorial as discussed below.

One of the most representative population-based chronic venous disease studies, the Edinburgh Vein Study[107] from Great Britain showed that a greater proportion of men demonstrated SVI and suffered from CVI. This study showed a significant increase in prevalence of chronic venous disease with age in men; whether this increased risk for disease progression in men is relative to greater tendency in women to seek treatment at an earlier stage of disease and thereby halting disease progression or based on pathophysiologic gender difference is not clear. In the same study men did have a higher prevalence of deep venous insufficiency (DVI), similar to the results for men under the age of 60 in the Bonn Vein Study[121] (Tables 6 and 7), which may partly explain the gender-related difference for CVI prevalence. Age may also contribute to the disagreement in the prevalence; the Bonn Vein Study showed no significant difference in the prevalence of SVI in both sexes under the age of 60 years (Table 7). However the rate of disease progression may be greater in women causing a divergent increasing trend in the prevalence of VVs and CVI in women after the age of 55 years. Similarly the French population study[116] showed that the overall prevalence was higher in women, however a significant difference was seen only in the distribution pattern of non-saphenous varicosities, which incriminates the distribution pattern of varicose veins as one of the contributory determinants of prevalence in population based studies. The same study also showed the occurrence of symptoms with both saphenous and non-saphenous varicosities, with a higher proportion of women being symptomatic as compared to men (symptomatic women: Saphenous - 70.1%, non-saphenous - 63.7%; symptomatic men: Saphenous - 36.4%, non-saphenous - 34.0%), which is perhaps why women seek treatment more commonly and earlier.

Table 6: Gender specific reflux prevalence in superficial and deep veins in the Bonn Vein Study[121].

Venous Systems	Male (n=1694) % (95%CI)	Female (n=1322) % (95%CI)
Superficial (overall)*	17.7 (15.7-19.9)	23.5 (21.5-25.7)
GSV (Proximal)*	11.8 (10.1-13.6)	16.4 (14.7-18.3)
GSV (Knee)*	9.3 (7.8-11.0)	15.1 (13.5-17.0)
SSV	3.5 (2.6-4.6)	3.5 (2.7-4.5)
Deep (overall)*	23.1 (20.9-25.5)	17.6 (15.8-19.5)
SFV*	14.7 (12.8-16.7)	11.1 (9.7-12.7)
PV*	11.0 (9.4-12.8)	7.2 (6.0-8.5)
PTV	1.0 (0.5-1.7)	0.5 (0.2-1.0)

Venous reflux defined as >0.5s on DUS. GSV – Great saphenous vein, SSV – Small saphenous vein, SFV – Superficial femoral vein, PV – Popliteal vein, PTV – Posterior tibial vein. *indicates statistically significant difference between men and women ($P < 0.05$).

Table 7: Age and Gender specific venous reflux prevalence in superficial and deep venous segments in the Bonn Vein Study[121].

	17-39 y %(95%CI)		**40-59 y %(95%CI)**		**60-80 y % (95%CI)**	
	Male (n=446)	Female (n=567)	Male (n=479)	Female (n=649)	Male (n=397)	Female (n=478)
Superficial (overall)	12.6 (9.6-16.0)	12.6 (10.0-15.6)	17.6 (14.3-21.3)	21.8 (18.7-25.2)	**23.7 (19.5-28.2)**	**39.1 (34.7-43.7)**
GSV (proximal)	9.6 (7.1-12.8)	10.3 (7.9-13.1)	12.8 (9.9-16.1)	14.0 (11.4-16.9)	**13.0 (9.8-16.7)**	**27.1 (23.1-31.3)**
GSV (knee)	3.2 (1.7-5.2)	6.7 (4.8-9.1)	10.9 (8.3-14.1)	13.9 (11.3-16.8)	**14.3 (11.0-18.2)**	**27.2 (23.2-31.5)**
SSV	2.2 (1.1-4.1)	1.1 (0.4-2.3)	2.9 (1.6-4.9)	3.3 (2.0-4.9)	5.6 (3.5-8.3)	6.7 (4.7-9.4)
Deep (overall)	**26.1 (22.1-30.5)**	**17.9 (14.8-21.3)**	**22.4 (18.7-26.4)**	**13.9 (11.3-16.8)**	20.7 (16.8-25.0)	22.3 (18.6-26.3)
SFV	18.6 (15.1-22.5)	13.4 (10.7-16.5)	**14.0 (11.0-17.1)**	**7.6 (5.7-9.9)**	11.1 (8.2-14.6)	13.3 (10.3-16.6)
PV	9.5 (6.9-12.6)	4.8 (3.2-6.9)	10.9 (8.2-14.0)	6.6 (4.8-8.8)	12.9 (9.7-16.6)	10.7 (8.1-13.8)
PTV	0.4 (0.1-1.6)	0.2 (0-1.0)	0.6 (0.1-1.8)	0.6 (0.2-1.6)	2.0 (0.9-4.0)	0.8 (0.2-2.2)

Venous reflux defined as >0.5s on DUS. GSV – Great saphenous vein, SSV – Small saphenous vein, SFV – Superficial femoral vein, PV – Popliteal vein, PTV – Posterior tibial vein. Figures in bold indicates statistically significant difference between men and women ($P < 0.05$).

Pregnancy and Female Hormones

Both physiologic states such as pregnancy, menopause and iatrogenic states due to hormone treatment, where in the levels of female hormones - oestrogen and progesterone are far greater than normal have been associated with varicose veins.

Pregnancy: multiparity has been associated with a greater prevalence of varicose veins than nulliparity[96 98 109 116 122 127-130]. Studies have even shown a proportional increase in the incidence with the number of full-term pregnancies[98 99 110 122 130 131]. In the Finnish population-based study[99], multi-adjusted odds ratio for varicose veins increased from 1.4 (95% CI 1.0-1.9) to 3.0 (95% CI 2.3-4.1) in women with one child or up to five children respectively in comparison to nulliparous women. A minority of studies[95 117 132] including the Edinburgh Vein Study[1], however did not find a significant association between prevalence and parity. This may have been due to failure to control for the confounding factor of age[102 105].

Popular explanation for the association of varicose veins and pregnancy is the increase in intra-abdominal pressure with the enlarging uterus which impedes venous return[133 134]. The contention to this hypothesis is that the varicose veins develop even prior to significant uterine enlargement suggesting the contribution of other factors[93]. There is a significant increase in blood volume secondary to plasma expansion during early pregnancy, causing an increased strain upon the capacitance of the venous system[135]. In addition, hormones associated with pregnancy such as relaxin and oestrogen mediate vasodilatation which in turn results in increased venous stasis and valvular dysfunction[136-139]. Progesterone is yet another hormone which is known to

weaken the structural integrity of vessel walls[137 139 140]. Both oestrogen and progesterone levels increase rapidly in early pregnancy.

Oral Contraceptives and Hormone Replacement Therapy (HRT): while a study from the USA[131] found an increased prevalence of telangiectasia and varicose veins in the population using the contraceptive pill, no such association was found in other population based studies[99 104 105 141]. Similarly the association of HRT in menopausal women and varicose veins has been inconsistent. Some studies have shown a significant difference in the age-adjusted prevalence of VVs in women (50 years or over) taking HRT as compared to those not exposed[99 120]. However such evidence was lacking in other studies[116], with the Edinburgh Vein Study even showing a reduced risk of trunk varices with the use of HRT[105].

Heredity

Familial predisposition to venous disease has been proposed for at least a century. However most of the available information is based on subject recollection in questionnaire based surveys rather than objective verification[117 142]. This information may be biased in that the varicose veins sufferers may only be more aware of other family members with similar problems than those not affected.[93]. In one of the studies[117], the correct reporting of varicosities ranged from 52% to 93%. Allowing for such reporting bias, there appears to be reasonable evidence of hereditary association with both varicose veins and CVI[95-98 101 104 116 143]. Both the Finnish and the French population based risk factor studies (Table 3-5) found that a positive family history of varicose veins in first-degree relatives was the strongest risk determinant, increasing the risk by up to 5 times[98 116].

There has also been disagreement on the heritability of venous disease; with studies contradicting each other on the dominant or recessive nature of inheritance[144] or the gene responsible for inheritance[145 146]. Although congenital syndromes associated

with venous disease are well recognized, no specific genetic mechanism has been found to associate heritability with primary venous insufficiency. Studies have hypothesized polygenic inheritance[147 148]; the current consensus is that both environmental and genetic factors are interlinked in the development of varicose veins[61 145 149]

Geography / Race

Occurrence of varicose veins has been studied in both general population and defined population groups. There are geographic variations in the occurrence of the disease, with studies suggesting that venous insufficiency is less common in the developing world as compared to Europe and North America; the variation being attributed to lifestyle factors such as high fibre diet and reduced constipation; less time spent standing; less tight fitting undergarments etc. There is however lack of substantive evidence and the reported difference could be due to differences in population sampling, definition and diagnosis of the condition and access to medical care, rather than an actual racial difference.

Body Mass Index and Height

The Bonn vein study found an association of increased SVI prevalence with a BMI of greater than 30[121]. Edinburgh and Framingham vein studies reported similar association only in women[1 101]. The reason for this gender difference was hypothesized to be due to increased availability of circulating oestrogen in obese women[93], which mediates vasodilatation leading onto venous stasis and valvular dysfunction[136-139]. The relatively higher prevalence found may also be due to obese women reporting varicose veins more often[150]. It is debatable however as to whether obesity worsens the symptoms / severity of venous disease or whether obesity causes general leg symptoms often incorrectly attributed to venous origin. Current evidence

for association of BMI with venous disease is weak as some studies report an association[96 99 104 121 128 134 151] and some do not[102 109 122 127 132].

Both the Edinburgh and Tampere vein studies showed a significant relationship between greater height and truncal varicosities in both sexes[98 105]. In the Tampere study (Table 3) height was also an independent determinant for varicose veins. Similar association was reported only in women in Finnish and French studies (Table 5)[99 116]; while no such association was found in either sexes in other population based studies[109 122 132]. Hence similar to BMI, the current evidence for association of height with venous insufficiency is weak.

Lifestyle

Western Lifestyle features such as low fibre highly refined diet, standing at work, sitting in chair, toilet posture, tight fitting undergarments, oral contraceptives, hormone replacement therapy, social class, education and smoking have all been implicated as potential risk factors for varicose veins[1 93 116 129 152], but not consistently proven in all epidemiological studies. Risk assessments of lifestyle factors are difficult to investigate as the information gathered by investigators are often self-reported by patients and difficult to quantify or verify.

Of the proposed lifestyle risk factors, popular ones are: association of diet deficient in fibre-rich plant foods and consequent constipation as potential cause for varicose veins[152-154]; the suggested mechanism being a loaded colon compressing on the pelvis veins and the effect of increased intra-abdominal pressure on straining at stools[152]. The evidence for this is again weak as other studies including the Edinburgh Vein Study did not show any association between the prevalence of trunk varices and dietary fibre intake in either sex[96 111 119 155 156]. Significant associations have been reported with the level of physical activity: with protracted standing[1 96 99 101 127 131 141 157], work involving heavy lifting[117], and lack of regular exercise[101 116 128] being related

to a higher prevalence of varicose veins. The Edinburgh[102], Framingham[101] and Israeli[96] epidemiological vein studies reported decreased risk of trunk varices in women predominantly seated at work. Some of the above findings have not been corroborated by other population based studies[99 105 110].

1.3 MANAGEMENT OF SUPERFICIAL VENOUS INSUFFICIENCY

The objectives of effective management of patients with varicose veins are to control symptoms and prevent complications, thereby preserving their quality of life. In this process, clinical evaluation to detect, localize and quantify the problem is a critical starting point. Advances in imaging technology have made clinical diagnosis easier and much more precise than conventional examination alone. Non-invasive methods such as duplex ultrasonography has made identification of underlying pathophysiology and the extent of disease process relatively simple, which in turn has facilitated selection of the most appropriate treatment modality. History and physical examination are also important to grade and classify its diverse presentation in a standardized manner as discussed below.

History

A wide range of symptoms have been ascribed to CVI. Commonly reported symptoms are aching, cramping, tired legs, swelling, heaviness, itching and restless legs. Cosmetic concerns with visible varicosities may often be the only presenting symptom. The San Diego population based study[158] reported on the prevalence of symptoms in those with duplex proven functional disease and those with visible venous disease alone (Figures 2 and 3). Aching legs was by far the most commonly reported symptom and in both categories symptom prevalence increased with increasing severity of the disease; women reported symptoms to a greater extent as compared to men[159 160]. The aching pain is due to pressure exerted by the dilated vessels on the adjacent network of subcutaneous somatic nerve fibres; hence the classical complaint of aching legs worse towards the end of the day or following

prolonged standing and usually relieved by elevation of the leg[161]. Compression stockings seek to combat this relative venous hypertension and promote antegrade flow of blood from the legs. Relief of symptoms with compression stockings may therefore indicate that the symptoms may be of venous origin. History of deep venous thrombosis; bilateral limb swelling; previous trauma to the leg; risk factors such as family history of VVs, pregnancy, hormone use, obesity and hypercoagulability should be sought. Type of occupation, general health, life style and the effect of the problem on activities of daily living should be elicited in order to help decide the best available treatment. History of previous conservative or surgical treatments is also helpful in deciding the next appropriate form of treatment. Not infrequently symptoms associated with varicose veins are non-specific and does not correlate well with the presence or extent of varicosities. This often poor relationship has been reported in clinical and population based studies[162]. These observations have implications towards care of symptomatic patients with seemingly uncomplicated VVs who may be denied treatment on the NHS in some geographic areas of UK.

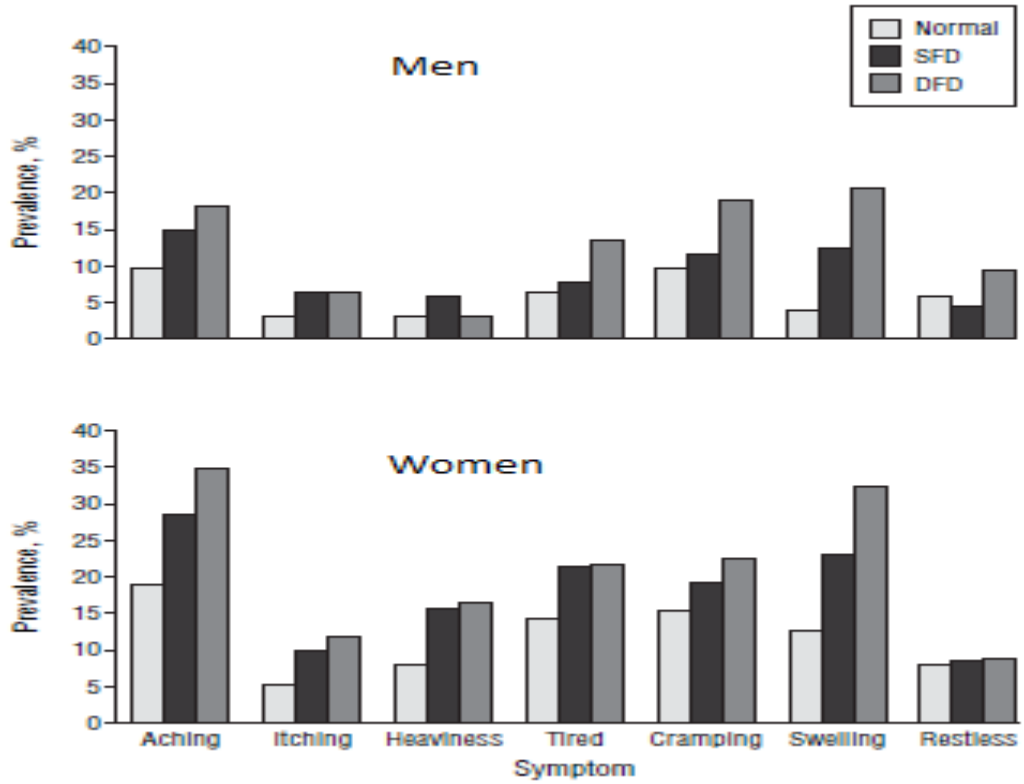


Figure 2: Prevalence of symptoms and functional venous disease by gender. San Diego Population Study[158].

SFD - superficial functional disease; DFD - deep functional disease.

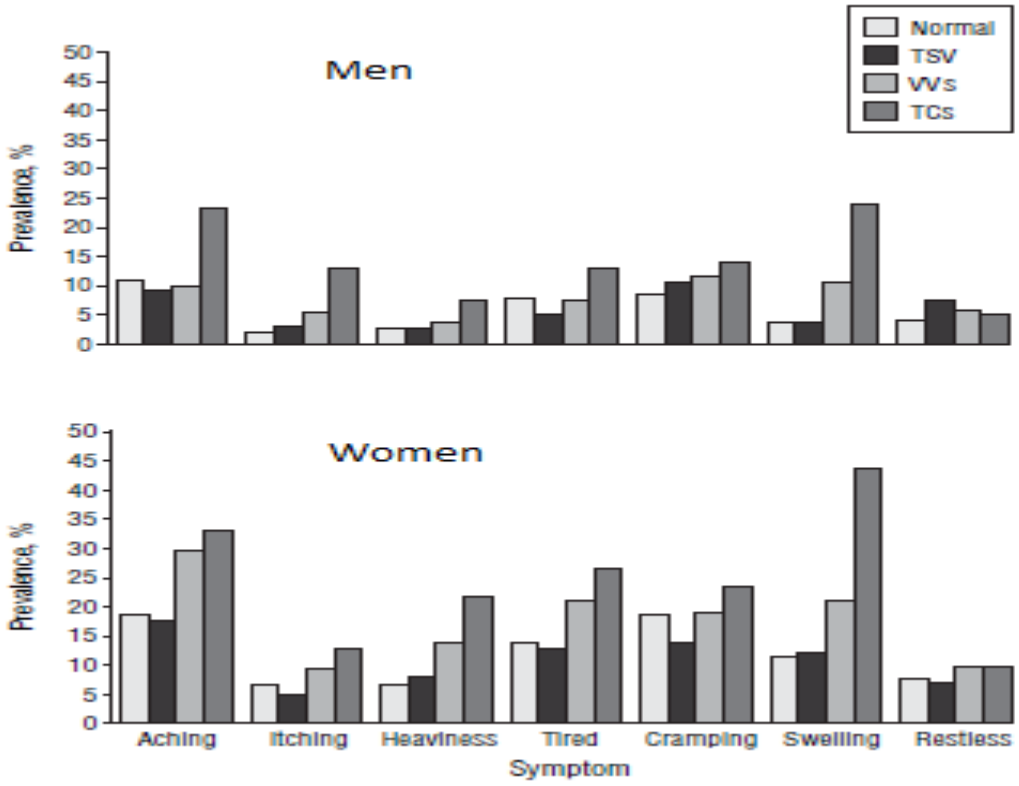


Figure 3: Prevalence of symptoms and visible venous disease by gender. San Diego Population Study[158].

TSVs - telangiectasias or spider veins; VV - varicose veins; and TCs - trophic changes.

Physical Examination

Examination of the limbs is best carried out in the standing position in a warm room, with good light[163]. Exposure from the umbilicus down to the toes facilitates examination over the front and the back, also allowing for comparison of the legs. Inspection and palpation are essential elements of the physical examination. Auscultation for presence of bruit may indicate varicose veins secondary to vascular malformations or arteriovenous fistulas.

Inspection: Distribution of visible varicosities may indicate the involvement of great saphenous or small saphenous venous system. Atypical distribution in areas such as the lower abdominal wall, pubis or bilateral varicosities may suggest co-existence of a secondary cause such as iliac vein obstruction or internal iliac vein or gonadal vein incompetence. Presence and distribution of stigmata of venous insufficiency such as telangiectasia (*thread veins* or *spider veins*), reticular veins, ankle swelling, pigmentation, corona phlebectatica (fan shaped pattern of telangiectasia on the ankle or foot thought to be an early sign of advanced venous disease), lipodermatosclerosis (diffuse fibrosis of skin and subcutaneous tissues accentuated by fat necrosis and chronic inflammatory changes), atrophie blanche (white skin patches due to reduced capillary numbers in areas of prior ulceration), eczema, dermatitis, skin discoloration, and signs of healed or active ulcers should be noted. Signs of varicose veins complications such as bleeding, superficial thrombophlebitis and venous hypertensive skin changes mentioned above are associated with significant morbidity and hence useful in guiding the urgency for treatment.

Palpation: Varicose veins can be palpated to confirm the distribution pattern as seen on inspection. A saphena varix (dilatation of saphenous vein at its junction with the CFV in the groin) could be clinically excluded by its compressible, reducible nature on lying, and palpable cough ‘thrill’. In addition examination of the peripheral pulses to exclude peripheral arterial disease and abdominal palpation to exclude any masses compressing on the IVC or iliac veins, precipitating venous hypertension should be undertaken. Classic tourniquet tests such as the Trendelenburg, Fegans and Perthes test to establish saphenous, perforator or deep venous incompetence have been described based on the anatomical and physiological principles underlying the development of venous disease. However these tests are rarely used in current clinical practice and are mostly of historical interest. Hand held Doppler is also used to complement physical examination; however a detailed and accurate evaluation

required for the planning of treatment is provided by the duplex ultrasound scan (DUS) which is considered the gold standard investigation for venous diseases.

Inspection, palpation and tourniquet tests may reveal dilated small saphenous vein (SSV) or tributaries behind the knee in the SSV territory, but do not provide any conclusive information on the competency of saphenopopliteal junction (SPJ). The hand-held Doppler, although considered by many to be a convenient way to record SPJ reflux, may however provide false-positive results that could lead to unnecessary popliteal fossa exploration in 10% of patients assessed by this method[164]. Also the variation in the anatomy of SPJ and its tributaries in the popliteal fossa cannot be ascertained by this method.

Duplex Ultrasound Scan (DUS)

DUS is the most frequently used and the recommended diagnostic investigation of first choice for all patients with suspected venous disease[165-167]. It is safe, non-invasive, cost-effective and reliable with a far superior diagnostic accuracy in the assessment of venous insufficiency as compared to continuous wave hand held Doppler[168 169]. It is labelled as the ideal non-invasive method to evaluate outcomes following treatment, giving both anatomic and haemodynamic information of the lower limb veins[3 165 166 170-174]. Serial DUS imaging can thus be invaluable in objectively understanding the patterns and causes of clinical recurrence[175].

Duplex doppler system uses conventional real-time B-mode (Brightness mode) to gather anatomical information of the site at which blood flow is to be examined and superimposes doppler information regarding the velocity and direction of blood flow onto the B-mode image. The ultrasound machine assigns colours to the magnitude of velocity and direction of flow, also known as colour doppler (Figures 4a, 4b). The colour is assigned on the basis of flow towards or away from the examining transducer. The image in a colour doppler is best understood as being formed of several pixels; flow in any pixel is detected and the velocity within the pixel which is

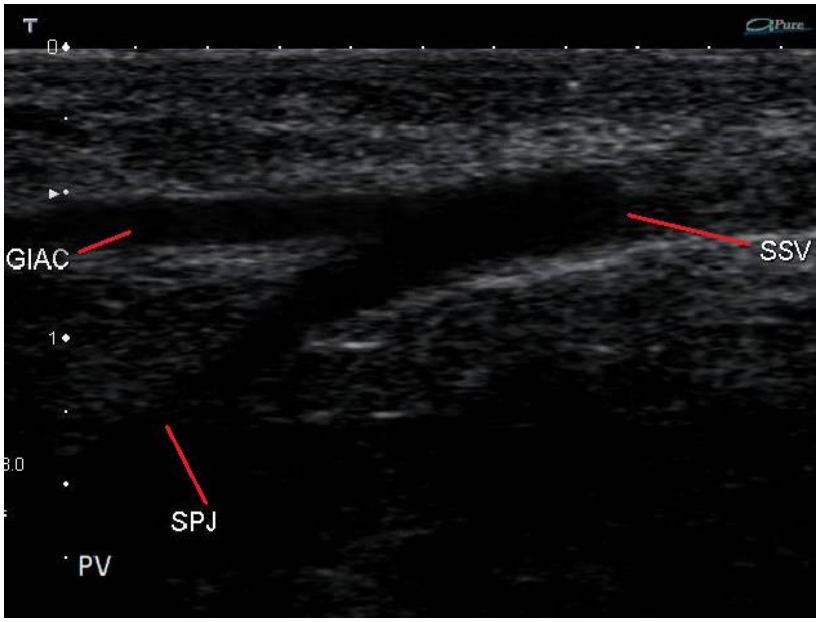
the average velocity of all movements within that pixel, is allocated a certain colour. The velocity component of the doppler beam and hence the allocated colours are interdependent on the direction of the beam (cosine θ dependence). Spectral doppler is another function that accurately computes velocity and direction of blood flow over time on a graph (Figure 5). Thus the combination of B-mode and doppler achieves an objective, detailed assessment of the anatomy and physiology of the venous system, making it the most frequently used and reported investigation. The Union Internationale de Phle´bologie (UIP) group has published consensus documents aiming to standardize the methods of DUS imaging and its reporting prior to and following treatment of lower limb varicose veins[165 175]. Such standardization measures also aims to address certain controversies such as DUS categorization of venous incompetence based on the interpretation of reflux duration. While most investigators accept reverse flow lasting more than 0.5 seconds to define significant superficial venous reflux, some argue that this "cut-off" duration may over estimate deep venous insufficiency (DVI). The Edinburgh vein study and the Bonn vein study saw little difference in prevalence of SVI based on 0.5 or 1.0 second thresholds for venous reflux[121 176]; however for the deep system, lowering the threshold to 0.5 seconds gave a two to four times increased prevalence of DVI. In the same studies, association of clinically evident venous disease with DUS reflux times showed a higher specificity for the 1.0 second cut-off threshold[107]. Hence the Society for Vascular Surgery and the American Venous Forum recommend threshold reflux duration of 1.0 second in the SFV and PV (deep veins) and 0.5 seconds in rest of the lower limb veins[167].

Clinical assessment with duplex ultrasound scan: A systematic DUS examination of the superficial and deep venous system helps delineate any segments of reflux or obstruction. Reflux can be elicited by the valsalva manoeuver (patient dependent) or calf compression and release (operator dependent) or by the use of standardized inflation/ deflation pneumatic cuff, where 95% of normal venous valves are expected

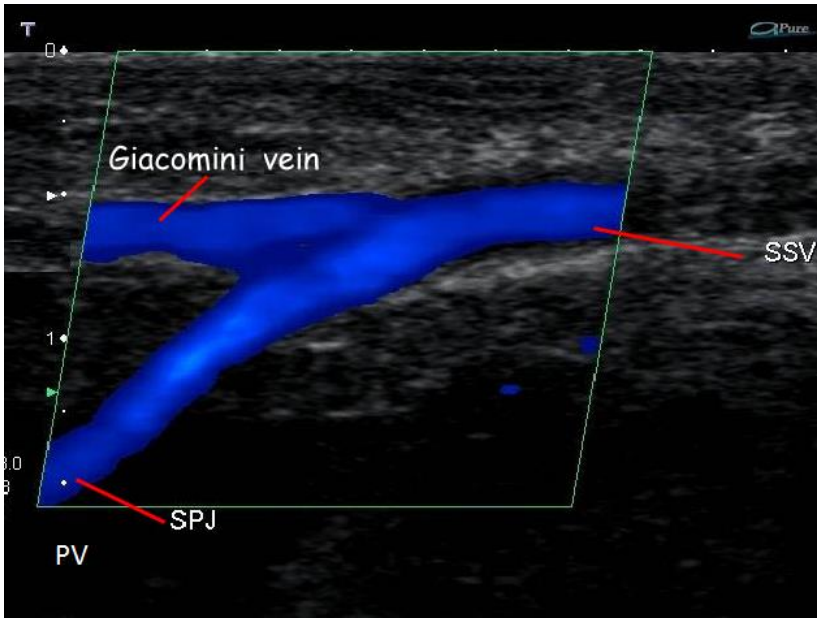
to close within 0.5 seconds of cuff deflation and any occurrence of prolonged retrograde flow can be demonstrated on the spectral display (Figure 5). The minimum requirements for pre-treatment DUS assessment as outlined by the UIP consensus document[175] are –

- Deep veins assessment for patency and reflux - common femoral vein (CFV) and popliteal vein
- Junctions assessment for reflux (terminal valve/pre-terminal valve) - saphenofemoral junction (SFJ) and saphenopopliteal junction (SPJ)
- Main trunks diameter measurement and assessment of reflux (in the saphenous compartment) - great saphenous vein (GSV), anterior accessory saphenous vein (AASV), posterior accessory saphenous vein (PASV), small saphenous vein (SSV), thigh extension of SSV/Giacomini vein
- Competency of tributaries and non-saphenous veins
- Perforating veins diameter measurement and assessment of reflux

Even though DUS is considered the gold standard investigation and widely available for the assessment of venous insufficiency, it does not grade the severity of venous reflux. Reflux duration, reflux velocity and even the calculated reflux volume have all been used to assess the severity of reflux[177]. These parameters at best provide a semiquantitative assessment of the severity of disease. There is weak correlation of the severity of disease by duplex imaging with both plethysmographic techniques and clinical manifestations.



4a



4b

Figure 4a: The Saphenopopliteal Junction (SPJ) in longitudinal section in B-mode and 4b: with colour Doppler.

SSV – small saphenous vein, PV – Popliteal vein.

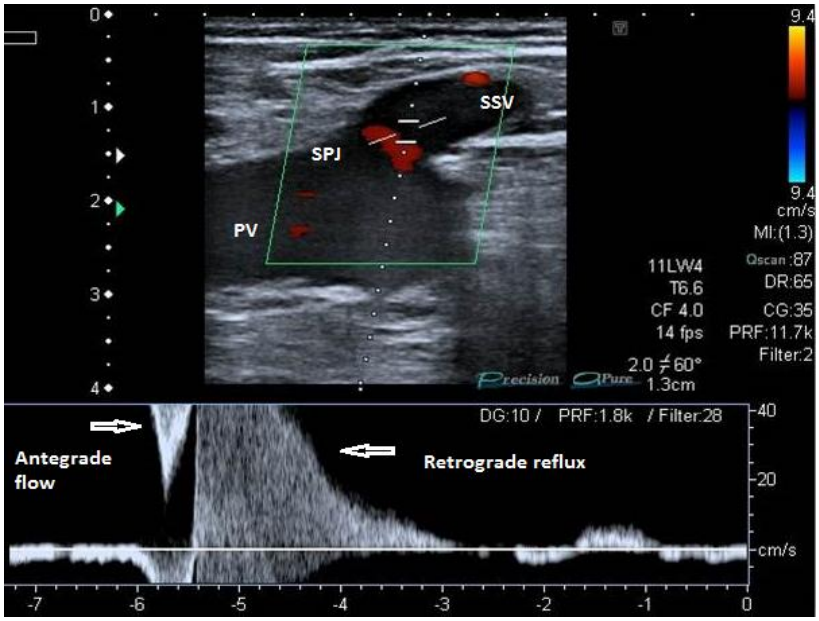


Figure 5: Spectral Doppler demonstrating SPJ incompetence with reflux into SSV in longitudinal section

Assessment of severity of venous reflux

DUS information is often adequate to guide treatment, however if the contribution of the extent of reflux to the global haemodynamics is required then further testing in the form of ambulatory venous pressure measurement and plethysmographic studies may be considered[177].

Ambulatory Venous Pressure (AVP): is the hemodynamic gold standard in assessing CVI[68]; it has been shown to be valuable in assessing its severity and clinical outcomes[67]. The technique involves insertion of a needle connected to a pressure transducer into the pedal vein. The pressure is charted at rest and after exercise (usually 10 tip toe movements) (Figure 6). The AVP (lowest pressure reached during exercise) and refill time (time taken to reach 90% of pre-exercise pedal venous pressure after exercise) are two parameters which have been shown to correlate with clinical severity of venous disease and the incidence of related complications.

Because of the invasive nature and alternative diagnostic modalities, AVP seldom is used in clinical practice.

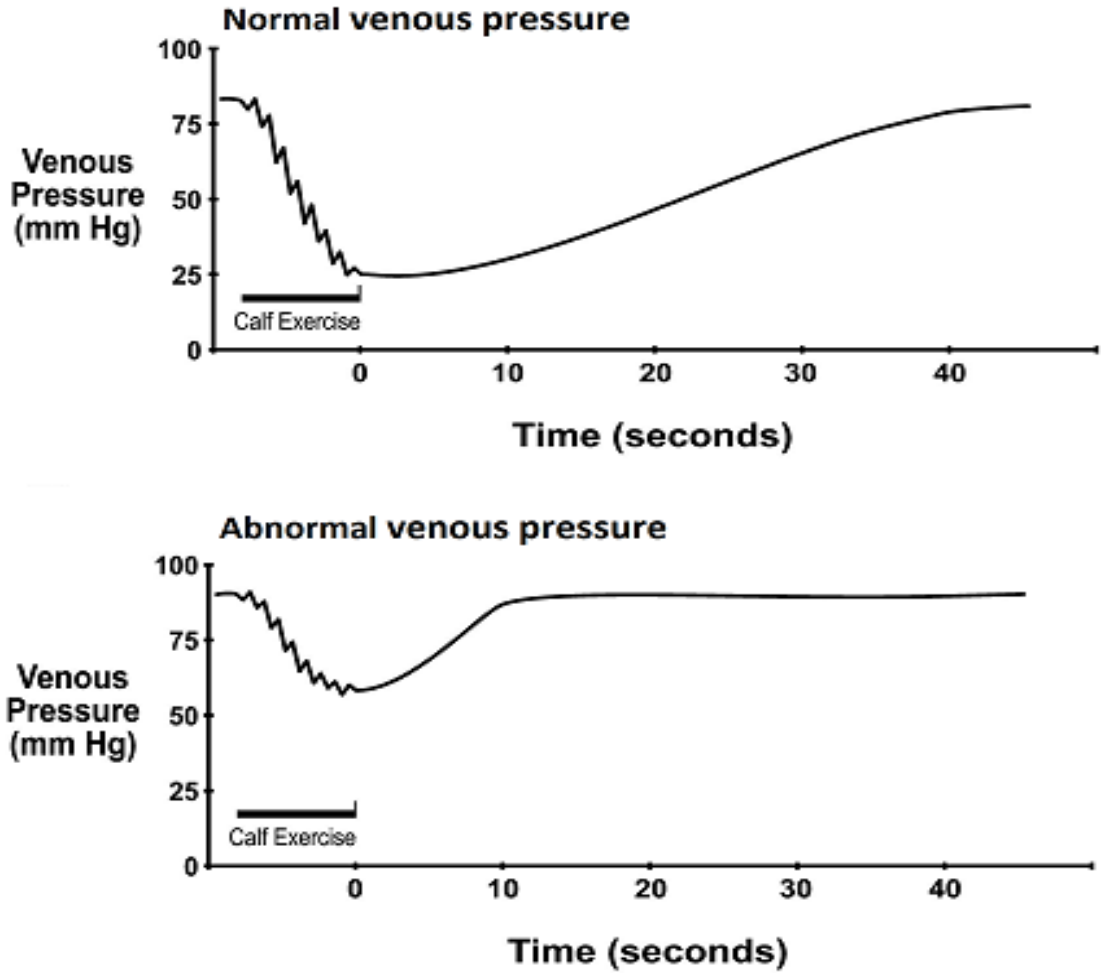


Figure 6: Illustrative ambulatory venous pressure measurements.

The resting standing normal venous pressure is ≈80-90 mm Hg. This pressure drops with calf exercise to ≈20-30 mm Hg (>50% decrease). The return in pressure is more gradual with refill taking >20 s. In deep venous reflux, drop in pressure with exercise is blunted (<50% decrease) - abnormal venous pressure. The return in venous pressure to the resting level is rapid because of a short refill time (<20 s).

Air-Plethysmography (APG): is a non-invasive investigation that provides quantitative information on various components of the calf-muscle pump, global venous reflux and venous outflow obstruction. Changes in limb volume are measured by air displacement in a cuff surrounding the calf during manoeuvres to empty and fill the venous system. The venous filling index (rate of venous reservoir filling as a result of standing); venous volume (amount of blood in the venous reservoir); the ejection volume and ejection fraction (as a result of a single tiptoe movement); the residual volume and residual volume fraction (as a result of 10 tiptoe movements) are all estimated. The venous filling index is the key parameter in the detection of abnormal reflux[178], and in combination with ejection capacity has been shown to correlate well with severity of reflux in CVI[179-181].

Photoplethysmography (PPG): is based on measurement of changes in the blood volume in limb dermis by measuring the backscatter of light emitted from a diode with a photosensor. A PPG probe is placed on the foot and calf muscle contraction manoeuvres undertaken to empty the foot. Venous refilling is detected by increased backscatter of light and the refill time is measured. A venous refill time >20 seconds suggests normal venous filling and time <18 to 20 seconds (dependent on the patient's position) is indicative of CVI[182 183]. The use of a tourniquet or low-pressure cuff also allows to distinguish between superficial and deep venous disease. Though the test does not provide information on specific anatomic distribution, information on regional venous function is accurate. A shorter rapid refill time suggests more severe reflux; however this is poorly correlated to the severity of disease[181]. PPG may provide an assessment of the overall physiological function of the venous system and is most useful to determine the absence or presence of disease[184].

Clinical assessment of disease severity

Clinical manifestation of venous insufficiency encompasses a spectrum of conditions ranging from simple telangiectasia or reticular veins to more advanced stages such as

skin fibrosis and venous ulceration. Early studies reported in literature lacked standardized definitions and classification systems that made estimation and comparison of disease severity unreliable. This was originally addressed by the Committee on Standards established by the Society for Vascular Surgery and the International Society for Cardiovascular Surgery. The original publication and its revision by an international consensus committee included detailed descriptive recommendations for venous manifestations[185]. A decade following the original consensus conference, its sponsor, the American Venous Forum (AVF), convened an international group to consider revision of the CEAP classification[42]. Publication of these documents in multiple international journals and widespread acceptance has resulted in international uniformity of the current literature focused on venous pathophysiology.

CEAP classification

The CEAP classification system (Table 8) defines the clinical class (C) or severity of venous disease, which is graded from 0 to 6. Each clinical subgroup can be followed by subscripts A or S to represent asymptomatic or symptomatic patients respectively; its aetiology (E), which is further subdivided into 3 main aetiological possibilities; anatomic (A) involvement; and pathology (P) indicating the pathophysiological cause for the underlying disease.

The CEAP classification encompasses the entire range of chronic venous disease and is a useful classification tool that allows comparison of outcomes between different studies. However some of the criticism to this system is that it is too precise and sometimes too elaborate for the purposes of clinical trials in a specific subgroup of patients; furthermore there is no grading of severity within each clinical class i.e. limbs with uncomplicated varicose veins are globally classed as C2 irrespective of the extent of varicosities. C4 class is also resistant to change and C5 class is permanent. These inherent resistances to clinically significant improvements following treatment

makes this classification system insensitive to changes observed in interventional studies[186-189].

Table 8: The revised CEAP classification[42]

Clinical	**C0**	**No visible / palpable signs of venous disease**
	C1	**Telangiectasia or reticular veins**
	C2	**Varicose veins**
	C3	**Oedema**
	C4a	**Pigmentation or eczema**
	C4b	**Lipodermatosclerosis or atrophy blanche**
	C5	**Healed venous ulcer**
	C6	**Active venous ulcer**
aEtiologic	Ec	Congenital
	Ep	Primary
	Es	Secondary (post-thrombotic)
	En	No venous cause
Anatomy	As	Superficial Veins
	Ap	Perforator veins
	Ad	Deep veins
	An	No venous cause
Pathology	Pr	Reflux / insufficiency
	Po	Obstruction
	Pn	No venous pathophysiology

Venous Clinical Severity Score

The American Venous Forum Committee on Venous Outcomes Assessment designed the Venous Clinical Severity Score (VCSS) to integrate directly with the CEAP clinical system. The measure was aimed at developing a system which was responsive to changes and provided a means of serial assessment of clinical findings commonly expected to change during the course of clinical observation and treatment[187 188 190]. The VCSS is heavily weighted toward the more severe features of CVI—inflammation, induration and ulceration (C4-C6 CEAP clinical class). Based on a maximal possible score of 30 generated by grading 9 different clinical characteristics of venous disease including the use of compression therapy (Table 9), disease is considered relatively severe in patients who generate scores greater than 8[186 187].

The criticism to the VCSS system arises from the inclusion of a simplified pain or discomfort estimation variable and the use of compression therapy. Pain or discomfort of venous origin is much clearly understood in context to the health related quality of life impairment it causes and is best measured using validated patient reported QoL instruments as discussed below. The use of compression is not standard practice and its use for control of symptoms relate to clinician and patient preference and compliance. Hence this variable may inadvertently result in differing VCSS outcomes for clinically similar patients due to differing compression practices thereby creating potential bias in comparative studies.

Table 9: The Venous Clinical Severity Score[190]

Component	Scores			
	0	1	2	3
Pain (or discomfort of presumed venous origin)	None	Occasional, not restricting ADL	Daily, interfering with ADL	Daily, limiting most or preventing ADL
Varicose veins (≥3mm)	None	Few, scattered, corona phlebectatica	Confined to thigh or calf	Involves thigh and calf
Oedema (of presumed venous origin)	None	Limited to foot and ankle	Extends above ankle, below knee	Extends to knee and above
Skin pigmentation (of presumed venous origin)	None or focal over a varicose vein	Peri-malleolar	Diffuse over lower third calf	Wider distribution above lower third calf
Inflammation	None	Peri-malleolar	Diffuse over lower third calf	Wider distribution above lower third calf
Induration (including lipodermatosclerosis and atrophy blanche)	None	Peri-malleolar	Diffuse over lower third calf	Wider distribution above lower third calf
Active ulcer(s)	0	1	2	>2
Active ulcer duration	NA	<3 months	3 months - 1 year	>1 year
Active ulcer diameter	NA	<2cm	2-6cm	>6cm
Use of compression therapy	None	Intermittent	Most days	Every day

Health related Quality of Life assessment

The treatment aim of venous disease is to improve QoL of the sufferer. In recent years, there has been much emphasis on QoL outcomes as one of the two important indices of treatment effectiveness; the other being the traditional clinical surrogate outcomes of technical success, complications and duplex imaging end points. Not only does such QoL outcomes provide valuable information on the patient-perceived burden of illness, but it is also essential for cost–utility analysis which is the underpinning attribute of economic evaluation in health technology assessment studies[191]. Thus it provides crucial information to both the user and providers of medical care, thereby facilitating appropriate allocation of limited health-care resources in the most cost-effective manner. In the UK, the concept of QoL has evolved from the confines of 'academic interest only' and it is now an essential component in the NHS to measure Health-Related Quality of Life (HR-QoL) before and after venous interventions[192 193].

QoL instruments are broadly categorized into those specific to a given disease and generic tools assessing the QoL impairment from any health condition. A number of validated questionnaires are in use for assessment of QoL in venous disease. The routinely used disease-specific questionnaires are Aberdeen Varicose Vein Questionnaire (AVVQ), Venous Insufficiency Epidemiological and Economic Study Symptom questionnaire (VEINES-Sym)[194], Chronic Venous Insufficiency Questionnaire (CIVIQ 2)[195] and Specific Quality of Life and Outcome Response–Venous (SQOR-V)[196], of which the AVVQ remains the most popular in the UK and USA and has undergone the most stringent validation process. The generic QoL instruments in common use are the Short Form-36 (SF-36) and the EuroQol-5D (EQ-5D). Generic instruments allow comparison of patient populations with different diseases but do not give a comprehensive picture of the impact of a specific disease condition on QoL. The disease specific instruments on the contrary are convergent on key aspects of QoL that are affected by a specific condition, and are more sensitive in

detecting even small but important changes in health resulting from interventions. Hence a combination of generic and disease specific instruments is recommended[35] [197] [198] and can provide valid and reliable strategies to assess patient-perceived health states and changes brought about by interventions to treat conditions such as venous disease. Using these in combination may also reveal differences in the "responsiveness" or sensitivity to assess QoL changes between generic and disease specific instruments following any intervention. This may be useful for future comparative studies and also benefit in making commissioning decisions with the help of the most appropriate tools.

Disease Specific Quality of Life Assessment

Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ is a disease specific instrument which measures the QoL impairment associated directly with venous disease[36]. It consists of 13 questions which mirrors those aspects that are commonly used in the clinical assessment of patients with varicose veins. The first question allows for graphical representation of the visible varicosities on an outline diagram of both lower limbs (Figure 7); a scoring grid (Figure 9) is then utilised to sum-up the numerical extent of recorded varicosities. The rest of the questions have two to four graded responses relating to different aspects of varicose vein problem as experienced by the patient in the previous two weeks (Figure 8). An index summary score (Table 10) thus computed ranging between 0 (no impairment) to 100 (maximum impairment in bilateral disease) relates to the effect on QoL. The AVVQ has been demonstrated to be specific, valid, reliable, and responsive[35-37]. It has been recommended for use as a pre-scoring tool to quantify the severity of disease present, and in turn be used as a means to identify those patients whose treatment could be deemed as most cost-effective.

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

Legs viewed from front Legs viewed from back

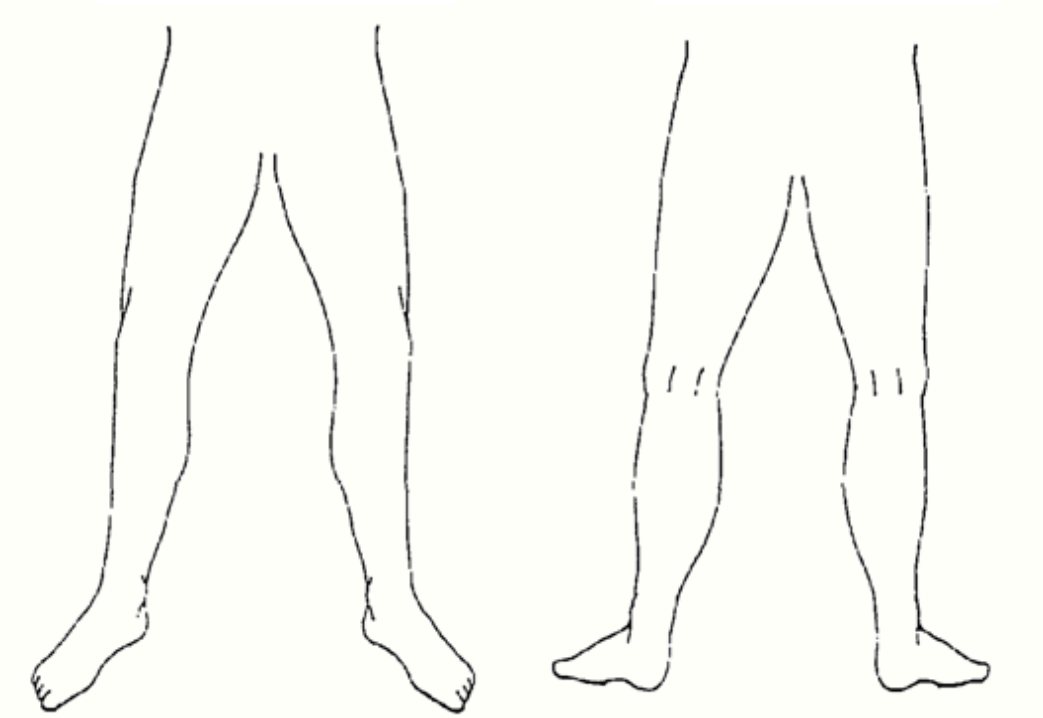


Figure 7: Question 1 of Aberdeen Varicose Vein Questionnaire[36]

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

(Please tick one box for each leg)

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

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

(Please tick one box)

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

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

(Please tick one box)

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

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

(Please tick one box for each leg)

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

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

(Please tick one box for each leg)

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

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

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes	☐	☐

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

(Please tick one box for each leg)

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

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

(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes	☐	☐

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

(Please tick one box)

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

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

(Please tick one box)

No	☐
Occasionally	☐
Often	☐
Always	☐

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

(Please tick one box)

No	☐
I have been able to work but my work has suffered to a slight extent	☐
I have been able to work but my work has suffered to a moderate extent	☐
My veins have prevented me from working one day or more	☐

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

(Please tick one box)

No	☐
Yes, my enjoyment has suffered to a slight extent	☐
Yes, my enjoyment has suffered to a moderate extent	☐
Yes, my veins have prevented me taking part in any leisure activities	☐

Figure 8: Questions 2-13 of the Aberdeen varicose veins questionnaire[36]

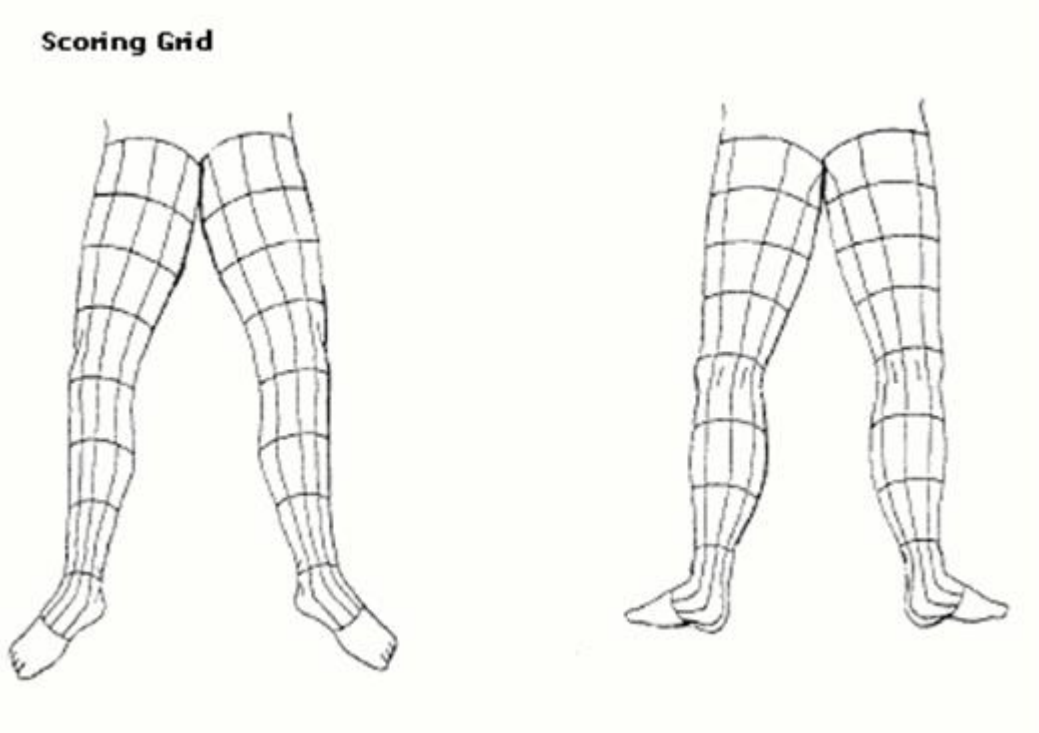


Figure 9: Scoring Grid for Question 1 of Aberdeen Varicose Vein Questionnaire.

Table 10: Recoding the Aberdeen Varicose Vein Questionnaire

Question	Left Leg	Right Leg	Maximum score per question
1. Score per box	0.172	0.172	22.016
2.	0 0 0.500 1.000 1.812	0 0.500 1.000 1.812	3.624
3.	0 0.812 1.625 2.437	0 0.812 1.625 2.437	2.437
4.	0 1.250 1.875		1.875
5.	0 1.374 2.000 5.496	0 1.374 2.000 5.496	10.992
6.	0 1.374 1.437 2.748	0 1.374 1.437 2.748	5.496
7.	0 2.000	0 2.000	4
8.	0 2.624 6.121	0 2.624 6.121	12.242
9.	0 9.118	0 9.118	18.236
10.	0 1.625 3.249 5.248		5.248
11.	0 1.625 2.624 3.998		3.998
12.	0 1.625 3.373 5.496		5.496
13.	0 1.625 2.437 3.998		3.998
Maximum possible Score			99.658

Generic Quality of Life Assessment

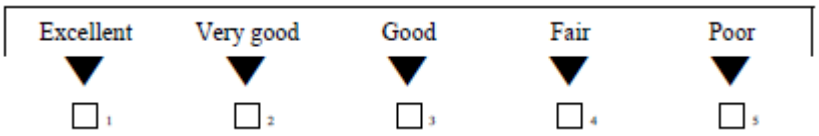
Short Form 36 (SF-36)

The SF-36[199 200] is a popular, validated, generic measure of health status which originated from the Medical Outcomes Survey[201] and the RAND health insurance experiment[202]. This is the most widely used generic QoL instrument in the world and is used across multiple conditions including varicose veins. It has a 36 item profile that measures QoL over eight health domains covering the range of physical and psychological wellbeing: physical function (10 items), role limitation due to physical disability (role – physical) (4 items), bodily pain (2 items), general health perception (5 items), vitality (4 items), social function (2 items), role limitation due to emotional problems (role – emotional) (3 items) and mental health (5 items). These eight domains broadly fit into physical or mental health status scales. The questionnaire (Figure 10) includes a single unscaled item that provides an indication of the patient's perceived change in health over the past year. The rest of the questions have a time frame of the previous 4 weeks. Item scores in each domain are coded, summed and transformed on to a scale from 0 (worst possible health state) to 100 (best possible health state). SF-36 is used to assess QoL changes following a wide variety of health interventions. It does facilitate identification of those specific health domains that contributed to overall change in QoL and is therefore a useful tool to estimate the impact of an intervention on a specific aspect of health and to compare such results between interventions. The SF-36 has been shown to be acceptable, valid, and reliable[203-207]; and has also been tested as an outcome measure to assess the effectiveness of interventions in the treatment of varicose veins[208-210]. The SF-6D is an index utility score which can be derived from responses to the SF-36 or the shorter SF-12 health profile[211 212]. The UK weights were derived by statistical modelling of 836 standard gamble responses from adults, to produce 18,000 health states. This scoring system allows for the calculation of quality-adjusted life years (QALYs),

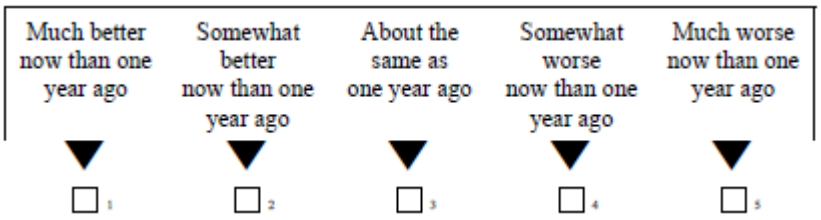
enabling cost–utility analysis. A benefit of this instrument is that it can be calculated from the results of previous studies not featuring dedicated utility assessment.

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:



2. <u>Compared to one year ago</u>, how would you rate your health in general now?



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?

	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 several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the <u>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>…

	All of the time	Most 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
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

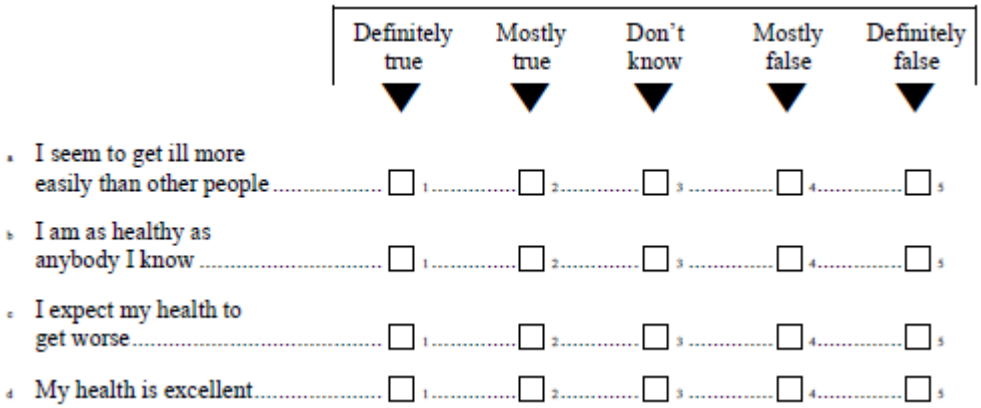


Figure 10: The Short Form 36 Questionnaire (UK V2)

EuroQol (EQ-5D)

The EuroQol was developed by a multidisciplinary group of researchers from five European centres[213]. It is a simple standardised instrument designed for use as a measure of generic QoL and is applicable to a wide range of health conditions and interventions. It measures health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of these five domains are stratified to one of the three possible responses (no problems, moderate problems and severe problems), which in turn reflects the patients' perception of their own health state (Figure 11). A unique health state can be defined by combining one level from each of the 5 domains. A total of 243 possible health states can be defined by such combinations. These can be transformed using the UK time trade-off tariffs into a single global index[214], scored on a scale of -0.513 (worst score) to 1 (best score); these scores quantify the 'utility' or 'value' ascribed by patients to these health states. Index utility scoring is also an essential element of health intervention assessment as it allows the calculation of QALYs, enabling cost–utility analysis[191]. Similar to SF-36, EQ-5D has also undergone extensive testing of validity and reliability including in the context of venous disease treatment[35-37 204 206-208 213 215 216].

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some 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 with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

Figure 11: The EuroQol Questionnaire

1.4 TREATMENT OF VENOUS INSUFFICIENCY

The treatment of varicose veins is guided by a full clinical assessment and its findings. It is chosen based up on the extent of symptoms, complication status, effect on quality of life and work, site and extent of varicosities, underlying pathophysiology as generally ascertained by duplex ultrasonography and outcomes from any previous treatment. Besides, it may also be influenced by patient's wishes, surgeon's experience or beliefs, available hospital resources and evidence based guidance as set out by organisations such as NICE. It may range from simple reassurance, to use of compression stockings, conventional surgical techniques, newer endovenous ablative techniques or a combination of the above. The objective of an optimal treatment being relief of symptoms attributable to superficial venous incompetence, prevention of complications, cosmetic improvement, less periprocedural morbidity, faster recovery and lower recurrence rates, all achieved in the most cost-effective manner.

Conservative treatment

Compression hosiery: remains the principal conservative treatment measure for venous insufficiency. It improves both symptoms and venous haemodynamics among patients with varicose veins[217-219]. Compression hosiery acts as an external support compressing the superficial veins to keep them collapsed and empty of blood, thereby promoting antegrade blood flow from the leg, improving calf muscle function and decreasing reflux, which in turn results in reduction of venous hypertension and leg swelling[220 221].

Whilst the benefits of compression in uncomplicated disease are well established, uncertainty exists regarding the optimal degree of compression required. Results of studies looking into these aspects may be biased due to compliance issues which are variable and difficult to assess. Poor compliance, among several reasons has been attributed to cost of stockings[222], lack of patient education[223], and cosmetic factors.

Difficulty to don compression hosiery, particularly in the elderly may also be an issue, with a study highlighting inability to apply in 15% of its study population and up to 26% needing considerable help[224]. Different lengths and grades of compression hosiery are available. Generally knee-length stockings are better tolerated and more acceptable to patients as compared to the thigh-length hosiery[222]. Also Class II stockings are better tolerated than Class III stockings (Table 11) i.e. lower degrees of compression have higher compliance rates[225]. Maximum symptom relief has been found for compression range between 18-35 mmHg (Class II to III)[226]. Although there is no substantive evidence that any degree of compression would actually influence disease progression.

Table 11: Compression hosiery standards.

Class of Stockings	British Standard (mmHg)	European/RAL Standard (mmHg)
I	14-17	18-21
II	18-24	23-32
III	25-35	34-46

Benefits of compression are similarly established in patients with CVI. A meta-analysis reported significant improvement in symptoms and swelling with the use of compression (10-20 mmHg) as compared to no compression at all for patients with CVI[227]. The study also did not find any added benefit of using higher compression pressures in this patient group. Compression treatment has an established role in the management of venous ulcers. Systematic reviews have reported the benefits of increased healing rates and reduction of recurrence with the use of graduated elastic compression as part of multi-component dressings for venous leg ulcers[228 229]. Similar to uncomplicated venous disease, benefits of compression in CVI is limited by compliance. High rates of non-compliance up to 63% have been reported after one

year[222 230]. Consequently ulcer healing rates are poorer and recurrence higher in non-compliant patients[231].

Lifestyle changes: Alongside compression therapy, self-help advice such as regular exercise, weight loss (if overweight), and avoidance of prolonged standing have been traditionally advocated as ways of reducing severity of symptoms and prevention of the progression of venous disease. Elevation of legs above the level of the heart when sitting down has also been suggested as useful in alleviating symptoms and swelling. There is however lack of objective evidence substantiating benefits of such general lifestyle advice[232].

Medical Treatment: for venous insufficiency is not in common use, however early evidence of their role in the treatment of venous ulcers holds promise. A meta-analysis evaluating effectiveness of pentoxifylline - a xanthine derivative, found its use in combination with compression was more effective in ulcer healing than placebo and compression RR 1.56 (1.14 - 2.13); pentoxifylline alone was more effective than placebo or no treatment RR 2.25 (1.49 - 3.39)[233]. Similarly, micronized purified flavonoid fraction (MPFF) has been shown to benefit ulcer healing times. In patients treated with MPFF and compression the mean healing time was 16 weeks as compared to 21 weeks in patients with compression alone[234]. The rationale for the use of such venoactive drugs is to increase the venous tone and capillary permeability, although the precise action of most of these drugs are unknown; flavonoids are also known to influence the inflammatory process by its action on leucocytes and endothelium[184]. The clinical and cost-effectiveness of such novel drugs and many more are yet to be validated by well-designed RCTs[235].

Interventions

Compression treatment is effective in countering venous hypertension; however it does not address the underlying pathology causing the hypertension. Thus the scope

and benefits of interventions in the management of venous disease is in correcting the underlying venous insufficiency. While conventional surgery has clearly shown to offer clinical and cost-effective benefits over conservative measures in the management of SVI[208] [236], there has been a revolution in this field with the introduction of minimally invasive endothermal ablative techniques which has sought to offer benefits without the trauma of conventional surgery. At the start of this trial endovenous laser ablation (EVLA) was the fore-runner of this endovenous revolution[237] (Figure 17) and hence was compared with conventional surgery which is considered the gold standard treatment and the most commonly performed intervention in the management of SVI[238].

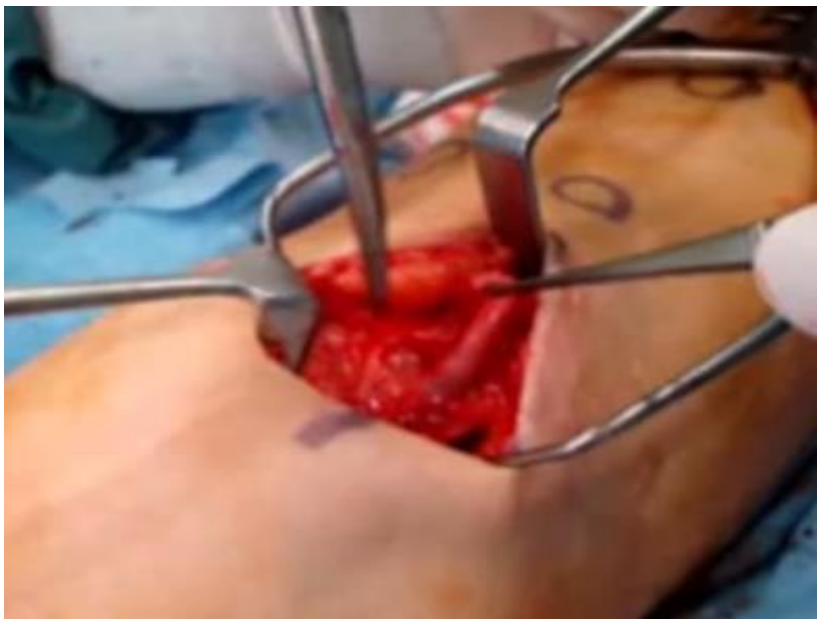
Surgical treatment

The aim of surgical treatment is to correct superficial axial and perforator incompetence and remove visible varicosities. This is classically achieved by flush ligation of the junction between the deep and the superficial systems to control the highest point of superficial reflux and stripping of the incompetent axial vein; visible tributary varicosities are removed by multiple phlebectomies. The standard practice of SFJ ligation and GSV stripping and the various modifications of this surgical technique in the treatment of commonly presenting GSV incompetence are beyond the scope of this study and hence surgery for SSV reflux only will be discussed below.

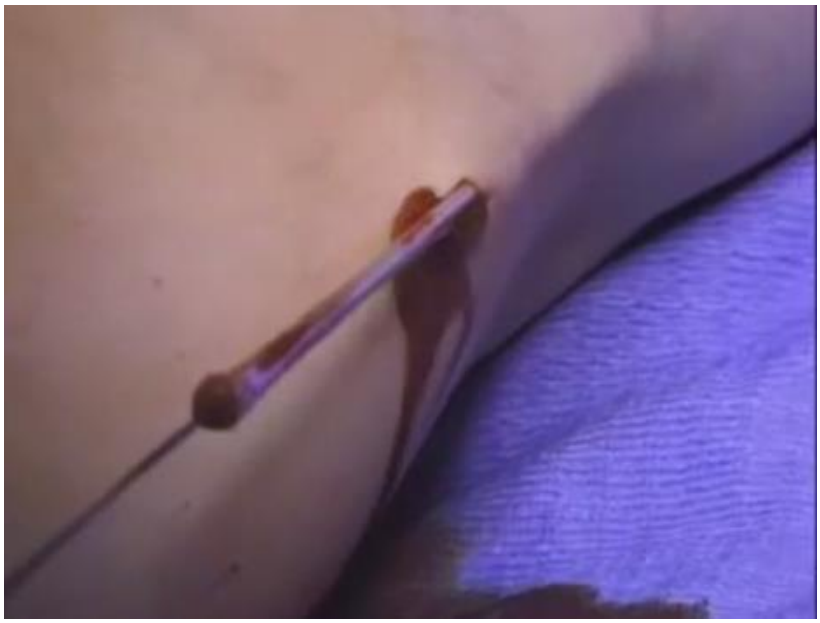
Conventional surgery for SSV reflux is performed under GA; although spinal and regional nerve blocks can also be used. Most surgeons favour the patient to be positioned prone in order to access the popliteal fossa or to place a higher incision for an incompetent SPJ that is located more proximally. A published survey of the Vascular Surgical Society of Great Britain and Ireland[11] (VSGBI) highlighted the lack of consensus amongst surgeons on the best surgical technique for small saphenous incompetence, the key areas of contention being the role of formal

popliteal exposure, and ligation of SPJ with stripping of SSV in primary small saphenous incompetence. In the above report most surgeons in the UK performed flush ligation of SPJ, although few undertook formal exposure of the popliteal fossa unless for recurrent SSV reflux. Approximately 15% routinely stripped SSV and the majority avulsed or excised as much SSV within the operating field[239]; some simply ligated the vein at the incision site without stripping it due to fear of damage to the sural nerve. The operative procedure is described in detail below (Operation protocol – Appendix 5, p. 293). There is sparse evidence to routinely ligate incompetent perforators during SSV surgery as the reflux in such perforators is often found to be secondary to SSV reflux rather than deep venous incompetence. In this study, adjunct perforator ligation and concomitant phlebectomies of visible varicose tributaries were undertaken as standard procedures in both treatment groups based on evidence that such one stop procedures reduce the need for secondary procedures, maximize QoL benefits and is in keeping with patient's preference[240-243] (Figures 12a, b and 13a, b).

The few published studies on the surgical treatment of small saphenous insufficiency reported on different techniques such as SPJ ligation, SSV excision, SSV stripping or both SPJ ligation and SSV stripping[8 9 173 244-247]. The number of limbs included in such studies ranged from 52 to 204; follow-up length were variable from as short as 6 weeks to as long as 5 years; success rates varied from as low as 24% to as high as 100% (Table 12). The studies that included USS surveillance post-surgery to evaluate the success of treatment, reported a disturbingly high recurrence rate of up to 52% at 3 years[174] and occurring as early as 6 weeks[9]. Sites of recurrence identified from these studies included reflux in an intact unstripped SSV following SPJ/SSV ligation as one of the commonest findings[247]; whereas in those with previous SSV stripping, reflux into SSV tributaries was the commonest pattern[173].

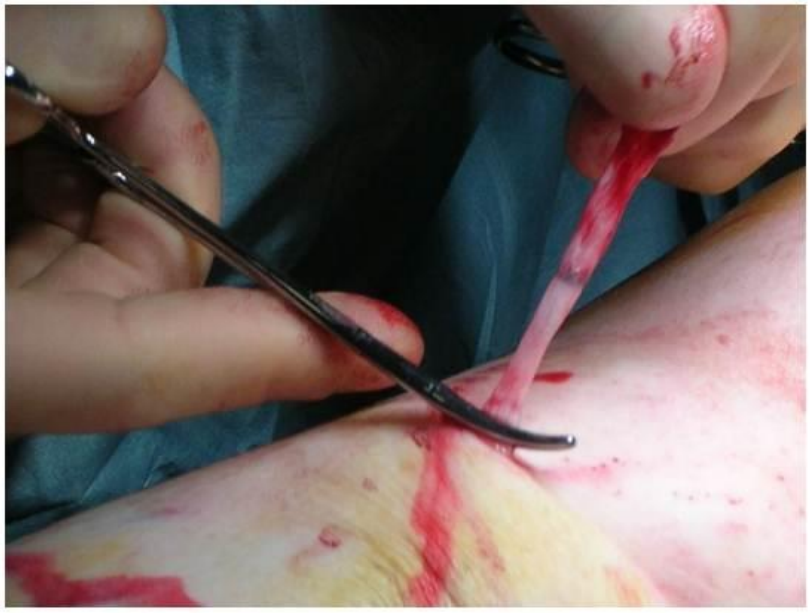


12a

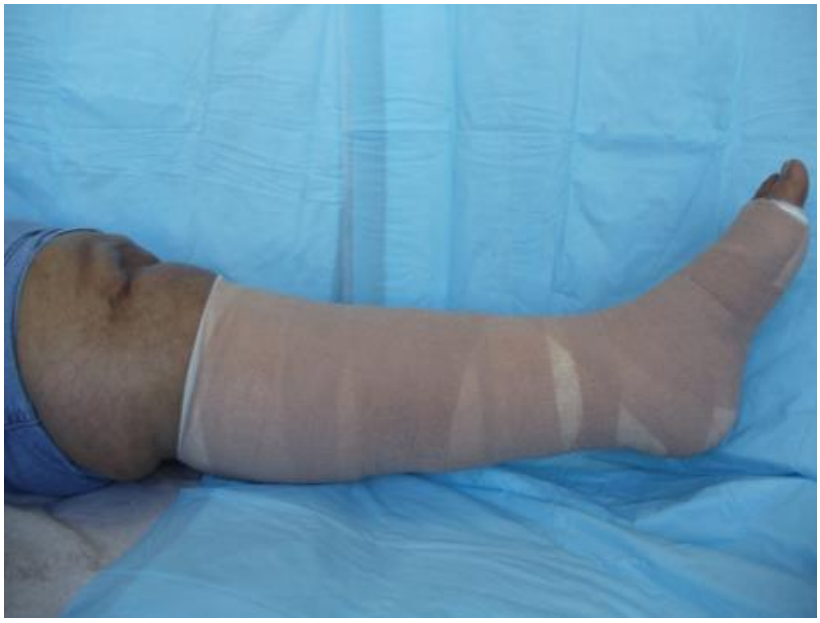


12b

Figure 12a: Popliteal fossa dissection to define SPJ. 12b: retrieving PIN stripper with vein through distal stab incision.



13a



13b

Figure 13a: Concomitant ambulatory phlebectomies of tributary veins. 13b: compression bandage dressing post-surgery.

Morbidity associated with surgery

Although varicose vein surgery *per se* is considered safe and a relatively minor procedure, it is often associated with significant morbidity and patient dissatisfaction. In the UK, the commonest single cause of litigation following any vascular surgical procedure is alleged injury to cutaneous sensory nerves, specifically the saphenous and sural nerves[248]. The VSGBI survey found that surgeons perceived a higher potential risk of nerve injury following SSV surgery, as two-thirds of those surveyed were more likely to warn patients of this complication for SSV surgery in comparison to GSV surgery[11]. The incidence of objectively established sural or common peroneal nerve injuries following SSV surgery has not been established and may be low[239]; sural nerve injuries are reported at 2 to 4%, whereas common peroneal nerve injury occurred in 4.7% in one series and 6.7% in another[249]. It is unclear as to what proportion of these nerve injuries can be ascribed to formal popliteal fossa dissection and/or to the process of SSV stripping. Paraesthesia, especially in the sural nerve distribution has been reported to range from 1.7-34% which was predominantly self-limiting over the follow-up period. No significant difference in the occurrence of paraesthesia was reported when comparing stripping of SSV with ligation alone[8 250]. Adjunct procedures such as phlebectomies and perforator ligation can be associated with nerve injuries, however there is little reliable data to quantify this risk and may only be speculated to potentially increase with the extent of such procedures.

Other morbidities including bleeding, subcutaneous haematoma, bruising, persistent pain, skin discolouration or pigmentation, phlebitis, thrombosis of residual veins, post-operative infection, scarring, popliteal vein injury, deep vein thrombosis and pulmonary embolism have all been reported with low rates of occurrence[8 9 245 246 250-252].

Patient satisfaction with surgical treatment has been reported in few studies showing symptom reduction on non-validated clinical severity scores[244 245]. In an observational

study, our unit reported significantly higher patient satisfaction in the group treated with SPJ ligation and SSV stripping as compared to SSV excision; in the same study disease specific AVVQ QoL scores were also significantly better in the SSV stripping group up to a follow-up period of 1 year[250].

Table 12: Literature review: outcomes of small saphenous varicose vein treatments[253]

Author	Year	Country	Study Type	Treatment	No. Limbs	Follow-up Months	Success rate	Definition of Outcome
Allegra	2007	Italy	2	Surgery	132	60	0.7	recurrence
Dumas	2007	Netherlands	3	Surgery	84	3.8	0.24	reflux
O'Hare	2008	UK	2	EVLA	204	12	0.4	reflux
Rashid	2002	UK	1	EVLA	59	1.5	0.59	disconnection SPJ
Whitely	2006	UK	1	EVLA	52	?	1.0	recurrence
Gibson	2007	USA	2	EVLA	210	3	0.96	occlusion
Huisman	2008	Netherlands	2	EVLA	169	3	0.98	occlusion
Jung	2008	Korea	1	EVLA	41	3	0.93	recurrence
Kontothanassis	2009	Italy	2	EVLA	229/ 66	2/24	0.99/0.97	recanalisation
Nwaejike	2008	UK	1	EVLA	66	14	1.0	recurrence/ recanalisation
Park 1	2008	Korea	2	EVLA	390	12	0.94	occlusion
Park 2	2008	Korea	2	EVLA	96	1/36	0.96/1.0	occlusion/ recanalisation
Proebstle	2003	Germany	2	EVLA	37	6	1.0	recanalisation
Ravi	2006	USA	2	EVLA	101/ 37	0.5/36	0.91/ 0.92	reflux/ recanalisation
Theivacumar	2007	UK	2	EVLA	68/48	3/6	1.0/1.0	occlusion
Darke	2006	UK	2	FS	23	1.5	1.0	occlusion
Smith	2006	UK	2	FS	141	11	0.82	occlusion

SPJ = Saphenopopliteal junction; EVLA = endovenous laser ablation; FS = foam sclerotherapy

Minimally invasive treatment

In the last decade newer alternatives to surgical treatment have been developed which are bearing a major impact on the management choices for varicose veins. These newer treatments for truncal venous incompetence are broadly classed as endovenous thermal (endovenous laser ablation, radiofrequency ablation, steam ablation) and chemical ablation techniques (sclerotherapy). The goal of these minimally invasive endovenous treatments is to accomplish haemodynamic elimination of truncal incompetence, which is achieved by endothermal or chemical damage of the vein wall with subsequent occlusion of the treated vein. A substantial amount of published clinical evidence evaluating efficacy, complications and clinical outcomes of these newer alternatives to surgery exists for commonly occurring GSV insufficiency; however much less is reported on the application of these techniques to lower limb varicosities due to SSV incompetence. Endovenous techniques and its literature review for small saphenous varicose veins are discussed below.

Endovenous Laser Ablation (EVLA)

EVLA utilises laser energy delivered via a laser fibre to obliterate the treated incompetent truncal veins. The emitted LASER (Light Amplification by the Stimulated Emission of Radiation) is a monochromatic (single wavelength), collimated (in parallel) beam of photons that are coherent (in-phase) thereby allowing for a controlled delivery of focussed intense energy. The technique to treat truncal varicosities involves ultra sound guided percutaneous placement of the optical laser fibre just distal to the incompetent junction and laser energy delivery through this fibre as it is withdrawn down the axial vein[28]. During this process the vein wall is irreversibly destroyed due to thermal injury, leading to occlusion of the target vein. It requires local tumescent anaesthesia and is an outpatient procedure that can be conveniently performed in an office setting. The 810-940nm (wavelength) diode lasers are more commonly employed with the power settings set between 5-14 watts

in the endovenous treatment of VVs. The EVLA technique for the treatment of SSV incompetence is described in detail below (EVLA protocol – Appendix 6, p.294).

The principal attributes governing laser induced thermal reaction are its wavelength, type of laser energy administered i.e. pulse or continuous form, and the amount of energy per surface area (fluence, J/cm^2) or energy per unit length (Laser Energy Density, J/cm) which in turn depends on the power, pulse duration and vessel surface area. In context to varicose veins treatment, shorter wavelength lasers (810, 940 and 980nm) are absorbed primarily by the haemoglobin component of red blood cells and longer wavelengths (1319, 1320 and 1470nm) are absorbed by intra and extracellular water, causing rapid heating of blood (700-1300^{o}C) which in turn generates steam bubbles; this along with some direct conduction of heat by the fibre tip (that can reach temperatures up to 800^{o}C) to the vein wall causes thermal endothelial denudation, collagen contraction, vein wall thickening, non-thrombotic occlusion, subsequent fibrosis and finally absorption of the vein[254-256]. Treatment in the Trendelenburg position, with the target vein collapsed and compressed by perivenous tumescent anaesthesia, increases contact surface area which would in turn influence the extent of direct vein wall injury. Of the few case series reported on the laser treatment of SSV incompetence[12 13 15 18 19 21 257-259], none have compared different wavelengths and the comparison of such heterogeneous studies is also not practical due to the variation in amount of energy delivery. The much debated literature on the relative merits of different wavelengths is all based on GSV treatment. These reports indicate benefits of lower post procedural pain, phlebitis and ecchymosis with longer wavelength lasers[260-262], possibly due to lesser energy requirement to cause vein wall damage[263]; although no studies have clearly established any significant differences in patient reported QoL measures on comparison of different wavelengths[260 261 264-266].

In the pulsed mode the target vein wall is exposed to a fixed amount of energy at equal distances, whereas in the continuous mode the fibre is pulled back at a constant

rate delivering uninterrupted energy; hence for fixed laser beam diameter and pulse duration, the total energy delivered depends on the power and the pullback speed. Early studies used the pulsed mode for energy delivery[267 268]; however the continuous delivery technique is favoured in recent years and was also used in this study, due to practical advantages of standardisation and reduced treatment duration. In contrast, estimation of total laser energy per unit length or area is more difficult with the pulsed mode, which may also be associated with a higher risk of vein perforation and bruising[269]; later studies however failed to confirm this hypothesis[270 271].

Several independent studies have established the magnitude of energy delivered as the most important predictor of technical success[272-274]. Fluence (J/cm^2) or laser energy density (LED, J/cm) are used to quantify the amount of energy delivered per unit area or unit length of the vein respectively. Due to practical difficulties of estimating venous wall surface area (cm^2), most studies report on LED (J/cm) as a surrogate marker of fluence[254]. A wide range of energy doses have been reported in the treatment of GSV incompetence ranging from 20-160 J/cm or equivalent fluence[265 275-277]. Increasing energy dose has been shown to cause more extensive vein wall damage in animal models[278], and improve occlusion rates in clinical studies[276 279]. Though there has been no randomised trials comparing different dosing regimens, a mathematical modelling report recommended a LED of 65 J/cm for a 3 mm vein and 100 J/cm for a 5 mm vein (in continuous mode)[263]. Other studies have also retrospectively compared LED doses for failed and successful treatments. A minimum LED of 60 J/cm for successful treatment was proposed by one of these studies[273]. In practice, a fibre withdrawal rate of 1 cm for every 5 s using 14W power achieves LED delivery of 70 J/cm, which was attempted in this study for the EVLA treatment of SSV incompetence. Even with relatively higher doses of LED, failures have been reported which may indicate a multifactorial basis for such occurrences. The optimal laser energy that would achieve maximal occlusion rates with minimal morbidity and complications is the subject of on-going debate, albeit is

predominantly centred on data from GSV studies without considering SSV treatment on its own.

The small number of case-series on EVLA treatment of SSV incompetence has reported encouraging success rates of 90 to 100% (Table 12). The number of limbs included in such reports varied from 37 to 390, with follow-up ranging from as short as 2 weeks to as long as 3 years[12-17 19-21 280]. Clinical recurrence rates corroborated by objective USS assessment ranged from 1% to 7.8%; the relatively higher incidence reported in one of the studies was a collective number that included recanalization, recurrence at treated tributary sites and new reflux at axial veins other than the treated SSV[15]. Studies that recorded recanalization of treated SSV, reported 1% to 9% occurrence between 1 to 12 months which in most cases occurred in veins greater than 9mm in diameter. No RCTs have been reported comparing recurrence rates for surgery and EVLA or other endovenous ablative techniques with EVLA. (Figures 14, 15a,b and 16)

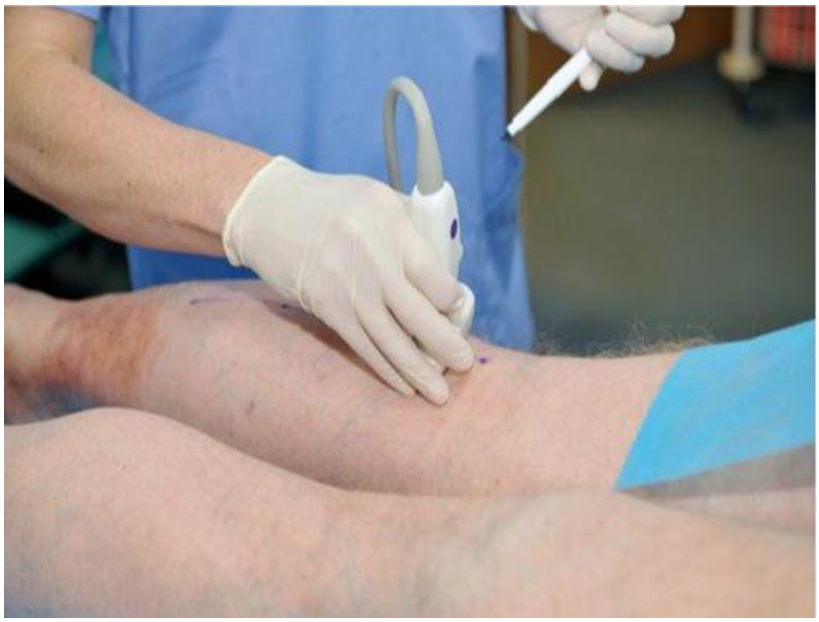
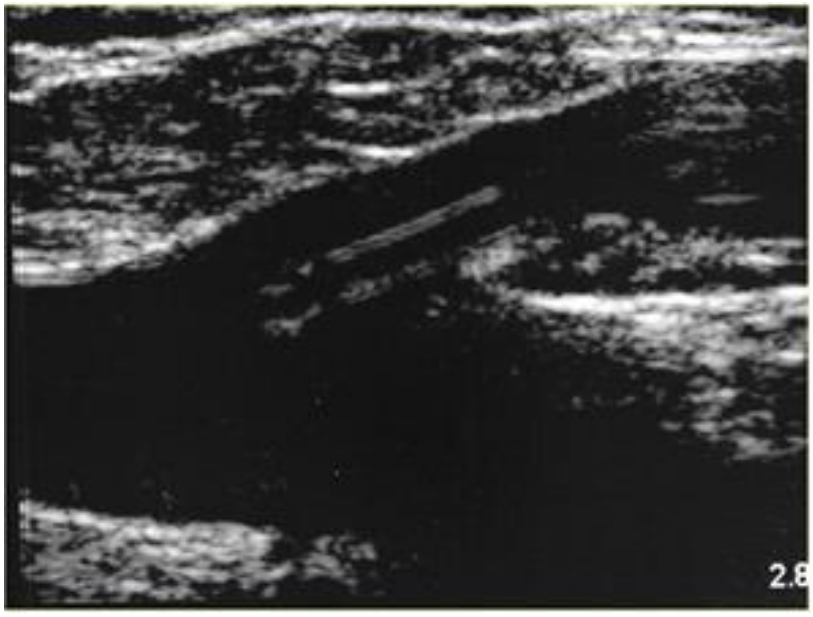
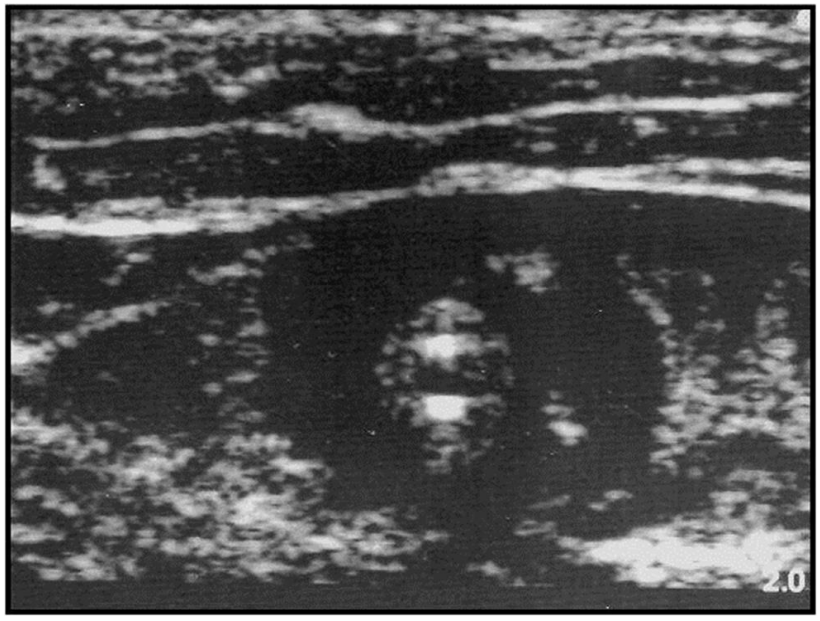


Figure 14: Defining venous anatomy with duplex ultrasound prior to intervention



15a



15b

Figure 15a: Laser catheter tip placement at SPJ. 15b: tumescent infiltration around SSV under DUS guidance

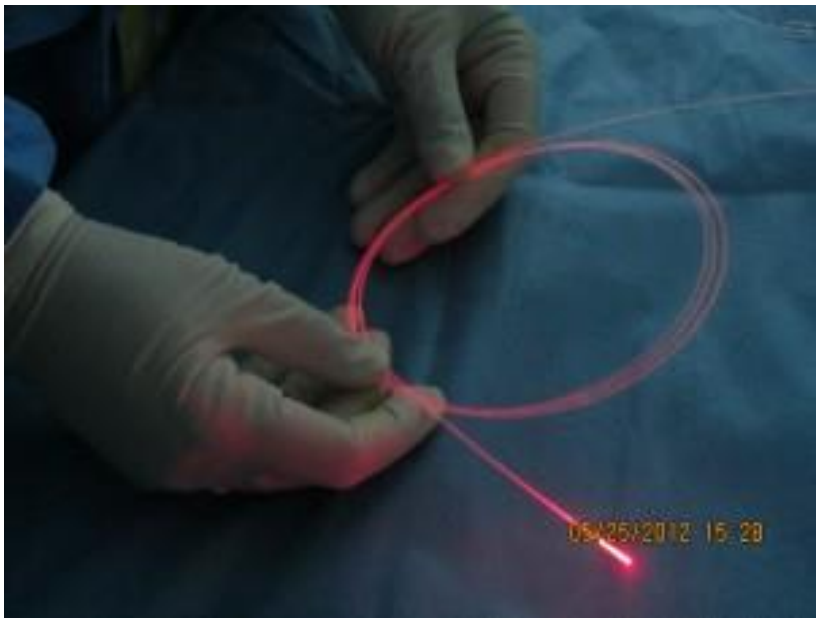


Figure 16: Laser Generator and fibre, set at 14W power and 810nm wavelength.

Morbidity associated with EVLA

Numerous studies especially in the treatment of GSV incompetence have consistently established the safety profile of EVLA; although the procedure is not completely free of complications, which may be minor to significant in severity. In the treatment of SSV, phlebitis or inflammation of the treated veins has been reported in 0-8% of the cases[13-15 17 19 21]. Minor complications of ecchymosis, induration and pain have been commonly observed which resolved by itself within a short period of time[17-19 21 257]. Significant complications of deep-vein thrombosis (DVT) have been reported at rates of 1.3% to 5.7%[15 19] which included thrombus extension from the treated SSV into the popliteal vein beyond the SPJ[12]; sensory disturbance rates of 1.3% to 11%[12-15 17-19 21], with one study reporting temporary paraesthesia of up to 40% experienced by patients in the 1st week post-procedure[257]. Rare complications such as pulmonary embolus (PE)[254 281], arteriovenous fistulae[282 283], skin burn[284] and misplaced catheter[285] have also been reported in the EVLA treatment of saphenous veins. Patient satisfaction with treatment and cosmetic outcome following EVLA treatment have been reported to be high, with concurrent improvement in symptoms[14 15 19 20]; studies using both generic and disease specific QoL tools demonstrated significant improvement following treatment[7 21 286].

Although trials comparing Surgical and EVLA treatment contain both GSV and SSV insufficiency patients, yet there is no evidence that these conditions have a similar impact on QoL or that they respond to treatment in a similar way. In these trials, there has been no attempt made to separately compare treatment results of GSV and SSV incompetence in order to establish whether the current evidence base (centred on GSV intervention) can be applied to SSV disease. This comparison was attempted in a retrospective cohort study, which interestingly demonstrated differences such as a lower pre-treatment disease specific VCSS score in SSV patients as compared to GSV patients ($P<0.001$), despite equivalent pre-treatment morbidity; following

surgical treatment, SSV patients scored worse on disease specific AVVQ scores (P=0.045) than GSV sufferers, but better following EVLA treatment (P=0.042). Patients with SSV disease tended to suffer more complications following treatment (sensory disturbance – P=0.003 and deep venous thrombosis – P=0.042) (Table 13)

Table 13: Complication rates following Surgical, EVLA treatment of GSV and SSV incompetence[286]

	Surgery		**EVLA**	
	GSV	SSV	GSV	SSV
DVT	0	2 (5.3)	0	0
Minor Complications	18 (17.8)	7 (18.4)	16 (8.3)	5 (13.2)
Sensory Disturbance	7 (6.5)	6 (15.8)	5 (2.6)	4 (10.5)
Haematoma	6 (5.9)	1 (2.6)	1 (0.5)	0
Pigmentation	0	0	4 (2.1)	0
Phlebitis	2 (2)	0	3 (1.6)	2 (5.3)

Number of complications in absolute figures, with percentages in brackets. GSV, great saphenous vein; SSV, small saphenous vein; EVLA, endovenous laser ablation; DVT, deep venous thrombosis

Radiofrequency Ablation (RFA)

RFA, first introduced in Europe (1998) as VNUS Closure® system, was developed as a minimally invasive alternative to incompetent GSV stripping. It involved application of radio frequency (RF) energy to the vein wall via bipolar electrodes with the intervening vein wall completing the circuit. In this process, radio-frequency

–resistive heating of the vein wall occurred causing vein shrinkage and luminal obliteration. The Closure® system was later abandoned due to high failure rates, slow withdrawal speed prolonging procedure times and occasional need for cleaning the clotted blood from around the active electrode tip which was perceived as cumbersome. Early procedures were performed under GA without tumescent local anaesthesia, which may have also contributed to its poor results. The VNUS ClosureFast® (VNUS Medical Technologies, San Jose, Calif), a refinement of the old system was subsequently introduced which relies on a 7cm long electrical heating coil which accurately maintains its temperature at 120^{o}C over a treatment cycle of 20 seconds. Segmental withdrawal of the catheter thus ensures faster treatment times and superior ablation rates of the treated length as compared to the old system. It is generally performed under tumescent local anaesthesia and the reported periprocedural pain, analgesia requirement and ecchymosis is lesser as compared to EVLA (810, 980-nm Diode Laser) in the treatment of GSV varices[242 287 288]. Although the above RCTs indicate better early clinical outcomes for the newer RFA device, at the time of initiation of this trial comparing minimally invasive endothermal technique with conventional surgery in the treatment of SSV varicosities, EVLA was still the forerunner amongst endovenous techniques as demonstrated by a meta-analysis[237] of outcomes for varicose veins treatment which indicated significantly better GSV ablation with EVLA than RFA (Figure 17); although the RFA data in this meta-analysis was predominantly derived from studies that used the older VNUS Closure® device.

Complications reported with RFA and as recorded in the Closure international registry include DVT (0.9%), skin burns (1.2%), superficial thrombophlebitis (2.9%), neuralgia and bruising. Although the overall incidence is low, the majority of occurences are with the older system in which tumescent anaesthesia was not used. Similarly published reports on the results of RFA in the treatment of SSV reflux is sparse due to the high incidence of transient sural neuralgia in the early stages,

although this has been reduced but not eliminated wth the use of perivenous tumescence with the newer system [289]. The available case-series on RFA treatment of SSV incompetence have reported high success rates of 95 to 100%, over a follow-up period ranging from 3 to 14 months. The number of limbs included in such reports varied from 27 to 80[290-292].

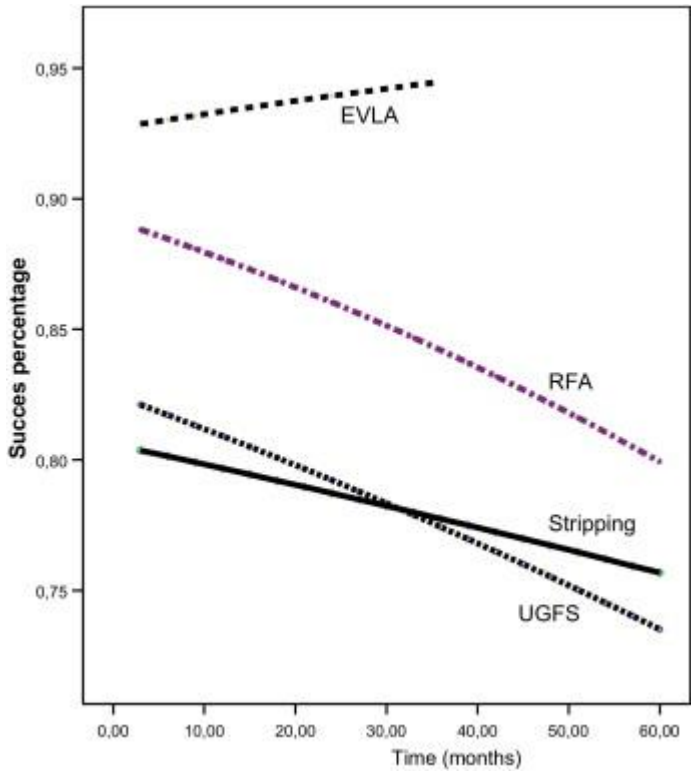


Figure 17: Anatomic success rates for different modalities of VVs treatment[237]

Steam ablation

Steam ablation is the third and the more recent endothermal technique in the treatment of axial incompetence. It has been introduced in Europe, but is yet to be used in clinical practice in the UK and USA. This technique uses superheated steam to cause thermal injury to the vein wall, thereby bringing about similar changes as

seen with other endothermal techniques such as endothelial denudation, fibrotic thrombosis, and major alterations in the collagen fibers of the media. The use of steam ablation for the treatment of SSV incompetence has not been reported in literature, other than in 3 patients as part of a small pilot study[293].

Chemical Ablation: Sclerotherapy

Sclerotherapy is the oldest of the minimally invasive techniques, once considered the treatment of choice for reticular and telengiectatic varicosities. The chemical nature of the sclerosant causes thrombophlebitis of the target vein followed by thrombotic occlusion and fibrosis of the vein wall[294]. Principles of sclerotherapy was described as early as 1855 by Chassiagnac[295] and popularised by Fegan in 1960 with the introduction of injection-compression technique[296]. High rates of recanalization and recurrence with the use of liquid sclerosants for axial and tributary reflux limited its popularity[297 298], until renewed interest was kindled with the introduction of foam sclerotherapy; a mixture of detergent sclerosant and physiologic gas to form foam that is injected into the incompetent vein under USS guidance (UGFS). Comparative studies have indicated greater efficacy of UGFS than liquid sclerotherapy[299 300] and is now being used increasingly in the treatment of both GSV and SSV incompetence, with reported success rates ranging from 84-95%[301 302]. The advantage conferred by foam over liquid sclerotherapy is that foam displaces blood, thereby preventing dilution and inactivation of sclerosant, thus allowing for a greater concentration of sclerosant to be in contact with the wall surface; this in turn improves the chemical irritation and sclerosing ability over a larger surface area. Further the gas-liquid mixture decreases the volume of liquid sclerosant required to treat incompetent axial veins and the potential side effects when used on its own. Various sclerosants, foam production and injection techniques have been described in literature which is beyond the scope of this study. The most commonly used sclerosants in the treatment of VVs are sodium tetradecyl sulphate (STS) and polidocanol. Tessari's technique is the most commonly used technique for foam production, with the use of a three-way tap

between two syringes to pump the sclerosant and air (ratio 1:3 or 1:4 respectively) mixture forwards to backwards (approximately 20 times) to produce foam which is stable to inject for approximately two minutes.

The published studies on UGFS for small saphenous varicosities reported success rates of 82% to 100%, mostly achieved with one treatment and occasionally requiring one or two further injections[302-304]. The follow-up varied from 6 weeks to 12 months and the number of legs included in such studies ranged between 23 and 331. One report suggested higher occlusion rates in smaller sized SSVs $\leq$5 mm. Reported complication were minor including thrombophlebitis (5%) and hyperpigmentation (24%) which resolved over time[303 304]. Major complication of symptomatic DVT was reported in one patient (1.0%)[302]. Complications such as skin necrosis, neurological events and anaphylaxis have been reported as rare but serious occurrences in the general treatment of SVI with foam sclerotherapy[301].

Endovenous Mechanochemical Ablation

This relatively newer technique combines mechanical and chemical ablation to occlude incompetent axial veins without the need for tumescent anaesthesia. Under DUS guidance, an infusion catheter with a motor drive is introduced percutaneously into the target superficial vein and advanced up to the junction with the deep system. Motorised rotation of the dispersion wire within the catheter brings about venous endothelial injury, and the sclerosant that is infused simultaneously as the catheter is withdrawn further supplements its sclerosing potential over a larger exposed surface area. Compression stockings are prescribed for at least 2 weeks following the procedure. The only study[305] evaluating efficacy and safety of mechanochemical ablation using the ClariVein® catheter (Vascular Insights, Madison, CT, USA) in the treatment of SSV varices, reported initial success of 100% in all 50 patients and 94% at the end of 1 year follow-up. Venous severity scores significantly improved over the same period. No major complications were observed; minor complications were self-

resolving and included localised ecchymosis (12%), induration at access site (12%) and superficial thrombophlebitis (14%).

To summarise, symptomatic small saphenous axis incompetence is significant and can result in greater disease-specific quality of life impairment than incompetence in the GSV axis when controlled for clinical disease severity[286]. SPJ ligation with or without stripping of SSV is currently the accepted gold standard surgical treatment of SSV axis incompetence[11]. This procedure is generally considered more challenging than groin dissection due to the varied SPJ anatomy and the close proximity to sensory and motor nerves. The risk of complications therefore increases with thorough exploration of the popliteal fossa whereas limited exploration potentiates the risk of recurrence[10]. This technical dilemma was also highlighted in a survey of VSGBI members wherein there was lack of consensus on the best surgical technique for SPJ/SSV incompetence[11]. In addition, disappointingly high residual and recurrent varicosities after SPJ ligation provide an impetus for surgeons to consider alternate treatment modalities[9]. Newer minimally invasive endothermal ablation procedures are being increasingly used for SSV reflux, with promising results in case series[13 18 21 257]. Although the advantages of minimally invasive procedures over conventional surgery in the treatment of the GSV are well established in the context of randomized trial and meta-analyses[209 237 270 306], no such evidence exists in the treatment of the SSV. There is some suggestion that the SSV may behave differently to the GSV after treatment[286], precluding extrapolation of the current evidence base centred upon GSV management. This study was thus conceived to generate level 1 evidence in the management of SSV reflux by comparing the safety, technical efficacy, and clinical effectiveness of conventional surgery and minimally invasive endovenous laser ablation treatment.

CHAPTER 2

METHODS

The study was conducted as a single-centre, prospective, non-blinded randomized controlled trial at the Academic Vascular Surgical Unit, Hull Royal Infirmary, Hull. The trial was referred to as the Hull Endovenous Laser Project -2 (HELP-2) and was approved by the local research ethics committee (Registration number: NCT00841178), and the institutional Research and Development Department. The study was also registered on the www.clinicaltrials.gov trials registry website.

STUDY POPULATION

The target population for this study were patients referred by their general practitioners (GPs) on a non-rationed basis, who had developed troublesome symptoms attributable to their varicose veins (even if they were classed as uncomplicated) and where the patient and their GP felt that the extent, site and size of the varicosities were significantly impacting on patient's quality of life. GP referral criteria were in keeping with the NICE referral guidelines[307] at the time which included symptomatic varicose veins, complications of venous insufficiency such as bleeding varicosities or potential re-bleeders, progressive and/or painful venous ulcers, progressive skin changes attributable to venous insufficiency, recurrent superficial thrombophlebitis. Such patients from the common UK NHS referral pool were reviewed in our dedicated one-stop varicose vein clinics, vascular outpatient clinics and at the vascular laboratory; eligible patients were clearly informed that participation in the study was entirely voluntary and that refusal to participate would in no way disadvantage them.

INCLUSION CRITERIA

- Age >18 years
- Ability to give informed written consent.
- C2 – C6 graded unilateral varicose veins.

- Demonstrated to have primary isolated SPJ incompetence and / or SSV reflux on Duplex scan (reflux was defined as retrograde flow >1s in duration on spectral doppler analysis).

- Both patient and surgeon occupy a position of equipoise over the relative merits of either intervention.

EXCLUSION CRITERIA

- Inability to give informed written consent

- Symptomatic varicose veins which on venous duplex were not attributable to SPJ incompetence and SSV reflux.

- Presence of reflux at the saphenofemoral junction.

- Evidence of deep venous reflux or occlusion on duplex scan

- Pregnancy

WITHDRAWAL CRITERIA

- Patient request
- Patient non-compliance with study protocol

INFORMED CONSENT

All patients presenting to the 'one-stop' varicose vein clinics or vascular outpatient clinics at the Hull Royal Infirmary were initially seen by the Consultant Vascular Surgeon or a senior Clinical Research Fellow. On clinical confirmation of presence of symptomatic varicose veins, these patients were referred to the Vascular Laboratory where duplex ultrasound evaluation was performed by the same consultant surgeon or senior research fellow. On establishing the anatomical suitability for inclusion into the trial by DUS evaluation, a detailed explanation of the DUS findings and the available treatment options including the benefits and risks of both conservative and

surgical options were given to the patient. Those patients, who wished to have definitive treatment, were given further explanation of the two treatment options of EVLA and conventional surgery available within the trial setting. The technique, benefits and risks of each of these procedures were also explained, aided by diagrams where necessary. In patients agreeing to participate in the trial, an informed consent form for participation was obtained prior to randomization (consenting protocol and consent form – Appendix 1 and 2, pp. 276-277). All patients were given a copy of the consent form, patient information sheet (Appendix 3, pp. 278-281), NICE guidance document (Appendix 4, pp. 282-292) before leaving the department. A contact telephone number for the research nurse was also provided to the patients, to address any queries or concerns that arose after reading the above documents. Simple queries were dealt by the research nurse or a further consultation or telephone call arranged with the consultant surgeon to resolve any other concerns. Those patients who requested some time before considering participation in the trial, were also given the above information and no time limit was placed for them to make contact regarding decision to participate in the trial. Such patients usually responded within a week of their visit to the vascular lab to confirm or refuse participation. Telephone contact was made to those patients who failed to respond within two weeks and either additional time granted to consider participation if requested by the patient, or reasons for their unwillingness to participate in the trial recorded. Such patients were offered conventional surgery. Patients randomized to conventional surgery were placed on a waiting list for the Consultant surgeon, most commonly as a day-care procedure. Patients randomized to EVLA were placed on a dedicated out-patient theatre list. Both groups signed a consent form (Form–1) used in the NHS, prior to having the procedure done. A separate consent form designed for medical illustration by the HYMS was used for obtaining patient photographs when required.

RANDOMISATION

After providing written informed consent, patients were randomized into two groups by means of sealed opaque envelopes, receiving either conventional surgery or EVLA. Randomisation was performed in the clinic or the vascular lab with the assistance of a research nurse, wherein the patients chose their own envelope and opened the sealed envelope to reveal the enclosed treatment option. This mode of randomization did not include any prior stratification to balance any variables between the two arms, as we did not believe this would ensure the true representation of the population sub-group being evaluated. Access to the envelopes was restricted to the personnel involved in the randomization process. No problems were encountered in the randomization process and all envelopes were accounted for at the end of recruitment into the study.

CONVENTIONAL SURGERY (CS)

Patients randomized to conventional surgery underwent formal exposure of the popliteal fossa with SPJ ligation, inversion stripping of the SSV with a PIN (Perforation-invagination) stripper when possible, and concomitant hook avulsions of the pre-operatively marked varicose tributaries. The junction was pre-operatively marked by DUS evaluation by the operating surgeon with accredited certification in the use of ultrasound. All operations were performed under general anaesthetic, predominantly as day-case procedures. These procedures were undertaken by a single Consultant vascular surgeon, in order to maintain the consistency of the operative technique. (Conventional Surgery protocol – Appendix 5, p. 293)

ENDOVENOUS LASER ABLATION (EVLA)

All procedures were performed under tumescent local anaesthesia in a dedicated clean procedure room in the outpatient department. Incompetent SPJ/SSV and perforators were marked preoperatively using DUS and any clinically obvious surface varicosities marked with the patient stood, to facilitate concomitant stab avulsions.

Ultrasound guided percutaneous cannulation of SSV was established distally at the site of venous reflux where the vein size was adequate (≥3mm). A 5 Fr catheter was introduced into the vein using the Seldinger technique, and its tip accurately positioned at the SPJ under ultrasound guidance. Perivenous tumescent local anaesthetic (20 ml of 2% lidocaine with 1:200,000 adrenaline and 20 ml 0.5% levobupivicaine in 1 L of 0.9% saline) was infiltrated along the axial vein and tributaries. A bare-tipped 600 nm laser fibre was then introduced via the catheter and laser energy delivered using an 810 nm diode laser generator at 14 W power with a continuous pull back rate of 2 mm/sec. Perforator ligation and ambulatory phlebectomies were performed concomitantly as a single procedure (EVLA protocol – Appendix 6, pp. 294-295). The Consultant Vascular Surgeon with sufficient experience in undertaking this intervention and/or a senior research registrar under the same Consultant's supervision carried out all the EVLA procedures.

OUTCOMES

Because of the nature of the interventions, it was not possible to blind the investigators or patients to the treatment methods. Patients were assessed at 1, 6, 12, and 52 weeks post procedure as detailed below.

Primary Outcome measure was early technical success, defined as abolition of SSV reflux at 6 weeks post procedure, objectively established by DUS assessment.

Secondary Outcomes included

- Assessment of safety of the two procedures, by prospective clinical evaluation and DUS assessment at each follow-up time point. A prospective log of complications was completed during the same time points.

- Post procedural morbidity which was assessed by recording the pain scores in the immediate postoperative period, alongside the requirement for supplementary

analgesia; recovery time was estimated by the time taken to return to work and normal activities.

- Patient satisfaction with the cosmetic outcome and with the overall intervention, that was recorded on visual analogue scales at 12 and 52 weeks.

- Clinical efficacy which was assessed by the Venous Clinical Severity Score (VCSS), a dynamic assessment tool to objectively demonstrate changes in clinical severity over time.

- Patient reported quality of life outcomes such as the disease-specific Aberdeen Varicose Vein Questionnaire (AVVQ); the generic Short Form Health Survey (SF-36 V2) and the EuroQol 5D instrument (EQ-5D) which was also used to derive a single index valuation, commonly used in the calculation of quality-adjusted life years (QALY) in economic evaluation.

- Cost-effectiveness which was assessed by comparing Cost/QALY and incremental cost effective ratio (ICER) for both treatment groups.

INTRA-OPERATIVE MEASURES

- Technical details of the procedure (Intra-operative record – Appendix 7, p. 296)
  - Ligation of SPJ
  - Length of SSV stripped or excised
  - Length of SSV ablated during EVLA
  - Total laser energy delivered and rate of pull back
  - Complications or adverse events
- Duration of the procedure
- Need for overnight stay

POST-OPERATIVE INSTRUCTIONS

Both treatment groups were instructed to keep the compression bandages on the treated leg until seen in the vascular lab 1 week following the procedure. Patients were asked to ambulate as frequently as possible; to return to normal functioning as they felt comfortable; elevate the limb when resting; and to take pain killers as necessary (discharged home with 2 weeks supply of Paracetamol and Diclofenac tablets) in the absence of intolerance or contraindications. Written after-care and emergency contact details were provided to all patients (Post-op instructions – Appendix 8, pp. 297-303).

POST-OPERATIVE ASSESMENT

All patients treated within the trial were followed-up in the Vascular Laboratory, where dedicated sessions were allocated for this purpose. Clinical evaluation of patients and collection of quality of life questionnaires were carried out by an experienced research fellow and research nurse respectively who had sufficient experience in undertaking these tasks. Duplex evaluation of the treated limbs was performed either by the Consultant Surgeon or a senior research Registrar, both of whom held accreditation in the use of ultrasound. Any abnormal or unusual findings were immediately reported to the supervising Consultant Surgeon for an expert opinion. All information was collected onto data collection templates specially designed for the trial purpose (Appendix 10, pp. 306-317). This information was transferred onto an electronic database by the researcher for the purpose of storage and analysis.

1 and 6 weeks assessment

- Peri-procedural morbidity assessment by clinical and patient reported methods.

- Pain: Average daily pain experienced by the patient over 1 week post procedure, charted on a pain diary (Appendix 9, p. 304) by using an unmarked 10-cm visual analogue scale (0, no pain; 10, worst imaginable pain)
- Analgesia requirement: dose and duration of simple analgesics used and requirement for any supplementary analgesia (Appendix 9, p. 305).
- Return to normal functioning: the time taken in days to return to work and full normal activity.
- Wound related complications: operative wound / phlebectomy site infection.
- Phlebitis
- Haematoma
- Skin burn
- Pigmentation
- Sensory disturbance: patient reported paraesthesia or dysaesthesia; clinical evaluation of numbness or altered sensation – area and distribution.
- Patient reported post-operative problems, warranting visit to the GP/ District nurse or visit to the casualty with or without subsequent in-patient admission.

• Quality of Life assessment

- Disease specific AVVQ
- Generic SF-36 (UK version 2.0) and Euroqol (EQ-5D)

• Duplex ultrasound scan

- For assessment of the deep venous system for evidence of deep vein thrombosis
- Evidence of reflux across the saphenopopliteal junction
- Evaluation of occlusion status in the treated segment of SSV following EVLA or absence of stripped segment of SSV post-surgery (primary outcome); flow status in the untreated distal SSV segment

12 and 52 weeks assessment

• Morbidity assessment by clinical evaluation and patient reported methods

- Pain
- Analgesic requirement for varicose veins related pain – dose and duration
- Persistent bruising
- Persistent pigmentation
- Residual or recurrent veins: recorded on the AVVQ chart
- Sensory disturbance: patient reported paraesthesia or dysaesthesia; clinical evaluation of numbness or altered sensation – area and distribution.
- Visit to GP/ practice nurse / vascular surgeon for varicose veins related problems.

- Patient satisfaction: with over-all treatment and with cosmetic outcome post procedure recorded on a 10-cm visual analogue scale (0, not satisfied at all; 10, completely satisfied)
- Patient's personal preference to have laser treatment in the future if needed.
- Objective assessment of venous disease severity: performed independently by the research nurse using the VCSS and the clinical grade of the CEAP classification system.
- Quality of Life assessment
  - Disease specific AVVQ
  - Generic SF-36 (UK version 2.0) and Euroqol (EQ-5D)
- Duplex ultrasound scan
  - Evidence of reflux across the saphenopopliteal junction
  - Evaluation of occlusion status in the treated segment of SSV following EVLA or absence of stripped segment of SSV post-surgery; flow status in the untreated distal SSV segment.
  - Assessment of competence of the deep venous system, SFJ, GSV and its major tributaries.
- Need for secondary procedures.

DUPLEX ULTRASOUND EVALUATION

Lower limb venous ultrasound evaluation was standardized as per the protocol followed in the Vascular Laboratory at HRI. All patients underwent DUS evaluation of the venous flow pattern in the standing position. All screening and follow-up duplex scans were undertaken in the Vascular Lab using standard equipment: Toshiba Aplio XV® device (Toshiba Medical Systems, Crawley, UK), with a 6-MHz linear array broadband transducer, and the same initial default settings. A portable duplex ultrasound (Micromaxx, Sonosite, Hitchin UK) machine was used intra-operatively to locate and mark the SPJ, incompetent SSV and perforators prior to either interventions.

- Pre-operative DUS assessment included

- Patency and reflux in the Deep veins and evidence of previous venous thrombosis: Common Femoral vein (CFV), Superficial Femoral vein (SFV) and the Popliteal vein (PV).
- Reflux across the junctions: SFJ and SPJ
- Competency, extent of reflux and vein diameter measurements of the main trunks: GSV, anterior accessory saphenous vein (AASV), posterior accessory saphenous vein (PASV), SSV, and thigh extension of SSV / Giacomini vein
- Origin and course of tributaries, if incompetent
- Competency, number, location of perforating veins and its size if incompetent.
- Non-saphenous veins when incompetent.

For the purpose of the trial, the following definitions were described in order to facilitate consistent interpretation of the duplex scan findings.

Reflux:

Retrograde flow on spectral doppler analysis lasting 1.0 second or more on distal augmentation method by calf compression–release or on valsalva manoeuvre, with the patient in the standing position[8 308 309]. Deep veins were assessed at three levels – femoral vein, and popliteal vein above and below the SPJ. Reflux in all examined segments was defined as total deep venous reflux. In case of the PV, only retrograde flow distal to the level of the SPJ was considered to represent true deep venous reflux[165] and termed segmental reflux.

Vein diameter measurements:

Antero-posterior outer vein wall diameter recorded in the transverse section of the ultrasound image. For the SSV the proximal vein measurement was taken 3 cms distal to the SPJ; mid segment measurement at the mid-calf level and the distal measurement at the distal calf level, avoiding measurements at any varix in the vein.

Early technical success (Primary Outcome):

Successful anatomical completion of the planned procedure as demonstrated by DUS at 1 and 6 weeks. In the surgical group flush ligation of the SSV at the popliteal junction and absence of the stripped incompetent SSV from the knee to mid-calf. In the EVLA group this required the treated segment of SSV to be occluded and non-compressible with absent flow. Visible flow within minor tributaries in the popliteal fossa or thigh extension of SSV and Giacomini vein was not regarded as initial technical failure as occlusion of such veins was not a treatment aim. The hypothesis for the study was that successful elimination of reflux in the incompetent SSV axis would reduce future recurrences and reoperation rates by disconnecting the mid-calf perforators and tributaries to the GSV system[8 173 247 289].

Anatomic success of EVLA:

Permanent occlusion of entire treated vein segment, demonstrated on DUS follow-up at 1 year and beyond. A partially occluded vein was defined as one with reflux immediately distal to the junction, but with no reflux beyond 5 cms from the SPJ.

Anatomic failure post EVLA:

SSV patency distal to the SPJ or proximal to the site of access with or without reflux in greater than 5-cm segment of treated vein. Anatomical failure could be due to non-occlusion i.e. failure to completely occlude from the time of treatment and during follow-up with or without reflux; or due to recanalization i.e. previously occluded vein as demonstrated by DUS, regaining partial or complete patency at a later time point.

Disease progression:

Defined as the development of new segments of incompetence or recurrence of preoperative reflux within superficial veins and perforators. Particular attention was given to signs of neovascularisation in the popliteal fossa and recanalization of a previously occluded SSV. **Neovascularisation** was defined as serpentine small vessels connecting the saphenous stump or the popliteal vein with the residual SSV or its tributaries, which were not present on duplex imaging at 1 or 6 weeks.

Primary ablation: ablation of SSV after initial EVLA procedure

Primary assisted ablation: successful retreatment of anatomic recanalization of SSV, prior to occurrence of clinical failure.

Secondary (retreatment) ablation: successful re-ablation of SSV in patients with both anatomic and clinical failure.

QUALITY OF LIFE (QoL) ASSESSMENT

Three standard instruments were used to measure HR-QoL (Figures 7, 8 and 10, 11): disease specific Aberdeen Varicose Vein Questionnaire (AVVQ) questionnaires,

generic Short Form 36 (SF-36®; Medical Outcomes Trust, Waltham, Massachusetts, USA) and EuroQol (EQ-5D; EuroQol Group, Rotterdam, The Netherlands).

All 3 questionnaires, the AVVQ, SF-36, and EuroQol are designed to be self-administered and were completed by patients pre-operatively (baseline) and post-operatively at 1, 6, 12 & 52 weeks. In order to reduce the possibility for certain patients scoring poorer responses on the QoL questionnaires thereby intending to obtain a preferred intervention ('faking bad'), the pre-op questionnaire was administered after the randomisation process into one of the two treatment categories. Post-op QoL questionnaires were completed during the follow-up visit at the vascular lab, prior to clinical and duplex evaluation. The English version of the questionnaires was used in all patients throughout the study. Completed questionnaires were collected and checked by a research nurse or research fellow in order to point out to the patients any incomplete sections that may have occurred by oversight; which in turn ensured a high response rate with these QoL tools.

POWER CALCULATION

Power calculation for the RCT was based on the reported duplex demonstrable 35.8% residual SSV reflux at 6 weeks following surgery (Joint Vascular Research Group study data)[8] versus an estimated 10% after EVLA; a chi-square test with continuity correction gave a statistically significant difference at the 5% level with 0.8 Power if 48 limbs were recruited into each group. Accounting for a 10% loss to follow-up / patient withdrawal, and assuming unilateral varicose veins in all patients, 53 patients were required and achieved in each group.

DATABASE

Patient information and data collected for trial purposes were held both on paper and electronically in a dedicated database (Microsoft® Access; Microsoft, Redmond, Washington, USA). It was registered with the Hull and East Yorkshire Hospitals

NHS Trust's Caldicott Guardian and was held in compliance with the Data Protection Act 1998.

STATISTICAL ANALYSIS

Statistical analysis on the collected data was done using SPSS® version 18.0 (SPSS, Chicago, Illinois, USA). Continuous data were first tested for normality (histograms, Kolmogorov–Smirnov and Shapiro–Wilks testing). Normally distributed data were presented as mean (s.d.), and hypothesis significance testing was performed with paired and unpaired *t* tests. If the data were not normally distributed, median (interquartile range) values were presented, with analysis using the Mann–Whitney *U* test (MWU) for unrelated samples and Wilcoxon signed rank (WSR) test for paired data. Friedman ANOVA (F-A) test was used to analyse multiple related samples across the study interval. Categorical data were analysed by means of Chi squared test (χ^2 test) or Fisher's exact test (FET) as necessary. The incidence and timing of patients lost to follow-up was established by the Kaplan–Meier analysis, with intergroup log rank testing for significance. Analysis was done by the principle of intention to treat.

COST ANALYSIS

Retrospective cost-utility analysis was carried out to determine whether the additional costs of laser consumables could be offset against estimated QALY values for EVLA treatment in comparison to conventional surgery. The results would then inform patients, health care professionals and commissioning bodies its feasibility and the economic impact of its future applications. In this process of cost comparison, estimated costs incurred by the hospital, by the general practice and by the patient for the loss of productivity from being unable to work during the post-operative convalescence were considered (Table 14). Costs arising from the extra follow-up hospital visits and duplex ultrasound scans as per the trial protocol were not included in the analysis as the number of events was evenly matched in both groups and the

extended follow-up would not generally take place outside of the trial setting; however the costs incurred with any unplanned visits were accounted for. In the employed patients, the difference in productivity between the two treatment groups was expressed as cost per working hour gained, which equates to the cost (to the Trust, practice and patient combined) for each extra hour of paid employment gained following EVLA over and above the cost of conventional varicose vein surgery. The difference in productive unpaid household work between the two treatment groups was expressed as cost per hour of household work gained following EVLA and conventional surgery as above.

The costs incurred by the hospital was estimated by tallying up the theatre costs, cost of in-patient stay and the cost of any un-planned outpatient visits or to the vascular lab for duplex ultrasound scans. The unit cost data was provided by the surgical division of the Hospital Trust Finance Department for the year 2011-2012. Estimation of theatre costs was based on the recorded mean total time spent in either the day surgery unit or the outpatients clean procedure room for CS and EVLA respectively; and the number of operating staff usually required for both types of procedures being compared in the trial. The operating staff for CS included one Consultant surgeon, one assistant (specialist registrar grade), one Consultant anaesthetist, one operating department assistant (ODA), one scrub nurse and one floor nurse; and for EVLA, one Consultant surgeon, one assistant (specialist registrar grade), one scrub nurse and one floor nurse. The staffs wage rates were taken as maximum of salary scale using 2011-2012 pay rates. Costs were allocated to theatre consumables, staff overhead and trust overhead in line with the trust accounting policy. 10% of direct theatre costs were allocated to theatre consumables. Staff overhead such as sterile services costs, administration, domestic services, laundry etc. was included in the trust overhead expenses as per standard trust accounting procedure; 30% of overall direct theatre costs were allocated to trust overhead which included costs of estates, energy, capital charges, administration etc. Additional costs for EVLA resulted from the use of

intraoperative duplex ultrasound scan (cost provided by the trust) and the disposable endovenous ablation catheter (prevailing purchase price of £ 275/- at the time of the trial for the year 2011-12. The capital cost of Laser generator and tumescent pump was not included in the costs incurred by the hospital as both these equipment were loaned for free to use both for trial and non-trial purposes. The operating consultant or research fellow performed all the intraoperative duplex scans and hence the additional cost for a vascular technician was not included in the above estimate.

The number of consultations during the postoperative period with patient's own family physician (GP) and or the district nurse (DN), either as a visit to the practice or as a home visit for any reasons directly or indirectly related to the operation was recorded by the research fellow during routine follow-up visits to the vascular lab. Estimated costs incurred by the patient's unplanned visit to the practice for reasons related to the treatment was obtained from the Unit Costs of Health and Social Care 2012 document published by the Personal Social Services Research Unit (PSSRU) University of Kent[310]. Although costs incurred by patient's unplanned visit to the hospital during the postoperative period or from purchase of medications such as antibiotics or analgesics over and above the supply of pain killers from the hospital were included in the costing analysis, such occurrences were rare and could be considered too small to make a significant difference to the overall costs.

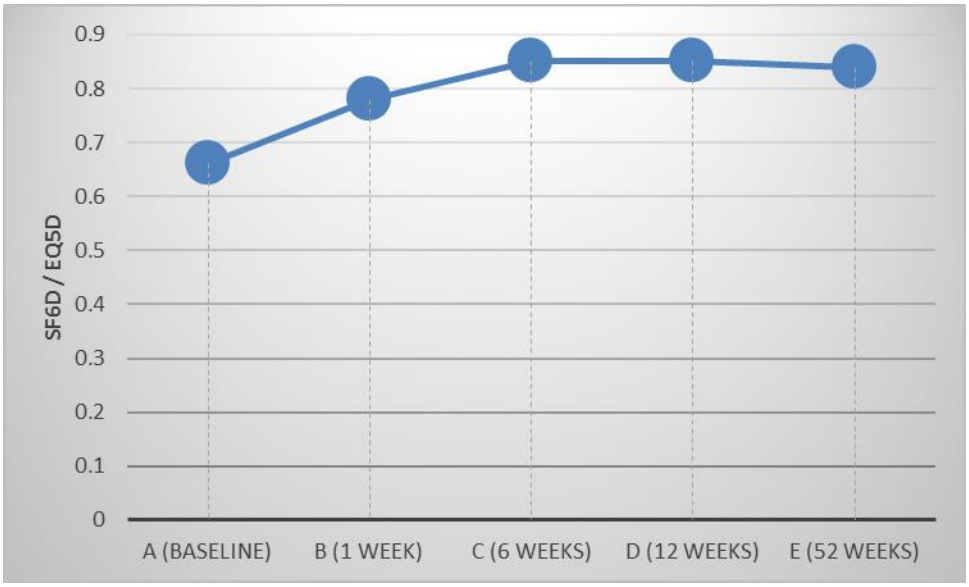
Utilities were calculated as quality adjusted life years (QALYs) as per NICE guidelines[191]. EQ-5D health utility index generated from the EuroQol generic quality of life questionnaire was used for calculation of QALYs. EQ-5D was calculated for each visit and plotted on a linear graph. QALY gain over the follow-up period of one year was estimated by calculating the area under the curve (AUC)[311] as shown below (Figure 18). The EQ-5D tool was chosen as it is frequently used and recommended by NICE for cost effective analysis in health technology appraisals[191].

Table 14: Categorisation of Costs incurred per patient

Cost I – Cost incurred by the Hospital • Cost of the operation (theatre costs) in DSU • Cost of procedure in the out-patient clean procedure room • Cost of non-protocol follow-up in the outpatients • Cost of non-protocol follow-up duplex scan. • Cost of treating recurrences
Cost II – Cost incurred by the General Practice • Cost of GP consultation • Cost of Practice Nurse consultation • Cost of non-protocol District Nurse home visit
Cost III – Cost incurred by the patient • Cost of practice visit (GP and/or Practice nurse) • Cost of non-protocol hospital visit • Cost of antibiotics • Cost of analgesia
Cost IV – Indirect Costs (loss of productivity) • Employed • Unemployed

Cost per QALY was calculated for individual patients by dividing the adjusted cost per treatment by the QALY gain over 1 year. The mean cost per QALY for the two treatment groups were then compared for statistical significance. Furthermore

incremental cost effective ratio (ICER) was calculated to determine which of the two procedures provide a more cost-effective treatment. ICER was calculated by dividing the difference in mean procedure costs with the difference in mean QALY gains. ICERs are commonly used in health economics to provide a practical approach in informing decisions prior to commissioning new health interventions, by determining whether the increase in the cost to the health care provider for providing the new treatment over the standard or current treatment is justified based on the incremental benefits/ effect in health status as determined by QALY gain. NICE determined threshold of £20,000 - £30,000 per QALY[312] was used to establish cost effectiveness of the two treatments and to compare them using ICER.



QALY= [{((A+B)/2) X 1}+{((B+C)/2) X5}+{((C+D)/2) X6}+{((D+E)/2) X40)}] / 52

Figure 18: QALY gain estimation by plotting utility index scores and calculating area under the curve.

CHAPTER 3

RESULTS

The results of the randomized trial are presented below. Descriptive texts are supported by tables which provide rapid overview of numerical data and results of statistical significance. 'P value' of < 0.05 is taken to be statistically significant. Data description and relevant tests used to determine statistical significance are mentioned in the legends of each table.

RECRUITMENT & BASELINE ASSESSMENT

A total of 767 patients were assessed for eligibility to participate in the trial during October 2005 to January 2010. 106 patients (106 legs) were randomized as planned, with strict adherence to inclusion and exclusion criteria specified in the protocol; and received treatment as intended. Figure 19 outlines the recruitment and the number of patients involved in the analysis at each stage of the study. There was no difference between the groups in terms of numbers lost to follow-up (P=0.339 FET) or the length of successful follow-up (P=0.249 Log Rank). There were no protocol violations in any of the stages of recruitment, treatment and follow-up.

Baseline demographic data including age, gender, laterality, smoking status, employment status, antiplatelet/anticoagulant usage, height, BMI, pre-op vein diameter, CEAP clinical grade, VCSS and QoL were comparable between the two groups with the majority being women, predominantly presenting with uncomplicated C2 venous disease (Table 15).

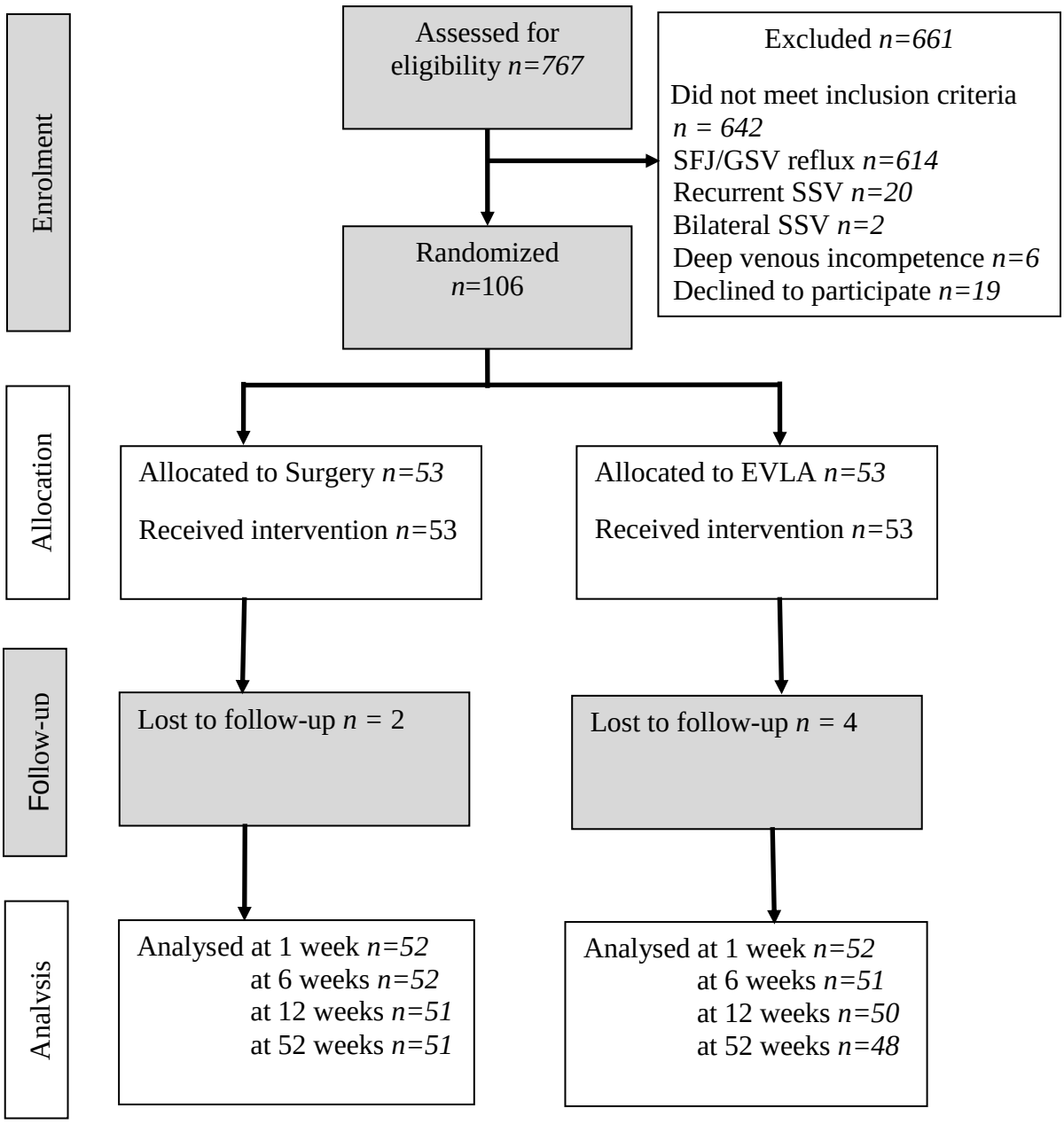


Figure 19: CONSORT chart depicting the progress of patients through the trial.

Table 15: Demographics and quality of life measures at baseline.

	Surgery	EVLA	Pϕ
Age (years)*	47.5 (12.9)	47.8 (12.2)	0.890 §
Women	40 (75.5%)	34 (64.2%)	0.204
Left Leg	23 (43.4%)	31 (58.5%)	0.120
Smoking status			
Ex-Smoker	15 (28.3%)	18 (34%)	0.396
Current Smoker	12 (22.6%)	15 (28.3%)	0.447
Employed	41 (77.4%)	42 (79.2%)	0.814
Antiplatelet / Anticoagulant	3 (5.7%)	6 (11.3%)	0.244†
Height‡ (m)	1.7 (1.63-1.79)	1.72 (1.63-1.81)	0.543 ¶
BMI* (kgm^{-2})	24.9 (5.3)	25.9 (3.2)	0.376 §
SSV diameter‡ (mm)			
At knee	6.9 (5.9-7.6)	6.5 (5.5-7.8)	0.348
At mid-calf	5.3 (4.4-5.9)	5.0 (4.1-6.0)	0.318
CEAP clinical grade			0.444
C2	46 (86.8%)	40 (75.5%)	
C3	1 (1.9%)	2 (3.8%)	
C4	4 (7.5%)	9 (17.0%)	
C5	2 (3.8%)	2 (3.8%)	
VCSS‡	3 (2-4)	3 (2-4.5)	0.299 ¶

AVVQ*		14.53 (6.02)	13.22 (5.97)	0.215 §
EQ-5D™‡		0.877(0.796-1.0)	0.808 (0.726-1.0)	0.249 ¶
SF - 36® domain profiles‡‡	Physical Function	90 (70-100)	90 (75-100)	0.891 ¶
	Physical Role	100 (50-100)	100 (50-100)	0.969 ¶
	Bodily Pain	74 (42-88)	74 (51-84)	0.826 ¶
	General Health	77 (52-87)	77 (53.2-84.2)	0.606 ¶
	Vitality	65 (50-80)	55 (46.2-75)	0.072 ¶
	Social Function	100 (75-100)	100 (75-100)	0.420 ¶
	Emotional Role	100	100 (75-100)	0.820 ¶
	Mental Health	80 (72-88)	78 (60-87)	0.167 ¶

Values are expressed as percentages unless otherwise specified; *mean (s.d.) and ‡medians (i.q.r.). P values are derived from ϕChi Squared test, except §student t test, †Fishers Exact test and ¶Mann–Whitney U test. EVLA, endovenous laser ablation; BMI, body mass index; CEAP, Clinical Etiologic Anatomic Pathophysiologic; VCSS, Venous Clinical Severity Score; AVVQ, Aberdeen Varicose Vein Questionnaire; EQ-5D™ , EuroQol 5D; SF-36®, UK Short Form 36 V2.

PRIMARY OUTCOME

The primary outcome measure of early technical success, defined as abolition of SSV reflux at 6 weeks post procedure on DUS assessment was significantly higher for EVLA 51 (96.2%) versus 38 (71.7%) patients in the Surgery group (P<0.001 FET) (Table 16). The relative risk of early success with EVLA as compared to Surgery was 1.34 (95% CI 1.11 to 1.44), giving a risk difference of 0.24 (95% CI 0.09 to 0.30). The NNT with EVLA rather than Surgery to avoid a residual refluxing SSV post procedure was 4.0 (95% CI 3.2 to 10.9). Residual reflux in the surgical group was

attributable to the inability to strip the SSV as previously discussed; whereas in the EVLA group three legs developed recanalization of the treated segments (having received energy densities of 90, 92 & 99 J/cm; and pre-procedural proximal vein diameters of 5.8, 10.7 & 10.4 mm respectively) between 3 to 12 months.

Table 16: Duplex ultrasound findings of small saphenous venous system at 6 weeks

	Surgery (n=52)				**EVLA** (n=51)			
DUS findings at 6 weeks	SPJ	Prox-SSV	Mid-SSV	Distal SSV	SPJ	Prox-SSV	Mid-SSV	Distal SSV
Ligated/ occluded / absent	46	38	25	0	45	51	51	12
Patent, no or flash reflux	2	0	13	35	6	0	0	31
Patent, reflux >1 sec	4	14	14	17	0	0	0	8

Values are aggregate number of limbs at the 6 week follow-up, for assessment of abolition of SSV reflux as the primary outcome

SECONDARY OUTCOMES

Peri-procedural outcomes

Interventions:

In the Surgery group the SPJ was identified and flush ligation possible in 51 (96.2%) legs, however inversion stripping of the SSV was only possible in 35 (66%) legs. In the remaining18 patients, stripping was not possible due to either vein tear, tortuosity, spasm or intraluminal valves restricting passage of the stripper distally or a combination of the above. Because of this, the median (i.q.r.) length of SSV stripped was only 10 (3-19) cm across the 53 patients, in comparison to the EVLA group

where the length of SSV ablated was 24.5 (18.3-30.5) cm (P<0.001 MWU). In the EVLA group, SSV access and thermal ablation was achieved in all 53 (100%) patients; the mean (s.d.) energy density delivered was 99.2 (18.6) J/cm. There was no significant difference in the mean (s.d.) procedure duration for Surgery and EVLA: 63.6 (16.6) versus 58.5 (14.8) min respectively (P = 0.111 *t* test).

Procedural settings:

Unsuitability for day-case general anaesthesia necessitated in-patient treatment in 4 of 53 (7.5%) patients in the surgical group, in comparison to 1 of 53 (1.8%) patients in the EVLA group who required over-night stay post procedure (P=0.362 χ^2). This compared well with the hospital database figures for varicose veins surgery for both interventions.

Pain scores:

Post-procedure, pain scores were significantly lower in the EVLA group as compared to surgical group between days 4 and 7 (Day 4, P=0.025; Day 5, P=0.008; Day 6, P=0.033; Day 7, P=0.042 MWU) (Table 17, Figure 20), despite having no difference in the frequency of analgesia intake (Table 18).

Analgesia requirement:

Although there was a significant difference in the post-operative pain scores between the groups during the latter half of the week, yet there was no significant difference in the analgesia intake between the surgical and EVLA groups (P>0.05 χ^2). (Table 18)

Table 17: Post-procedural pain scores.

Day	**Surgery**	**EVLA**	**P-value** ¶ (Intergroup)
1	2.9 (0.8-5.8)	1.6 (0.9-4.1)	0.134
2	2.7 (0.3-5.3)	1.2 (0.4-2.6)	0.116
3	2.0 (0.1-5.1)	1.1 (0-1.9)	0.060
4	2.0 (0-4.7)	0.8 (0-1.8)	0.025
5	2.1 (0.3-3.8)	0.5 (0-1.8)	0.008
6	1.6 (0-3.1)	0.2 (0-2.0)	0.033
7	0.9 (0-2.7)	0 (0-1.6)	0.042
P*(Intragroup)	<0.001	<0.001	

Values indicate the median (i.q.r.) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). ¶Mann Whitney U Test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison.

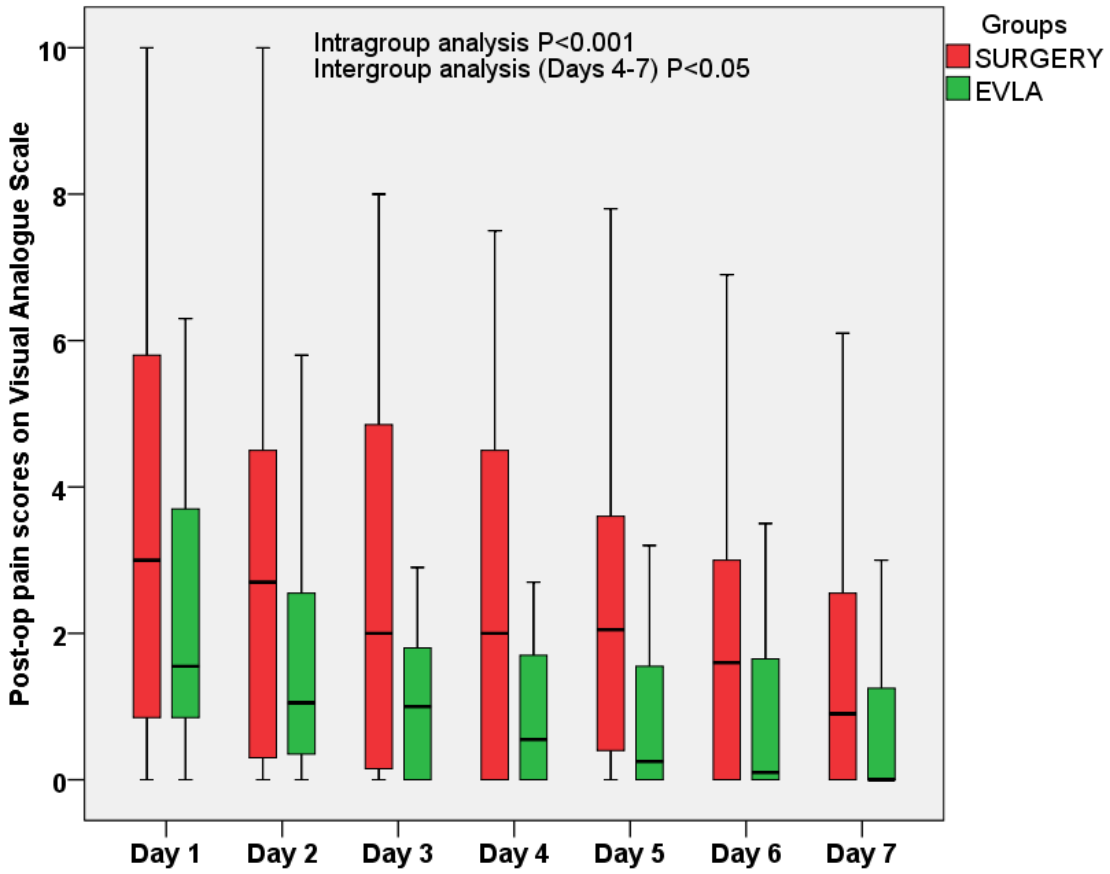


Figure 20: Post-procedural pain scores.

Pain after surgery or EVLA recorded on a visual analogue scale from 0 to 10, starting on the day of the procedure (Day1) until Day 7. Median (line within box), interquartile range (box), and range of data with 1.5 × i.q.r. below the first quartile and above the third quartile (error bars).

Table 18: Analgesia requirement by groups

Day	Analgesia Surgery Group				Analgesia EVLA Group			
	None	PCM+ NSAID	Co-codamol	Other	None	PCM+ NSAID	Co-codamol	Other
1	24.5	49.1	15.1	1.9	35.8	52.8	3.8	0
2	28.3	49.1	11.3	1.9	41.5	47.2	3.8	0
3	35.8	39.6	13.2	1.9	52.8	35.8	3.8	0
4	49.1	32.1	7.5	1.9	63.3	32.7	3.8	0
5	52.8	35.4	4.2	2.1	64.2	26.4	1.9	0
6	58.5	28.3	1.9	1.9	64.2	24.5	3.8	0
7	64.2	22.6	1.9	1.9	69.8	18.9	3.8	0

Values are percentage of patients requiring analgesia over the first week post-procedure by groups. PCM, Paracetamol; NSAID, Non-steroidal anti-inflammatory drug; other- supplementary analgesia other than the above dispensed by hospital.

Recovery:

The difference in the post-operative pain scores were reflective in the time taken to return to normal activities and employment in that the EVLA group returned faster to normal activities as compared to surgical group; median (i.q.r.) 7 (2-14) versus 14 (7.5-26) days (P=0.001 MWU). Return to work among employed individual was similarly sooner in the EVLA group in comparison to the surgical group; median (i.q.r.) 7 (3-14) versus 14 (11.5-21.75) days (P < 0.001 MWU) (Figure 21).

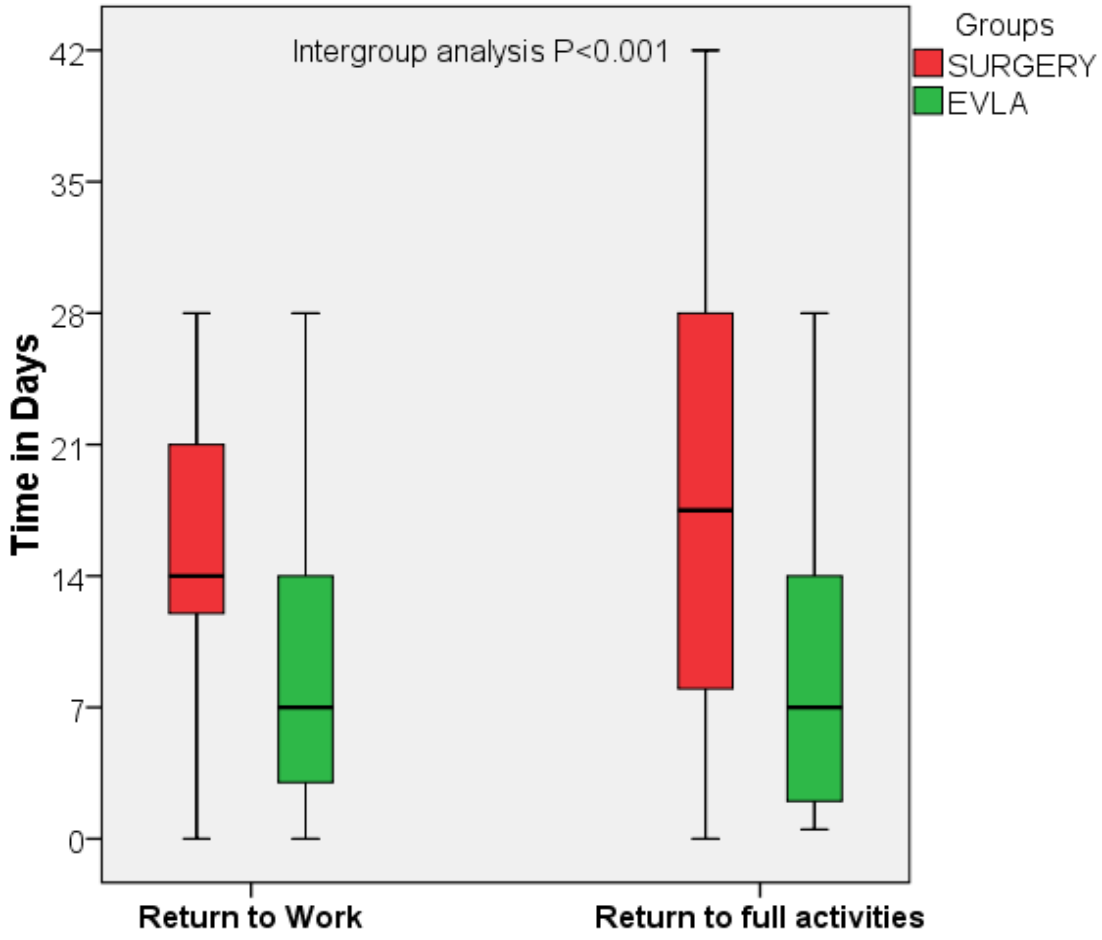


Figure 21: Time taken to return to work and normal activities post procedure

Complications:

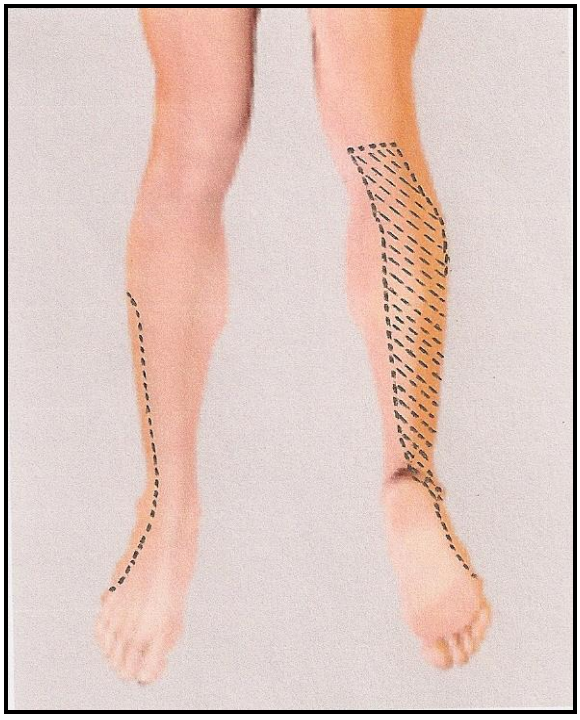
Complications were relatively rare and minor in both groups, which were self-limiting and did not increase costs (Table 19). However, there was a significantly higher incidence of early sensory disturbance in the surgical group, 14 (26.4%) patients compared to 4 (7.5%) patients in the EVLA group (*P*=0.009 FET) over the 6-week follow-up period. These sensory disturbances were most frequently observed along the sural nerve distribution (Figures 22a and 22b). The majority of these cases

however improved spontaneously leaving persistent sensory disturbance in only 5 (9.4%) surgery patients and 2 (3.7%) EVLA patients (*P*=0.434 FET) at the end of 1 year. A single major complication of deep vein thrombosis (DVT) in the popliteal vein (PV) was recorded during the 1 week DUS evaluation post-surgery. This otherwise asymptomatic patient was treated with three months of oral anticoagulation; the DVT had completely resolved over this time, leaving a patent and competent popliteal vein and no clinical evidence of PE.

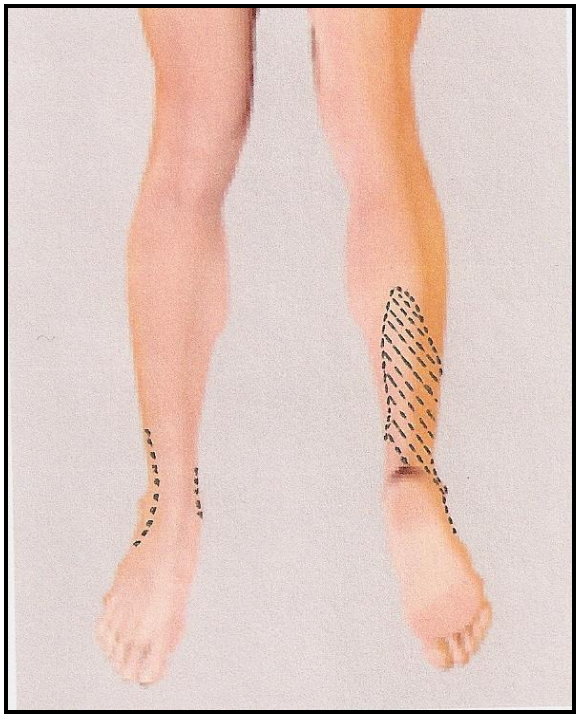
Table 19: Complications following treatment

Complications:	**Surgery**	**EVLA**	**P-value***
Sensory disturbance			
at 6 weeks	14 (26.4%)	4 (7.5%)	0.009
at 52 weeks	5 (9.4 %)	2 (3.7%)	0.434
Phlebitis	1 (1.9%)	3 (5.7%)	0.309
Infection (phlebectomy site)	1 (1.9%)	0	0.500
Skin pigmentation	0	2 (3.8%)	0.248
Haematoma	2 (3.8%)	0	0.248
DVT	1 (1.9%)	0	0.500

P-values are derived from*Fisher's exact test. DVT, deep vein thrombosis.



22a



22b

Figure 22a: Overall distribution of early sensory disturbance in Surgical Group and 22b: EVLA group (shaded area with dotted line on the front and back of same leg)

Late Outcomes

Venous Severity Scores:

Objective clinical assessment of venous disease severity saw significant improvement (lower scores) in the VCSS scores over the follow-up period in both surgery and EVLA groups, median (i.q.r.) of 3 (2-4) pre-op to 0 (0-1) at the end of 12 months (P<0.001 F-A). There was no significant difference in scores between the groups at any time points (Table 20, Figure 23).

Table 20: Venous Clinical Severity Scores over time

VCSS over time	**Surgery**	**EVLA**	**P-value** ¶ (Intergroup)
Pre-op	3 (2-4)	3 (2-4.5)	0.299
At 12 weeks	0	0 (0-1)	0.230
At 52 weeks	0 (0-1)	0 (0-1)	0.829
P*(Intragroup)	<0.001	<0.001	

Values indicate the median (i.q.r.) scores. ¶ Mann Whitney U Test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. VCSS, venous clinical severity scores.

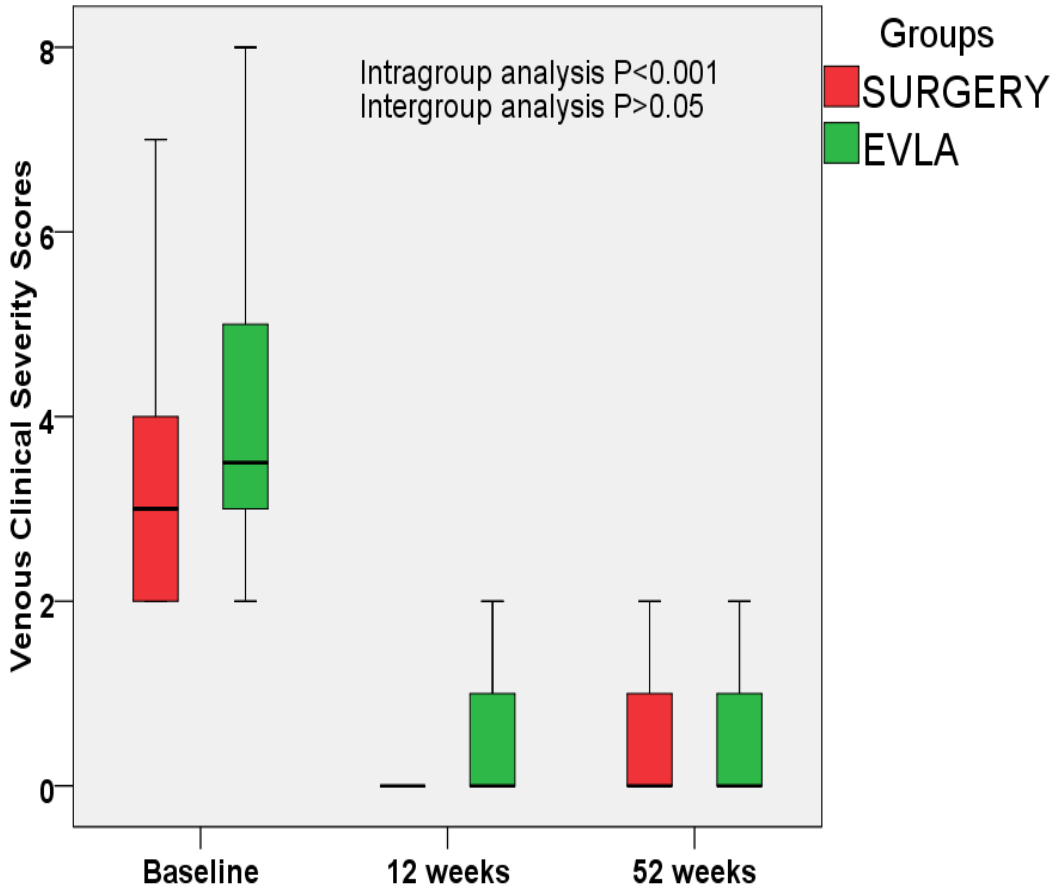


Figure 23: Clinical Severity of Venous Disease, using the Venous Clinical severity score, over time, by group

Clinical Recurrence:

Clinical recurrence (defined as clinically evident varicose veins at least 3 mm in diameter not present at 1 or 6 weeks, but becoming apparent during subsequent follow-up) over the 1 year follow-up period was low in both Surgical and EVLA groups: 9 (16.9%) versus 5 (9.4%) legs respectively (P=0.390 χ^2). The NNT with EVLA to avoid one clinical recurrence post-surgery was 14. This analysis was based on those undergoing clinical assessment at the end of 1 year.

Following conventional surgery clinical recurrence was most commonly seen in association with residual incompetent SSV, 8 of 9 (88.9%) recurrences, attributable to

anatomical failure to strip SSV following SPJ ligation. 3 of the above 8 patients were symptomatic and were treated with EVLA of the residual SSV and concomitant ambulatory phlebectomies. 1 of 9 (11.1%) recurrence in the surgical group demonstrated disease progression by developing neoreflux in a previously competent anterior accessory saphenous vein. This symptomatic patient was treated by ambulatory phlebectomies of the superficial tortuous AASV under local anaesthesia. 10 of 18 patients (55.5%) with intact un-stripped SSV did not develop clinical recurrence, however at the end of 1 year follow-up all of these 10 patients continued to have duplex demonstrable SSV reflux.

In the EVLA group two patients developed asymptomatic SSV recanalization, having received LED of 90 & 92 J/cm, compared to an overall mean (SD) of 99 (18.6) J/cm; these patients did not want further treatment at this time. Similarly another patient who demonstrated disease progression with neoreflux in both antero-lateral thigh branch (ALTB) and a mid-calf perforator remained asymptomatic and did not consider further treatment. One patient each in the same group developed symptomatic reflux in calf perforators and posterior thigh perforator which were all ligated under local anaesthesia (Table 21).

Secondary Procedures:

A total of 6 patients underwent secondary procedures. There was no significant difference between surgical and EVLA groups in the number, timing and type of additional procedures performed over the span of 1 year (P>0.05 FET). 3 symptomatic surgical patients had additional EVLA procedures for residual incompetent SSV; all of these 3 recurrences were amenable to EVLA prior to initial surgical treatment and at the time of recurrence requiring intervention. Further, 1 surgery and 2 EVLA patients underwent additional phlebectomies with or without perforator ligation under local anaesthesia as described previously. No patients in

either groups demonstrated residual symptomatic tributary varicosities warranting additional secondary procedures.

Table 21: Proportion of patients by group with clinical recurrence over 1 year

	Surgery	**EVLA**	**P-value**
Over 52 weeks	9 (16.9%)	5 (9.4%)	0.390
Pattern of recurrence	Incompetent SSV – 8 (88.9%) Incompetent AASV – 1	Recanalization – 2 (40%) Incompetent ALTB + calf perforator – 1 Incompetent posterior thigh perforator – 1 Incompetent calf perforator – 1	

P-value is derived from Chi-square test. AASV, Anterior accessory saphenous vein; ALTB, Antero-lateral thigh branch.

Duplex Findings:

Duplex ultrasound findings of the SSV for both treatment groups, over the follow-up period are listed in Table 22.

Late Complications:

No late complications were observed in either group up to the 1 year follow-up period.

Table 22: Duplex ultrasound findings of small saphenous venous system

		Surgery				EVLA			
Time		SPJ	Prox-SSV	Mid-SSV	Distal SSV	SPJ	Prox-SSV	Mid-SSV	Distal SSV
Pre-op	Median (i.q.r.) vein diameter (mm)		6.9 (7.6-5.9)	5.3 (4.4-5.9)	3.0 (3.9-2.6)		6.5 (7.8-5.5)	5.0 (6.0-4.1)	3.1 (4.0-2.8)
	Perforators, reflux >1sec		0	1(MCP)	0		1(PT)	2(MCP)	0
	Patent, no or flash reflux		0	3	28	2	0	3	31
	Patent, reflux >1 sec	53	53	50	25	51	53	50	22
At 1 week	Ligated/ occluded/absent	51	38	30	0	45	52	52	10
	Patent, no or flash reflux	0	0	13	37	7	0	0	37
	Patent, reflux >1 sec	1	14	9	15	0	0	0	5
At 6 weeks	Ligated/ occluded/absent	46	38	25	0	45	51	51	12
	Patent, no or flash reflux	2	0	13	35	6	0	0	31
	Patent, reflux >1 sec	4	14	14	17	0	0	0	8
At 12 weeks	Ligated/ occluded/absent	43	38	24	0	44	47	46	6
	Patent, no or flash reflux	3	0	13	32	4	0	0	34
	Patent, reflux >1 sec	5	13	14	19	2	3	4	10
At 52 weeks	Ligated/ occluded/absent	46	38	28	3	44	45	43	3
	Patent, no or flash reflux	3	3	13	32	4	0	0	33
	Patent, reflux >1 sec	2	10	10	16	2	3	5	12

Values are aggregate number of limbs at the various time points. i.q.r. interquartile range; MCP, mid-calf perforator; PT, posterior thigh perforator.

Quality of Life Outcomes

Generic SF-36 profile intragroup analysis:

1 week post-procedure, both groups demonstrated statistically significant deterioration in 4 each of the 8 SF-36 QoL domains. Surgery group: Physical Function (P=0.001 WSR), Role Physical (P=0.001 WSR), Bodily Pain (P=0.009 WSR) and Social Function (P<0.001 WSR). EVLA group: Physical Function (P=0.043 WSR), Role Physical (P=0.002 WSR), Bodily Pain (P=0.013 WSR) and Mental Health (P=0.013 WSR) (Table 23)

Following this initial deterioration, the surgical group demonstrated significant overall improvement in 6 of 8 QoL domains over the 1 year follow-up period: Physical Function (P<0.001 F-A), Role Physical (P<0.001 F-A), Bodily Pain (P<0.001 F-A), Vitality (P=0.050 F-A), Social Function (P=0.001 F-A), Mental Health (P=0.028 F-A); and the EVLA group in 3 of 8 QoL domains: Role Physical (P<0.001 F-A), Bodily Pain (P<0.001 F-A) and Vitality (P=0.020 F-A).

Generic SF-36 profile intergroup analysis:

The relative preservation of QoL in both Surgical and EVLA groups resulted in there being no statistically significant difference on comparison between the groups over the 1 year follow-up period (Table 23).

Generic SF6D index scores

SF-6D index utility scores were derived from responses to the SF-36 health profile. There was a significant increase (improvement) in scores for both surgery and EVLA groups over the study period (P<0.001 F-A). On comparison, there was no significant difference in scores between the groups over the follow-up time points (Table 24)

Table 23: Generic SF-36 quality of life domains

Domains†	Week	Surgery	EVLA	P-value ¶ (Intergroup)
Physical function	0	90 (70-100)	90 (75-100)	0.891
	1	70 (50-90)	80 (61.2-95)	0.095
	6	95 (85-100)	95 (75-100)	0.708
	12	95 (85-100)	95 (80-100)	0.766
	52	95 (85-100)	95 (77.5-100)	0.896
	P*(Intragroup)	< 0.001	0.069	
Role Physical	0	100 (50-100)	100 (50-100)	0.969
	1	50 (0-100)	50 (0-100)	0.277
	6	100 (25-100)	100 (31.2-100)	0.644
	12	100 (75-100)	100 (50-100)	0.779
	52	100	100 (75-100)	0.502
	P*(Intragroup)	< 0.001	< 0.001	
Bodily Pain	0	74 (42-88)	74 (51-84)	0.826
	1	52 (41-74)	62 (41-84)	0.325
	6	74 (54-100)	84 (62-100)	0.469
	12	84 (62-100)	84 (62-100)	0.483
	52	84 (61.7-100)	84 (62-100)	0.280
	P*(Intragroup)	< 0.001	< 0.001	
General Health	0	77 (52-87)	77 (53.2-84.2)	0.606
	1	77 (53.2-92)	77 (55.5-82)	0.341
	6	82 (67-92)	77 (57-89.2)	0.175
	12	77 (64.5-91)	74.5 (62-87)	0.403

	52	82 (67-92.7)	72 (57-86.5)	0.077
	P*(Intragroup)	0.253	0.491	
Vitality	0	65 (50-80)	55 (46.2-75)	0.072
	1	60 (45-73.7)	62.5 (45-73.7)	0.690
	6	70 (60-85)	68.3 (45-80)	0.325
	12	70 (50-80)	70 (45-80)	0.774
	52	75 (53.7-85)	65 (50-75)	0.136
	P*(Intragroup)	0.050	0.020	
Social Function	0	100 (75-100)	100 (75-100)	0.420
	1	75 (50-100)	87.5 (62.5-100)	0.082
	6	100 (62.5-100)	100 (75-100)	0.198
	12	100 (75-100)	100 (75-100)	0.877
	52	100 (78.1-100)	100 (75-100)	0.364
	P*(Intragroup)	0.001	0.054	
Role Emotional	0	100	100 (75-100)	0.820
	1	100	100 (66.7-100)	0.498
	6	100	100	0.582
	12	100	100 (66.6-100)	0.155
	52	100	100	0.510
	P*(Intragroup)	0.542	0.325	
Mental Health	0	80 (72-88)	78 (60-87)	0.167
	1	84 (68-91)	78(65-92)	0.680
	6	84 (76-92)	80 (68-92)	0.369
	12	88 (74-92)	84 (72-92)	0.456

	52	88 (72-92)	80 (68-90)	0.071
	P*(Intragroup)	0.028	0.256	

†values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. SF-36 – UK Short Form-36 V2, Role-Physical – Role limitation due to physical disability, Role-Emotional – Role limitation due to emotional problems.

Table 24: SF-6D utility index scores

Week	**Surgery†**	**EVLA†**	**P-value** ¶ (Intergroup)
0	0.803 (0.713-0.846)	0.772 (0.703-0.828)	0.390
1	0.745 (0.655-0.800)	0.743 (0.683-0.814)	0.366
6	0.817 (0.693-0.846)	0.809 (0.718-0.861)	0.497
12	0.830 (0.758-0.868)	0.821 (0.717-0.864)	0.321
52	0.839 (0.728-0.875)	0.813 (0.746-0.865)	0.292
P*(Intragroup)	<0.001	<0.001	

† values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. SF-6D – Short Form – 6D.

Generic EQ-5D index scores

The Surgical group demonstrated significant decrease (worsening) in the EQ5D scores at 1 week (P=0.004 WSR), whereas the EVLA group showed a non-significant worsening of scores (P=0.286 WSR). Following the initial decrease, there was a significant increase (improvement) in scores over the study period: Surgery (P<0.001 F-A), EVLA (P=0.009 F-A). On comparison there was no significant difference between the groups at any time points (Table 25, Figure 32).

Table 25: Euroqol Health Index scores

Week	**Surgery†**	**EVLA†**	**P-value** ¶ (Intergroup)
0	0.877 (0.796-1.0)	0.808 (0.726-1.0)	0.292
1	0.766(0.691-0.877)	0.796 (0.699-1.0)	0.256
6	1.0 (0.806-1.0)	1.0 (0.841-1.0)	0.802
12	1.0 (0.848-1.0)	0.965 (0.760-1.0)	0.095
52	1.0 (0.807-1.0)	0.929(0.783-1.0)	0.119
P*(Intragroup)	<0.001	0.009	

† values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. EQ-5D – EuroQol – 5D questionnaire.

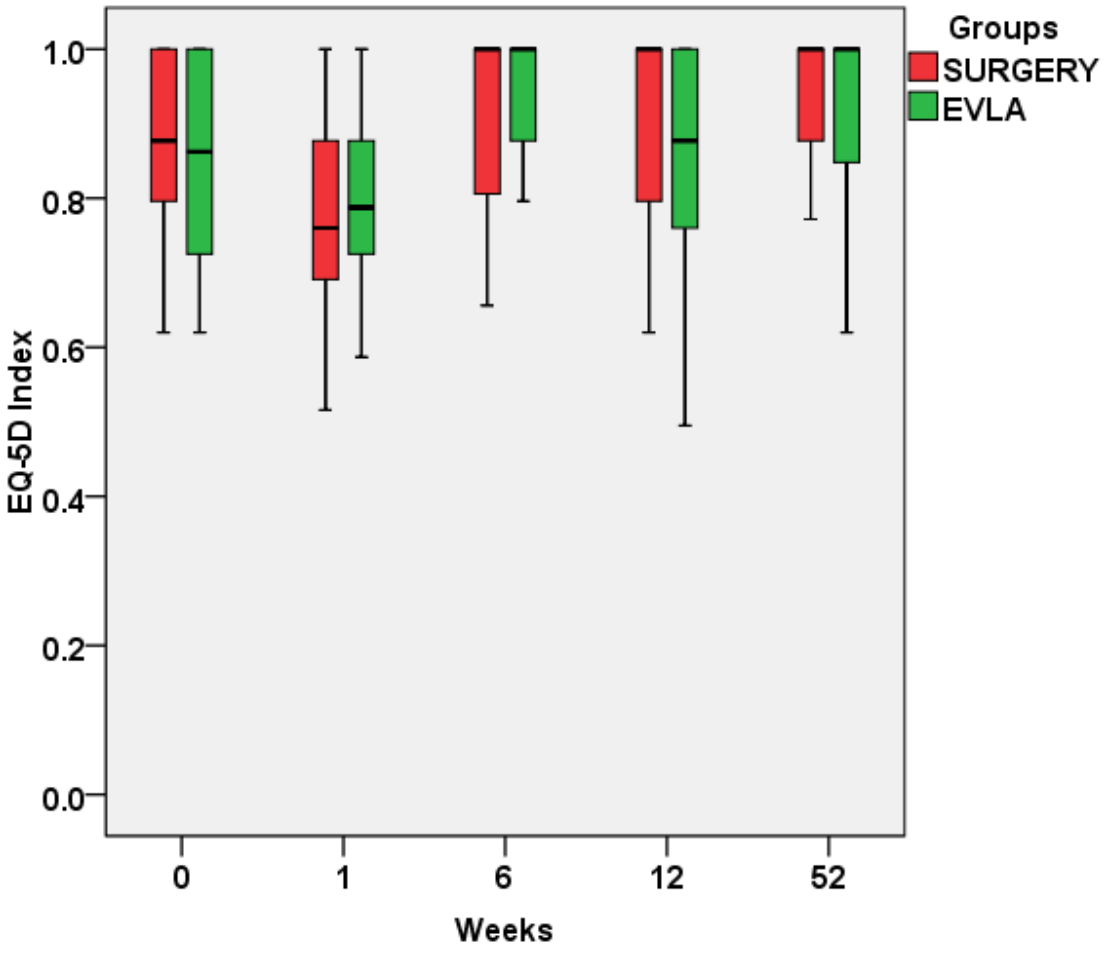


Figure 24: Euroqol Utility Index Scores, over time, by group.

Disease specific AVVQ quality of life outcomes:

Both groups demonstrated significant increase (worsening) in AVVQ scores at 1 week post interventions: Surgery (P=0.007 WSR), EVLA (P=0.003 WSR). Subsequently there was a decrease (improvement) in the AVVQ scores over the follow-up period as compared to base line in both groups (P<0.001 F-A). There was no significant difference in AVVQ scores seen between the groups at any time points (Table 26, Figure 33)

Table 26: Disease specific AVVQ Scores

Week	**Surgery†**	**EVLA†**	**P-value** ¶ (Intergroup)
0	14.53 (6.02)	13.22 (5.97)	0.215
1	17.92 (6.41)	16.22 (6.19)	0.092
6	8.77 (5.52)	8.78 (7.22)	0.996
12	5.23 (5.28)	5.05 (4.87)	0.787
52	5.30 (5.74)	4.22 (5.95)	0.327
P*(Intragroup)	<0.001	<0.001	

† values are expressed as mean (SD). ¶student t-test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. AVVQ – Aberdeen Varicose Vein Questionnaire.

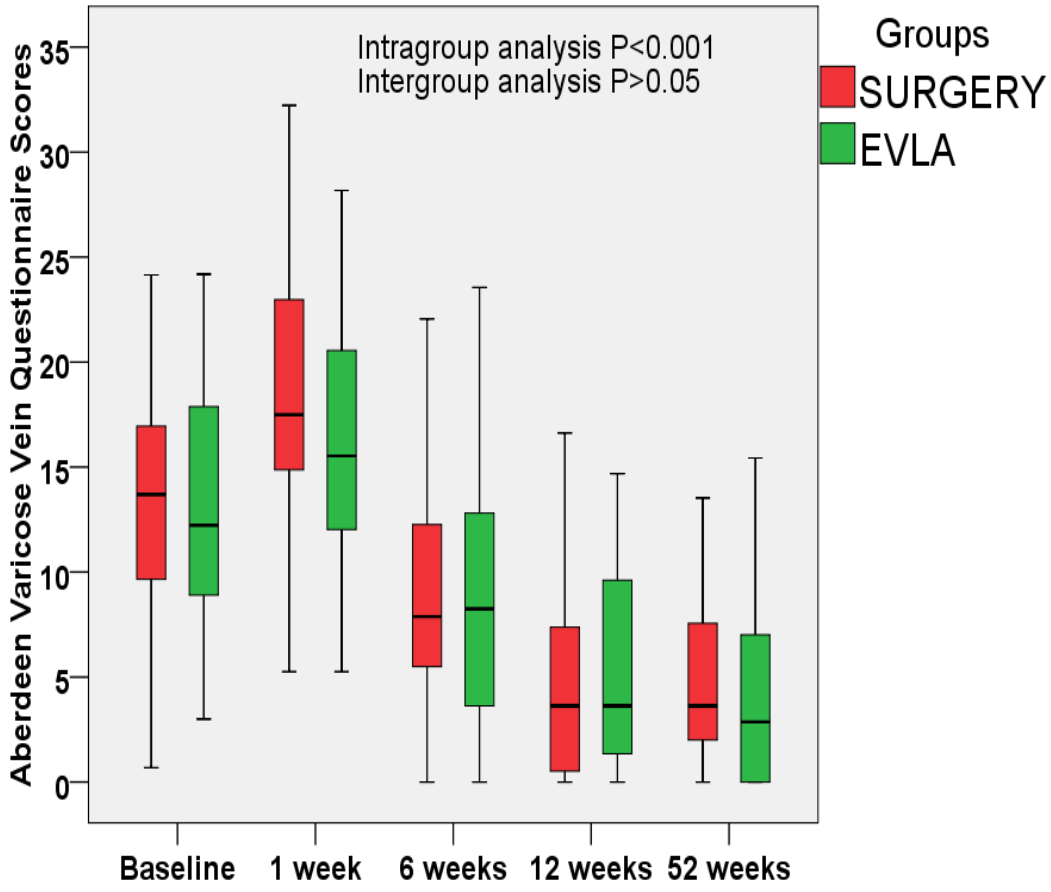


Figure 25: Disease specific quality of life AVVQ scores, over time, by group.

Patient Satisfaction

Patient satisfaction was high with both treatments and there were no significant differences between the groups: at 1 year, patient satisfaction with the overall treatment for Surgical group was median (i.q.r.) 9 (8-10), for EVLA 10 (9-10) (P=0.171 MWU); and cosmetic outcome of the treated leg was 8 (7-10) versus 9 (7.2-10) (P=0.196 MWU) in the surgical and EVLA groups respectively (Figure 34).

The EVLA patient sub-group with early evidence of clinical recurrence demonstrated a declining trend in terms of overall satisfaction, median (i.q.r) 9 (8-9.5) versus 10 (9-

10) (P=0.046 MWU) in the non-recurrent patients; and cosmesis 8 (6-8) versus 9 (8-10) (P=0.030 MWU) respectively. Such declining trend did not reach significance in the surgical recurrence sub-group (P>0.05 MWU) (Figure 35 and 36).

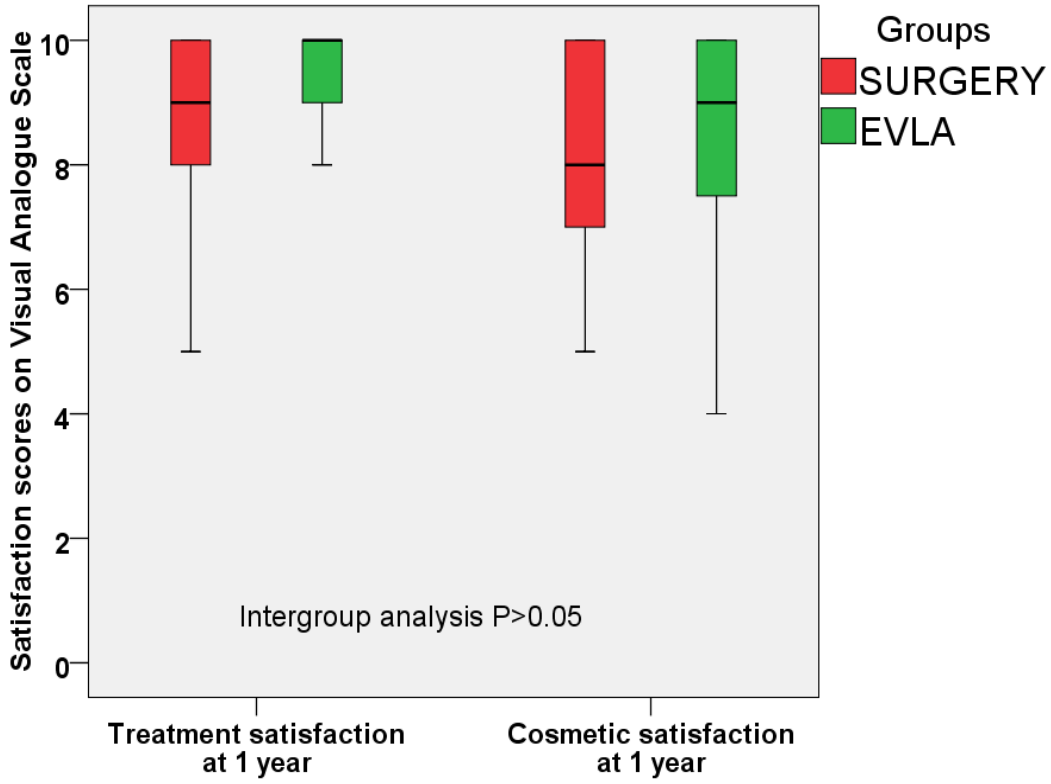


Figure 26: Patient reported satisfaction with overall treatment and cosmetic outcome by treatment groups.

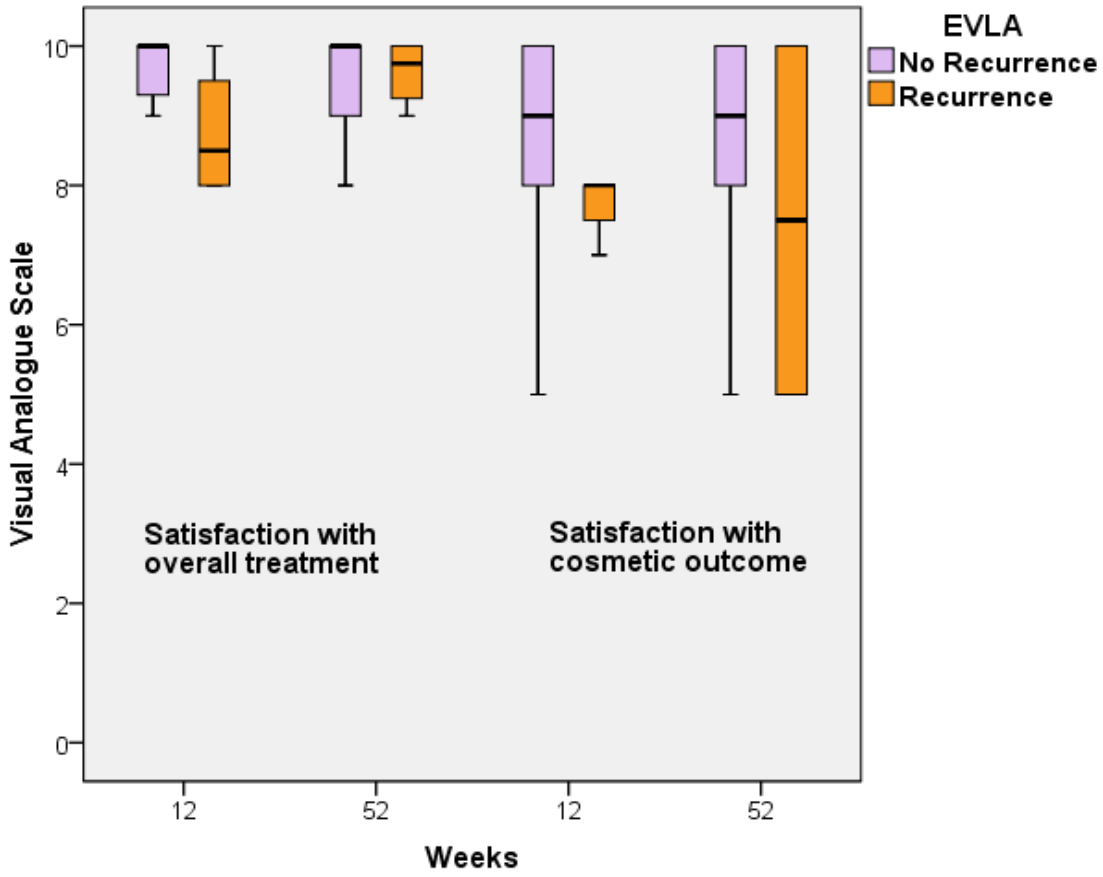


Figure 27: Satisfaction with overall treatment and cosmetic outcome of EVLA group with & without clinical recurrence.

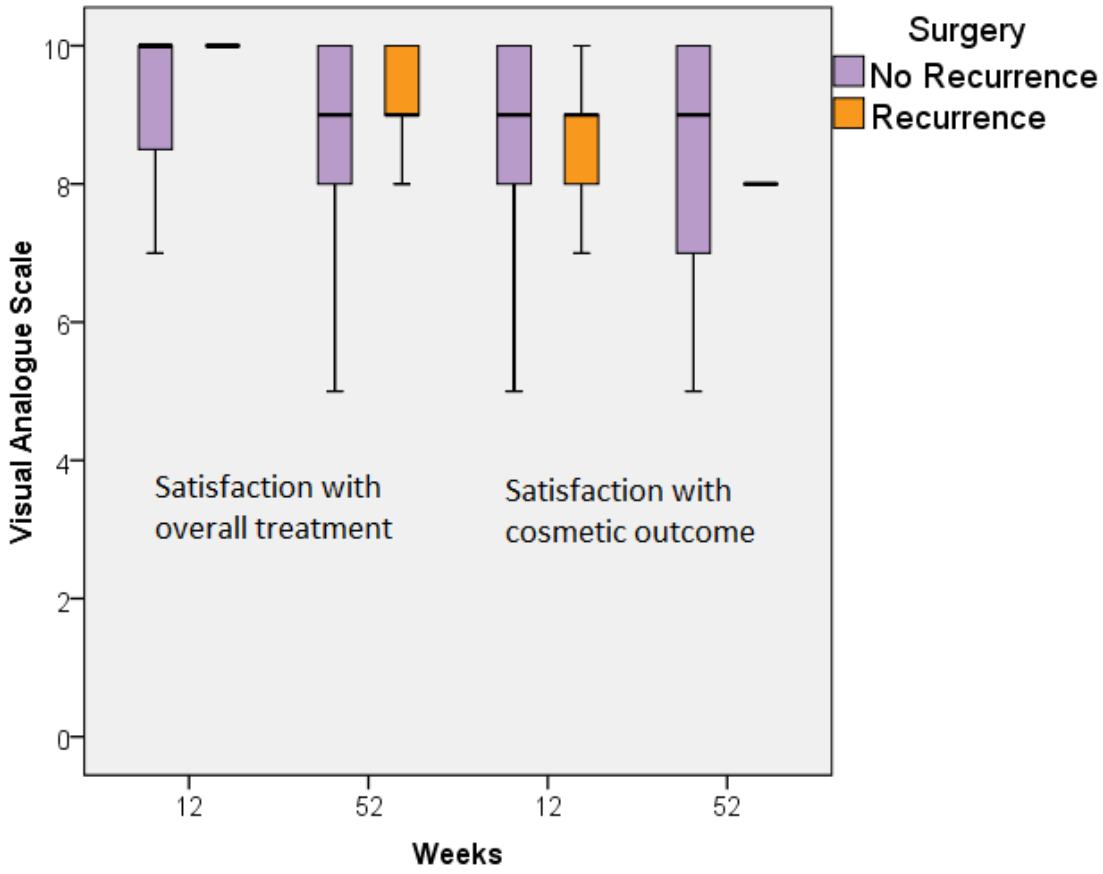


Figure 28: Satisfaction with overall treatment and cosmetic outcome of Surgical group with & without clinical recurrence.

COST ANALYSIS

This was calculated per patient under 4 categories (COST I to IV, Table 27 to 31). The mean theatre costs (s.d.) per patient were £663 (173.10) for Surgical group and £675.56 (95) for EVLA group (P=0.659 *t* test) which excluded the capital costs of laser generator and tumescent pump (both were loaned for free). The overall mean hospital costs (s.d.) were £730.77 (304.82) for Surgical group and £690.31 (121.66) for EVLA groups (P=0.390 *t* test). The mean difference in the overall cost between the two procedures equated to a saving for the hospital of £40.45 (95% CI -52.47 to

133.39) per patient receiving EVLA treatment (Table 27). The mean costs incurred by the General Practice and by the patient themselves were small indicating that the demand placed by either treatment on community services was not significantly different between the groups (P>0.05) (Table 28 and 29).

Patients who were in employment returned to work earlier following EVLA treatment when compared to Surgery by a mean of 9.6 (95% CI 4.9 to 14.3) days (which included 2 non-working weekend days). 41 patients in the surgical group and 42 patients in the EVLA group in this study were in employment. Using national data for employees in the UK (obtained from the 2012 Annual Survey of Hours and Earnings, published by the Office of National Statistics), the median gross adult weekly earnings for full time employees was estimated to be £506 (39.1 hours at £12.94 per hour); and for all employee jobs to be £405 (33.1 hours at £12.23 per hour). This was the monetary value for loss of productivity with each week of delayed return to work after either procedure. Thus the increased cost of EVLA consumables could be offset by patients returning to work 9.6 days earlier than following surgery. The mean (s.d.) overall cost for Surgery and EVLA was £2157.50 (792.69) and £1408.86 (667.65) respectively for the full time employees; £1871.18 (641.70) and £1264.58 (541.10) for all employee jobs respectively. The resultant difference in the overall cost of the two procedures was expressed as cost per working hour gained: £13.96 (95% CI 7.41 to 20.5) for full time employees and £13.36 (95% CI 7.10 to 19.62) for all employee jobs (Table 32, 33 and 34). The break-even point (defined as cost of Surgery equivalent to EVLA, when loss of productivity from being unable to work is considered) would be achieved if, following surgery, patients returned to employment 15 days (full time) or 15.1 days (all employee jobs) earlier than after EVLA, rather than after 7.6 working days as seen in this trial.

Among the unemployed, patients who underwent EVLA (n=11) returned to their full level of normal household activities 10.1 days earlier than those undergoing Surgery

(n=12). The cost of an hour of unpaid household work was estimated at £4.72 and the average time spent on household activities was 142 minutes per day, based on the Office of National Statistics Lifestyle Survey 2005. The increased cost of EVLA consumables could be partly offset by the ability of unemployed patients to return to full household activities earlier than after Surgery. The estimated difference in the cost of the two procedures was expressed as cost per hour of household work gained, which was calculated to be £12.35 (95% CI 0.45 to 24.26) (Table 31 and 34).

Although there was no significant difference in the mean (s.d) QALYs gained by the surgical group 0.8823 (0.1614) and the EVLA group 0.8258 (0.1892) (P=0.101 *t* test), using the above cost estimates, the mean (s.d.) cost per QALY gain for the two groups was calculated at £2123.48 (1084.54) and £1652.58 (966.20) respectively (P=0.032 *t* test). Since the mean cost per QALY in the EVLA group was significantly lesser than the surgical treatment group, therefore by simple discounting EVLA was found to be more cost effective. Alternatively if EVLA was to be considered as the standard treatment, then the incremental cost effective ratio (ICER) for Surgery compared to EVLA was estimated at £13250.26 per QALY, which is below the NICE determined cost-effectiveness threshold of £20,000 - £30,000 per QALY. From the above estimates, although both treatments are cost effective, EVLA is the more cost effective treatment option of the two.

Table 27: Cost incurred by the Hospital per patient [a, b]

Cost of the Operation (DSU / OPD clean procedure room)	Scale (if relevant)	Quantity	Unit Cost (£)	Surgery (£)	EVLA (£)
Mean Total Theatre time (min)				63.6	58.5
Surgeon (Consultant)		1	185	196	179
Assistant (Registrar Grade)		1	51	54	50
Anaesthetist (Consultant)		1	151	160	NA
Anaesthetic Assistant (ODA)	Band 6	1	21	22	NA
Scrub Nurse	Band 6	1	27	29	26
Floor Nurse	Band 2	1	12	12	12
Theatre Consumables†		1	10% of direct	47	27
Other trust overheads, including staffing overhead*			30% of direct	141	81
EVLA catheter (bare tip 600 nm fibre)		1		NA	275

EVLA generator including accessories		1	On loan for free	NA	0
Tumescence consumables		1		NA	25
Tumescence pump		1	On loan for free	NA	0
Duplex scanner		1	Research department's portable scanner used	0	0
Cost of inpatient hospital stay (single night)		CS – 4 of 53 Pts EVLA – 1 of 53 Pts	230	17.35	4.33
Cost of non-protocol OPD visit		CS – 1 visit for 53 pts	114	2.15	0
Cost of non-protocol duplex scan		CS – 1 visit for 53 pts	49	0.92	0
Cost of secondary procedures		CS – 3 Pts of 53, further EVLA CS – 1 Pt & EVLA – 2 Pts of 53, further phlebectomies +/- perforator ligation		38.20 4.65	9.30
Mean (s.d.) Cost (I)				**£730.77** (304.82)	**£690.31** (121.66)

a. Cost data as provided by Finance Department, Hull Royal Infirmary, Hull, UK for financial year 2011-12.

b. Calculations based on 1 Consultant Surgeon, 1 Specialist Registrar in Surgery, 1 Consultant Anaesthetist, 1 Anaesthetic ODA (operating department assistant), 1 Scrub Nurse, 1 Floor Nurse involved with the procedure, with staff wage rates at maximum of salary scale for year 2011-12 pay rates.

†Standard overheads based on overall costs - 10% of direct theatre costs were allocated to theatre consumables.

*Standard trust overheads based on overall costs - 30% of overall direct theatre costs (includes costs of staff overheads, estates, energy, capital charges, administration etc.)

Table 28: Cost incurred by General Practice per patient

Consultation	Unit Cost (£)*	Surgery		EVLA	
		Total contacts	Cost per Pt. (£)	Total contacts	Cost per Pt. (£)
GP (11.7 min. session)	43.00 [a]	3 contacts for 53 pts.	2.43	1 contact for 53 pts.	0.81
Practice nurse (15.5 min. session)	13.70 [b]	2 contacts for 53 pts.	0.25	none	0.00
Non-protocol district nurse home visit	39.00 [c]	none	0.00	none	0.00
Mean (s.d.) Cost (II)		**3.12** (12.60)		**0.87** (6.14)	

*Unit costs of Health and Social Care 2012 published by the Personal Social Services Research Unit (PSSRU) University of Kent[310]

a. includes the cost of training and direct care support staff cost

b. includes the cost of training

c. includes cost of training and cost incurred in travel

Table 29: Cost incurred by each patient

	Unit Cost (£)*	Surgery		EVLA	
		Total contacts	Cost per Pt. (£)	Total contacts	Cost per Pt. (£)
Practice visit (GP/ Practice nurse/ OPD visit)	9.10	6 contacts for 53 pts.	1.03	1 contact for 53 pts.	0.17
Cost of Antibiotics	7.65	1 in 53 patient	0.14	none	0.00
Cost of other prescription drugs	7.65	2 in 53 patients	0.28	1 patient	0.14
Mean (s.d.) Cost (III)		**1.39** (4.02)		**0.34** (2.39)	

*Unit costs of Health and Social Care 2012 published by the Personal Social Services Research Unit (PSSRU) University of Kent[310]

Table 30: Indirect Costs (loss of productivity in the employed group – CS=41, EVLA=42)

	Surgery	EVLA
Mean (s.d.) Time to return to work (days)	19 (11.7)	9.4 (8.7)
Mean (s.d.) gross adult earnings(full time employees) at £506/week	**£1421.61** (822.53)	**£699.36** (626.63)
Mean (s.d.) gross adult earnings(all employee jobs) at £405/week	**£1137.85** (658.35)	**£559.76** (501.55)
Unplanned time off work	NA	NA

Cost of a week of work for employees in the UK†

Mean weekly paid hours for ***full time employees*****.*** 39.1 hours

Mean gross adult weekly earnings for full time employees (where earnings were not affected by absence) £ 506.00

Mean weekly paid hours for ***all employee jobs.*** 33.1 hours

Mean gross adult weekly earnings for all employee jobs in the UK (where earnings were not affected by absence) £ 405.00

† Based on 2012 Annual Survey of Hours and Earnings (ASHE), published by the Office of National Statistics. (http://www.ons.gov.uk/ons/dcp171778_286243.pdf - last accessed 10/01/2014)

*Full-time defined as employees working more than 30 paid hours per week (or 25 or more for the teaching professions)

Table 31: Indirect Costs (loss of productivity in the unemployed group – CS=12, EVLA=11)

	Surgery	EVLA
Mean (s.d.) Time to return to normal household activities (days)	15.3 (11.7)	5.2 (6.5)
Mean (s.d.) Cost of unpaid household work at £4.72/hour	**£171.27** (131.24)	**£64.78** (74.24)
Unplanned time off household work	NA	NA

Cost of normal housework for the unemployed may be calculated as

Average duration of unpaid household work per day (excluding child care) 142 mins†

Average hourly rate for unpaid household work £4.72

†average time spent per person per day on housework is 142 mins – Based on the Office of National Statistics time use survey 2005. (www.ons.gov.uk/ons/rel/lifestyles/time-use/2005-edition/time-use-survey-2005--how-we-spend-our-time.pdf - last accessed 10/01/2014)

Table 32: Final Cost Analysis (Full time employees)

	Surgery (£)	EVLA (£)
Hospital costs (COST I)	730.77	690.31
General Practice costs (COST II)	3.12	0.87
Patient costs (COST III)	1.39	0.34
Indirect costs (COST IV)	1421.61	699.36
Mean (s.d.) TOTAL	**2157.50** (792.69)	**1408.86** (667.65)
Mean (95% CI) DIFFERENCE	**748.63** (397.76 to 1099.50)	
Cost per working hour gained	748.63/53.62 = **13.96**	

Table 33: Final Cost Analysis (all employee jobs)

	Surgery (£)	EVLA (£)
Hospital costs (COST I)	730.77	690.31
General Practice costs (COST II)	3.12	0.87
Patient costs (COST III)	1.39	0.34
Indirect costs (COST IV)	1137.85	559.76
Mean (s.d.) TOTAL	**1871.78** (641.70)	**1264.58** (541.10)
Mean (95% CI) DIFFERENCE	**606.60** (322.41 to 890.79)	
Cost per working hour gained	606.60/45.39 = **13.36**	

Table 34: Final Cost Analysis (Unemployed Group)

	Surgery (£)	EVLA (£)
Hospital costs (COST I)	730.77	690.31
General Practice costs (COST II)	3.12	0.87
Patient costs (COST III)	1.39	0.34
Indirect costs (COST IV)	171.27	64.78
Mean (s.d.) TOTAL	**1031.40** (418.19)	**736.04** (100.55)
Mean (95% CI) DIFFERENCE	**295.36** (10.78 to 579.94)	
Cost per working hour gained	295.36/23.90 = **12.35**	

CHAPTER 4

SUBGROUPS ANALYSIS

Subgroup analysis on the roles of extended stripping of SSV in primary small saphenous incompetence was undertaken in order to test the hypothesis that saphenopopliteal ligation (SPL) with extended stripping of SSV increased the incidence of complications especially nerve injuries, whereas SPL without stripping increased the recurrence of varicose veins as reported in literature[8 10]. Similarly, the theoretical plausibility of increase in endothermal nerve injury with distal site of EVLA access, due to the close proximity of SSV and sural nerve distally at the ankle[12 21], was also evaluated in this study.

SPJ LIGATION WITH & WITHOUT STRIPPING OF SSV

As discussed earlier (Peri-procedural outcomes Pg.144) SPJ was positively identified and ligated in 51 (96.2%) legs. Attempted inversion stripping of SSV was only possible in 35 (66%) legs; and in the remaining 18 (34%), complete stripping was not possible due to the vein snapping, tortuosity, spasm, or a combination of the above. Surgical patients were hence retrospectively subgrouped into SPL with inversion stripping of SSV ≥5 cm (n=35) and short segment excision <5 cm (n=18). Demographic variables between the two groups were comparable at baseline (P>0.05) except the higher percentage of women (P=0.04 FET) and higher mental health profile (P=0.002 MWU) of the SF-36 QoL domain in the short excision group (Table 35).

Technical Outcomes

There was no significant difference in median (i.q.r.) procedure duration between the inversion stripping and short excision groups 64 (54–75) versus 60 (49–75) minutes respectively (P=1.000 MWU). The median (i.q.r.) length of SSV removed was 16.5 (9.8–20.6) versus 3 (2-3) cm in the inversion stripping and short excision groups respectively (P<0.001 MWU).

Table 35: Demographics & QOL: inversion stripping and short excision subgroups.

	SPL with inversion stripping ≥ 5cm (n=35)	SPL with short segment excision <5cm (n=18)	P-Value[Φ]
Age (years)†	50 (38-57)	46 (36-57.7)	0.679
Women	23 (65.7%)	17 (94.4%)	0.040 [§]
Left Leg	13 (37.1%)	10 (55.6%)	0.200 [¶]
Smoking status			0.744 [¶]
Ex-Smoker	11 (31.4%)	4 (22.2%)	
Current Smoker	8 (22.9%)	4 (22.2%)	
Employed	27 (77.1%)	14 (77.8%)	1.000 [§]
Antiplatelet / Anticoagulant	1 (2.9%)	2 (11.1%)	0.263 [§]
Height (m)†	1.71 (1.63-1.80)	1.66(1.61-1.73)	0.217
BMI (kgm^2)†	24.8 (23.4-28.2)	23.7 (20.8-28.9)	0.549
SSV diameter (mm)†			
At knee	7.3 (6.0-8.4)	6.2 (5.5-7.5)	0.179
At mid-calf	5.4 (4.7-5.8)	5.0 (3.9-6.2)	0.255
CEAP clinical grade			0.372 [¶]
C2	30 (85.7%)	16 (88.9%)	
C3	0	1 (5.6%)	
C4	3 (8.6%)	1 (5.6%)	
C5	2 (5.7%)	0	

VCSS†		3 (2-4)	3 (2-4.25)	0.415
AVVQ†		13.48 (9.63-16.91)	15.30 (12.74-20.34)	0.112
EQ-5D™†		0.877 (0.796-1.0)	0.877(0.796-1.0)	0.528
SF - 36® domain profiles†	Physical Function	90 (67.5-100)	95 (85-100)	0.354
	Physical Role	100 (25-100)	100 (62.5-100)	0.355
	Bodily Pain	73 (48.5-88)	74 (42-94)	0.679
	General Health	79.5 (50-90)	75 (62-87)	0.818
	Vitality	62.5 (46.2-80)	70 (60-80)	0.258
	Social Function	87.5 (75-100)	100 (87.5-100)	0.095
	Emotional Role	100 (33.3-100)	100	0.177
	Mental Health	76 (64-84)	88 (77-92)	0.002

Values are expressed as percentages unless otherwise specified; †medians (i.q.r.). P-values are derived from ϕMann–Whitney U test, ¶Chi Squared test and §Fishers Exact test. BMI, body mass index; CEAP, Clinical Etiologic Anatomic Pathophysiologic; VCSS, Venous Clinical Severity Score; AVVQ, Aberdeen Varicose Vein Questionnaire; EQ-5D™ , EuroQol 5D; SF-36®, UK Short Form 36 V2

Clinical Outcomes

Pain Scores

There were no significant differences in the median (i.q.r.) pain scores between the inversion stripping and short excision groups (P>0.05 MWU) (Table 36). By day 7 pain scores had significantly improved in both groups (P<0.001 F-A).

Table 36: Post Surgery pain scores

Day	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision <5cm (n=18)**	**P-value** ¶ (Intergroup)
1	3.3 (1.3-5.2)	2.6 (0-6.8)	0.489
2	2.9 (0.8-3.9)	1.5 (0-6.6)	0.704
3	2.3 (0.8-4.9)	1.6 (0-5.7)	0.568
4	2.3 (0.3-4.7)	1.4 (0-4.7)	0.484
5	2.2 (0.4-3.9)	1.4 (0-3.7)	0.512
6	1.4 (0.2-3.2)	1.8 (0-3.1)	0.750
7	1.0 (0-2.6)	0.2 (0-3.0)	0.410
P*(Intragroup)	<0.001	<0.001	

Values indicate the median (i.q.r) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). ¶Mann Whitney U Test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison.

Return to work and normal activities

There was no significant difference between the inversion stripping group and short excision group for the time taken to return to work, median (i.q.r.) 21 (10-26.5) versus 17.5 (14-21) respectively (P=0.977 MWU); and return to normal activities, median (i.q.r.) 21 (8-35) versus 13 (2.7-21) respectively (P=0.123 MWU), following surgery.

Complications and Recurrence

Minor complications recorded included phlebitis in one leg (2.9%) and infection in another (2.9%) at a phlebectomy site requiring antibiotic treatment, in the inversion stripping group (P=1.000 FET). Symptoms of sural neuropathy, predominantly numbness in the sural nerve distribution, was present in 12 legs (34.3%) in the inversion stripping and 2 legs (11.1%) in the short excision groups, at six weeks postoperatively (P=0.102 FET). Sensory disturbance persisted up to a year in 4 legs (11.4%) and 1 leg (5.6%) in the inversion stripping and short excision groups respectively (P=0.651 FET). The only major complication was the duplex confirmed DVT in the popliteal vein of an asymptomatic patient in the inversion stripping group, noted at the routine one week follow-up. This patient was treated with three months of oral anticoagulation as mentioned before.

Over the 1-year follow-up period, clinical recurrence in the short excision and inversion stripping groups were 8 (44.4%) versus 1 (2.9%) legs respectively (P<0.001). All 8 recurrences in the short excision group were due to the residual unstripped incompetent SSV, whereas the single recurrence in the inversion stripping group was due to disease progression with neoreflux in a previously competent AASV which was superficial and tortuous and hence was treated with ambulatory phlebectomies under local anaesthesia. 3 symptomatic patients out of 8 recurrences in the short excision group were treated with EVLA of the incompetent residual SSV with concomitant ambulatory phlebectomies as secondary procedures.

Venous Severity Scores

In both groups, there was significant improvement in the venous severity scores post procedure, sustained over the follow-up period of one year (P<0.001 F-A). There was no significant difference in VCSS between the groups during the same period (Table 37)**.**

Table 37: Venous Clinical Severity Scores over time, surgical subgroups

VCSS over time	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision <5cm (n=18)**	**P-value** ¶ (Intergroup)
Pre-op	3 (2-4.0)	3 (2-4.25)	0.415
At 12 weeks	0	0 (0-0.25)	0.791
At 52 weeks	0 (0-1)	0.5 (0-1.25)	0.126
P*(Intragroup)	<0.001	<0.001	

Values are expressed as median (i.q.r.) scores. ¶Mann Whitney U Test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. VCSS, venous clinical severity scores.

Patient satisfaction and Quality of Life scores

Patient reported satisfaction with overall treatment and cosmetic outcome of the treated leg was comparable in both inversion stripping and short excision subgroups at 3 and 12 month follow-up (P>0.05 MWU) (Table 38). However, in the short excision group there was a significant deterioration of patient satisfaction with treatment (P=0.034 WSR) and cosmesis (P=0.021 WSR) by the end of 1 year.

Both groups reported significant improvement in generic SF-36 (5 and 3 of the 8 QoL domains in the inversion stripping and short excision groups respectively) and EQ-5D scores over the one year follow-up period (P<0.05 F-A) (Table 39 and Table 40). The relative preservation of QoL in both the surgical subgroups resulted in there being no statistically significant difference between the groups over the same follow-up period (P>0.05 MWU). The disease specific AVVQ scores were significantly better (lower

scores represent better outcomes) in both surgical subgroups over the follow-up period (P<0.001 F-A), with no significant difference seen on intergroup comparison (P>0.05 MWU) (Table 41)

Table 38: Patient satisfaction with treatment and cosmetic outcome, surgical subgroups

Patient satisfaction at follow-up	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision <5cm (n=18)**	**P-value** ¶ (Intergroup)
Overall treatment			
at 3 months	10 (8-10)	10 (9-10)	0.380
At 12 months	9 (8-10)	9 (8-10)	0.937
P* (intragroup)	0.134	0.034	
Cosmetic outcome			
at 3 months	9 (8-10)	9 (8-10)	0.105
At 12 months	8 (7-10)	9 (7.25-10)	0.294
P*(intragroup)	0.549	0.021	

Values are expressed as median (i.q.r) scores. ¶Mann–Whitney U test for intergroup comparison. * Wilcoxon Signed Rank test for intragroup comparison.

Table 39: Generic SF-36 quality of life domains for Surgical subgroups

Domains	**Week**	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision < 5cm (n=18)**	**P-value** ¶ (Intergroup)
Physical function	0	90 (67.5-100)	95 (85-100)	0.354
	1	70 (50-86.2)	75 (53.7-90)	0.787
	6	95 (80-100)	92.5 (83.7-100)	0.688
	12	95 (80-100)	95 (90-100)	0.578
	52	95 (75-100)	95 (90-100)	0.727
	P*(Intragroup)	0.002	0.008	
Role Physical	0	100 (25-100)	100 (62.5-100)	0.355
	1	37.5 (0-100)	50 (0-100)	0.626
	6	100 (25-100)	87.5 (25-100)	0.716
	12	100 (25-100)	100 (93.7-100)	0.445
	52	100 (75-100)	100	0.233
	P*(Intragroup)	0.002	0.027	
Bodily Pain	0	73 (48-88)	74 (42-94)	0.679
	1	53 (38.5-74)	51.5 (38.5-74)	0.969
	6	74 (56-100)	84 (50.7-88)	0.822
	12	84 (54-100)	84 (70-100)	0.556
	52	84 (51-100)	92 (74-100)	0.455
	P*(Intragroup)	0.002	0.007	
General Health	0	79.5 (50-90)	75 (62-87)	0.818
	1	79.5 (52-92)	77 (55.2-88.2)	0.736

	6	87 (69-96)	77 (57.7-83.2)	0.090
	12	82 (62-92)	77 (65.7-90.5)	0.835
	52	83.5 (65.7-92.7)	79.5 (68.2-94.5)	0.772
	P*(Intragroup)	0.149	0.561	
Vitality	0	62.5 (46.2-80)	70 (60-80)	0.258
	1	55 (43.7-71.2)	62.5 (48.7-80)	0.274
	6	70 (57.5-85)	65 (60-81.2)	0.677
	12	70 (45-80)	75 (67.5-80)	0.248
	52	72.5 (53.7-85)	77.5 (53.7-83.7)	0.692
	P*(Intragroup)	0.083	0.760	
Social Function	0	87.5 (75-100)	100 (87.5-100)	0.095
	1	62.5 (50-87.5)	87.5 (71.8-100)	0.023
	6	100 (68.7-100)	87.5 (59.3-100)	0.529
	12	100 (62.5-100)	100 (87.5-100)	0.136
	52	100 (87.5-100)	100 (62.5-100)	0.232
	P*(Intragroup)	<0.001	0.148	
Role Emotional	0	100 (33.3-100)	100	0.177
	1	100 (91.6-100)	100 (83.5-100)	0.861
	6	100	100 (75-100)	0.422
	12	100	100	1.000
	52	100	100	0.910
	P*(Intragroup)	0.337	0.740	
Mental Health	0	76 (64-84)	88 (77-92)	0.002
	1	80 (68-88)	86 (76-92)	0.088

	6	84 (74-92)	84 (76-92)	0.831
	12	88 (68-92)	92 (80-92)	0.497
	52	88 (72-92)	88 (76-92)	0.566
	P*(Intragroup)	0.003	0.449	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. SF-36 – UK Short Form-36 V2, Role-Physical – Role limitation due to physical disability, Role-Emotional – Role limitation due to emotional problems.

Table 40: Euroqol health index scores for surgical subgroups

Week	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision <5cm (n=18)**	**P-Value** ¶ (Intergroup)
0	0.877 (0.796-1.0)	0.877 (0.796-1.0)	0.528
1	0.760(0.691-0.859)	0.802(0.708-0.969)	0.303
6	1.0 (0.806-1.0)	1.0 (0.856-1.0)	0.799
12	1.0 (0.796-1.0)	1.0 (0.877-1.0)	0.533
52	1.0 (0.806-1.0)	1.0 (0.825-1.0)	0.807
P*(Intragroup)	<0.001	0.018	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. EQ-5D – EuroQol – 5D questionnaire.

Table 41: Disease specific AVVQ Scores, surgical subgroups

Week	**SPL with inversion stripping ≥ 5cm (n=35)**	**SPL with short segment excision <5cm (n=18)**	**P-Value ¶** (Intergroup)
0	13.48 (9.63-16.91)	15.3 (12.74-20.34)	0.112
1	18.34 (15.11-23)	17.4 (12.23-24.33)	0.722
6	7.99 (5.54-11.47)	7.52 (3.62-15.17)	0.848
12	2 (0.51-6.87)	7.21 (1.24-9.52)	0.163
52	3.25 (0.51-7.84)	5.34 (1.0-10.24)	0.410
P*(Intragroup)	<0.001	<0.001	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. AVVQ – Aberdeen Varicose Vein Questionnaire.

EVLA & SITE OF SSV ACCESS

The risks and benefits of EVLA in context to the site of SSV access was evaluated by recording the site of endovenous access as either at or above mid-calf (AMC) (n=30) or below mid-calf (BMC) (n=23). The exact site of SSV cannulation was determined by an adequate sized (≥ 3mm) distal vein segment in which venous reflux was demonstrable on DUS. The two EVLA subgroups thus formed retrospectively were comparable in terms of baseline demographics including venous severity and QoL scores (P>0.05) except the obviously wider distal vein segment in the BMC group (P=0.024 MWU) (Table 42).

Technical Outcomes

There was no significant difference in median (i.q.r.) procedure duration between AMC and BMC groups 60 (45–75) versus 55 (45–62) minutes, respectively (P=0.233 MWU); the median (i.q.r.) length of SSV treated was 19 (14.2–23.5) versus 31 (28-33.5) cm respectively (P<0.001 MWU). The longer length of SSV treated in the BMC group was reflected in the total laser energy (TLE), median (i.q.r.) AMC 1806 (1193-2295) versus BMC 3134 (2575-3810) Joules (P<0.001 MWU); however there was no significant difference in the laser energy density (LED) delivered to the two groups median (i.q.r.) 95 (82-115) versus 99 (92-104) J/cm respectively (P=0.705 MWU).

Table 42: Demographics & QOL: above mid-calf and below mid-calf endovenous access subgroups.

	AMC Group (n=30)	**BMC Group (n=23)**	**P-Value$^{\phi}$**
Age (years) †	44.5 (39-55.7)	49 (39-53)	0.660
Women	22 (73.3%)	12 (52.2%)	0.111 ¶
Left Leg	18 (60%)	13 (56.5%)	0.799 ¶
Smoking status			0.422 ¶
Ex-Smoker	8 (26.7%)	10 (43.5%)	
Current Smoker	9 (30%)	6 (26.1%)	
Employed	24 (80%)	18 (78.3%)	1.000 §
Antiplatelet / Anticoagulant	4 (13.3%)	2 (8.7%)	0.687 §
Height (m)†	1.68(1.62-1.79)	1.75 (1.64-1.82)	0.429
BMI (kgm^2)†	25.7 (22.9-27.9)	27.3 (24-29.6)	0.258
SSV diameter (mm)†			
At knee	6.4 (5.4-7.6)	6.7 (5.7-8.0)	0.673
At mid-calf	4.7 (3.9-5.3)	5.5 (4.2-6.1)	0.074
At distal-calf	2.9 (2.7-3.4)	3.8 (2.8-4.8)	0.028
CEAP clinical grade			0.547 ¶
C2	23 (76.7%)	17 (73.9%)	
C3	2 (6.7%)	0	
C4	4 (13.3%)	5 (21.7%)	
C5	1 (3.3%)	1 (4.3%)	

VCSS†		4 (2.75-5.25)	3 (3-4)	0.569
AVVQ†		11.98 (8.31-15.62)	13.95 (10.07-18.86)	0.289
EQ-5D™†		0.796 (0.725-1.0)	0.877 (0.727-1.0)	0.537
SF - 36® domain profiles†	Physical Function	90 (77.5-100)	85 (75-95)	0.437
	Physical Role	100 (37.5-100)	100 (50-100)	0.839
	Bodily Pain	72 (51-84)	74 (51-100)	0.436
	General Health	77 (52-82)	77 (57-87)	0.406
	Vitality	55 (42.5-75)	60 (50-75)	0.553
	Social Function	87.5 (62.5-100)	100 (75-100)	0.379
	Emotional Role	100 (66.6-100)	100	0.560
	Mental Health	72 (60-84)	80 (60-88)	0.233

Values are expressed as percentages unless otherwise specified; †medians (i.q.r.). P values are derived from ϕMann–Whitney U test except ¶Chi Squared test and §Fishers Exact test. BMI, body mass index; CEAP, Clinical Etiologic Anatomic Pathophysiologic; VCSS, Venous Clinical Severity Score; AVVQ, AberdeenVaricose Vein Questionnaire; EQ-5D™ , EuroQol 5D; SF-36®, UK Short Form 36 V2.

Clinical Outcomes

Pain Scores

The overall post procedural pain scores were low in both AMC and BMC groups. On Day 1 post-procedure the pain score was significantly lower in the AMC group median (i.q.r.) 1.3 (0.4-3.4) versus 2.1 (1.3-4.5) in the BMC group (P=0.033 MWU); however there were no significant differences between the groups on days 2 to 7

(Table 43). By day 7, the recorded pain scores had significantly improved in both the groups (P < 0.05 F-A).

Table 43: Pain scores in EVLA access subgroups

Day	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-value†** (Intergroup)
1	1.3 (0.4-3.4)	2.1 (1.3-4.5)	0.033
2	1(0.2-2.6)	1.7 (0.8-3)	0.362
3	1.2 (0-2)	1 (0-2)	0.810
4	0.5 (0-1.7)	1 (0-2.1)	0.427
5	0.3 (0-1.5)	0.7 (0-2)	0.486
6	0.1 (0-1.4)	0.8 (0-2)	0.755
7	0 (0-0.6)	0.2 (0-2.2)	0.226
P* (intragroup)	<0.001	0.003	

Values indicate the median (i.q.r) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). †P-values for intergroup comparison are derived from the MWU test. *Friedman-ANOVA test for intragroup comparison.

Return to work and normal functioning

There were no significant differences between AMC and BMC groups in the time taken to return to work, median (i.q.r.) 4 (2-14) versus 7 (3.7-18) days (P=0.280 MWU) and normal activities median (i.q.r.) 3.5 (1-8.5) versus 10 (2-21) days (P=0.062 MWU) respectively following EVLA.

Complications and Recurrence

Minor complications recorded in the AMC and BMC groups included phlebitis in 2 (6.7%) and 1 (4.3%) limbs (P=0.600 FET); and paraesthesia in the sural nerve distribution in 2 (6.7%) and 2 (8.7%) limbs at 6 weeks (P=0.588 FET), persisting up to a year in 1 (3.3%) and 1 (4.3%) limbs (P=0.684 FET) respectively. Skin tract pigmentation along the treated SSV segment was found in 1 limb each of the AMC (3.3%) and BMC (4.3%) groups (P=0.684 FET).

Clinical recurrence was recorded in 3 (10%) and 2 (8.7%) limbs (P=0.627 FET), in the AMC and BMC groups, respectively. Duplex demonstrated patterns of recurrence in these 5 limbs were incompetent mid-thigh perforator feeding superficial tributaries; concurrent calf perforator and anterolateral thigh branch incompetence; giacomini vein incompetence causing recanalization in the entire length of SSV, in the AMC group and incompetent calf perforators in one limb; proximal SSV recanalization due to junctional reflux in another of the BMC group. One limb in AMC group underwent ambulatory phlebectomies for residual symptomatic varicosities and one limb in BMC group open perforator ligation, under local anaesthesia (P=0.684 FET). The rest were asymptomatic and declined secondary interventions.

Venous Severity Scores

In both AMC and BMC groups, there was significant improvement in the venous severity scores post procedure, sustained over the follow-up period of one year (P<0.001 F-A). There was no significant difference in VCSS between the groups during the same period (P>0.05 MWU) (Table 44).

Table 44: Venous severity scores, EVLA subgroups

VCSS over time	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-value †** (Intergroup)
Pre-op	4 (2.75-5.25)	3 (3-4)	0.569
At 12 weeks	0 (0-0.5)	0 (0-1)	0.301
At 52 weeks	0 (0-1)	0 (0-1)	0.947
P* (intragroup)	<0.001	<0.001	

Values are expressed as median (i.q.r.) scores. †Mann Whitney U Test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. VCSS, venous clinical severity scores.

Patient satisfaction and Quality of Life scores

Both subgroups recorded high VAS scores for satisfaction with overall treatment and cosmetic appearance of the leg following EVLA, with no significant difference seen between the subgroups (P >0.05 MWU) (Table 45). Although at the end of 1 year, satisfaction with overall treatment was significantly lower in the AMC group (P=0.011 WSR) but was sustained in the BMC group (P=0.739 WSR). Cosmetic satisfaction with treatment remained high in both groups over the same period (P>0.05 WSR).

Table 45: Patient satisfaction with treatment and cosmetic outcome, EVLA subgroups

Patient satisfaction at follow-up	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-value †** (Intergroup)
Overall treatment			
at 3 months	10 (9.1-10)	10 (8.5-10)	0.160
At 12 months	9.8 (8-10)	10 (9-10)	0.179
P* (intragroup)	0.011	0.739	
Cosmetic outcome			
at 3 months	9 (8-10)	8.7 (7.5-10)	0.888
At 12 months	9.8 (7-10)	9 (8-10)	0.989
P*(intragroup)	0.782	0.782	

Values are expressed as median (i.q.r) scores. †Mann–Whitney U test for intergroup comparison. * Wilcoxon Signed Rank test for intragroup comparison.

AMC and BMC subgroups reported improvement in the post-procedural generic SF-36 QoL measures over the follow-up period. Of the 8 SF-36 health domains, 3 in the AMC & 2 domains in the BMC group reached statistical significance at the end of 1 year ($P<0.05$ F-A) (Table 46). On comparison there was no significant difference in the domain scores due to similar improvement in the QoL measures over the same period. The Euroqol health index scores also improved in both groups with the BMC group demonstrating significant improvement over the follow-up period ($P=0.002$ F-A); no significant difference was seen on intergroup comparison ($P>0.05$ MWU) (Table 47). Similarly, with the disease specific AVVQ QoL scores, both subgroups showed significant improvement (lower scores represent better outcomes) over the follow-up period ($P<0.001$ F-A), with no significant difference seen between the groups ($P>0.05$ MWU) (Table 48).

Table 46: Generic SF-36 quality of life domains for EVLA subgroups

Domains	**Week**	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-value** ¶ (Intergroup)
Physical function	0	90 (77.5-100)	85 (75-95)	0.437
	1	80 (60-95)	85 (65-95)	0.911
	6	90 (75-100)	95 (80-100)	0.378
	12	95 (80-100)	95 (70-100)	0.950
	52	90 (68.7-100)	100 (85-100)	0.288
	P*(Intragroup)	0.727	0.058	
Role Physical	0	100 (50-100)	100 (37.5-100)	0.839
	1	50 (0-100)	50 (0-100)	0.916
	6	100 (25-100)	100 (50-100)	0.517
	12	100 (75-100)	100 (81.2-100)	0.379
	52	100	100 (68.7-100)	0.580
	P*(Intragroup)	0.020	0.030	
Bodily Pain	0	72 (51-84)	74 (51-100)	0.436
	1	62 (41-84)	72 (51-74)	0.642
	6	84 (51-100)	84 (63-100)	0.906
	12	84 (53.7-100)	84 (67-100)	0.589
	52	84 (62-100)	74 (72-100)	0.883
	P*(Intragroup)	0.003	0.011	
General Health	0	77 (52-82)	77 (57-87)	0.406
	1	77 (52-83.5)	77 (57-82)	0.691
	6	72 (52-82)	82 (67-91)	0.142

	12	74.5 (62-87)	77 (59.5-91)	0.571
	52	67 (49.5-86)	72 (62-87)	0.288
	P*(Intragroup)	0.184	0.076	
Vitality	0	55 (42.5-75)	60 (50-75)	0.553
	1	60 (45-70)	65 (45-75)	0.385
	6	60 (45-75)	75 (55-80)	0.120
	12	70 (47.5-75)	77.5 (46.2-85)	0.361
	52	67.5 (48.7-76.2)	65 (50-75)	0.885
	P*(Intragroup)	0.760	0.083	
Social Function	0	87.5 (62.5-100)	100 (75-100)	0.379
	1	87.5 (62.5-100)	100 (62.5-100)	0.129
	6	100 (75-100)	100 (75-100)	0.755
	12	100 (75-100)	100 (75-100)	0.619
	52	93.7 (75-100)	100 (75-100)	0.348
	P*(Intragroup)	0.034	0.809	
Role Emotional	0	100 (66.6-100)	100	0.560
	1	100 (66.6-100)	100	0.249
	6	100	100 (83.3-100)	1.000
	12	100 (66.6-100)	100 (66.6-100)	0.970
	52	100 (83.5-100)	100	0.307
	P*(Intragroup)	0.177	0.720	
Mental Health	0	72 (60-84)	80 (60-88)	0.233
	1	76 (62-88)	80 (68-92)	0.181
	6	84 (72-92)	80 (68-94)	0.867

	12	84 (69-91)	90 (76-95)	0.235
	52	84 (63-92)	80 (72-88)	0.854
	P*(Intragroup)	0.432	0.626	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. SF-36 – UK Short Form-36 V2, Role-Physical – Role limitation due to physical disability, Role-Emotional – Role limitation due to emotional problems.

Table 47: Euroqol health index scores for EVLA subgroups

Week	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-Value** ¶ (Intergroup)
0	0.796 (0.725-1.0)	0.877 (0.727-1.0)	0.537
1	0.826 (0.751-1.0)	0.772(0.691-0.841)	0.102
6	1.0 (0.833-1.0)	1.0 (0.836-1.0)	0.972
12	0.827 (0.769-1.0)	1.0 (0.818-1.0)	0.379
52	1.0 (0.796-1.0)	0.982 (0.869-1.0)	0.830
P*(Intragroup)	0.153	0.002	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. EQ-5D – EuroQol – 5D questionnaire.

Table 48: Disease specific AVVQ Scores, EVLA subgroups

Week	**AMC Group (n=30)**	**BMC Group (n=23)**	**P-Value** ¶ (Intergroup)
0	11.98 (8.31-15.62)	13.95(10.07-18.86)	0.289
1	14.83 (12-19.73)	15.95 (12.9-21.22)	0.450
6	8.15 (2-12.72)	8.01(4.71-13.52)	0.325
12	4.04 (1.48-9.62)	3.31 (0.37-10.19)	0.731
52	2.86 (0-8.77)	0 (0-4.04)	0.280
P*(Intragroup)	<0.001	<0.001	

Values are expressed as medians (i.q.r.). ¶Mann–Whitney U test for intergroup comparison. *Friedman-ANOVA test for intragroup comparison. AVVQ – Aberdeen Varicose Vein Questionnaire.

CHAPTER 5

DISCUSSION

Non-randomised case series reported in literature have centred on technical and safety outcomes of EVLA, more often within the remit of GSV studies and results extrapolated to SSV management without actually comparing the technical efficacy, safety and clinical effectiveness of EVLA with conventional surgery, which is still considered the 'gold standard' treatment in the management of small saphenous insufficiency. Conventional surgery involves exploration of the popliteal fossa with SPJ ligation and stripping of the SSV to eliminate the hydrostatic forces of saphenous reflux. Variability of the venous anatomy in the popliteal fossa and failure to locate the SPJ, thereby requiring extensive dissection have often been attributed to the higher recurrence rates and incidence of major neurovascular injuries[313]. In addition, unlike the clear benefits demonstrated by stripping of GSV[314 315], the role of stripping SSV has been controversial, with reports of increased sural nerve injury deterring surgeons from combining SPL with SSV stripping[239 248]. There is thus scope to build upon the principles of conventional surgical treatment by aiming to achieve the same or even better results with less surgical trauma; which could then speed up post-op recovery and be beneficial to both individual patients and society as a whole. In the minimally invasive treatment of SSV incompetence, EVLA is one of the newer endovenous thermal ablative techniques that has been shown to minimise surgical trauma, as there is no need for popliteal dissection or vein stripping and aid quicker return to employment and normal activities; safety and effectiveness have also been established from published case series. Whilst these benefits on their own holds promise for the future, rigorous scientific scrutiny of both early and late outcomes, including the cost feasibility should be undertaken in a comparative setting prior to the procedure being offered as the primary treatment to suitable patients, in a set-up such as the UK National Health Service (NHS). In this era of evidence based medicine, a prospective randomised controlled trial comparing EVLA with the current gold standard treatment of conventional surgery would be the best means of

finding out these facts, rather than simply relying on reports of effectiveness from heterogeneous case series.

HELP-2 Trial

This is the first randomized trial to compare a minimally invasive endovenous treatment with conventional surgery in the treatment of isolated SPJ incompetence and small saphenous insufficiency. It is the only trial up to date that is also adequately powered to objectively compare the early technical outcomes following interventions for SSV incompetence, with the hypothesis that effective abolition of SSV reflux would reduce future recurrence rates[8 11]. The results of this study have clearly demonstrated that both treatments are safe and effective; they both improve the clinical severity of venous disease, thereby resulting in tangible benefits in both generic- and disease-specific QOL. Of the two, EVLA was found to offer superior early technical success, similar to results from other non-comparative observational studies[12 13 18-21 257]; cause less post-procedural pain, allowing an earlier return to work and normal activities, which in turn translated into EVLA being a relatively more cost-effective option for both patients and health care providers combined. The cost-effectiveness comparison was made from a NHS care provision perspective, in order to inform commissioning bodies the future applicability of EVLA as a routine procedure for SSV treatment within the NHS. Although preliminary results from this trial focussed on short-term clinical outcomes and cost comparison between EVLA and CS, patient follow-up is planned to continue up to 5 years following the index procedure; the long-term follow-up is intended to provide useful information on recurrence rates and its impact on patient's QoL. Nonetheless, when a relatively new treatment is being compared with an established one, NICE recommended health technology appraisal components[316] of scope; clinical effectiveness; cost effectiveness can be addressed with short-term results, which could subsequently lead to the development of guidelines and recommendations.

Inclusion & Exclusion Criteria

In an RCT comparing two treatments it is important to have clear, well-defined inclusion and exclusion criteria for patient selection. In this study, it also ensured that the two groups were comparable, not requiring any stratification methods to balance potential confounding variables. Only patients presenting with primary, symptomatic, unilateral SSV incompetence due to isolated SPJ reflux were included. Symptomatic patients with both uncomplicated and complicated SVI due to SPJ and SSV reflux (i.e. $C_{2\text{-}S}$ to $C_{6\text{-}S}$ clinical class of the CEAP classification) were included, in order to represent the entire spectrum of symptomatic SVI presenting to the outpatient clinics, unlike some studies that excluded higher CEAP clinical class ($C_{5\text{-}6}$), citing longer duration to manifest post-operative changes or improvement as compared to the uncomplicated C_2 clinical class[317]. For inclusion purposes, incompetence on DUS was defined as retrograde flow of ≥1 second on spectral Doppler after distal augmentation. Although the more recent guidelines from the Society of Vascular Surgery and the American Venous Forum recommend reflux duration threshold of 0.5 seconds in lower limb superficial venous segments; at the start of the trial a cut off of 1 second was chosen as was the standard practice at the time. Also, subsequent studies found that there was little difference in prevalence of SVI using a cut off of 0.5 seconds when compared to 1 second[107 121 176]. When considering reflux association with clinically evident venous disease, reflux duration of 1 second improved the specificity to 95.7% as compared to 87.9% with 0.5 seconds reflux threshold[107].

Among the patients who were assessed for eligibility to participate in the trial, the more common GSV axis incompetence (80%); ipsilateral recurrences following previous treatment (2.6%); and bilateral SSV (0.2%) varicosities were excluded, as their simultaneous treatment were likely to affect outcomes, making analysis and interpretation of results difficult. The same is true with interpreting results from studies comparing similar treatments primarily in context to GSV insufficiency that

cannot simply be extrapolated for small saphenous dysfunction as discussed above. The other well documented exclusion criteria included duplex confirmed deep venous obstruction (0.7%) due to risk of occluding varicosities which may be acting as the only collateral channels to bypass the deep venous pathology; patients younger than 18 years; inability to give informed consent or complete questionnaires during participation in the trial, which also facilitated in a high follow-up rate and data collection; pregnancy and peripheral vascular disease were stated exclusion criteria, however none of the screened patients were found to have the latter conditions.

Recruitment and Randomisation

Of the screened patients presenting to the one-stop varicose veins clinic with lower limb varicosities, 80% had GSV incompetence, 16.3% had isolated SPJ incompetence and SSV reflux, which roughly correlates with the 15% estimate of all patients with lower limb varicosities reported in literature[5 6 318]. Of the 125 patients eligible for recruitment 19 (15%) declined to participate, predominantly due to personal preference for the newer minimally invasive EVLA procedure performed under local-tumescent anaesthesia. Such refusal to participate in trials by patients seeking non-conventional surgical alternatives has been previously noted in published studies [240 319 320]. Of all the eligible patients for recruitment, there were no patient exclusions due to anatomical reasons such as large calibre of SSV or tortuosity of the vein that would prevent safe passage of the laser catheter; progressive operator experience with ultrasound and guide-wire techniques has been recognised to render the vast majority of patients suitable for the array of catheter based enodovenous thermal ablative techniques[270 319 321]. Randomisation was achieved with the assistance of a research nurse, wherein patients themselves chose an opaque sealed envelope to reveal the concealed treatment option. Access to the sealed envelopes was strictly restricted to the personnel involved in the randomization process. Although the sealed envelope technique was the only practical means of randomization at the start of the trial, the

stringency in its administration provided validity to the process, without any scope for allocation bias[322].

Conventional Surgery, EVLA procedure and complications

All patients randomized to either treatment groups received the intended treatment. CS was performed under general anaesthesia as day case procedures in the majority of patients; and EVLA under tumescent anaesthesia in a clean procedure room in the outpatient department. 4 (7.5%) patients in the surgical group and 1 (1.8%) in the EVLA group required over-night stay post-procedure predominantly due to social reasons and were discharged home within the expected time. This compared well with the hospital database figures for varicose veins treatment. The procedures were undertaken by a single consultant vascular surgeon to maintain the consistency in operating standards.

Preoperative duplex marking of the SPJ facilitated in its positive identification and ligation in 51 of 53 (96.2%) limbs[323 324]. This is in stark contrast to some of the studies that have reported no better outcomes with preoperative duplex marking, with one study reporting technical success as low as 59% with formal SPJ dissection[9 325]. The superior results in this trial may have been influenced by the experience of the vascular surgeon who also held an accredited qualification in the use of ultrasound and routinely performed the preoperative duplex scanning. This may have helped the operator in planning the popliteal fossa exploration and to anticipate technical difficulties that may arise due to anatomical variations. Formal exploration of the popliteal fossa to identify and ligate SPJ in all 53 limbs did not increase the risk of neurovascular complications in this study; overall there was one major complication of DVT recorded in a patient with SPL and inversion stripping of SSV, which resolved completely within three months of warfarin treatment. The preoperative duplex marking and the formal exploration of the popliteal fossa thus seems to have

positively influenced the abolition of deep to superficial venous reflux at the SPJ without significantly increasing the risk of complications.

SPL alone without stripping of SSV would not abolish venous reflux and is likely to result in recurrence; the evidence for this though is by no means as strong as it is for GSV management. Stripping SSV should theoretically reduce recurrence and reoperation rates by disconnecting the mid-calf perforator and tributaries to the GSV system[173 247 289]. Yet, it is not part of standard practice, at least in the UK, largely because of concerns over injuring the closely applied sural nerve[11 251]. However, there is very little evidence in the literature to support this approach. A study comparing complete SSV stripping with selective stripping of only refluxing segments reported signs of sural nerve injury in 21% versus none respectively; however, their description of the operative techniques was very brief and delayed neurological examination was carried out only in a proportion of their patients[326]. Another practice is to perform sequential avulsion i.e. after identifying and dividing the SSV in the popliteal fossa, the knee is bent up so that a length of 5–10 cm SSV can be drawn into the wound and excised. Although in theory this should be safer as the surrounding tissues could be protected under direct vision, yet there is no evidence that this technique is in fact safer than 'blind' stripping. The method of SSV stripping in this study was standardized to inversion stripping with a PIN stripper, based on level-1 evidence demonstrating better clinical and QoL outcomes in GSV stripping with the PIN technique[327 328]. SSV stripping was possible in 35 (66%) legs and in the remaining 18 (34%) it was not possible due to either vein tear, tortuosity, spasm or intraluminal valves restricting passage of the stripper distally or a combination of the above. Antegrade stripping or distal approach was not attempted after failure to strip SSV in the usual manner. Although attempting this may have succeeded in eliminating the axial vein reflux in some cases, but it was not done so because of the potential for additional surgical trauma increasing the procedural morbidity and recovery; also, such adjunct technique was not in common practice at the beginning

of the trial. The length of SSV stripped was measured at the time of procedure and was compared against the length of SSV ablated. The median length of SSV ablation achieved was significantly greater than the length stripped; and with higher rates of early occlusion achieved with EVLA (as discussed below), bears implications for considering such an alternative endothermal ablative intervention as a standard treatment in the management of SSV insufficiency.

The advantage of EVLA technique in comparison to surgery for SSV incompetence is that it does not involve popliteal dissection or stripping of SSV, thus avoiding the surgical trauma altogether. The same benefit of stripping an incompetent axial vein is achieved by obliterating the vein lumen more effectively, as seen in this trial. SSV access and immediate thermal ablation was achieved in all 53 (100%) patients. Intra-operative technical success is important in achieving durable abolition of venous reflux as demonstrated by the high occlusion rates of 96.2% achieved with EVLA versus 71.7% with surgical stripping, at the 6 week follow-up which was also the primary outcome of this study. Technical success with EVLA could be attributed to the accurate placement of the catheter tip at the SPJ (when present) that ensured abolition of reflux from the deep to the superficial system at the junction; and the delivery of adequate magnitude of laser energy, aiming for the 810 nm laser threshold of at least 70 J/cm or equivalent fluence for each leg. This was achieved by a consistent fibre pullback speed of 1 cm for every 5 s at 14W power. The magnitude of energy delivery, which has been proven to be the most important predictor of EVLA success, is dependent on the power setting and the laser exposure times (dependant on the catheter withdrawal rate) for a fixed laser beam diameter and pulse duration[329]. Thus the surgeon's experience with ultrasound and endovenous catheter techniques facilitated effective occlusion of incompetent SSVs from the junction down to the distal site of venous access. Most practitioners of EVLA do not aim for flush occlusion of the junction due to concerns of popliteal vein thrombosis, compounded by the anatomical variations at the SPJ[12 19]. Despite placing the fibre tip at the SPJ, no

incidence of DVT or thrombus protrusion into the deep vein was found in this study; one reason for this is the surgeon's technique to create peri-luminal compression of the junction with copious infiltration of tumescent anaesthesia around the SPJ, preventing the physical transmission of heat energy from the tip of the fibre beyond and into the deep system.

Some surgeons are reluctant to use thermal ablation in the management of SSV insufficiency, despite using it in the treatment of GSV and many opt for foam sclerotherapy instead. One reason for this is a perceived difficulty in passing the wire through the SPJ. Flush occlusion of the SPJ (as mentioned above) was aimed for in this study; and it was found that in the vast majority of cases, if the junction was a significant source of reflux, the wire could be easily passed. The use of a hydrophilic wire could also help with a difficult junction, in conjunction with a little rotational torque. In cases where the true source of reflux is a cranial extension of the SSV or Giacomini vein, the wire often passed preferentially into this vein from the SSV rather than into the deep system. In such cases, ablation of the refluxing segment (in some cases as far as the groin) could be undertaken. Ablating past the SPJ rather than up to it typically leaves either an occluded SPJ or a competent junction receiving flow from the gastrocnemius veins (GV). If the GV is also incompetent pre-procedure, it is worth initially passing a wire separately through the SPJ and if required a further wire through the cranial extension or Giacomini vein. A further anxiety regarding SSV thermoablation rests with the potential for sural nerve damage; however it seems, as noted with the GSV, EVLA results in less damage to the accompanying nerve than stripping. This is due to the use of tumescent anaesthesia during EVLA that acts as a "heat shield" protecting the paravenous structures from thermal injury, which are pushed away by the tumescence envelope. The rates of injury following stripping and hence the procedural morbidity may also be reduced by tumescent use, although this is not in common practice and could be considered in future studies.

Postoperative Follow-up

Follow-up visits were achieved as planned with high rates of attendance in both treatment groups. Attendance numbers at the end of one year follow-up was still high enough to retain the study's power to detect true differences in technical and clinical outcomes. Follow-up rates were far superior compared to similar trials of venous interventions where continued and complete follow-up have been reported to be suboptimal and challenging. The possible reasons for this could have been the incentive of a thorough examination including DUS assessment over an extended period of follow-up that provided a sense of assurance and motivation for the patients. It may have also resulted from the quality of information and standard of care received during the course of the trial. This high follow-up rate in turn ensured that potential for bias, due to attrition or loss to follow-up was minimised.

Postoperative Pain, Analgesia requirement

Pain is an important component of all QoL measurement tools. Postoperative pain is a direct result of surgical trauma and reflects the invasive nature of the procedure. It bears a definite impact on patients' postoperative recovery and satisfaction with the procedure. In this study, postoperative pain was measured comprehensively using a pain diary that recorded pain on a visual analogue scale and the simultaneous usage of analgesia on a daily basis for the first week post procedure. All patients were given standard analgesic packs and advice on taking them. Postoperative pain scores were relatively lower in the EVLA group throughout the week post-procedure as compared to the surgical group; between days 1 and 3 the difference did not reach statistical significance however between days 4 and 7 the scores were significantly lower in favour of EVLA; similar findings have also been reported in non-randomised case series[21 330]. Although the analgesia intake was not statistically different between the two treatment groups, by Day 3 following EVLA 57% (28/49) had stopped taking any analgesia compared to 39.6% (19/48) in the surgical group. This trend is

reflective of the minimally invasive nature of EVLA, which is expected to result in lesser pain, faster recovery and return to routine activities for the patients.

Return to activities

Patients in both treatment arms were given the same standard instruction regarding mobilization within the limits of pain or discomfort following treatment; no restrictions were placed on return to routine activities or employment if these could be undertaken comfortably and safely. As expected, patients in the EVLA group experienced less disruption to their activities of daily living and returned to both routine activities and employment at least a week earlier than patients receiving conventional surgery; similar to results borne out by studies comparing the same treatments in GSV insufficiency[209 270]. EVLA resulted in 60% of patients returning to normal routine activities within the first week as compared to 25% following surgery; amongst the employed, 56% returned to employment within the first week following EVLA, whereas only 15% could do so following CS. The time taken to return to work following varicose veins treatment is known to be influenced by multiple factors[331 332]. However, both groups in this study were well matched at baseline, and given the same advice regarding recovery and the expected convalescence. Thus the median difference of 7 days in favour of EVLA reported here is likely to be real.

Post-procedural Morbidity

Despite concerns regarding sural nerve injury resulting from SSV stripping[239], this technique has been shown to decrease recurrence rates after SPJ ligation by disconnecting the mid-calf perforators and communicating veins to the GSV system[8 289]. As this study was powered to compare the relationship of technical outcomes and recurrence, rather than specifically exploring periprocedural morbidity in depth, SSV stripping was selected as a necessary component in the surgical treatment arm. In the literature, early paraesthesia in the sural nerve distribution following SSV stripping has been reported between 0 - 40%, persisting in some even up to a year. Such rates

are often derived from small case series and reports where both SSV and GSV operations were analysed together and often the operative and assessment methodologies were incompletely described. This makes any interpretation or comparison extremely difficult; although permanent damage to the nerve is reported only as a rare complication. In this trial, SSV ablation or stripping was attempted to the level of distal calf with demonstrable incompetence. The incidence of early sensory disturbance was significantly higher in the surgical group (26.4%) as compared to the EVLA group (7.5%). These sensory disturbances were most frequently observed along the sural nerve distribution. The majority of these cases however improved spontaneously leaving persistent sensory disturbance in 9.4% of surgical group and 3.7% of EVLA group at the end of 1 year. The relatively higher incidence of sensory disturbance in both treatment groups of this study as compared to those reported in the literature, could have also been the result of detailed subjective and objective assessment of the treated legs at each follow-up visit.

A single major complication of deep vein thrombosis (DVT) in the popliteal vein (PV) was recorded in the surgical group (1.9%). This otherwise asymptomatic patient was treated with three months of oral anticoagulation to resolve the DVT completely. The incidence of DVT with surgical treatment of SSV has been reported between 0 – 3%; and with EVLA between 0 – 6%. The relatively higher incidence with EVLA has been attributed to the variable anatomy of the saphenopopliteal junction and the operator's learning curve with SSV treatment[12]. Incidence of other minor complications such as phlebitis, infection, haematoma and skin pigmentation were low and comparable between the groups. They were self-resolving and did not lead to increased costs or affect postoperative recovery for the patients.

Late outcomes – venous severity

Both treatments produced significant improvement in objectively evaluated venous severity scores (VCSS), which were well established as early as 12 weeks post

procedure and sustained over the entire follow-up period of 1 year. This confirmed that both treatments were equally effective in achieving symptomatic and clinical correction in patients with SSV incompetence. This was achieved across the spectrum of uncomplicated and complicated venous disease patients ($C_{2\text{-}S}$ to $C_{5\text{-}S}$ clinical class of the CEAP classification) in both treatment groups. Although the majority of patients in this trial belonged to the uncomplicated $C_{2\text{-}S}$ clinical class of SVI, where outcomes following treatment are more readily obvious; positive results with either treatment even in the higher $C_{4\text{-}S,}$ $C_{5\text{-}S}$ clinical class are encouraging for future consideration of these treatments especially minimally invasive interventions such as EVLA as feasible alternative options for patients with clinically worse venous disease, who generally tend to be poor candidates for a surgical intervention under general anaesthesia due to significant comorbidities.

Recurrence

With the sample size of the current study, clinical recurrence rates were similar at one year, but long-term follow-up will establish the fate of those with residual incompetence after failed stripping and the rates of disease progression in a population with successfully treated SSV insufficiency. In this study, the fact that all of the residual, incompetent, unstripped SSVs failed to revert to competence supports the hypothesis that it is the elimination of SSV reflux that is important and that ligation of SPJ alone is insufficient. It is interesting that despite the technical inadequacies of SSV surgery, the clinical recurrence rates were significantly less at one year than those observed after successful saphenofemoral junction ligation and stripping[306]. The reason for this is unknown, but this highlights another difference between the management of these 2 distinct clinical patterns.

Any new treatment of varicose veins requires long-term follow-up to determine recurrence rates and its impact on patients QoL, hence further follow-up will be undertaken in this trial. Recanalization has been reported after EVLA of SSV[12 18 257]

and may compromise long-term outcomes; a large observational series of 229 SSV EVLAs found a recanalization rate of 1.3% at 2 years[15], whereas prospective data from this RCT indicates an early rate of 5.6% (3 patients), although it would be inequitable to compare results between studies using different wavelengths and energy densities. In this trial, 1 patient developed full-length SSV recanalization due to neoreflux from a previously competent Giacomini vein, whereas the other 2 developed junctional incompetence with reflux into proximal SSV segments; all 3 having been treated above the 810-nm energy density threshold of 70 J/cm.[273] These may be related to the vein diameter rather than the energy density alone, both of which have been implicated with increased occurrence of recanalization[15 18 257].

Quality of Life

Contrary to the previously held misconception of varicose veins being a minor cosmetic problem, various studies have conclusively established the relationship between QoL impairment with CVI. As a result, the focus of treating varicose veins has not only been to alleviate symptoms but also to improve patient's QoL. In the UK, QoL analysis has evolved from a research role and it is now compulsory in the NHS to measure QoL before and after venous interventions[192 193]. In this study, QoL was assessed using a combination of disease specific and generic tools to assess the effects of small saphenous varicose vein disease on QoL and to detect any changes brought about by the two interventions. The AVVQ being disease-specific was expected to be sensitive to changes in health as a result of interventions aimed at treating varicose veins causing impairment of health related QoL; AVVQ significantly improved following both EVLA and Surgery, being sustained over the follow-up period of one year. At the end of the year, the AVVQ score for EVLA was better but not statistically significantly different to that of surgery. However, less pain, faster recovery and lower recurrence rates after EVLA seem promising, having also been alluded to by previous nonrandomized studies[12-16 18-21 330]. It is possible that the use of tumescent anaesthesia before stripping may also improve post-procedural

pain, immobility, and nerve injury, but this was not standard practice and hence not used in this study.

Over the follow-up period, significant improvement was seen in six of the eight SF-36 health domains in the surgical group and three of the eight in the EVLA group; improvement in both treatment groups were predominantly in the physical domains, suggestive that despite being perceived as a minor ailment with predominantly cosmetic implications, treatment of varicose veins by either conventional surgery or the newer EVLA technique contributed to overall improvement of physical health status. When compared against each other, there was no statistically significant difference in any of the health domain scores. In common with the early RCTs comparing EVLA and conventional surgery for GSV insufficiency[270 333 334] this study was underpowered for detailed QoL analysis and therefore could not confirm or refute any true benefit of EVLA over surgery in this area. Possibly due to the same reason, there was no significant difference in the generic EQ-5D questionnaire scores between the two treatments over the follow-up time points. There was however, a relatively greater deterioration in scores immediately after surgery corroborating well with the early clinical outcomes of worse pain and slower return to work and routine activities, as compared to the EVLA treatment group. Despite this initial deterioration, significant improvement was seen and sustained over the follow-up period with both treatments establishing their effectiveness in the management of SSV insufficiency.

Patient Satisfaction

Along with well-known patient reported outcomes such as health-related QoL and current health state, patient satisfaction provides the ultimate end point for quality of health care provision. Thus, it is an essential part of quality assessment addressed from the patient's perspective. Advent of newer treatments for varicose veins has made this assessment even more important in the evaluation of such interventions.

Patient satisfaction with overall treatment and cosmetic outcomes following both procedures were assessed on a visual analogue scale (VAS), which is a numerical scale that can be easily analysed, interpreted and used for comparison between treatments and different studies. Patient satisfaction data was collected at 3 and 12 month time points post procedure to gain a more accurate measure of patients' views or understanding of the success or failure of their treatment, having recovered completely and returned back to their routine activities. Patient satisfaction is known to be low following venous surgery[335] and it was reassuring to see such high rates following either treatment. At the end of one year, patient satisfaction with overall treatment and cosmetic outcome was relatively higher for EVLA but did not reach statistical significance. The EVLA sub-group with early evidence of clinical recurrence demonstrated a significant decline in overall satisfaction and cosmesis, as compared to the non-recurrence patients in the same group; this may suggest a higher level of expectation with the treatment and its cosmetic outcomes with the newer minimally invasive endovenous intervention, which perhaps led to a greater degree of dissatisfaction on developing clinical recurrence. Such declining trend did not reach significance in the surgical recurrence sub-group.

Cost-time Effectiveness

In the past, the focus on post-operative clinical results and the indifference to QoL outcomes has meant that the cost-effectiveness of treatment has been sparingly discussed in literature. In the current era, economic analysis is increasingly recognised as a critical component of health technology assessment and service provision. Economic modelling strategy has established the superiority of conventional surgery when compared to conservative management in the treatment of SVI in the REACTIV trial[208]. In context to the modern management of SVI, there has only been one high quality analysis up to date, which suggested that EVLA carried out under tumescent anaesthesia had the highest probability of being cost effective at the commonly quoted UK NHS threshold of £20 000 per QALY[336]. No studies have looked

into specifically comparing the cost effectiveness of newer treatments with conventional surgery for SSV treatment.

The attempt at cost effectiveness analysis in this trial should be interpreted with caution. Conventional surgery for SSV incompetence is commonly performed by vascular surgeons in both tertiary referral centres and district general hospitals, whereas EVLA may not be as widely available. Additionally endovenous techniques require specialist ultrasound scanning skills which may be limited to surgeons with a special interest in venous disease (as in this study). The costs of training and learning-curve effects were not considered in this study as both procedures were performed by a single surgeon with additional ultrasound qualifications; thus the clinical outcomes and the associated costs could vary depending on the expertise and case-volume load for the surgeon and the treating centre as a whole. The hospital costs in this study were calculated based on theatre time and maximum wage rates for the personnel involved and hence would be sensitive to changes if either or both these parameters differed in other hospital settings. The method of allocation of standard overheads may also vary between hospitals. At the start of the trial, the cost incurred by the hospital per procedure was anticipated to be higher for EVLA due to the additional cost of the disposable laser catheter, however the cost analysis at the end of the trial proved otherwise; one of the reasons for this being, the cost of the laser catheter which became cheaper over the years as a result of its growing popularity and expanding consumer market. The fixed cost of the laser generator and the tumescent pump, both essential for EVLA procedures was not included in the hospital costs as they were being used for both trial and non-trial patients even before the start of this trial and was loaned for free to the hospital. This fixed cost would have to be considered when setting up a new EVLA service; although at current competitive prices it is unlikely to change the cost evaluation significantly. Similarly, another factor to consider is the cost accrued with routine duplex scanning following endovenous procedures to assess treatment success and/or rule out complications

such as DVT; unlike after conventional surgery when no routine scans are carried out unless indicated. The follow-up duplex scan costs in this trial were discounted as both groups underwent equal number of duplex assessment for an extended period as per trial protocol for research purposes. As the safety and effectiveness profile of EVLA in the treatment of SVI grows stronger, it is likely that the customary early post-operative duplex scanning practice may change to as indicated only basis, similar to post-surgical management. The cost calculations from this trial may then become relevant to clinical practice outside of a trial setting.

Health economics analysis is traditionally carried out from a healthcare system perspective often alluded to as the 'third party payer'. Whilst this is useful to make comparisons between different healthcare systems globally, in the UK, the society is the third party payer and a societal view on the impact of minimally invasive endovenous treatment on loss of productivity and time off work is fundamental. The results from this study has demonstrated a clear winner in EVLA over conventional surgery in terms of short-term outcomes of return to work, routine daily activities and their estimated cost gains. The indirect-cost analysis for the employed group was based on national employment data which were taken from Annual Survey of Hours and Earnings (ASHE) 2012 and also estimated for unpaid household work from Office of National Statistics time use survey 2005. The 2005 rates for unpaid household work were applied due to lack of similar data for the reference year 2012. This may explain the smaller cost difference between the groups when comparing the total costs for the unemployed patients. The imputed monetary value of unpaid household work is low and is unlikely to be accurately estimated even with more recent rates; the analysis in the smaller group of unemployed patients was carried out to obtain an approximate idea of the treatment costs in this subgroup as well. The faster return to routine household activities ensured that the estimated overall cost for EVLA treatment was cheaper than conventional surgery, similar to the employed group. To understand the cost comparison between the two treatments in a utilitarian

manner, outcomes for the employed group were reported as cost per hour of work gained and break even points. Prospective QoL data collection also allowed for cost per QALY gain and ICER estimation, which are NICE recommended standard cost-effectiveness analysis tools that can be applied for health technology assessment in context to NHS hospital practices in the UK. Since both surgery and EVLA were equally effective in the clinical management of small saphenous insufficiency, the lack of significant difference in QALY gain was explicable, however the cost gains with the EVLA procedure being carried out in a clean procedure room under tumescent anaesthesia not requiring full theatre, general anaesthetic services, and the economic advantages of faster return to work and routine activities resulted in establishing the cost-effectiveness of EVLA over conventional surgery in the short-term. For healthcare providers, these results may make EVLA an attractive and feasible first-line treatment option in the treatment of small saphenous insufficiency. The economic analysis in this trial did account for the small number of early recurrences, its impact on QoL and costs associated with secondary procedures. This may not be a true reflection of the natural history of recurrences and patient attitudes to seek treatment when not being intentionally followed up as in this trial. However, in order to establish the most cost-time effective treatment of the two, further long term data on recurrences, its QoL impact and economic implications is vital to inform economic models that would then facilitate extrapolation of such results to an appropriate time frame i.e. the patient's life-time following varicose vein treatment.

ADDITIONAL FINDINGS

SPJ ligation and stripping of SSV: To strip or not to?

The surgical management of small saphenous incompetence is relatively challenging and technically demanding compared to that of great saphenous venous system. Variability of the venous anatomy in the popliteal fossa and failure to locate the SPJ imposing extensive dissection have often been attributed to the higher recurrence

rates and incidence of major neurovascular injuries[313]. In addition, unlike the clear benefits demonstrated by stripping of GSV[314], the role of stripping SSV has been controversial, with reports of increased sural nerve injury deterring surgeons from combining SPL with SSV stripping[239 248]. Owing to these very reasons, there has been no randomized controlled trial undertaken to validate the clinical outcomes of SPL with or without SSV stripping.

The operative aim for all 53 limbs was to perform SPL with inversion stripping of SSV, although the extended stripping was not possible in a proportion. This is one of the shortfalls of this study (as discussed in the Critique section below, Page 224) wherein the SPL short excision group was not unstripped by choice, but due to failed attempts. Whether preoperative duplex evaluation could have predicted the feasibility of SSV stripping or not in this study is debatable, as the majority of patients in both subgroups had refluxing incompetent SSVs up to mid-calf level or lower, thereby providing enough length of SSV to perform inversion stripping; only one limb each in both subgroups had tortuous SPJ/proximal SSV segments which could be anticipated to cause difficulty in passing the PIN stripper (PS) past the tortuosity without causing proximal vein tear in these limbs. Venous spasm during attempts to introduce PS or resistance by intraluminal valves restricting passage of the stripper or a combination of both could be speculated as the likely causes for inversion stripping failure. The inability to strip SSV post-SPL in nearly a third of the operated limbs, despite elective planning to do so, also bears implications for considering alternative endovenous ablative treatments with higher technical success of SSV occlusion[12-16 18-21 257]. The rationale for planned stripping was extrapolated from the best long-term results and reduced rates of late re-operations reported in literature with GSV stripping[315]. The method of SSV stripping was standardized to inversion stripping with a PS, based on level 1 evidence demonstrating better clinical and QoL outcomes in GSV stripping with the PIN technique[327 328]. Contrary to the reported morbidity associated with SSV stripping, the subgroup analysis showed no significant increase

in sural nerve injury in comparison to the short excision group, nor was there an increased incidence due to formal exposure of popliteal fossa as discussed above[8]. Whether these low rates of nerve injury were influenced by the use of PS, which is known to cause less perivenous trauma, is difficult to determine as there have been no randomized studies carried out comparing PIN technique to conventional stripping for SSV[337 338].

Similar to the results seen with SFJ ligation and GSV stripping[314 339], SPL with SSV stripping may be expected to decrease the risk of recurrence due to removal of the SSV run-off channel into which new veins could otherwise drain. In this subgroup analysis the incidence of clinical recurrence was significantly higher in the short excision group, which could be predominantly attributed to the residual incompetent SSV that could not be stripped. These findings are identical to the Joint Vascular Research Group (JVRG) UK[8] results and their observation that the stripping component of SSV surgery was more important than the extent of the surgery at the SPJ. This in turn would make a stronger case for adoption of endovenous methods that principally target and obliterate the incompetent truncal vein. In the meanwhile, the significant improvement in venous severity, generic- and disease-specific QoL measures up to one year in both surgical subgroups of this study establishes the effectiveness of SPL with or without stripping in the treatment of SSV incompetence; although the increased rates of recurrence, declining patient satisfaction with overall treatment and cosmetic outcomes in the short excision group favours management of SSV incompetence with SPL and extended stripping, without any increased risk of significant nerve injury.

EVLA of SSV and site of access

The retrospective subgroup analysis based on the level of EVLA access; above mid-calf (AMC) or below mid-calf (BMC) did not show a significant difference in the paraesthetic complications between the groups. This finding is contrary to the results

from a recent randomized-controlled trial performed by Doganci et al[259] who found a significant increase in sensory paraesthesia associated with endovenous access established distally at the ankle. The investigators attributed such increase in paraesthesia to the level of puncture site, having refrained from concomitant phlebectomies in all their patients. In this study, SSV access in the BMC subgroup was predominantly between mid and lower calf, never requiring cannulation at the ankle, which may have been the elementary reason for increased rate of paraesthetic complications in Doganci's RCT. The 2 sensory complications in the BMC group may have however been a direct consequence of increased LED delivery of more than 100 J/cm in both these limbs and at least 1 of the 2 limbs in the AMC group. Logistic regression analysis to quantify such an association was not possible due to the small numbers that received LED over 100 J/cm and an even smaller number that developed sensory disturbance. Temperatures within the vein have been reported to reach between 700^{O}C and 1300^{O}C with EVLA[267], and although the tumescence ''heat sink'' significantly lessens the heat transfer to paravenous structures, even temperatures of 45^{O}C may cause irreversible nerve injury[21]. In the case of SSV treatment, the fascial sheath envelope around the vein makes creation of a perivenous tumescence ''halo'' relatively easy, and with ample volumes of tumescence should in turn adequately separate the paravenous structures along its entire length[12 15]. Thus, the senior author of the study recommends meticulous tumescence administration as well as lower laser energy delivery at 60 to 80 J/cm for SSV treatment; based on the best evidence from our own practice, to reduce the incidence of post procedural paraesthetic and phlebitic complications without decreasing treatment efficacy[13 21].

One of the limitations in the design of this study (as discussed in the Critique section below, Page 225) is that concomitant phlebectomies which were performed as standard adjuvant treatment in both subgroups, did not assist in determining the contribution of such stab avulsions to potentially cause nerve injuries. The paraesthetic complication in both AMC & BMC groups was low and comparable to

other studies reporting on EVLA (810 nm) of SSV alone without adjuvant procedures[13 21], thereby suggestive of weak correlation between occurrence of nerve injuries with phlebectomies. However, such speculation could have only been resolved by comparing with a control group (outside the context of this RCT), undergoing EVLA alone without adjuvant phlebectomy procedures. Concomitant phlebectomies however did significantly reduce the number of secondary procedures required for residual varicosities post-SSV EVLA[15] (1.8% in the current study) as compared to the rates reported in studies (between 18% and 100%) offering EVLA alone without concomitant treatment of tributary varicosities[13 21 259], which is likely to have significant impact on the indirect costs of the treatment and on patient's expectations[335].

Clinical recurrence rates were low in both subgroups, with no significant difference in its occurrence in context to the extent of treated SSV. The majority of recurrences (3 of 5 limbs) occurred due to new reflux in the extra-axial locations, unrelated to the ablated SSV. In the AMC group, a single case of clinical recurrence due to SSV recanalization at 3 months post treatment resulted due to reflux from a previously competent giacomini vein into SSV (treated with 104 J/cm LED; preoperative proximal vein diameter of 5.8 mm). Similarly, in the BMC group, the only recurrence due to SSV recanalization occurred due to junctional reflux into proximal SSV segment (treated with 92 J/cm LED; preoperative proximal vein diameter of 10.7 mm). Based on two cases of clinical recurrence due to recanalization, it is difficult to make any meaningful inferences as to whether treatment failure was due to anatomical cause or technical reasons. In the literature, saphenous vein size over 9.0 mm and magnitude of energy delivery less than 60 J/cm have been implicated with increased occurrence of recanalization[15 18 257].

Post-operative pain following EVLA was significantly worse for the BMC group only on Day 1, which may reflect the immediate morbidity associated with

endothermal injury of a relatively longer length of axial vein. However there was no such difference in pain or analgesia requirement on subsequent days; nor was there any difference between the subgroups in the time taken to return to work or routine activities. Patient satisfaction with overall treatment declined in the AMC group, whereas the generic EQ-5D QoL significantly improved in the BMC group over the follow-up period of 1 year. Objectively assessed venous severity and disease specific AVVQ QoL measures significantly improved in both subgroups, over the same time period. With these small numbers, early results suggest a slight advantage in accessing the SSV below mid-calf, without increasing sensory complications. Therefore the site of SSV cannulation will continue to be determined by an adequate sized (≥ 3mm) distal vein segment in which venous reflux is demonstrable on DUS. Irrespective of the site of access, EVLA of SSV with concomitant phlebectomies of the incompetent tributaries has been shown to be safe and effective, improving clinical severity and QoL outcomes in the short term. With its increasing applications, results from this study could also be utilised for ‘‘procedure refinement’’ of the EVLA technique in context to SSV treatment.

CRITIQUE

One of the limitations of this study, in common with most trials of surgical interventions, is that the patients, surgeons, and assessors could not be blinded to the two techniques being compared due to the contrasting nature of these interventions. It was not possible to blind the assessors to the type of intervention during the assessment of post-operative clinical outcomes as the presence of popliteal fossa scar and the DUS images of the treated area were easily distinguishable differentiating features between the two interventions in the early post-operative period. Risk of observer bias was however reduced as much as possible by recording outcomes (both primary and secondary) with objective, validated instruments, and standardized protocols employed by assessors with relevant qualifications and experience. It may be argued that from the patients’ perspective, preliminary information provided to

them regarding the invasive nature of conventional surgery and minimally invasive nature of a relatively newer endovenous intervention may have potentially influenced the subjective evaluation of post-operative outcomes. However the influence of such reporting bias, if any, on the independently reported QoL outcomes was likely to be small with the use of both disease-specific and generic instruments providing a valid and reliable strategy to assess patient reported health states after treatment of their venous disease[35 197]

Patients in the surgical arm underwent conventional inversion stripping under general anaesthesia, which is the common practice by proponents of SPL and inversion stripping of SSV in the UK; whereas EVLA was performed with tumescent anaesthetic infiltration around the treated vein. It is possible that the use of tumescent anaesthesia before surgical stripping may improve post procedural pain, immobility, and nerve injury rates, but this was not used in this study as this modified technique was not commonly practiced in the UK when planning this study. Also, such a use described more recently with GSV stripping has shown little convincing evidence that such a technique will significantly improve short-term outcomes following surgery[333 340].

The incidence of incomplete SSV stripping was 34% (18/53) i.e. 1 in 3 SSVs could not be completely stripped despite attempting to do so; this was mostly due to vein tear, tortuosity, spasm or intraluminal valves restricting passage of the stripper distally or a combination of the above. In this context a counter-argument would be that the primary outcome of technical success may not have been worse for conventional surgery in comparison to EVLA, had the surgeon been successful in stripping all SSVs by using alternate means such as antegrade stripping in those veins that snapped or offered resistance to retrograde advancement of the PIN stripper. Antegrade stripping was not employed in this study as any re-attempt at this adjunct procedure may have caused further soft tissue trauma leading to worsening pain,

discomfort, reduced mobility that may have prolonged recovery; there was also an increased potential to cause sural nerve injury and its associated morbidity from trying the distal approach. The emphasis of this pragmatic study was to compare the true outcomes of these two interventions without attempting to modify standard practices adopted in the UK, so that the results from this study could then be generalized.

Another criticism is that all patients in both groups underwent concomitant phlebectomies of tributary varicosities and/or perforator ligation (when indicated), the extent of these adjunct procedures was not controlled between individuals, nor was any attempt made to match the number of stab avulsions between the groups. Although there is a theoretical plausibility of nerve injuries with more extensive phlebectomies, it is difficult to differentiate the contribution of stab avulsions *per se* apart from SSV treatment itself in the form of stripping or endothermal ablation, to cause nerve injuries and paraesthetic complications. Concomitant phlebectomies, however did result in no secondary procedures being required for residual tributary varicosities following either treatment, in comparison to the rates reported in literature following SSV treatment alone without concomitant phlebectomies which ranged between 18% and 100%[13 21 259]. The need for such secondary procedures is likely to have a significant impact on patient's quality of life, expectations for a one-stop treatment[240 335 341 342] and also the indirect costs of the treatment.

FURTHER RESEARCH

The results from this first RCT comparing a newer minimally invasive technique with the gold standard conventional surgery in the treatment of small saphenous varicosities raises a number of questions worthy of future research.

Long-term outcomes of EVLA in terms of recanalization and re-treatment of SSV are yet to be reported. Following surgical treatment of SVI, prevalence of recurrent reflux is known to increase over time with more than half of the patients developing

recurrence within 10 years of treatment[174 315 343]. Although the short-term results of SSV recurrence rates with EVLA is promising[12 15 18 257], whether this will be sustained over the long term and how it would compare with other endothermal / chemical ablation methods is to be explored.

The optimal magnitude of energy delivery effecting maximal venous occlusion rates and minimal complications is a subject of ongoing contentious debate. While independent studies have demonstrated the 'key success predictor' status of energy density[272-274] and the linear relationship of occlusion rates with increasing energy delivery[276 279], what is at the heart of the debate is the issue of treatment-related complications. Linear and logistic regression statistical models have established the safety of increasing laser energy delivery on morbidity or complications for GSV insufficiency[33 277]. Such energy delivery and outcome aspects have not been studied exclusively for the SSV axis, with much variation between operators reported in SSV studies.

The more recent introduction of higher wavelength lasers and specialized fibre-tips makes the above debate on optimal energy delivery even more complex and interesting. Although the available evidence is predominantly based on GSV studies, to date there is no conclusive evidence supporting improved results with these higher wavelength or modified laser fibres and caution should prevail in interpreting the available data. The thermodynamic and absorption profile of different wavelengths of laser are different and are more water specific at higher wavelengths; the rationale being better vein wall penetration and endothermal injury, which in turn improves venous occlusion with less procedural morbidity. However, the water absorptive wavelength fibres could also transfer higher magnitudes of energy to the perivenous tumescent anaesthetic attenuating its effect as a "heat shield"[344]. It is also incorrect to assume that the SSV recanalization rates for shorter wavelength lasers at specific energy densities can be generalized to the new wavelengths or fibre tips altering the

density of laser delivery. Hence, these advances in technology and their potential outcomes need validating in context to SSV treatment as well.

A further area requiring urgent studies is the role of minimally invasive endovenous interventions in long-term healing and recurrence rates for venous ulcers, which is a particularly challenging problem that results in significant impairment of quality of life, and its treatment places a heavy financial burden on healthcare systems. Conventional surgery for SVI has been shown to reduce ulcer recurrence rates[236 345], but is an unpopular and often unsuitable option for many patients. The efficacy of the newer, minimally-invasive endovenous thermal ablative techniques has been established in uncomplicated superficial venous disease, and these techniques are now beginning to be used in the management of venous ulceration, though the evidence for this treatment is currently unclear[346]. It is hypothesised that, when used along with compression, ablation may further reduce pressures in the leg veins, resulting in improved rates of healing. This hypothesis needs to be proven by research.

CONCLUSIONS

Small saphenous incompetence does cause significant impairment in health-related QoL and hence warrants treatment. They behave differently to GSV incompetence following treatment, and therefore available evidence for GSV cannot be extrapolated to SSV management; rather, they should be considered as two distinct entities.

The results from this RCT suggest equivalent improvements in clinical severity, and at least non-inferiority of EVLA compared with CS in the treatment of small saphenous incompetence. EVLA is shown to be safe and effective offering immediate postoperative benefits of less pain, faster recovery and return to routine activities that also translated into it being a more cost-effective option. It offered better short-term technical outcomes with lower morbidity in comparison to CS. Additionally, from a procedure refinement context; EVLA access of SSV at the distal calf is safe and

effective without appearing to influence potential neural complications or recurrence rates.

As for conventional surgical treatment of SSV incompetence, it can be performed on all patients with varicosities where indicated, without the limitations placed on endovenous catheter based interventions regarding patient selection, although in this study all eligible patients could undergo EVLA irrespective of the anatomy of SSV axis. CS also improves disease severity, QoL and symptoms in majority of patients undergoing this procedure and differs from the newer endovenous interventions in the entailed short-term morbidity and increased sensory disturbance following stripping of incompetent SSV. The results from this study have however restated the need to strip SSV in order to reduce recurrences and risk of reoperation. This aspect would also make a strong case for adoption of endovenous methods that principally targets and obliterates the incompetent SSV axis without the morbidity associated with surgery.

In this ever changing world of modern medicine where excellence and betterment of treatment methods are being constantly pursued, the results from this first RCT would support the consideration of EVLA as the standard feasible treatment for small saphenous insufficiency[347], provided the long-term results are no worse than following surgery.

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APPENDICES

APPENDIX 1: Consent Guidelines

□ Establish need and willingness for surgical treatment of VVs

□ Fulfil inclusion and exclusion criteria

□ Explain conventional surgery: Procedure, Benefits, Risks, Post-op recovery, Recurrence.

□ Explain EVLT: Technique, Advantages, Risks, inability to complete procedure and hence conversion to open surgery at a later date, our experience and results thus far.

□ Introduction to Trial comparing conventional surgery Vs. EVLT

□ NICE guidance: use of EVLT within trial settings.

□ Emphasis:

- Participation in the trial purely voluntary
- Decision to participate after being fully satisfied with the given information
- To contact Research Nurse / Research Fellow / Consultant for any further information / queries.
- Randomisation by opaque envelope method following informed consent.
- Waiting list is the same within and outside the trial.
- EVLT available only within the trial
- Outside trial – conventional surgery – one routine follow-up
- Within trial – CS/EVLT – extended follow-up for 5 years

APPENDIX 2: Consent Form

Centre Number:
Study Number:
Patient Identification Number:

CONSENT FORM

Study 2; A new method of surgically treating varicose veins and venous ulcers- a study to assess clinical and economic value; Surgery versus EVLT for lower limb varicose veins

Name of Researcher: Mr Ian C Chetter
Consultant Vascular Surgeon
Academic Vascular Unit, Alderson House,
Hull Royal Infirmary
Hull, HU3 2JZ
Tel: 01482 674765 / 674703

1. I confirm that I have read and understood the information sheet dated 12/08/05 (version 1) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals (company name) or from a regulatory authority where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

----------	----------	----------
Name of Patient	Date	Signature
----------	----------	----------
Name of Person taking Consent	Date	Signature
----------	----------	----------
Name of Researcher	Date	Signature

APPENDIX 3: Patient Information Sheet

Study 2: A new method of surgically treating varicose veins and venous ulcers – a study to assess clinical and economic value; surgery versus EVLT for varicose veins.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to take part.

Thank you for reading this.

The purpose of this study:

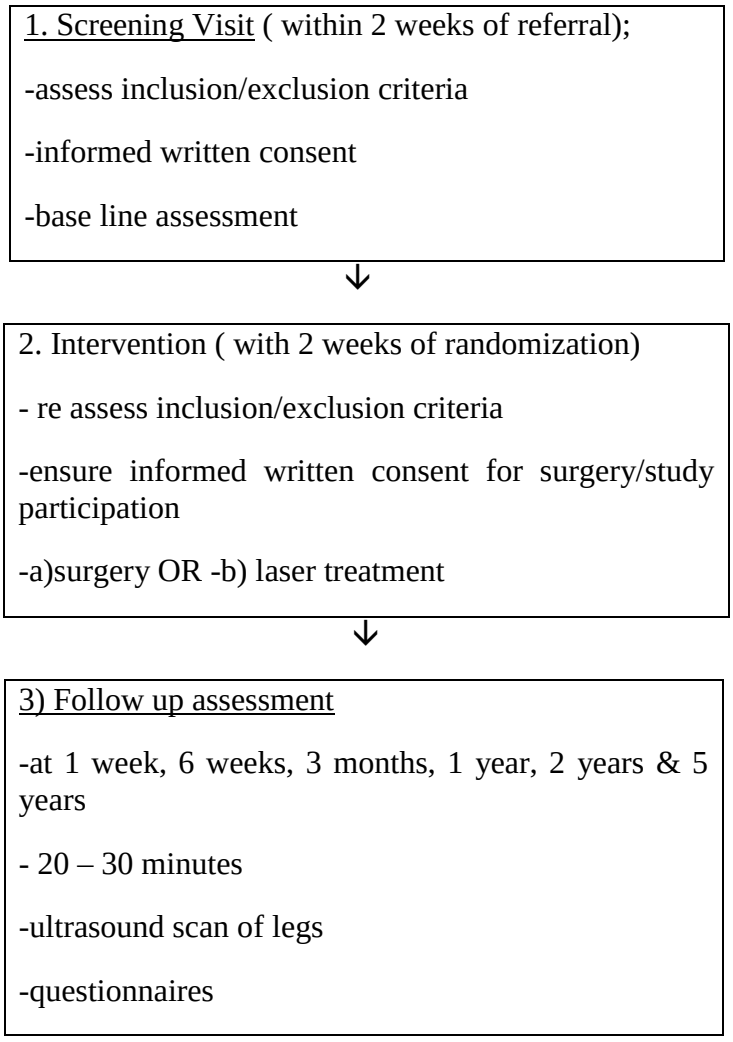
Lower limb venous disease is a common problem which frequently interferes with patient's quality of life. A promising new therapy for lower limb venous disease has been developed which uses laser therapy under local anaesthetic. This study aims to compare this new treatment to traditional treatments for lower limb venous disease in terms of clinical outcome and value for money over a 5 year period.

You have been chosen because you have significant lower limb venous disease, which, in the opinion of your surgeon, merits treatment. You are suitable for both traditional and the new laser therapy. In total we aim to study approximately 100 patients.

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving any reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

If you choose to participate in the study you will be assessed to confirm your suitability. This is a randomized trial because we do not know which way of treating patients is best. We need to make comparisons; therefore, people will be randomly put into groups and then compared. The groups are selected by a computer which has no information about the individual – i.e. by chance. Patients in each group then have a different treatment and these are compared. You will be randomized to either surgery or the laser treatment for your varicose veins. Surgery will be performed under a general anaesthetic (you will be asleep); an operation will be performed in the back of your knee to tie off the major incompetent vein which will then be removed to the calf, and removal of the rest of the varicose veins in your leg will be pulled out using small incisions. Laser therapy will be performed under local anaesthetic (you

will be awake); a laser wire will be passed along the vein to destroy it. Any residual veins will be treated subsequently with injections. There is a one in two chance you will be allocated the new laser treatment. Compression stockings will then be worn during the day for 6 weeks. Following treatment you will be followed up for a total of five years with assessment performed at 1 week, 6 weeks, 3 months, 12 months, 24 months and 60 months. At the assessments you will undergo a scan and be asked to complete questionnaires assessing your symptoms from lower limb venous disease and your quality of life. Each follow up assessment should take only 20 – 30 minutes.



Laser therapy compared to traditional surgery:

1. Potential disadvantages

- The long term result of laser treatment is unknown. The risks of your varicose veins recurring may be higher, we do not know.

-the small varicose veins in the lower leg are not removed with the laser treatment, thus the number of residual veins may be higher. We do not know that a large proportion of these varicose veins shrink and any that remain troublesome can be treated with injections.

- Skin burns and nerve irritation were highlighted as potential problems but in practice do not appear to be.

2. Potential advantages

-avoid a general anaesthetic, thus no need for pre op fasting and no complications associated with general anaesthesia e.g. nausea & vomiting, chest infections.

-avoids incision over back of knee, thus no local complications e.g. wound infection

-less invasive thus less pain and quicker return to normal activities.

We hope that both treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with varicose veins better.

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about this and discuss with you whether you want to continue the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interest to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

At the end of the study (5 years), the vast majority of patients will be cured from their varicose veins, and if satisfied with the results patients will be discharged from the hospital care back to their GP. If not satisfied with the results (approximately 5% of patients will have recurrent varicose veins at 2 years), you will undergo further investigation/treatment, if desired. If you are harmed by taking part in this research project there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have

to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it. Once the study is completed (approx. 5 – 6 years), the result will be published in the medical literature. You will not be identified in any report/ publication. These results will be available on request from the local study organiser.

Thank you for participation in this study.

You will be given a personal copy of this patient information sheet and a signed consent form to keep.

For further information please contact;

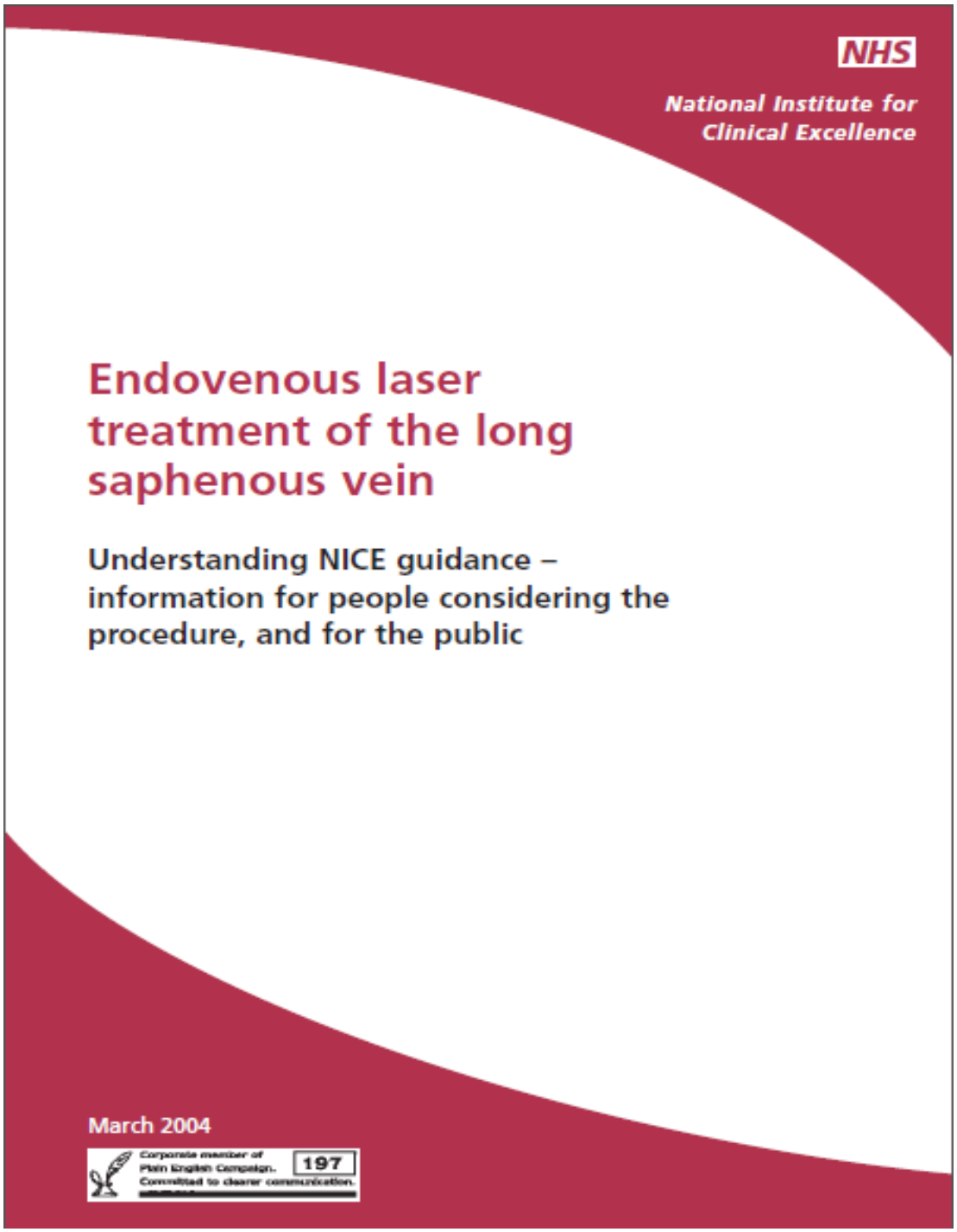
Mr.Ian Chetter,

Consultant Vascular Surgeon,

Hull Royal Infimary

01482 674765

APPENDIX 4: NICE Guidance



Endovenous laser treatment of the long saphenous vein
Understanding NICE guidance – Information for people considering the procedure, and for the public

Issue date: March 2004

To order copies
Copies of this booklet can be ordered from the NHS Response Line; telephone 0870 1555 455 and quote reference number N0500. A version in Welsh and English is also available, reference number N0501. Mae fersiwn yn Gymraeg ac yn Saesneg ar gael hefyd, rhif cyfeirnod N0501. The NICE interventional procedures guidance on which this information is based is available from the NICE website (www.nice.org.uk). Copies can also be obtained from the NHS Response Line, reference number N0499.

National Institute for Clinical Excellence

MidCity Place
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Contents

About this information

This information describes the guidance that the National Institute for Clinical Excellence (NICE) has issued to the NHS on a procedure called endovenous laser treatment of the long saphenous vein. It is not a complete description of what is involved in the procedure – the patient's healthcare team should describe it in detail.

NICE has looked at whether endovenous laser treatment is safe enough and works well enough for it to be used routinely for varicose veins (in this case for a particular vein in the leg, called the long saphenous vein).

To produce this guidance, NICE has:

- looked at the results of studies on the safety of endovenous laser treatment and how well it works
- asked experts for their opinions
- asked the views of the organisations that speak for the healthcare professionals and the patients and carers who will be affected by this guidance.

This guidance is part of NICE's work on 'interventional procedures' (see 'Further information' on page 10).

About endovenous laser treatment of the long saphenous vein

Varicose veins are veins (usually in the legs) that have lost their elasticity and bulge with blood as a result. They happen if the valves in a vein become weak and let blood go the 'wrong way' back through the vein. Over time, the vein has to become wider to cope with the extra blood and this eventually means it loses its elasticity. A person with varicose veins can feel pain in the affected area, their legs can feel tired and can swell, the skin can start to look different and ulcers can appear in the area. Most commonly, a vein called the long saphenous vein is affected, which runs from the foot to the groin.

Endovenous laser treatment is a method of closing off the long saphenous vein. The doctor puts a narrow tube called a catheter into the vein. Ultrasound images are used to make sure it's in the right place. A tiny laser device is then placed through the catheter and is passed up into position at the top of the vein. Local anaesthetic is injected into the area, and the doctor then pulls the laser device slowly along the vein while watching the laser tip with ultrasound pictures. The laser is gradually pulled back until it reaches the place where it was first put in. The laser fires short bursts of energy as it moves along the vein, and this heats the vein and makes it seal up.

A common alternative to closing the vein in this way is to remove it in a process called 'stripping'.

How well it works

What the studies said

NICE found five studies that looked at what happened in patients who had endovenous laser treatment. The vein was sealed up in nearly everyone who had the procedure (the results of the studies went from 90% to 100%, meaning that the 'worst' result was that nine out of ten people had their vein closed and the 'best' result was that ten out of ten people had their vein closed). One study that checked on 40 patients 3 years afterwards showed the long saphenous vein had not reopened in any of them.

What the experts said

The experts did not agree about how well endovenous laser treatment worked. One expert said it had not been shown to work well. Another said that it looked as if the results were good over a short period of time, but that it wasn't known if the effects lasted for a long time. A third expert thought that it had been shown that the results lasted quite a long time.

Risks and possible problems

What the studies said

The most common problems with endovenous laser treatment were pain and bruising. In one study, most patients felt a tightening along their leg and about a quarter of the patients had bruising afterwards (though these disappeared within a month). The vein became inflamed in a small number of patients (this is called phlebitis).

What the experts said

The experts thought that a loss of feeling, burns on the skin and damage to other veins were all possible problems. One expert said that fewer problems were likely with endovascular laser treatment than with the standard operation. Another expert didn't think enough was known about how often problems happened.

What has NICE decided?

NICE has considered the evidence on endovenous laser treatment of the long saphenous vein. It has recommended that when doctors use it, they should be sure that:

- the patient understands what is involved and agrees (consents) to the treatment, and
- the results of the procedure are monitored.

NICE noted that the studies it looked at only checked on patients up to 3 years after the procedure. NICE has also encouraged doctors who perform endovenous laser treatment to collect information about how well it works in patients over a longer period of time.

Other comments from NICE

NICE pointed out that although the studies showed that the procedure usually closes up the vein, there wasn't much information on how this improved patients' symptoms.

What the decision means for you

Your doctor may have offered you endovenous laser treatment. NICE has considered this procedure because it is relatively new. NICE has decided that the procedure is safe enough and works well enough for use in the NHS. Nonetheless you should understand the benefits and risks of endovenous laser treatment of the long saphenous vein before you agree to it. Your doctor should discuss the benefits and risks with you. Some of these benefits and risks may be described above.

Further information

You have the right to be fully informed and to share in decision-making about the treatment you receive. You may want to discuss this guidance with the doctors and nurses looking after you.

You can visit the NICE website (www.nice.org.uk) for further information about the National Institute for Clinical Excellence and the Interventional Procedures Programme. A copy of the full guidance on endovenous laser treatment of the long saphenous vein is on the NICE website (www.nice.org.uk/IPG052guidance), or you can order a copy from the website or by telephoning the NHS Response Line on 0870 1555 455 and quoting reference number N0499. The evidence that NICE considered in developing this guidance is also available from the NICE website.

If you want more information on varicose veins, a good starting point is NHS Direct (telephone 0845 4647) or NHS Direct Online (www.nhsdirect.nhs.uk).

Date: March 2004

NHS

National Institute for Clinical Excellence

National Institute for Clinical Excellence

MidCity Place
71 High Holborn
London
WC1V 6NA

www.nice.org.uk

N0500 1P POD Mar 04

APPENDIX 5: Conventional Surgery Protocol

Anaesthesia: General Anaesthesia (standard technique)

Antibiotic: Single dose of antibiotic at induction

Skin preparation and Drape: 10% Povidone-Iodine in water (Betadine®). In case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChloraPrep®) to be used.

Position: Prone, reverse Trendelenburg position.

Operation:

- Adequate length incision over popliteal fossa or higher as indicated.

- Dissect to expose SPJ and tributaries of SSV if any.

- Ligate and divide tributaries; ligate SSV flush to popliteal vein (PV) with 2-0 uncoated Polyglactin 910 (Vicryl®) and divide; if the SSV joins the gastrocnaemius vein (GV) before the PV, then ligate at the level of this junction with the GV; if the SSV extended cranially above the SPJ, then this should also be ligated; if there is no SPJ present within the popliteal fossa and the SSV extended cranially terminating in a junction with the deep vein below the mid-thigh, then it should be ligated at that junction.

- Pass a PIN (Perforation-invagination) stripper down the divided proximal end of SSV to emerge at the mid-calf. Incise the skin distally over the tip of stripper, secure vein at the proximal end of stripper and pull it down to emerge at the calf level and out of the exit wound, thus stripping SSV. If SSV stripping is not possible, then excise a short proximal segment (at least 5 cm) SSV under direct vision.

- Close popliteal wound in layers with 2-0 uncoated Polyglactin 910 (Vicryl®).

- Perform stab avulsions of previously marked tributary veins using vein hook.

- Incompetent perforators (if any) identified pre-op should be ligated via small incisions.

- Skin closure with absorbable 3-0 Poliglecaprone 25 (Monocryl®) subcuticular stitches. Infiltrate 0.5% Levobupivacaine LA into popliteal wound.

- Steri-strips™ to stab wounds. Apply cotton wool, gauze and Panelast® elastic compression dressings from mid-thigh or knee down to foot.

APPENDIX 6: EVLA Protocol

Anaesthesia: Local Tumescent Anaesthesia

Duplex Scan: Confirm SSV incompetence; mark the skin over the distal site of cannulation and the course of vein up to the SPJ. Surface varicosities and perforators should also be marked in the dependant position pre-operatively.

Skin preparation and Drape: 10% Povidone-Iodine in water (Betadine®). In case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep®) to be used.

Position: Prone, reverse Trendelenberg position.

Vein Access:

- Inject 1-2 mls of 1% Lignocaine over the site of access. A small incision is made and ultrasound guided percutaneous access of the distal incompetent segment gained with 18G or 19G needle.

- A 0.035″ guide wire is inserted through the needle up the SSV and its position confirmed with DUS; the needle is now removed. Using Seldinger technique, place a 5F catheter in the SSV and position its tip accurately at the SPJ using DUS. The wire can now be removed.

- slide the catheter into the PV and withdraw into SSV so that the tip lies exactly at the SPJ. Endoluminal position is also confirmed by aspirating venous blood.

Tumescent anaesthesia:

- Put the patient in the Trendelenburg position and administer perivenous local anaesthetic (20 ml of 2% Lignocaine with 1:200,000 Adrenaline and 20 ml of 0.5% Levobupivacaine in 1 litre of 0.9% Sodium Chloride solution) under DUS guidance along the SSV and tributary veins, which need concomitant phlebectomies. A 22 G spinal needle may be used with tumescent pump for infiltration.

Endovenous laser ablation:

- A bare-tipped 600 nm laser fibre is introduced via the catheter up to the 1st marked site, indicative of the tip being flush with the catheter tip. Now withdraw the catheter up to the 2nd marked site by holding the fibre steady, to unsheathe the distal 3 cm of laser fibre. Reconfirm position of fibre tip at SPJ with DUS and aiming beam if required.

- Ensure laser safety specs are worn by the patient and all staff in the operating room prior to starting laser ablation.

- Endovenous laser energy will be delivered using an 810 nm diode laser generator (Diomed® / Angiodynamics®, Cambridge, UK) at 14 W power and continuous delivery mode. Withdraw the catheter at a rate of 2 mm per second; aiming for a specified target energy delivery of 80-100 J/cm.

- Once laser ablation complete, perform stab avulsions of previously marked tributary veins using vein hook.

- Incompetent perforators (if any) identified pre-op should be ligated via small incisions. Skin closure with absorbable 3-0 Poliglecaprone 25 (Monocryl®) subcuticular stitches.

- Steri-strips™ to access site and stab wounds. Apply cotton wool, gauze and elastic compression dressings from mid-thigh to ankle.

APPENDIX 7: Intra-operative Record

Treatment Data

Date	
Hospital Number	
Treatment Group	EVLT ☐ Surgery ☐ (14 Watts)
Start Time (apply prep)	
Total Laser Dose (EVLT)	
Total length Vein Treated (EVLT)	_____cm
Extent of Vein Stripped	_____cm
Rate of pullback (EVLT)	_____pulse/cm
Surgeon / Laser operator	
Assistant present	YES ☐ NO ☐
Finish Time (patient off table)	
Any Comments	

Please ensure patients have the analgesia diary and pain scores to complete

APPENDIX 8: Post-operative Instructions

The Day Surgery Service

Advice Sheet

Varicose Vein Surgery

Sapheno Popliteal Ligation

Hull and East Yorkshire NHS Trust

Elastic Stockings:

Before you are discharged your bandages will be removed and you will be fitted with an elastic stocking, which must be left undisturbed for 1 week.

On the 8th day you should take a bath and soak off the stocking. The steristrips may come off on their own, but they can also be soaked off.

You will have been given a spare stocking at discharge. You should wear this stocking during the day until your leg feels comfortable without it.

Complication:

Complications following varicose veins surgery are unusual but if your leg becomes red, swollen or painful OR there is any significant bleeding you should seek medical advice. Contact the Day Surgery Unit, the ward or your doctor immediately.

Driving:

You may drive when you feel comfortable to do so, provided you are able to accomplish an emergency stop.

Work and Activity:

You may return to work when you feel well enough to do so. After your operation you are encouraged to walk as much as possible but to avoid heavy exertion and strenuous sports for 3 weeks. Avoid standing for long periods.

Follow Up clinic:

The surgeon may wish to see you in the weeks following your surgery. An appointment will be made for you if required and will follow in the post.

Your Consultant is:- …….

Your Surgeon is: - …….

Your Named Nurse is:- …….

If you have any problems or need further advice please contact

The Duchess of Kent Day Surgery Unit

Hull Royal Infirmary

8am – 8pm

01482 675066 / 5073

After 8pm and weekends

Contact Ward 7 HRI Tel: 01482 675007

Aftercare Advice:

Stitches:

The surgery usually involves an incision behind the knee to tie off the main incompetent vein in the leg. In addition to this small branches of the vein are removed through multiple small cuts usually below the knee. The knee wound is usually closed with absorbable stitches which will take several weeks to dissolve but do not need removing. This is covered with an adhesive dressing. The small cuts are covered with steristrips (paper dressings)

Bruising:

It is not unusual to develop quite marked bruising, especially in the calf. This should settle in time but if it does not seem to be settling or if you are worried please contact us.

Pain:

It is not unusual for your leg to feel sore.

We will give you pain relief to take home. The instructions on the packet will tell you the maximum dose you can take.

Important:

Because you have had a General Anaesthetic today we advise you not to attempt to drive, operate machinery or household appliances, Drink alcohol or make any important decisions for 24 hours.

As part of your care when you come into hospital, information about you is shared between members of the heath care team, some of whom you may not meet and who may not be directly involved in your care.

Information we collect may be used after you have been treated to help train other staff or to help us improve and maintain the quality of care we give or to research into new developments.

We may pass on information to other health organisations to help improve the quality of care provided by the NHS generally.

All information is treated as strictly confidential and is not given to anyone who does not need it. If you have any concerns please speak to a member of staff.

Under the Data Protection Act 1988, Hull and East Yorkshire NHS hospital Trust is responsible for maintaining the confidentiality of any information we hold about you.

May 2011 ~ review May 2012

DAY SURGERY SERVICE

ENDOVENOUS LASER TREATMENT OF VARICOSE VEINS

HULL AND EAST YORKSHIRE HOSPITAL NHS TRUST

Advice following your laser treatment

Before leaving the hospital by taxi or car you should walk continuously for 15 minutes.

Dressings

After your treatment a bandage will be applied to your leg. This should be left in place for one week, after which you may remove it. If the bandage is removed before one week the treatment may be less successful. Keep the bandage dry. Once the bandage has been removed you may take a bath or shower.

If the bandage is too tight you may develop swelling of the foot, numbness of the toes or a blue discolouration of the toes. These symptoms may appear 2-4 hours after the bandage has been applied. If you develop any of these problems you must telephone the contact number and seek advice immediately.

When you remove the bandage after one week you may notice mild bruising and perhaps some lumpiness on the inside of your thigh. The bruising will disappear over the next 7-10 days. The lumpiness will also disappear although this takes longer than the bruising to settle down.

The stocking which you were given after your laser treatment should be worn for a further six weeks during the day only and may be taken off at night.

Pain

You may experience some mild pain following your operation. Paracetamol or something similar (not aspirin) should give adequate relief. Please follow the instructions on the container.

Work and exercise

Once you have returned home after your treatment you can walk as much as you like but should avoid standing still for the next 48 hours. You may return to work and normal activities on the day of your treatment although you should refrain from sport, vigorous activity and swimming for 10 – 14 days.

Your Consultant is:-

Your Surgeon is: -

Your Named Nurse is:-

If you have any problems or need further advice please contact

Monday to Friday 8am to 7pm

Liaison Nurse

Duchess of Kent Day Surgery Unit

Hull Royal Infirmary

Tel 01482 675066

At other times, **only in an emergency**

Hull Royal Infirmary, Ward 6

Tel. 01482 875875

Special Instructions;-

After your operation:

Should you need to consult your doctor with a problem related to your operation within three weeks of surgery we would appreciate you contacting the Duchess of Kent Day Surgery Unit. This will enable us to monitor your progress. Please speak to the Liaison Nurse (01482 675066)

If you need any further help or advice please telephone the unit – we are open from 8 a.m. to 7 p.m. Monday to Friday (01482 675066), At other times, **only in an emergency,** please telephone Hull Royal Infirmary, Ward 7 (01482 674759).

The Duchess of Kent Day Surgery Unit is continually striving to improve patient information. If you feel we could improve our information we would be pleased to hear from you.

December, 2004

APPENDIX 9: Pain Diary

PAIN DIARY

Pt Initials: __ __ __

Study No: __ __ __ __ __

Date: __ __ / __ __ / __ __

Each day please record how much pain you have had by placing a cross on the line below:

Day 1 (Day of Treatment)	No Pain	worst imaginable pain
Day 2	No Pain	worst imaginable pain
Day 3	No Pain	worst imaginable pain
Day 4	No Pain	worst imaginable pain
Day 5	No Pain	worst imaginable pain
Day 6	No Pain	worst imaginable pain
Day 7	No Pain	worst imaginable pain

APPENDIX 9: Analgesia Record

ANALGESIA DIARY

Pt Initials: __ __ __

Study No: __ __ __ __ __

Date: __ __ / __ __ / __ __

Each day, please make a note of how many painkillers you took. If you didn't need to take any painkillers, or if you took them for something else other than for your legs (e.g. headache), please leave the space blank.

	Name of Painkiller	Dose of each tablet	Number of tablets taken over 24 hrs
Day 1 (Treatment Day)			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

APPENDIX 10: Baseline & Follow-up assessment

Front sheet for EVLT Trial

Name:	Unit No:
DOB	Consultant:
Address:	Sex: M/F
Tel No:	Ht; Wt; BMI;

Site to be tretaed; Left / Right / Bilateral

Procedure Listed;

CEAP classification; C0 /C1 /C2 /C3 /C4 /C5 /C6

VCSS

Pain;	0 /1 /2 /3	Induration;	0 /1 /2 /3
VV's;	0 /1 /2 /3	No. of Ulcers;	0 /1 /2 /3
Oedema;	0 /1 /2 /3	Ulcer duration;	0 /1 /2 /3
Pig't;	0 /1 /2 /3	Ulcer size;	0 /1 /2 /3
Inflamm;	0 /1 /2 /3	Comp Therapy;	0 /1 /2 /3
TOTAL;			

Past venous history

Surgery;	yes/no……..
Sclerotherapy;	yes/no
DVT;	yes/no
Fracture;	yes/no
Ulcer (active/healed);	yes/no
Phlebitis;	yes/no
+ve FH;	yes/no……..

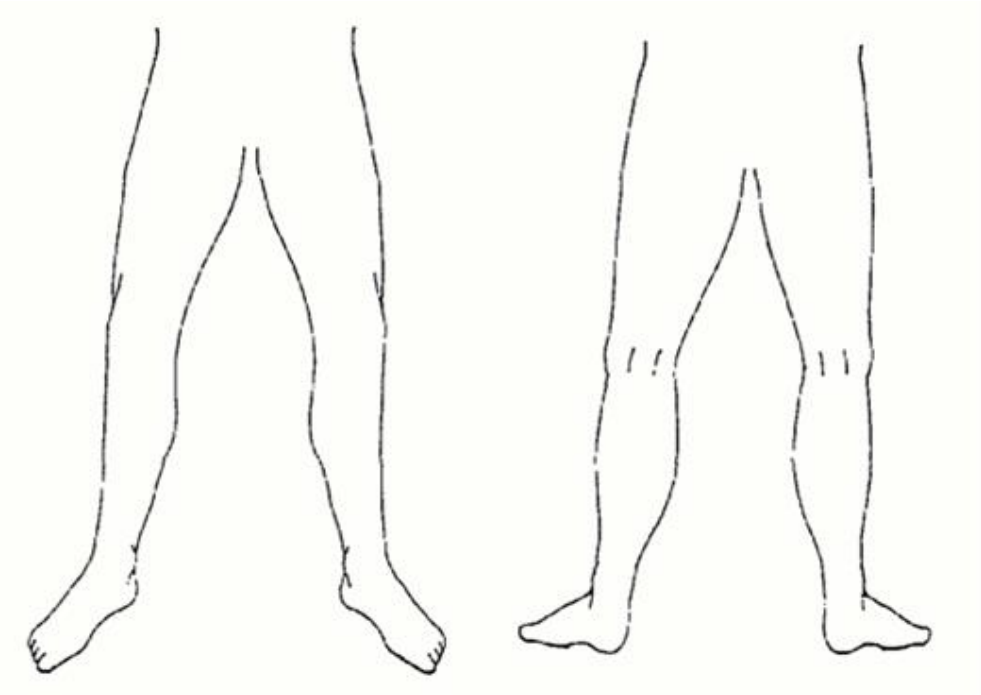
Past medical history

Drugs antiplatelets yes/no
others……..
……
……

Allergies Smoker; current/ex/never

Distribution of varicose veins (drawing); legs viewed

From Front From back



Hand held Doppler; yes/no

	Right	Left
Groin reflux	Yes/No	Yes/No
Popliteal fossa	Yes/No	Yes/No

Duplex; yes/no

Ultrasound Assessment	
Diameter SSV (while standing) in min	2cm distal to SPJ ☐ Mid Calf ☐ Distal ☐
Echogenecity SSV	Iso ☐ Hyper ☐ Hypo ☐
Compressibility SSV	Not ☐ Partially ☐ Completely ☐
Flow SSV	No flow ☐ <1sec reflux ☐ >1sec reflux ☐

EVLT TRIAL 2 – FOLLOW UP 1

Please complete for all the patients at the first follow-up appointment (1week).
Also collect ANALGESIA DIARY and PAIN SCORES.

Date (today)	
Patient Details (ID label if avaliable)	Name: DOB: Hospital Number:
Side of Treatment	Left ☐ Right ☐
SSV Phlebitis (clinical assessment)	Yes No
Time to work (if employed) in days	
Time to nomal activity (days)	
Ultasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complication eg: sensory loss, infection, haeatoma	

EVLT TRIAL 2 – FOLLOW UP 2

Please complete for all trial patients at second follow-up appointment (6 weeks)

Date (today)	
Patient Details (ID label if avaliable)	Name: DOB: Hospital Number:
Side of Treatment	Left ☐ Right ☐
SSV Phlebitis (clinical assessment)	Yes ☐ No ☐
Time to work (if employed) in days	
Time to nomal activity (days)	
Ultrasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complication eg: sensory loss, infection, haeatoma	

EVLT TRIAL 2 – FOLLOW UP 3

Please complete for all trial patients at third follow-up appointment (12 weeks)

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital Number:
Side of Treatment:	Left ☐ Right ☐
Patient satisfaction (with overall treatment)	Very Unsatisfied Completely satisfied _____
Patient view on cosmesis	Not at all Pleased Very pleased _____
Would patient have laser again?	Yes ☐ No ☐
Complication eg. neuritis, infection, haematoma (describe any and outcome)	
Sclerotherapy required	Yes ☐ No ☐
Number of visits for sclerotherapy	
VCSS score	_____/30
CEAP Score	C____ E___ A___ P____.

FOLLOW UP 3 (12 WEEKS)

Number days in Hospital/DCU	
Number of Outpatients Visits	
Ultrasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complications eg sensory loss, infection, haematoma	

EVLT TRIAL 2 – FOLLOW UP 4

Please complete for all trial patients at fourth follow-up appointment (52 weeks)

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital Number:
Side of Treatment:	Left ☐ Right ☐
Patient satisfaction (with overall treatment)	Very Unsatisfied Completely satisfied _____
Patient view on cosmesis	Not at all Pleased Very pleased _____
Would patient have laser again?	Yes ☐ No ☐
Complication eg. neuritis, infection, haematoma (describe any and outcome)	
Sclerotherapy required	Yes ☐ No ☐
Number of visits for sclerotherapy	
VCSS score	_____/30
CEAP Score	C____ E___ A___ P____.

FOLLOW UP 4 (52 WEEKS)

Number days in Hospital/DCU	
Number of Outpatients Visits	
Ultrasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complications eg sensory loss, infection, haematoma	

EVLT TRIAL 2 – FOLLOW UP 5

Please complete for all trial patients at fourth follow-up appointment (2 Years)

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital Number:
Side of Treatment:	Left ☐ Right ☐
Patient satisfaction (with overall treatment)	Very Unsatisfied Completely satisfied _____
Patient view on cosmesis	Not at all Pleased Very pleased _____
Would patient have laser again?	Yes ☐ No ☐
Complication eg. neuritis, infection, haematoma (describe any and outcome)	
Sclerotherapy required	Yes ☐ No ☐
Number of visits for sclerotherapy	
VCSS score	_____/30
CEAP Score	C____ E___ A___ P____.

FOLLOW UP 5 (2 Years)

Number days in Hospital/DCU	
Number of Outpatients Visits	
Ultrasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complications eg sensory loss, infection, haematoma	

EVLT TRIAL 2 – FOLLOW UP 6

Please complete for all trial patients at fourth follow-up appointment (5 Years)

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital Number:
Side of Treatment:	Left ☐ Right ☐
Patient satisfaction (with overall treatment)	Very Unsatisfied Completely satisfied _____
Patient view on cosmesis	Not at all Pleased Very pleased _____
Would patient have laser again?	Yes ☐ No ☐
Complication eg. neuritis, infection, haematoma (describe any and outcome)	
Sclerotherapy required	Yes ☐ No ☐
Number of visits for sclerotherapy	
VCSS score	_____/30
CEAP Score	C____ E___ A___ P____.

FOLLOW UP 6 (5 Years)

Number days in Hospital/DCU	
Number of Outpatients Visits	
Ultrasound Assesment Cilcle appropriate response	SPJ -flush occlusion; yes no -patent proximal segment; yes no - incompletent; yes no Proximal tribs -present; yes no - incompetent; yes no SSV Knee -present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Calf (above puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete SSV Distal (below puncture) present; yes no -diameter (mm); yes no -flow; yes no -reflux; yes no - echogenecity; hyper iso hypo -compressibility; not partial complete
Complications eg sensory loss, infection, haematoma	