THE UNIVERSITY OF HULL

Minimally Invasive Treatment of Venous Insufficiency using
Endovenous Laser Ablation

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by

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Prizes

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Abstract

Background

Venous insufficiency is very common and causes significant quality of life (QoL) impairment. Conventional open surgery featuring junction ligation, stripping of the axial vein and phlebectomy is known to offer significant benefits over conservative management; resulting in improved QoL. Additionally this treatment has been shown to be highly cost-effective. Despite these advantages, surgery is associated with significant post-operative morbidity; in the form of pain and immobility, even in the absence of complications. Additionally, in the long term; high recurrence rates have marred these promising early results, eventually returning patients to their pre-operative state. Unsurprisingly recurrence is unpopular with patients and patient satisfaction has been observed to be disappointingly low.

At the end of the 20th century, new minimally invasive endovenous interventions were developed. Rapidly gaining popularity; it was hoped that they could address some of the limitations of surgery. Following initial cases series; the endothermal technique of endovenous laser ablation (EVLA) appeared to have the highest technical efficacy with a good safety record.

Objectives

Three studies were performed with the aim of perfecting the ablative procedure and evaluating it against the gold standard of conventional surgery.

Study 1 was designed to establish the optimal management of saphenous tributaries and perforators following ablation of the saphenous axis.

Study 2 was designed to directly compare the outcomes of EVLA with surgery to establish whether EVLA can match the effectiveness of surgery, whilst addressing its limitations.

Study 3 was designed to explore the association between the magnitude of energy delivered during EVLA, procedural safety and periprocedural morbidity; in the context of evidence suggesting lower recanalisation rates following more aggressive use of laser energy.

Methods

Studies 1 and 2 were randomised clinical trials. Participants had primary, symptomatic, unilateral venous insufficiency, with isolated saphenofemoral junction incompetence, leading to reflux into the great saphenous vein (GSV). Study 1 randomised 50 patients to EVLA alone (Control) or EVLA with concomitant ambulatory phlebectomies (EVLTAP). Study 2 randomised 280 patients equally into groups receiving either surgery or EVLA. Outcomes were: QoL, Venous Clinical Severity Score (VCSS), technical success, requirement for secondary procedures, pain scores, time taken to return to normal function, recurrent varicose veins on clinical examination, patterns of reflux on duplex ultrasound examination, and the effect of recurrence on quality of life. Assessments were at 1, 6, 12 and 52 weeks after the procedure.

Study 3 used linear and logistic regression models to study the effect of energy delivery on outcome. The models controlled for age, gender, BMI, pre-operative QoL and vein dimension. The outcomes were QoL, complications, recovery time, pain scores and analgesia requirements. The sample size calculation established that 115 patients would be required to detect any significant relationship.

Results

Study 1: EVLTAP took longer, but significantly decreased the requirement for subsequent interventions. There was no impairment in immediate post-procedural pain or QoL with EVLTAP. Median (IQR) Venous Clinical Severity Score (VCSS) at 3 months was lower (better) for EVLTAP than for Control (0 (0-1) versus 2 (0-2); $P < 0.001$), with lower (better) disease specific QoL (Aberdeen Varicose Vein Questionnaire (AVVQ) scores) at 6 weeks (7.9 (4.1-10.7) versus 13.5 (10.9-18.1); $P < 0.001$) and 3 months (2.0 (0.4-7.7) versus 9.6 (2.2-13.8); $P = 0.015$). At 1 year, there were no differences in VCSS or AVVQ scores.

Study 2: Both groups had significant improvements in VCSS after treatment ($P < 0.001$), which resulted in improved disease-specific QoL (AVVQ, $P < 0.001$) and quality-adjusted life year (QALY) gain ($P < 0.001$). The pain and disability following surgery impaired normal function, with a significant decline in five of eight SF-36 domains ($P < 0.001$ to $P = 0.029$). Periprocedural QoL was relatively preserved following EVLA, leading to a significant difference between the two treatments in pain scores ($P < 0.001$), six of eight SF-36 domains ($P = 0.004$ to $P = 0.049$) and QALYs ($P = 0.003$). As a result, surgical patients took longer to return to work and

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normal activity (14 versus 3 days; P < 0.001). Complications were rare. Initial technical success was greater following EVLA: 99.3 versus 92.4% (P = 0.005). Surgical failures related mainly to an inability to strip the above-knee GSV. The clinical recurrence rate at 1 year was lower after EVLA: 4.0 versus 20.4% (P < 0.001). The number of patients needed to treat with EVLA rather than surgery to avoid one recurrence at 1 year was 6.3 (95 per cent confidence interval 4.0 to 12.5). 12 of 23 surgical recurrences were related to an incompetent below-knee GSV and ten to neovascularisation. Of five recurrences after EVLA, two were related to neoreflux in the groin tributaries and one to recanalisation. Clinical recurrence was associated with worse QoL (AVVQ scores) (P < 0.001).

Study 3: 232 patients were included. The mean (range) age was 50 (18-83) years. 63% were women. The mean (range) energy delivery was 89.8 (44.5-158.4) Jcm^{-1}. There was no significant effect on any outcome related to increasing energy delivery.

Conclusions

Concomitant phlebectomy with EVLA prolonged the procedure, but reduced the need for secondary procedures and significantly improved quality of life and the severity of venous disease. This supports a recommendation that phlebectomy is performed routinely in conjunction with EVLA.

EVLA was as effective as surgery for varicose veins, but importantly had lower periprocedural morbidity as evidenced by less negative impact on early post-intervention QoL and furthermore clinical recurrence rates were also significantly

lower than observed following conventional surgery. This suggests that EVLA with phlebectomy is superior to conventional surgery in the management of primary superficial venous insufficiency.

Study 3 clearly confirms that EVLA is a safe procedure and that for the range of energies studied, there was no evidence demonstrating an increase in complication rates or the periprocedural morbidity of EVLA.

These findings support the adoption of EVLA and concomitant phlebectomy as the gold standard treatment for primary superficial venous insufficiency.

Contents

List of Figures

List of Tables

Glossary of Abbreviations

95% CI	95% confidence interval (See *p170*)
ASV	Anterior saphenous vein (See *p28*)
AVVQ	Aberdeen varicose veins questionnaire - disease specific quality of life instrument (See *p85*)
BMI	Body mass index
CVI	Chronic venous insufficiency (See *p33*)
DUS	Duplex ultrasound (See *p100*)
DVI	Deep venous insufficiency (See p36)
EQ5D	Euroqol utility index - generic quality of life instrument (See *p90*)
EVLA	Endovenous laser ablation
F-A	Friedman ANOVA - statistical test (See *p170*)
FET	Fisher's Exact Test - statistical test (See *p170*)
g	gram - unit of weight (may be prefixed by k - kilo, m - milli)
GA	General anaesthetic
GSV	Great saphenous vein (See *p28*)
IQR	Inter-quartile range (See *p170*)
J	Joule - unit of energy
l	litre - unit of volume (may be prefixed by m - milli)
m	metre - unit of length (may be prefixed by c - centi, m - milli, n - nano)
MWU	Mann Whitney U Test - statistical test (See *p170*)

NNT	Number needed to treat (See *p170*)
OR	Odds ratio (See *p170*)
qds	quater die sumendus (4 times per day)
QoL	Health related quality of life
RCT	Randomised clinical trial
RD	Risk difference (See *p170*)
RR	Relative risk (See *p170*)
s	second - unit of time
SF-36	Short form 36 UK version 1 profile - generic quality of life instrument (See *p90*)
SF6D	Single utility index (derived from SF-36) - generic quality of life instrument (See *p90*)
SFJ	Saphenofemoral junction (See *p28*)
SSV	Small saphenous vein (See *p28*)
SVI	Superficial venous insufficiency (See p36)
SW	Shapiro-Wilk - statistical test (See *p170*)
tds	ter die sumendus (3 times per day)
W	Watt - unit of power
WSR	Wilcoxon Signed Rank - statistical test (See *p170*)
χ^2	Pearson's Chi-Square test - statistical test (See *p170*)

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..."the only thing that is permanent

is change"

Dr Charles Horace Mayo

1931

Chapter 1 - Introduction

Opening Statement

The venous system itself, along with its associated diseases; is by its very nature variable and inconsistent. This chapter draws from over half a century of detailed research, but in many regards a clear understanding remains elusive. The aim of this introduction is to discuss the highest quality of evidence available, analysing for points of consensus and contradiction, in order to set the scene for three new studies. Each of these studies aims to answer a specific management question, with the intention of improving the care received by current and future suffers of venous disease.

1.1 The Venous System

History

An awareness of the importance of the circulatory system can be traced back as early as prehistoric times; where cave paintings of bison and mammoth display an indication of the anatomical position of the heart. A useful target for hunters; haemorrhage was quickly linked to death and as time passed, the flow of blood became linked to the fundamental concepts of life, spirituality and medicine[1].

The early writing on the circulation, present in the Ebers Papyrus (written around 1550BC; thought to be a transcription of a documents from around 3400BC), were

developed over time by giants such as Hippocrates and Galen, before the 17th Century science of William Harvey and Marcelo Malpighi established the basic structure of the circulatory system known today.

The first documented attempts at the treatment of varicose veins also come in the Ebers papyrus and noted that surgery upon "leg serpents" can result in fatal bleeding. Ambulatory hook phlebectomy was performed by the Romans in the first century and a primitive form of ligation and stripping described by Albucasis of Cordova towards the end of the first millennium. This technique was developed and popularised by Friedrich Trendeleburg at the end of the 19th century, where saphenous ligation led to around five weeks hospitalisation. The first varicose vein operation to be performed under anaesthetic was done so in Finland in 1897[2]. Invagination stripping was introduced and developed by Keller and Mayo 15 years later[3,4]. With the exception of the introduction of modern anaesthetic techniques, the concepts surrounding surgery for superficial venous insufficiency (SVI) changed little until the end of the 20th century.

Sclerotherapy was described by Chassaignac in 1855, but did not become popular until the middle of the 20th century and this was relatively short lived, due to high recurrence rates and side-effects. There was a renaissance of this approach with the development of foam sclerotherapy at the turn of the 21st century.

The management of leg ulcers again has its origins in ancient times with bandaging known to have been used since at least 3500BC[5]. In the fourth century BC, Hippocrates recommended regular cleaning, debridement and removal of excess

granulation tissue and noted that excess moisture was detrimental. He also observed that incisions made into skin with the changes of chronic venous insufficiency may result in ulcer formation. Celsus is thought to be the first to recommend compression of ulcers in the first century and despite many subsequent attempts at surgical techniques and topical treatment, nothing beyond compression to date has been shown to improve venous ulcer healing rates other than the treatment of active infection.

Anatomy and Physiology

Blood delivers oxygen, nutrients and hormones to the tissues whilst passing through the capillary network. Following this, deoxygenated blood carrying metabolites, leaves the capillaries; entering into the systemic venous tree. The peripheral venous system can be divided anatomically into the superficial venous system, which is located within the superficial tissues and the deep venous system, which typically accompanies the arterial tree, beneath fascial planes, deep in the body. The superficial veins drain into the deep system, either at junctions or via fascial perforating veins, and the deep veins then return blood to the right atrium of the heart. Venous anatomy is characteristically variable. The terminology used below is consistent with international consensus[6].

Considering the lower limb, the deep venous system commences with the medial and lateral plantar veins in the sole of the foot. These unite behind the medial malleolus to form the posterior tibial vein, which ascends the leg adjacent to the

posterior tibial artery. A similar arrangement is seen with the anterior tibial and peroneal veins, which commence as a confluence of the venae comitantes of their accompanying nominate artery and also ascend with the arteries until the three vessels to unite around the level of the knee to form the popliteal vein, which continues to become the superficial femoral vein (SFV), ascending onwards in the thigh adjacent to its artery. The profunda femoris vein commences deep in the thigh and accompanies its artery to the groin where it unites in the groin with the SFV to become the common femoral vein (CFV) and onwards through the iliac veins to the inferior vena cava and then the right atrium of the heart.

Far more anatomical variations exist within the superficial veins of the lower limb, but it usually contains 2 systems or axes. As the sole of the foot is often placed under significant pressure, the majority of the venous drainage of the foot is into the dorsal venous arch, running in the subcutaneous tissues over the metatarsal heads. The medial end of this arch drains into the first axis: the great saphenous vein (GSV). This is the longest vein in the body and the most frequently affected by superficial insufficiency. The GSV passes anterior to the medial malleolus and ascends the leg accompanied by the saphenous nerve in the superficial tissues medial to the tibia, looping posteriorly at the level of the medial condyle of the femur and continuing in the medial thigh. In the groin, it unites with tributaries corresponding to the arterial branches of the common femoral artery, before piercing the cribiform facia covering the saphenous opening (approximately 3cm below and lateral to the pubic tubercle) and terminates by draining into the CFV at the saphenofemoral junction (SFJ). Throughout its course the GSV unites variably

with other superficial tributaries. The anterior (accessory) saphenous vein (ASV) is one of the most common. This is often seen originating around the lateral border of the knee, although sometimes originates as low as the lateral end of the dorsal venous arch. Occasionally this vein may also course down the medial aspect of the thigh, anterolateral to the GSV following its course. In this instance its origin is typically a confluence of small tributaries around the knee. There is usually an in-line GSV axis passing uninterrupted from the foot (in some cases this may be hypoplastic), but this pattern of ASV is commonly mistaken for the GSV itself (Some surgeons will call this a duplex GSV; a true duplex GSV is rare). The ASV may drain into the GSV in the thigh at any point from the SFJ down, but is typically at or near the junction itself. Another variable tributary of note is the Giacomini vein, which is discussed below.

The small saphenous vein (SSV) originates from the lateral side of the dorsal venous arch and accompanies the sural nerve as it passes posterior to the lateral malleolus, then upwards in the posterior midline of the leg. Its termination commonly occurs by piercing the fascia of the popliteal fossa to drain into the popliteal vein at the saphenopopliteal junction (SPJ), however this junction is highly variable and the vein may terminate as low as the mid calf. The SSV may extend cranially beyond the SPJ; in which case it is known as either a cranial extension of the SSV which terminates by piercing the fascia in the posterior thigh to drain into the deep system or the Giacomini vein which communicates with the GSV system occasionally joining the GSV at or about the SFJ. In some cases, the

SSV doesn't terminate at or below the popliteal fossa (i.e there is no junction with the deep venous system), but continues on as described above.

The purpose of the systemic venous system is primarily to return blood back to the heart so that it can be delivered into the pulmonary circulation. The systemic venous system contains approximately 60% of the total blood volume with an average pressure of around 5-10 mmHg. Mechanical factors (discussed below), alongside the autonomic nervous and endocrine systems, control the rate at which blood is delivered to the right atrium. Through its effects upon myocardial contractility via the Starling mechanism; venous return is one of the factors responsible for determining cardiac output.

The mechanical factors at work are the muscle and respiratory "pumps." As most venous flow is against gravity; these pumps are necessary to allow successful antegrade flow towards the heart. The peripheral deep veins run in proximity to skeletal muscle. During standing without skeletal muscle activity, venous pressures in the legs are determined by the hydrostatic component and capillary flow, and they may reach 80 to 90 mm Hg[7]. Contraction of these muscles, compresses the relatively thin walled veins, resulting in flow within the vessel. Even very small leg movements can provide this important pumping action. Additionally during inspiration, expansion of the volume of the thorax results in a decrease in intra-thoracic pressure, also resulting in antegrade venous flow. Competent venous valves ensure that venous blood flows toward the heart, thereby emptying the deep and superficial venous systems and reducing venous pressure, usually to less than 30 mm Hg[7].

The success of these mechanisms relies upon the valves found in healthy veins, preventing retrograde flow and these valves are variable in number and location. There are typically more valves in the lower limb than in the upper limb, which seems intuitive as there is a shorter column of blood below the heart upon which gravity will act; promoting retrograde flow. In the superficial system; the GSV has a median of 6 valves with a range of 4-25 in its full length[8]. 85% of people have a valve within 2-3cm of the SFJ[8]. The SSV has a median of 7 valves, with a range of 4-13[9]. In general the number of valves in the lower limb also tends to decrease above the knee and in the deep system; the CFV and external iliac veins have only one valve between them in about 63% of cases[9], whilst in 17-37% there is no valve between the CFV and the heart[10-12].

1.2 Venous Insufficiency

Definition

Venous insufficiency, otherwise known as incompetence or reflux, occurs when the veins become diseased, interfering with the normal mechanisms of antegrade flow. This failure of efficient venous return, coupled with turbulent and retrograde flow within the vessels results in a relative venous hypertension.

Venous hypertension promotes the development of a spectrum of clinical syndromes from simple varicose veins to ulceration and these syndromes are

associated with symptoms, which impair a sufferer's health related quality of life (QoL).

The Scale of the Problem

Venous disease is one of the most common conditions facing western health care systems (See: *Prevalence p58*). This high prevalence along with the chronic nature of its complications, such as venous ulceration, leads to extremely high costs to society. The direct costs account for 1-3% of the entire healthcare budget[13-15]. In the USA alone, treatment of venous ulcers costs around $3 billion per year[16].

Clinical Features

Lower limb venous insufficiency causes a relative venous hypertension, which through the proposed mechanisms outlined below (see *Pathophysiology*, p48) results in pathological, clinically evident features. Clinical studies have clearly shown this association[17-23] and have related the number of incompetent venous systems to the clinical severity of disease[19,21-23].

The clinical features of venous insufficiency lie on a spectrum of severity, although this spectrum is by no means linear or continuous and clinical features may not be cumulative or additive; some patients may present with severe features in the absence of lesser findings[24].

The following clinical features are commonly seen (these definitions are consistent with international consensus[25]):

- **Telangectasia** (thread veins, spider veins, and hyphen webs) - These represent tiny intradermal venules less than 1mm in diameter

- **Reticular vein** – small dilated "bluish" subdermal vein between 1 and 2.9mm in diameter, usually tortuous, can be difficult to distinguish this from a normal subdermal vein in someone white thin transparent skin

- **Varicose vein** – subcutaneous dilated vein 3mm in diameter or larger. They are frequently elongated and tortuous, with intermittent "blowouts", but are defined by the presence of reflux and may be tubular in morphology

- **Corona phlebectatica** (malleolar flare) – a fan shaped pattern of telangectasia on the ankle or foot. Thought to be an early sign of advanced venous disease

- **Oedema** – increased volume of fluid in the skin and soft tissues of the leg. Commonly starts distally and moves more proximally with increasing venous dysfunction. Classically this is "pitting oedema", with firm digital pressure leaving an indentation in the soft tissues

- **Eczema** – an erythematous dermatitis, often appears minor, although may be associated with significant itching and discomfort. In extreme cases it may progress to blistering and weeping

- **Pigmentation** (haemosiderosis) – a brownish discolouration of the skin, usually permanent, this is usually seen around the ankle, but is also seen in proximity to varicose veins and incompetent perforators

- **Lipodermatosclerosis** (LDS) – chronic inflammation and fibrosis of the skin and subcutaneous tissues, resulting in a tight, contracted, "woody" leg on examination. Occasionally results in significant contractures of the Achilles tendon. This is a sign of severe chronic venous disease

- **Atrophy blanche** – localised areas of atrophic, white skin, often surrounded by telangectasia and pigmentation. Some authors distinguish this from the white scarring left by ulceration, others do not. Either way this is a sign of severe chronic venous disease

- **Venous ulcer** – full-thickness skin loss, usually around the ankle, which fails to heal spontaneously and is propagated by continuing venous hypertension and the changes associated with chronic venous disease

Eczema, pigmentation, LDS and atrophy blanche are often referred to as trophic skin changes, whilst the presence of oedema, eczema, pigmentation, LDS, atrophy blanche and ulceration are usually implied by the use of the term chronic venous insufficiency (CVI).

Typically ulcers start with trivial wounds but tend to be stubborn, chronic wounds; difficult to heal and prone to relapse. In a UK based population study, the median

duration of ulceration was 9 months, 20% of ulcers had not healed in 2 years, and 66 percent of patients had recurrent episodes of ulceration lasting longer than five years[26].

The clinical classification systems, alongside the symptoms and QoL impairment associated with venous insufficiency, will be discussed later (See: *Quality of Life Impairment, p40, The Clinical Assessment of Patients with Superficial Venous Insufficiency, p79 and* Assessing the Quality of life Impairment Associated with Superficial Venous Insufficiency, *p84*).

Patterns of Reflux

Venous insufficiency may involve the superficial venous system (superficial venous insufficiency – SVI), the deep venous system (deep venous insufficiency – DVI) or both causing mixed venous insufficiency.

It is clear that SVI is more common than DVI or mixed insufficiency and that when the superficial veins are considered, the GSV is affected in many more cases than either the SSV or non-saphenous veins.

In a study of women with uncomplicated varicose veins[27]; of 590 limbs, 80% had GSV or SSV reflux. 77% had GSV reflux (in 60% this was isolated), 20% had SSV reflux (but only 3% were isolated) and 17% had combined reflux. Additionally non-saphenous reflux was noted in 20%. Deep venous reflux was only noted in 2% and perforating vein reflux in 23%.

This pattern was also demonstrated at a population level in the Bonn vein study[22] (*Table 1*) and confirmed in a patient population by Myers et al[23] (*Table 2*).

Site of Reflux		No disease (n=290)	Thread veins (n=1777)	VV (n=432)	Oedema (n=407)	Trophic skin changes (n=86)	Ulcer (n=22)
System	Superficial	2.4 (1.0-4.9)	5.0 (4.1-6.2)	49.2 (44.3-54.1)	24.1 (19.9-28.6)	67.1 (55.8-77.1)	72.7 (49.8-89.3)
	Deep	16.6 (12.5-21.3)	9.8 (8.4-11.2)	18.8 (15.2-22.8)	12.3 (9.3-15.9)	24.1 (15.4-34.7)	54.5 (32.2-75.6)
Superficial vein	GSV	2.1 (0.8-4.4)	3.4 (2.6-4.3)	32.2 (27.7-36.9)	16.5 (13.0-20.6)	41.7 (31.0-52.9)	57.1 (34.0-78.2)
	SSV	0.0 (0.0-2.5)	0.6 (0.3-1.1)	8.6 (6.2-11.7)	3.0 (1.5-5.1)	12.9 (6.6-22.0)	22.7 (7.8-45.4)
Deep vein	FV	13.1 (9.4-17.5)	6.3 (5.2-7.5)	10.0 (7.3-13.2)	6.9 (4.6-9.8)	12.8 (6.6-21.7)	36.4 (17.2-59.3)
	PV	3.8 (1.9-6.7)	3.5 (2.7-4.5)	9.7 (7.1-12.9)	6.6 (4.4-9.5)	12.9 (6.6-22.0)	36.4 (17.2-59.3)
	PTV	0.0 (0.0-1.3)	0.2 (0.1-0.6)	0.5 (0.1-1.7)	0.5 (0.1-1.8)	3.6 (0.7-10.1)	25.0 (8.7-49.1)

Table 1: *The association between venous insufficiency and severity of venous disease by venous system and individual vein (as a percentage (95%CI))[22].* **These figures are irrespective of the coexistence of insufficiency elsewhere. VV – uncomplicated varicose veins, GSV – great saphenous vein, SSV – small saphenous vein, FV – femoral vein, PV – popliteal vein, PTV – posterior tibial vein**

Site of Reflux		Uncomplicated VV	LDS	Ulcer
System	Superficial only	429 (55%)	27 (39%)	36 (38%)
	Deep only	12 (2%)	5 (7%)	8 (8%)
	Superficial and deep	137 (18%)	24 (34%)	46 (48%)
Superficial vein	GSV only	327 (58%)	29 (57%)	33 (40%)
	SSV only	104 (18%)	9 (18%)	21 (26%)
	GSV and SSV	135 (24%)	12 (25%)	28 (34%)
Deep vein	CFV	95 (61%)	14 (48%)	30 (56%)
	SFV	59 (38%)	11 (38%)	27 (50%)
	PV	79 (51%)	12 (41%)	33 (61%)
	PTV	33 (21%)	12 (41%)	24 (44%)

Table 2: *The association of venous insufficiency with severity of disease by system and then each system by vein[23] (as number of patients (percentage)).* **VV – varicose veins, LDS – lipodermatosclerosis, GSV – great saphenous vein, SSV – small saphenous vein, CFV – common femoral vein, SFV – superficial femoral vein, PV – popliteal vein, PTV – posterior tibial vein**

The methodology of the second study was such that many patients with obvious GSV reflux on hand-held Doppler were excluded (as they did not go on to have DUS mapping prior to intervention) and therefore the authors believe that the true rates of GSV insufficiency will be higher with a smaller proportion attributable to the SSV.

Studies of isolated SVI have unsurprisingly shown the same patterns; with 67-86% of patients having GSV insufficiency (48-60% in isolation) and 3-33% having isolated SSV insufficiency[19,21,27-32]. Currently, there is no explanation for why the GSV is affected more commonly than the SSV. Some authors suggest this may be due to the greater number of tributaries draining into the GSV and the higher number of valves in the SSV (per unit length; each vein contains a similar number of valves) may be responsible[19,33,34].

The degree of reflux influences the magnitude of venous hypertension and is therefore associated with a worsening in clinical severity. The Bonn vein study, the Edinburgh vein study and Myers et al all demonstrated that increasing numbers of insufficient trunks are associated with clinical severity[17,22,23]. Increases in the diameter of the trunks themselves is also associated with increased severity[21], as is the length of the incompetent segment within the vein[19] (*Table 3*).

Reflux in particular segments of vein is especially important as demonstrated by the greater association of CVI with below knee GSV insufficiency[19] (*Table 3*) and SFJ, SPJ and perforator incompetence[21,23].

Extent of reflux	Ache	Swelling	Skin Changes	Ulceration
Above knee only	11 (46%)	8 (33%)	1 (4%)	0
Below knee only	12 (57%)	13 (62%)	10 (48%)	0
Full Length	63 (81%)	71 (91%)	42 (58%)	6 (8%)
Total	86 (70%)	92 (75%)	53 (43%)	6 (5%)

Table 3: *The association of the extent of isolated great saphenous vein reflux with the symptoms and signs of venous insufficiency*

Previously it was thought that venous ulceration was due to secondary DVI, but a meta-analysis of 13 studies of 1153 legs with venous ulceration found isolated SVI in 45%, isolated DVI in 12% and 43% had reflux in both, confirming that SVI has an important part to play in the pathogenesis[35]. This has important implications when considering the treatment of venous ulceration, as SVI is eminently amenable to treatment (See *Interventional Treatment, p115*).

Quality of Life Impairment

Venous insufficiency rarely threatens a patient's life. The rationale for intervention therefore must be with the aim of improving QoL. Consequently it is of paramount importance that the QoL impairment associated with SVI is investigated to understand the nature of this association, whether this impairment is addressed by intervention, how to select which patients will benefit and whether such improvements are robust over time.

Patients with SVI complain of a range of symptoms; which are often fairly non-specific and it can be challenging to delineate which of these symptoms are related specifically to their venous insufficiency. Similar symptoms are also common in the background population who do not have demonstrable insufficiency. This issue was highlighted and rationalised during population level studies. Early work was fairly crude and was undertaken prior to the widespread use of validated disease specific QoL analysis in this area. The focus of such studies was to link simple physical symptoms to venous disease, rather than a specific quantification of the strength of this association, or the contribution of individual elements to the overall morbidity and impact upon a sufferer's daily life and career. Functional and psychosocial issues were not addressed. Typically venous symptoms are worse when the legs are dependant, particularly when standing for long periods and are usually relieved on elevation. This clearly has occupational implications.

The Edinburgh vein study studied patients randomly drawn from the general population[36]. They found that symptoms typically associated with venous disease were common, increased with age and were significantly more prevalent in women. For example 44.9% of women with no evidence of varicose veins complained of aching legs. Nonetheless, symptoms were shown to be more common with worsening degrees of varicose veins, particularly aching, heaviness and itching. The strength of this association was weak, particularly in men and the authors concluded that history taking alone was no enough to gauge who would and would not benefit from treatment. This analysis relied upon very simple questionnaire outcomes; there was no detailed enquiry of the QoL impairment and no validated QoL assessment scores were used. Some of the patients without clinically obvious varicose veins may have had early subclinical disease with underlying insufficiency which had not yet manifested itself in varicose veins.

Another population based study found a stronger association and was able to quantify this; varicose veins were an independent risk factor for "venous symptoms" OR 2.37 (1.19-4.72) – men and 2.11 (1.43-3.13) – women[37]. The extent of actual reflux seen on DUS has also been linked to the proportion of patients reporting symptoms (*Table 3, p39*)[19].

Women are significantly more likely to report symptoms than men (51.3% of women compared with 20.4% of men)[37]; which has also been noted on QoL modelling, where women reported a greater disease specific QoL impairment than men, controlling for the clinical severity of disease and other demographic and

anatomical factors[38].   This is perhaps the motivation behind women presenting earlier and in greater numbers, for treatment.

Validated instruments designed to study QoL have been developed and have offered much more insight into the nature of the QoL impairment associated with venous disease. The instruments themselves will be discussed in detail in a later section (See *Assessing the Quality of life Impairment Associated with Superficial Venous Insufficiency p84*).   Detailed study using such instruments has demonstrated not just the physical symptoms and disability, but also the emotional impact; leading in some cases to depression and social isolation, particularly in advanced disease[39-41].

Large studies have linked venous disease to a marked deterioration in QoL, which becomes more profound with increasing severity[42,43].   A QoL modelling study of 561 patients[44] clearly demonstrated that increasing severity of disease had a greater impact upon a range of QoL measures (*Figure 1 - Figure 7*) (For details of these outcome measures and CEAP clinical grading see *The CEAP Classification p80 and Assessing the Quality of life Impairment Associated with Superficial Venous Insufficiency p84*)
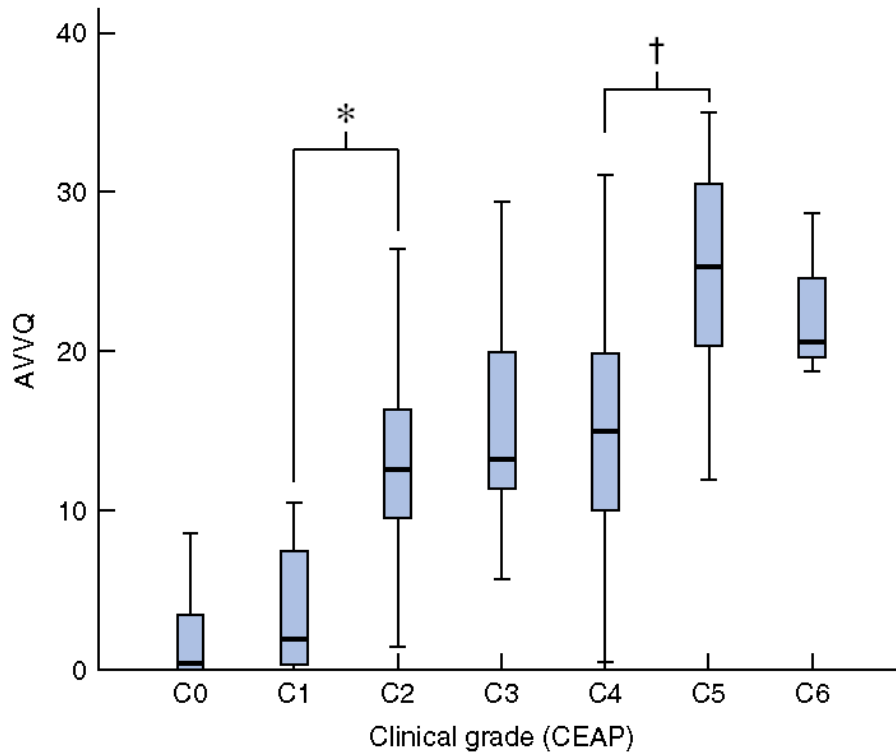
Figure 1: *Aberdeen Varicose Vein Questionnaire (AVVQ) scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* *P < 0.001, †P = 0.006 (intergroup Mann–Whitney *U* testing with Bonferroni correction). Higher AVVQ scores represent worse disease specific QoL[44].
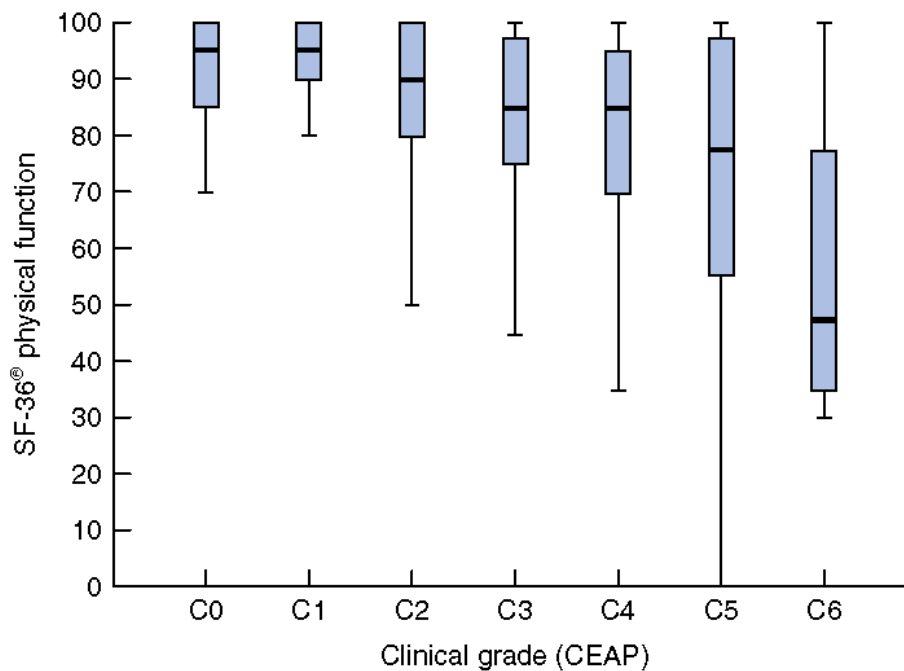
Figure 2: *Physical function scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* Lower physical function scores represent worse QoL[44].
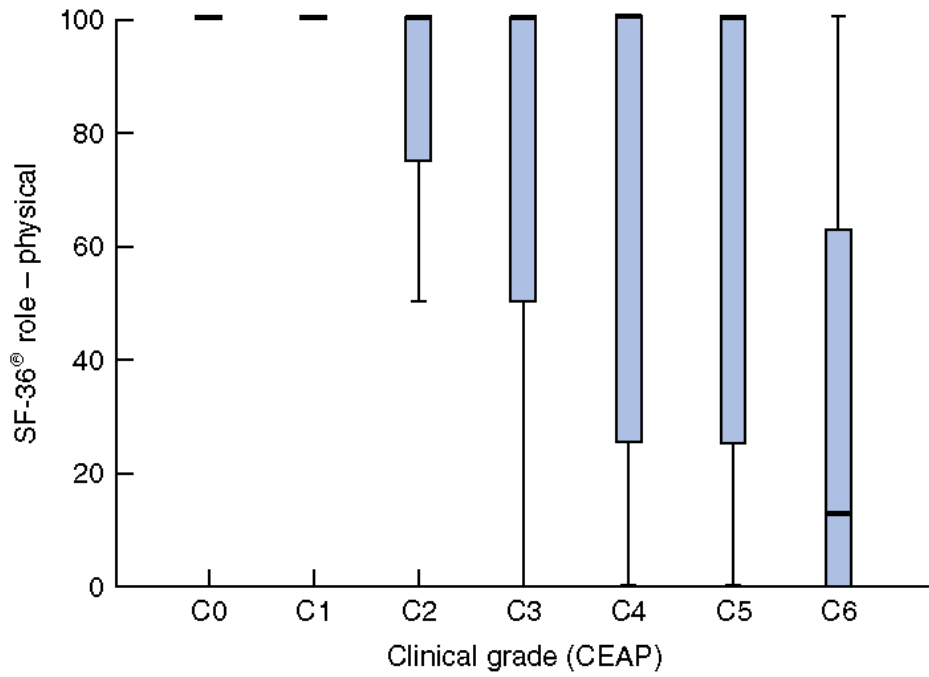
Figure 3: *Role limitation due to physical disability scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* **Lower role-physical scores represent worse QoL[44].**
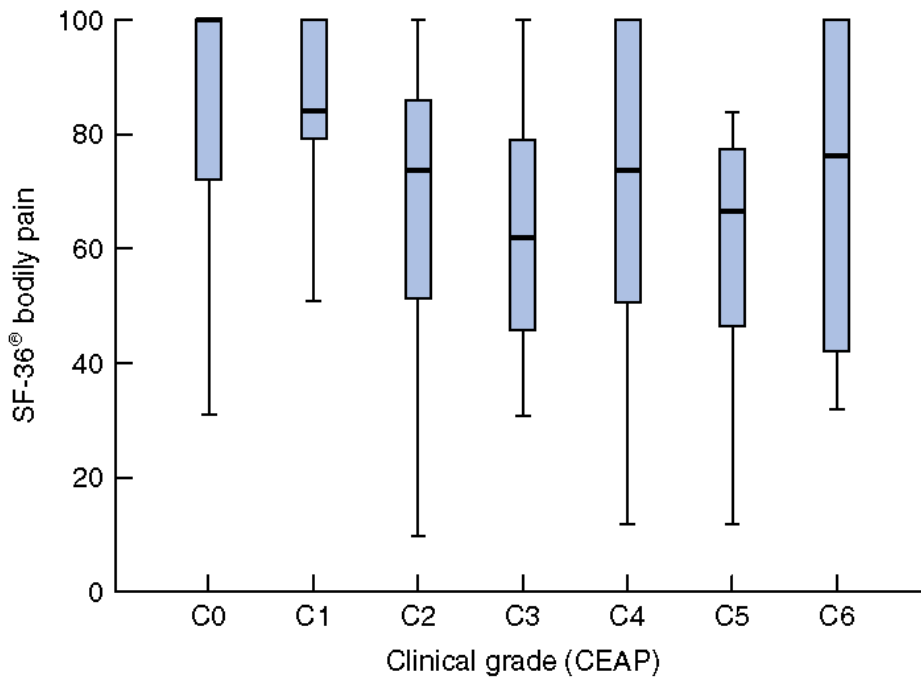
Figure 4: *Bodily pain scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* **Lower bodily pain scores represent worse QoL[44].**
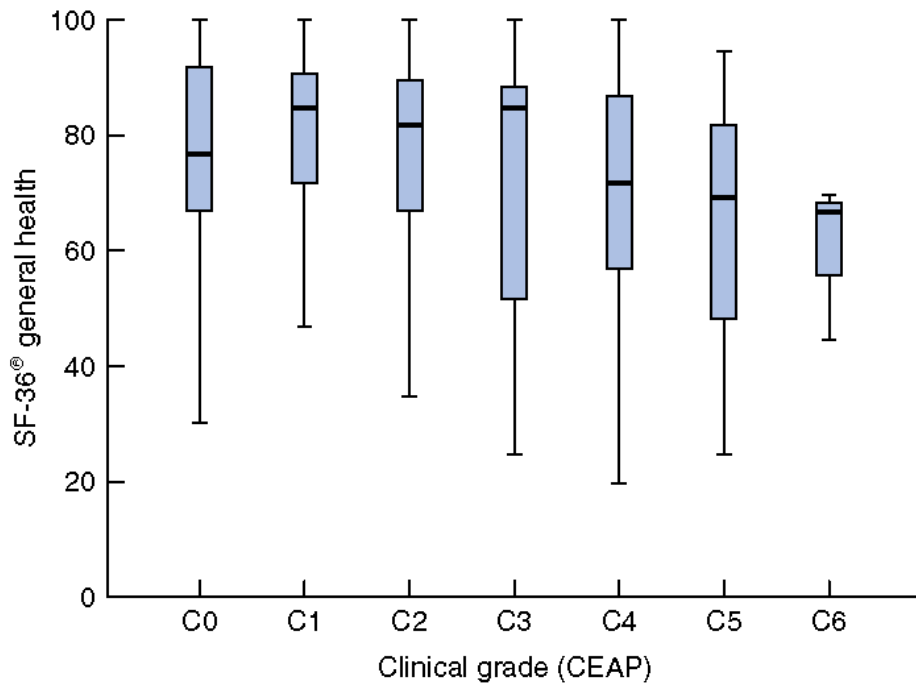
Figure 5: *General health scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* Lower general health scores represent worse QoL[44].
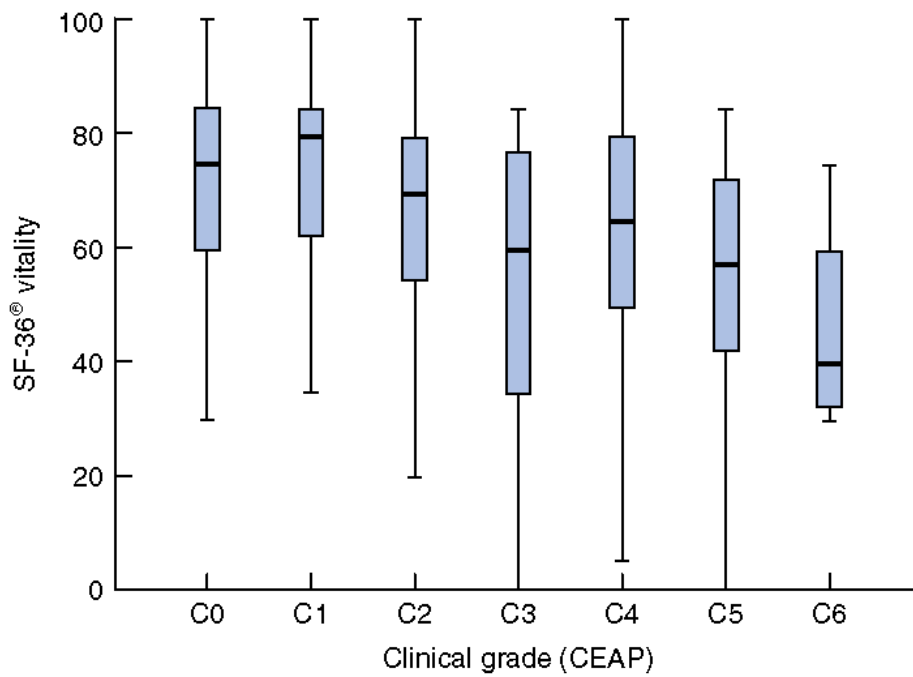
Figure 6: *Vitality scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* Lower vitality scores represent worse QoL[44].
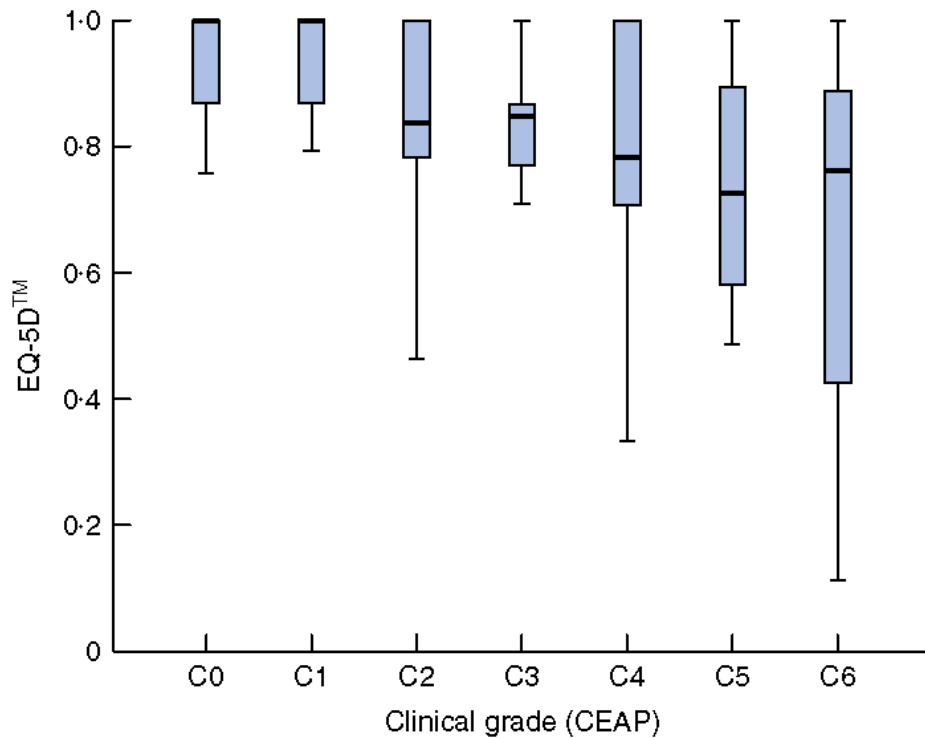
Figure 7: *Euroqol index (QALY) scores by Clinical aEtiologic Anatomic Pathophysiologic (CEAP) clinical grade.* **Lower EQ5D scores represent worse QoL**[44].

Disease specific QoL measurement (in this case with the AVVQ) as the name implies, is the most sensitive to the direct QoL impairment associated with the disease itself. It is interesting to note that even with a sample size this large, there was no appreciable difference between patients with uncomplicated varicose veins (C2) and those with skin changes short of ulceration (C3 & C4). This was an important finding, as it decouples objective clinical severity from the impairment in QoL resulting from these grades of disease. Another study found similar results and also discovered that QoL impairment could not be predicted from haemodynamic outcomes such as venous refill times[45]. This leads to the conclusion that patients cannot be selected for intervention based upon any

clinician observed outcome in common use currently, but the decision must be made based upon the patient reported symptoms and their consequent impairment of health related QoL.

When considering the generic scores, the QoL impairment was observed in predominantly physical (rather than psychological) domains. Cosmetic concern is most closely associated with mental health[46], however this domain was not primarily affected in this and other studies[46-48]. This domain was unaffected in this study. With regard to index utility scores (EQ5D), a patient with uncomplicated varicose veins will experience a loss of 0. 7 (95% CI 0. 3 to 1. 2) QALYs over 10 years (undiscounted) compared with someone in full health, if left untreated. This rises to 1. 0 (0. 5 to 1. 6) QALYs with skin changes and 2. 0 (0. 5 to 3. 6) QALYs with venous ulceration. These results are of a clinically significant magnitude[49]. The REACTIV trial[50] demonstrated a 1-year improvement in EQ-5D scores of 0. 1 following surgery, suggesting that the estimated morbidity observed in the present analysis was indeed reversible. To contextualize these results, patients with symptomatic disease can have bodily pain scores comparable to those of reference patients with recent acute myocardial infarction; whilst those patients with venous ulceration can suffer physical function and role limitation comparable to those in patients with congestive cardiac failure or chronic obstructive pulmonary disease[51]. Such profound QoL impairment has also be noted by other authors[52] and provides a clear mandate for the development and application of interventions to address this suffering and increase the health and well-being of the population.

Pathophysiology

A normal venous system depends on the integrity of the valves, vein wall and the haemodynamics of venous blood flow. These components are interdependent and the disruption of one affects the integrity of the others[53].

Insufficiency is the result of valvular dysfunction permitting retrograde venous flow in the leg. The aetiology may be congenital or secondary to thrombosis, but the vast majority of cases have no clear underlying cause and are said to be primary (at least 80% of cases[54]). As disease severity increases, the aetiology and the pathophysiology become increasingly multifactorial, for instance in venous ulcer disease, the association of previous DVT may be as high as 32%[35].

Congenital causes include Klippel-Trenaunay syndrome (manifesting as varicose veins, limb hypertrophy and dermal capillary haemangioma). Such patients have a range of venous abnormalities including atresia, agenesis, valvular incompetence and venous aneurysms. Klippel-Trenaunay syndrome, along with other congenital disorders associated with venous insufficiency is rare[55-57].

Whilst insufficiency is the most common cause of venous dysfunction, venous obstruction may also exist in isolation or in conjunction with it. Obstruction may be mechanical or functional (in the case of muscle pump failure). True mechanical obstruction is very rare, being involved in less than 0.2% of cases[23].

The Pathogenesis of Primary Venous Insufficiency

The descending theory is the classical hypothesis of the pathogenesis of primary venous insufficiency. This constitutes a mechanical failure of the junctional valvular structure, thought to be caused by back pressure acting on a background of years of battling against gravity in a bipedal gait, perhaps exacerbated by increased intra-abdominal pressure, secondary to constipation, pregnancy or chronic cough. After the proximal valves fail, increasing pressure is then propagated down the vein's axis causing dilatation and degradation of the vein and subsequent valves, which fail one after another. This appears to explain the most commonly seen patterns of SVI and is supported by pathological evidence of absence, deformity and distortion of the valves at a macroscopic level[58,59], in addition to structural changes and inflammatory infiltration[60,61] at a cellular level.

The descending theory however, fails to explain some inconsistencies in the patterns of reflux observed. Although it is common to see incompetence at the SFJ with reflux going down the GSV, it is also common to observe contradictory patterns[20,62]:

- Varicose veins with no incompetence in the trunk, junction or perforator

- Axial incompetence and dilatation below competent valves

In 1 study, 24% of 139 limbs with SVI had saphenous vein trunk or tributary reflux in the absence of an incompetent junction or perforator[63]. In the Bonn vein study; a large population based epidemiological study, around half of those with uncomplicated varicose veins had no trunk insufficiency demonstrated[22]. If left,

such patterns can be seen to progress proximally as well as distally[30]. The concept of insufficiency starting low in the leg and propagating proximally is known as the ascending theory of venous insufficiency.

This alternate theory cannot be explained by the proposed mechanism of a primary mechanical failure of the junctional valve and recent research has started to uncover a different, more intricate mechanism in action.

The acute effects of increased venous pressure have been studied in animal models. In rats, production of an arteriovenous fistula between the femoral artery and vein abruptly increased the pressure in the femoral vein to approximately 90 mm Hg. Although the valves were stretched immediately by the increased pressure, reflux did not occur until at least two days later and then increased with time in association with features of progressive inflammation. This process culminated in morphologic changes in the valves; there were reductions in leaflet height and width, and some valves disappeared. This suggests that valves can tolerate high pressures for limited periods, but when there is prolonged pressure-induced inflammation, valve remodelling, loss and reflux occur[64-66].

Inflammation plays a key role in the pathogenesis of primary venous insufficiency. Rather than being a secondary change, it is possible that this may be a significant driver of the process.

A vicious cycle exists (*Figure 8*): inflammation results in structural changes in the valves and the veins wall; weakening them. This in turn causes incompetence, precipitating venous hypertension, which then drives further inflammation. This

cycle can be initiated at any point in the venous system, but is often multifocal, with gradual propagation over time.
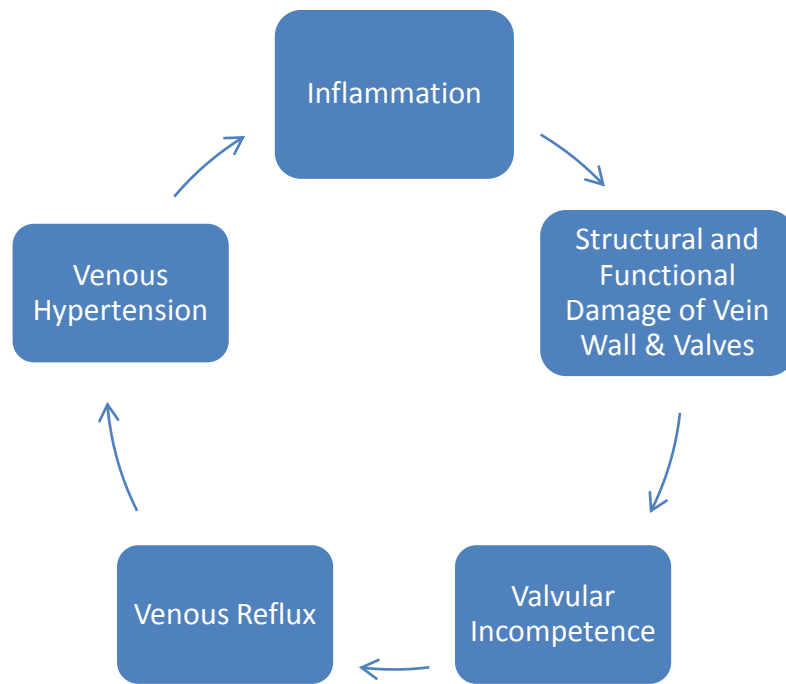
Figure 8: *The Vicious Cycle of the pathophysiology of primary venous insufficiency*

Inflammation and Degradation of the Venous Structure

Prolonged high pressure on the venous endothelium causes an imbalance in its endogenous humoral control of venous tone, resulting in relaxation[67-70]. Over distension also causes endothelial cells to release inflammatory mediators and growth factors[62,69,71,72]. Mast cells, macrophages and leukocytes are attracted to these areas of inflammation[64-66,73-75], releasing superoxide anions and proteases which act to break down the extracellular matrix[62,72], undermining the structural integrity of the vein wall. The growth factors initiate remodelling of the structure of the vein wall[62,69,72,76], which becomes stiffer and less elastic due to smooth muscle cell proliferation, collagen imbalance[77] (more type I, less type III) and a reduction in the elastin content of the media[78-82]. This is compounded by fragmentation of the collagen and elastic laminae[82-87]. The smooth muscle cells themselves are also dysfunctional, with impaired contractile function, dedifferentiation and structural disorganisation[88,89]. These processes may be mediated by dysfunctional apoptosis[53] and it is this patchy distribution of stiffened, inelastic media alternating with structurally compromised, fragmented media, prone to distension, which gives varicose veins their classical appearance.

Further damage to the extracellular matrix is mediated by matrix metalloproteinases (MMPs). In health, the structural matrix of the vein is modelled by the competing actions of MMPs and their tissue inhibitors (TIMPs)[68,69,90,91]. MMPs break down the constituents of the extracellular matrix[68,91] and reduce venous tone[92]. Normal homeostasis depends on balancing

the actions of MMPs and TIMPs, but inflammation and vein wall tension[92-94] causes imbalance of this mechanism, resulting in varicose veins[64-66,91].

Triggering the Cycle

It is unclear what factors are responsible for the initiation of the pathological cycle of venous insufficiency, but it is possible that venous stasis and hypertension results in venous wall hypoxia, mechanical stress and changes in shear stress and mechanical load[62,72].

Venous stasis has 2 elements; increasing pressure and absence of normal flow. When a rat mesenteric venule was experimentally occluded, the effects of increased pressure could be separated from the effects of reduced flow by comparing regions on either side of the occlusion; flow was essentially zero at both sites, but only the upstream site had high pressure. Leukocyte rolling, adhesion, and migration, as well as micro-haemorrhage and cell death, were all increased at the high-pressure site[95], indicating that it may be pressure rather than absence of flow acting as an initiator.

Venous valves are operated by pressure[96]. Venous flow is normally phasic, and whilst a person is standing, valves open and close approximately 20 times per minute. When the leaflets are fully open, they do not touch the sinus wall, causing flow to separate into an antegrade jet and a vortical flow into the sinus pocket behind the valve cusp. This vortical flow prevents stasis in the pocket and exerts a shear stress upon all surfaces of the valve[97]. Valve closure occurs when the

pressure caused by the vortical flow exceeds the pressure on the luminal side of the valve leaflet because of the antegrade flow. This ensures that minimal reflux occurs and endothelial surfaces are not generally exposed to reverse blood flow. Pulsatile, laminar shear stress in the endothelium causes the release of factors that reduce inflammation and the formation of reactive free radicals. By contrast, low or zero shear stress, caused by disturbed, turbulent or retrograde flow promotes inflammation and thrombosis[98-101]. These processes also operate in the arterial systems, where they may underlie the observation that atherosclerotic lesions occur preferentially in regions of low or reversing shear stress[102,103].

It is not known for sure what triggers initiate the inflammatory events in venous valves and walls, but plausible mechanisms are now known. Prolonged pooling of blood causes distension of lower limb veins. This initiates inflammation and distorts venous valves, allowing leakage and exposing endothelial cells to flow reversal. Venous stasis, even in the absence of reflux, produces regions of low or zero shear stress, whereas subsequent structural changes and irregularities in vessel walls may induce regions of disturbed and even turbulent flow. All of these events can initiate and propagate inflammatory reactions described above. Overall, it appears that inflammatory processes involving leukocyte-endothelial interactions and triggered largely in response to abnormal venous flow are important in causing the adverse changes within venous valves and vein walls. The extent and rate of progression of the different changes will depend on the interplay of many factors, producing wide variation among patients.

The Pathogenesis of Chronic Venous Insufficiency

The venous hypertension associated with CVI results in the oedema and skin changes which are apparent clinically. Higher post-exercise venous pressure is associated with a greater severity of skin damage[104]. A study of 236 limbs found that post-exercise venous pressures of less than 30 mm Hg are not associated with venous ulceration, whereas 100% of those with pressures of more than 90mm Hg had venous ulcers[105].

Venous hypertension increases the capillary hydrostatic pressure causing an imbalance in the net hydrostatic pressure across the capillary wall. This increased net filtration pressure causes increased movement of protein-free plasma into the interstitium, resulting in oedema.

There is greater uncertainty regarding the mechanisms behind trophic skin changes and two main hypotheses exist: the fibrin cuff and leukocyte trapping with inflammation:

The Fibrin Cuff Hypothesis: Increased venous pressure transmitted to the capillaries results in elongation and widening of the pores between endothelial cells[106], allowing the exudation of fibrinogen into the tissues[107]. This, along with defective fibrinolysis[108] causes fibrin cuffs to form around the capillaries. These cuffs are then purported to interfere with gas exchange, resulting in tissue ischaemia and cell death[109,110].

The Leukocyte Trapping Hypothesis: A more contemporary hypothesis is centred on inflammation and can be traced back to the observation that the blood returning from feet that have been passively dependent for 40 to 60 minutes is depleted of leukocytes, especially in patients with chronic venous disease[111,112]. This finding suggests that leukocytes accumulate in the leg under conditions of high venous pressure. It is likely that this is largely due to leukocyte adhesion to the capillary endothelium mediated by decreased shear force[113] and up-regulation of adhesion molecules in response to venous hypertension[114-116]. Evidence for this theory shows that in the presence of venous hypertension, levels of adhesion molecules on circulating leukocytes decreases, reflecting the trapping of these cells in the microcirculation. Simultaneously, plasma levels of soluble adhesion molecules increases, demonstrating the shedding of these molecules from leukocyte surfaces during leukocyte-endothelial adhesion[114,115]. Following trapping in the capillaries, the leukocytes then migrate into the tissues and are activated, initiating an intense inflammatory reaction, thought to be responsible for the skin changes[117-120].

During inflammation, tissue injury is mediated by increased expression and activity of MMPs (especially MMP-2) in LDS[121] and in ulcers[122,123]. In contrast, levels of TIMP-2 are lower in these conditions[121,122], resulting in unrestrained MMP activity breaking down the extracellular matrix. This process promotes ulcer formation and impairs healing.

Shoab et al[124] found that plasma levels of vascular endothelial growth factor (VEGF) are increased in patients with chronic venous disease, compared to

controls during venous hypertension induced by 30 minutes of standing and are higher in patients with CVI than those with uncomplicated varicose veins[125]. VEGF is thought to cause morphological changes in LDS, making the skin capillaries elongated and tortuous and inducing proliferation of the capillary endothelium in more advanced cases[126]. VEGF also increases microvascular permeability[127].

Pappas et al[128] discovered elevated levels of active TGF-β_1 in skin taken from the lower calf of patients with CVI, compared to skin from their thigh region or skin from the calves of controls. This fibrogenic cytokine; stimulates collagen production by dermal fibroblasts, culminating in dermal fibrosis[128]. Altered collagen synthesis by dermal fibroblasts in apparently healthy areas of skin in patients with varicose veins has also been reported[129].

Skin pigmentation is a product of capillary hyper-permeability; with extravasation of red cells leading to elevated levels of ferritin and ferric iron trapped inside phagocytes in affected skin[130,131]. Rather than being a benign cosmetic problem, this process may cause oxidative stress, MMP activation, and the development of a microenvironment that exacerbates tissue damage and delays healing[132]. Supporting this view; the haemochromatosis C282Y mutation is associated with an increase in the risk of ulceration by a factor of nearly seven in patients with chronic venous disease[133].

Epidemiology

The only population based follow-up study to date, estimates the incidence of varicose veins to be 39 per 1000 years in men and 52 per 1000 years in women (between the ages of 40 and 89)[134]. However, the chronic nature of venous disease escalates the prevalence; making it one of the most common ailments seen in developed countries. Some aspects of venous disease, such as thread veins are so common that they are considered by many to be "normal".

Prevalence

Much of the epidemiological data is old and estimates of the prevalence of clinical disease and the significance vary widely[135] (*Table 4*). There are a range of possible explanations for this: There are methodological differences in the studies, with some using self-reporting of disease status, others clinical examination and some imaging investigations such as duplex ultrasound (DUS) (See: Assessing Anatomical and Haemodynamic Dysfunction, p100). Early studies did not benefit from standardised classification systems such as the CEAP and venous clinical severity score (VCSS) (See: *The Clinical Assessment of Patients with Superficial Venous Insufficiency, p79*) and there was consequent disagreement regarding definitions[135,136]. Additionally there were differences in sample selection methodology; with some using samples drawn from the general population and others using patient or occupational groups. There were inconsistencies in the age and gender distributions, which can have a marked effect, when not corrected for

as these are independent associative factors in their own right (See below). It is also plausible that a proportion of these differences may also be due to genuine geographical and ethnic differences in prevalence, along with lifestyle changes over the many years of research.

Year	Country	Sample Size	Prevalence (%)	
			Male	Female
1942	USA	536	40.7	73.2
1958	Denmark	1684	18.4	38.0
1966	Bohemia	15060	6.6	14.1
1969	England	504		32.1
	Egypt	467		5.8
1970	New Zealand	232	25.0	42.0
1972	N. India	354	6.8	
	S. India	323	25.1	
1973	USA	6389	12.9	25.9
1973	Switzerland	610		29.0
1974	Switzerland	4376	57.0	68.0
1975	New Guinea	728	5.0	0.1
	Tokelau Island	286	2.9	0.8
1975	Cook Island	377	2.1	4.0
		417	15.6	14.9
	New Zealand	721	33.4	43.7
		356	19.6	37.8
1977	Tanzania	1259	6.1	5.0
1978	Switzerland	4529	56.0	55.0
1981	France	7425	26.2	
1981	Czechoslovakia	696		60.5
1981	Israel	4802	10.4	29.5
1986	Brazil	1755	37.9	50.9
1988	Sicily	1122	19.3	46.2
1989	Germany	2821	14.5	29.0
1990	Japan	541		45.0
1992	England	1338	17.4	31.6
1993	Finland	5568	18.0	42.0
1994	Turkey	856	34.5	38.3
1995	Finland	8000	6.8	24.6
1998	Italy	1319	17.0	35.2
1999	Scotland	1566	39.7	32.2
2000	Croatia	1324	18.9	34.6
2003	USA	2211	15.0	27.7
2008	Germany / Lithuania	3072	31.4	

Table 4: *Summary of studies of the estimated prevalence of varicose veins*

In order to obtain reliable estimates for societal prevalence, samples must be taken without bias, from the general population. Three high quality population based epidemiological studies, involving expert clinical assessment have been performed in recent years:

The Edinburgh vein study[18] selected an age stratified random sample from 12 general practice registers. There was a response rate of 54% giving a sample size of 1556. It was found that minor stigmata of venous disease are incredibly common with 80% of subjects having evidence of thread veins. Adjusting for age, 39.7% of men and 32.3% of women had varicose veins, and 9.4% of men and 6.6% of women had evidence of CVI.

French population study[37] randomly drew household phone numbers from four geographical areas of France for inclusion in a study on Reynaud's phenomenon. Each household was invited to enrol aiming for a target sample size of 2000. In a subsequent offshoot study; 835 of these patients were examined for the presence of venous disease and analysis of risk factors. 30.1% of men and 50.5% of women were reported to have varicose veins, whilst 5.4% of men and 2.8% of women had evidence of CVI on clinical examination.

Finally the **Bonn vein study**[22] was set in Germany and Latvia. Subjects were randomly selected from population registries. The response rate was 59% and 3072 people were examined. 90.4% had some clinical evidence of venous insufficiency; (59% - thread veins, 14.3% - varicose veins, 13.5% - oedema, 2.9% - trophic skin changes, 0.7% - ulcers).

All such studies carry the same possible biases in that response rates tend to be fairly low (not reported in the French study), leaving uncertainties around the degree to which this data can be generalised to the whole population. There is no way of knowing that there were no significant differences between the study population and the 41-46% of people choosing not to participate. Clearly with such a great proportion, even small differences will have a significant effect upon the estimated population value following extrapolation. Additionally if it is assumed that venous disease is progressive; when populations with different health care systems are studied, the relative timeliness, availability and quality of treatment may have an impact upon prevalence many years into the future.

Despite these issues; on the whole, the quality of these studies was high and many working within this field accept that the majority of the population carry minor evidence of venous disease, around a third suffer from varicose veins, 5-10% have trophic skin changes and around 1% suffer with venous ulcer disease[137,138].

Risk Factors and Associations

Many potential risk and / or associative factors have been identified and studied over the years and all have their proposed pathophysiological basis. Overall, as with the other epidemiological evidence, much of the data is very old, involving highly selected groups and fails to control for other potential confounding factors, such as age[139-141], which has a strong association with venous insufficiency.

Age

There is strong evidence that the prevalence and severity of venous disease increases with age[18,21,134,140-150]. Both the Edinburgh[18,140,144] and Bonn vein studies[22] establish a clear link between the prevalence of SVI and increasing age (*Table 5*).

Unsurprisingly this increase in pathological reflux, results in an increase in both the prevalence of varicose veins (*Table 6*) and CVI (*Table 7*).

Some of the best data on risk factor modelling comes from the Tampere varicose vein study in Finland. Questionnaires were sent to all 40, 50 and 60 year old people in a city and 5568 people responded (response rate 75% men and 86% women)[147]. Both this data and that of the French population study[37] was used to perform multiple logistic regression analyses to estimate the independent effect of risk factors upon clinical disease (*Table 8 - Table 10*). Both studies confirm the significant association of age and clinical venous disease.

Age	17-39		40-59		60-80	
Venous System	Male (n=446)	Female (n=567)	Male (n=479)	Female (n=649)	Male (n=397)	Female (n=478)

Superficial		Male (n=446)	Female (n=567)	Male (n=479)	Female (n=649)	Male (n=397)	Female (n=478)
	GSV Proximal Thigh	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 Distal Thigh	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)
	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)**
Deep	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)
	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)

Table 5: *The prevalence (as a percentage (95%CI)) of venous reflux >0.5s on DUS by age, gender and venous segment*[22]. **GSV – Great saphenous vein, SSV – Small saphenous vein, SFV – Superficial femoral vein, PV – Popliteal vein, PTV – Posterior tibial vein. Figures in bold indicate a statistically significant difference between men and women (α≤0.050)**

Age	18-24	25-34	35-44	45-54	55-64
Male	20.0	15.5	36.1	42.0	61.4
Female	5.3	13.9	22.6	41.9	50.5
Total	11.5	14.6	28.8	41.9	55.7

Table 6: *The prevalence of saphenous varicose veins (as a percentage) by age and gender in the Edinburgh vein study*[144]

Age	18-24	25-34	35-44	45-54	55-64
Male	0.0	0.0	2.53 (0.69-6.28)	7.73 (4.31-12.74)	25.25 (19.25-31.62)
Female	1.32 (0.03-7.11)	1.25 (0.15-4.44)	3.76 (1.48-7.48)	7.93 (4.87-12.52)	12.27 (8.17-17.20)

Table 7: *The prevalence of chronic venous insufficiency (as a percentage (95% CI)) by age and gender in the Edinburgh vein study[144]*

Risk Factor		OR (95% CI)
Female		2.3 (1.8-2.9)
Age (years)*	50	2.2 (1.9-2.6)
	60	2.8 (2.4-3.3)
Weight (Kg)	>65 (F), >80 (M)	1.2 (1.1-1.4)
Height (m)	>1.65 (F), >1.75 (M)	1.4 (1.1-1.6)
Mainly standing posture at work		1.6 (1.4-1.8)
FH (1st degree relative)		4.9 (4.2-5.7)
Parity	1	1.2 (1.0-1.6)
	2	1.7 (1.3-2.1)
	3	1.9 (1.4-2.5)
	4+	2.7 (1.9-3.9)

Table 8: *Independent Odds ratios (95%CI) for the association of proposed risk factors with varicose veins[147]. *The baseline age comparator is 40 years*

Despite this association with age; venous dysfunction has been demonstrated to commence early in life, for example; 2.5% of 518 school children aged 10-12 were found to have saphenous incompetence on ultrasound, increasing to 12.3% after 2 years and 19.8% by the age 18-20. This in turn was associated with 2.5% having visible varicose veins by 14-16 and 8.3% by the age of 18-20[151].

Risk Factor	Men	Women
	Varicose veins	
Age*	1.05 (1.02-1.07)	1.04 (1.02-1.05)
FH	3.53 (1.91-6.54)	3.47 (2.38-5.07)
Exercise+	1.97 (1.08-3.61)	NS
Previous Pregnancy	NA	1.98 (1.20-3.25)
Height >1.65m	NS	1.32 (1.08-1.62)
	Chronic Venous Insufficiency	
Age*	1.08 (1.04-1.13)	
FH	2.81 (1.03-7.71)	

Table 9: *Independent Odds ratios (95%CI) for the association of proposed risk factors with varicose veins and chronic venous insufficiency*[37]. **Controlling for activity, socioeconomic status, Body mass index, history of thromboembolic disease, geographical area, smoking status, alcohol consumption, level of education and oestrogen therapy in women. FH – Family history of a first degree relative, NS – no significant relationship, NA – not applicable. * - Odds ratio per year of age, + less than once per week**

Risk factor	Proportion of Variance Explained (%)	
	Men	Women
Age 50 years	23	12
Age 60 years	21	18
FH	38	31
Weight*	12	12
Height+	12	4
Standing at work	12	15
Parity	NA	24

Table 10: *The proportion of variance (as a percentage) in the prevalence of varicose veins explained by risk factor*[147]. **(Derived from the multiple logistic regression models detailed in** *Table 8***)**

There is also evidence that aside from the prevalence of venous dysfunction in general, the severity of venous disease increases with age[140], indeed; venous ulcers are uncommon below the age of 60, but their prevalence then increases with age[152-154].

Scott et al[141] performed a case control study in an outpatient clinic setting. This compared 222 patients with varicose veins or CVI against 113 "general surgery patients" with no clinical evidence of venous disease. A multivariate logistic regression analysis was subsequently performed (*Table 11*). The results should be interpreted with caution; as the chosen controls are likely to be significantly different from the general population. This resulted in some discrepancies, such as the apparent "protective effect" of age in the development of varicose veins. However, when patients with varicose veins are compared with those suffering CVI, it is apparent that age is a risk factor in progression from uncomplicated to complicated disease.

This association of worsening disease severity with age seems to support the theory of the progressive overall deterioration in clinical condition of people with unaddressed venous incompetence over time.

	Risk Factor	OR (95%CI)
VV compared with Controls	Age	0.96 (0.93-0.99)*
	Female Gender	5.00 (2.20-12.50)
	History Phlebitis/DVT	6.30 (1.80-22.30)
	"Family History VV"	21.50 (10.00-46.30)
CVI compared with controls	Age	1.06 (1.03-1.09)*
	Male Gender	2.90 (1.30-6.40)
	BMI	1.06 (1.01-1.10)+
	History Phlebitis/DVT	25.70 (7.60-86.50)
CVI compared with VV	Age	1.07 (1.04-1.10)*
	Male Gender	8.00 (3.50-18.30)
	BMI	1.07 (1.01-1.13)+

Table 11: *Independent Odds ratios (95%CI) for the association of proposed risk factors comparing controls with varicose veins and chronic venous insufficiency*[141]. **DVT – Deep vein thrombosis, VV – varicose veins, BMI – Body mass index. * - Per year, + - Per Kgm^{-2}**

Gender/Pregnancy

It is a widely held belief, that venous insufficiency is more common in women than men. It is certainly true that women present more often for treatment[142,145-148,150,155,156] and there is evidence from population based studies that the prevalence of varicose veins is indeed higher[21,22,37,143,147], however on closer inspection of the evidence; a complicated relationship with gender becomes apparent.

Firstly considering the findings of insufficiency upon venous duplex imaging: Women were observed to have a higher prevalence of SVI in the Bonn vein study[22], but it is men who appear to have the highest prevalence of DVI (*Table 12*). In the Edinburgh vein study men also had higher rates of DVI, but there was no significant difference in the superficial venous duplex findings between genders[18].

	Venous System	Male (n=1694)	Female (n=1322)
Superficial	GSV Proximal Thigh	**11.8 (10.1-13.6)**	**16.4 (14.7-18.3)**
	GSV Distal Thigh	**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)
	Overall	**17.7 (15.7-19.9)**	**23.5 (21.5-25.7)**
Deep	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)
	Overall	**23.1 (20.9-25.5)**	**17.6 (15.8-19.5)**

Table 12: *The prevalence (as a percentage (95%CI)) of venous reflux >0.5s on DUS by gender and venous segment in the Bonn Vein Study[22].* GSV – Great saphenous vein, SSV – Small saphenous vein, SFV – Superficial femoral vein, PV – Popliteal vein, PTV – Posterior tibial vein. Figures in bold indicate a statistically significant difference between men and women (α≤0.050)

These deep venous findings are based upon a definition of pathological reflux lasting more than 0.5 seconds; however, many believe that reverse flow of less than 1 second in deep veins, particularly in men; is physiological and that a cut off below this will erroneously label veins as incompetent (See *Assessing Anatomical and Haemodynamic Dysfunction, p100*). These gender-related differences in the

deep veins become less prominent when a cut off of 1 second is used, however, some difference is still evident and men judged to have no clinical evidence of venous disease have similar reflux durations to those seen in women.

There is disagreement in the literature as to whether women or men have a higher prevalence of varicose veins. Most studies find this to be higher in women[21,22,37,143,147] (*Table 8*), but the Edinburgh vein study showed the opposite[18] (See: *Prevalence*, p58). What does seem clear is that a greater proportion of men suffer with CVI[18,21,37,141,143] and male gender may be a risk factor for progression from varicose veins to CVI (*Table 11*)[141]. It is uncertain as to whether this increased risk of CVI is an indication of a greater tendency to have venous disease treated at an earlier stage in women or differing pathophysiology between men and women, (perhaps seen in the differences in DVI rates discussed above).

Age may have a part to play in the disagreement in varicose vein prevalence: *Table 5* (*p64*) shows that there is no significant difference in the prevalence of SVI between men and women in those under the age of 60 years. *Table 6* and *Table 7* (*p64-65*) echo this; showing significant divergence in the prevalence of varicose veins and CVI after 55 years. Prevalence therefore increases with age in both genders, but this may be at a greater rate in women, causing a gradual divergence between the rates seen in men and women.

With higher rates of SVI seen in women, it seems probable that the prevalence of varicose veins will be higher and interestingly the pattern of the varicosities may be different. The French population study[37] supported the evidence that overall,

varicosities are more common in women (See *Prevalence*, *p58*), however these followed a different distributional pattern. Both sexes had the same proportion of varicose veins coming from saphenous axial incompetence, but women had significantly more non-saphenous varicosities (*Table 13*).

Source	Women	Men
GSV and main tributaries	14.8	14.3
SSV	4.8	3.4
Non-Saphenous	**26.9**	**8.7**

Table 13: *The prevalence of varicose veins (as a percentage) by gender and distribution[37]. GSV – great saphenous vein, SSV – Small saphenous vein. Figures in bold indicate a statistically significant difference between men and women (α≤0.050)*

Women are significantly more likely to report symptoms than men (51.3% of women compared with 20.4% of men)[37]; which has also been noted on QoL modelling, where women reported a greater disease specific QoL impairment than men, controlling for the clinical severity of disease and other demographic and anatomical factors[38]. This is perhaps the motivation behind women presenting earlier and in greater numbers, for treatment.

Another interesting observation is that varicose veins from both saphenous and non-saphenous origins are associated similarly with the presence of symptoms (Saphenous - 70.1%, non-saphenous - 63.7% - women. Saphenous - 36.4%, non-saphenous - 34.0% - men), however saphenous varicosities had greater association with trophic skin changes (Saphenous 13.4%, non-saphenous 4.2%)[37].

To further complicate things, when CVI is looked at in detail, further inconsistencies are observed. Despite the higher rates of trophic skin changes in men, venous ulceration is 2 to 3 times more common in women[140]. This has not been satisfactorily explained, but may indicate differing pathological mechanisms or additional factors are involved.

Pregnancy is a proposed explanation for the increased incidence of varicose veins in women, with multiparity being associated with a greater prevalence than nulliparity[37,142,146,147,157-162] (*Table 8 - Table 10*, *p65-66*). There is even evidence of a "dose response" with incidence increasing with the number of full term pregnancies[147,148,150,155,158,160,163]. This is not a unanimous view however and some of these studies may be biased by a failure to control for age[139,140].

There are several proposed mechanisms to explain the association of venous incompetence and pregnancy. The most obvious is that the increase in intra abdominal pressure associated with the enlarging uterus impedes venous return[164,165], however this is debateable as varicose veins often develop prior to significant uterine enlargement[135], suggesting that other factors are important. There is also clinical evidence that weight gain is not an independent risk factor for varicose veins in pregnancy[158].

During early pregnancy there is a significant increase in blood volume due to plasma expansion placing an increased strain upon the capacitance of the venous system[166]. In addition to the increased demands upon the venous system, the

hormonal changes associated with pregnancy have a likely role. Relaxin causes softening of connective tissues. The primary function of this is in preparing the pelvic structures for delivery, but it also, works alongside oestrogen to mediate vasodilatation; which in turn results in increased venous stasis and valvular dysfunction[167-171]. Another hormone; progesterone, is known to weaken the structural integrity of blood vessels[167,169,171,172]. Concentrations of both oestrogen and progesterone increase rapidly in early pregnancy, but both are produced through a woman's reproductive life and it may be that even low levels have a cumulative deleterious effect upon venous integrity.

A further possible explanation of the increasing gender divergence with age is that there may be a differential weakness of the muscle pump with aging, due to the more rapid drop off in musculoskeletal mass in females.

Heredity

It is difficult to establish the role of genetics in venous insufficiency as venous disease is so common and most studies rely upon questionnaires to establish family histories rather than the independent objective verification of pedigrees. Subjects with venous disease are often more likely to be aware of others in the family, than those unaffected[135]. There is also some evidence that the number of reported "false positives" of a family history may be higher in those with venous disease[173].

Accepting this, there appears to be reasonable evidence of a hereditary association with both varicose veins and CVI (*Table 8 - Table 10*, *p65-66*) [37,134,141,142,145,147,174,175]. Two large population based risk factor studies found that a family history of a first degree relative with venous insufficiency was the most powerful risk factor for developing the disease, increasing the risk by approximately 3.5 to 5 times[37,147] (*Table 8 & Table 9*). Given the high rates of prevalence of venous insufficiency; it may be more correctly stated that an absence of family history is highly protective.

A detailed study of heritability was performed in Germany. 2701 patients with venous disease were recruited and a questionnaire based pedigree likelihood approach was applied. The heritability or proportion of phenotypic variance attributable to genetic inheritance was calculated to be around 17% and was stable throughout the clinical disease spectrum[175].

Hirai et al[146] studied 541 Japanese women, finding 42% of those with varicose veins had a positive family history compared with just 14% of women without disease. Importantly; this difference decreased with age, suggesting that genetic factors may be involved in the early development of disease.

There are known congenital syndromes associated with venous disease, but to date, no genotypes have been convincingly associated with the heritability of primary venous insufficiency[53].

Geography/Race

Once again, there is little contemporary data on this. Venous disease is not a research or health priority in the developing world as it cannot compete with other more pressing health and social issues in these areas. Previous work has suggested that venous insufficiency is less common in the developing world than in Europe and North America and it was suggested that this was mainly due to lifestyle issues[176-178]. Although there is little clear evidence, mechanisms such as reduced constipation; secondary to a high fibre diet, toilet habit, less time spent standing and less tight undergarments have been suggested, alongside the possibility of a genetic ethnic link[162].

A classic study compared 358 female cotton workers in the north of England with 467 of their counterparts in Egypt[149]. The prevalence of venous disease was higher in England (32% v 6%), when controlling for age.

Differences are noted between continents, even following immigration. In a community study in Jerusalem, Abramson et al[142] found a lower prevalence of varicose veins in immigrants from North Africa (13.2% - men, 30.2% - women) compared with immigrants from Europe and America (26.9% - men, 48.8% - women) and from other parts of Asia (22.4% - men, 39.7% - women). However, a more recent paper studied UK Asian men as they attended a Mosque in Birmingham, finding similar rates of varicose veins and CVI as reported in the white British population[179].

The most detailed study to date on ethnicity within an immigrant population consisted of 2211 current and retired university employees in San Diego[143]. The cohort was broken down into non-Hispanic white (58%), Hispanic (15%), African Americans (14%) and Asians (12%). There were no differences in the prevalence of varicose veins, trophic skin changes or venous ulcers. Hispanics were less likely to have oedema (OR 0.29), and Asians were less likely to have SVI on DUS (OR 0.65).

Beaglehole et al[155] studied 2301 people in New Zealand and the Pacific islands (*Table 14*). In New Zealand the western settlers (Pakeha) had a lower prevalence of varicose veins than the native Maori. There was an even a larger difference between the Rarotonga and the Pukapuka in the Cook Islands. As island communities tend to display greater genetic diversity between each other than those living on the great land masses, perhaps this gives more evidence as to the impact of genetic factors upon venous insufficiency.

Location	People	Male	Female
New Zealand	Maori	33.4	43.7
	Pakeha	19.6	37.8
Cook Islands	Rarotonga	15.6	14.9
	Pukapuka	2.1	4.0
Tokelau Island		2.9	0.8

Table 14: *The age standardised prevalence (as a percentage) of varicose veins by people and location in the South Pacific*[155].

Differences have also been noted within continents; Guberan et al[180] found the prevalence of varicosities was significantly lower among women from Southern Europe (Italy and Spain) than among women from Switzerland, France, and other Central European countries.

Other detailed studies have failed to attribute any significance to geographical variations within countries[22,37].

Body Mass Index

Evidence on the significance of body mass index is mixed and much of it is very weak. Amongst the most convincing evidence is seen in the Bonn vein study[22], which found an increase in the prevalence of SVI associated with a BMI of greater than 30. Other studies also support a link[22,141,142,150,155,161,163], which may only be relevant in women[134,144,157]. The reason for this differential relationship is speculation, but may be mediated by an increase in bioavailable circulating oestrogens in obese women[135]. Further studies have failed to identify any link[139,146,159,160,180]. Interestingly, obese women are more likely to report varicose veins[181]. It is possible that obesity may worsen the clinical severity or symptoms rather than having a direct effect upon prevalence, or perhaps obesity causes leg symptoms which are mistaken as venous in origin.

Lifestyle

Although lifestyle risk factors have long been blamed for variation in prevalence, there is little high quality evidence to support their role. Lifestyle factors are difficult to investigate as many studies rely on self reported data, which is difficult for the investigators to verify.

There is some support for the view that periods of protracted standing predisposes to venous insufficiency[134,142,144,150,159,163,182]. The Edinburgh vein study found that sitting at work is protective in women (OR 0.75 (0.57-0.99))[139]. This appears to be corroborated by the Israeli and Framingham epidemiological studies[134,142] again mainly in women.

Constipation has been suggested as a potential cause, with a loaded colon compressing the pelvic veins and the effect of straining at stool on intra abdominal pressure as suggested mechanisms[176]. There is currently little supportive evidence for this hypothesis and detailed analysis in the Edinburgh vein study failed to demonstrate an association[139].

The evidence to support any association between varicosities and other lifestyle factors such as social class, education, tight undergarments, toilet posture, chair sitting, oral contraceptives, hormone replacement therapy and smoking is also lacking[37,135,144,162].

1.3 The Management of Superficial Venous Insufficiency

Assessment

The Clinical Assessment of Patients with Superficial Venous Insufficiency

It is clearly important to be able to objectively evaluate the clinical severity of disease suffered by a patient in a manner which is standardised across the literature. As discussed earlier, many of the early studies into venous disease were hampered by a lack of consensus upon how to grade and classify its diverse spectrum. This was addressed in 1994 by an international ad hoc committee at the American Venous Forum annual meeting.   The result was the CEAP classification system published in 1996 and revised in 2004[25,183].

The CEAP Classification

The C is for clinical severity and runs from 0 to 6. Each clinical subgroup may be followed by the subscript A (asymptomatic) or S (symptomatic). E is for aEtiologic and divided into the 3 main aetiological mechanisms. A is for anatomic, detailing which veins are involved and finally P is pathologic, representing the pathophysiological mechanism underlying the disease.

Figure 9 provides a detailed breakdown of the classification system.

Clinical	C0	No visible / palpable signs of venous disease
	C1	Telangectasia 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

Figure 9: *The revised CEAP classification*[25]

Clearly full CEAP evaluation requires the use of objective clinical observation in conjunction with imaging and physiological assessment. Whilst the CEAP system offers descriptive precision; some criticise that it becomes too precise and complex in some cases; furthermore it is a poor outcome for clinical interventional studies for several reasons. There is no indication as to the severity within each of the clinical classes. A single 1cm long varicosity of 3mm diameter scores the same as severe tortuous veins covering 90% of the leg's surface area. This makes the C2 relatively resistant to change and in practise C4 is highly resistant to change and C5 permanent. This inherent resistance to clinically significant improvements makes this instrument insensitive to the variation observed in interventional studies[184-187].

The Venous Clinical Severity Score

In a bid to produce a clinical severity classification system which is responsive to changes a further ad-hoc committee of the American Venous Forum produced the Venous Clinical Severity Score (VCSS), which was designed to supplement the CEAP and provide a method for serial assessment[184,186,188]. It was also designed to give additional weight to more severe manifestations of chronic venous disease (CEAP clinical class 4 and class 6). The VCSS has been shown to withstand differences in intra-observer and inter-observer reproducibility and to be responsive to change[185].

Figure 10 provides a detailed breakdown of the classification system.

The VCSS is not without its critics however with some criticising the inclusion of a observer assessed valuation of pain and discomfort and the use of compression therapy. The quality of life impairment associated with venous disease is clearly a critical issue; but one best left to assessment using validated patient reported quality of life assessment instruments, which will be discussed later. The use of compression is a multifactorial issue, relating to clinician, patient and societal preference as much as to the control of symptoms. In clinical studies, this is clearly open to bias as this factor is eminently under investigator control and differing compression practices may result in very different VCSS outcomes for clinically similar patients.

Component	Score			
	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

Figure 10: *The Venous Clinical Severity Score*[188]. ADL – activities of daily living

Assessing the Quality of life Impairment Associated with Superficial Venous Insufficiency

Venous insufficiency does not significantly alter the length of life, but can have a profound impact upon the quality of that life (See Quality of Life Impairment, p40). Therefore the principle aim of any treatment is the improvement of a patient's QoL. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends the consideration of treatment for varicose veins that impact on QoL[189], irrespective of the coexistence of complications. This makes patient centred QoL assessment the primary outcome for any study on venous insufficiency and as such; must be studied in detail. Accurate information regarding the QoL value of the health states associated with venous disease is also essential for cost–utility analysis, the keystone of economic evaluation in the context of health technology assessment[190]. In the UK, QoL analysis has evolved from this research role and it is now compulsory in the NHS to measure QoL before and after venous interventions[191,192].

Broadly speaking there are two categories of QoL instrument; those specific to a given disease and generic systems assessing the QoL impairment from any condition.

Disease Specific Quality of Life Assessment

At the time this research was commenced, most was known about the performance characteristics of the Aberdeen varicose vein questionnaire (AVVQ). This is a disease-specific instrument that measures the QoL impairment associated directly with venous disease and is the most widely used and stringently validated instrument in this role[47]. Disease specific measures have potential advantages over generic instruments[47]:

- It may be more sensitive to small yet clinically significant changes in health status

- It may have greater power to discriminate between patients whose health is only mildly affected by their varicose veins

- The questions will be familiar to patients, and the resulting questionnaire will be acceptable and present them with few difficulties

The questionnaire was based on questions commonly used in the clinical assessment of patients with varicose veins, as indicated by a review of the clinical literature. An "expert panel" of two consultant surgeons was convened to assess the content validity (whether the questions are representative of the disease). Each question was then independently scored by the surgeons. 0 was the score for responses considered to be normal and the other responses were given a score in proportion to what is believed to be the associated morbidity. The two sets of scores were then averaged and rescaled to yield total scores between 0 and 100; 0

is reserved for patients with no features or evidence of venous disease and 100 for patients ticking the most severe response to each question. A patient focus group was used to assess the wording of the questions for comprehension and ambiguity. Factor analysis was used to identify any questions which did not contribute significantly to the overall score. Such questions were removed; along with any where greater than 80% of respondents gave the same answer or gave all responses to a question; as these questions did not add to the questionnaire's ability to discriminate between different levels of morbidity. Finally the questionnaire was validated by a sample of patients and the general population. It was found that variation in the AVVQ was associated with variation in previously validated generic instruments such as the Short Form 36 (SF-36®; Medical Outcomes Trust, Waltham, Massachusetts, USA)[47].

Question 1 of the questionnaire invites the subject to draw the distribution of their varicose veins on an unmarked diagram of the front and rear aspects of the legs. The investigator then uses an acetate overlay with a grid pattern to score the number of affected segments (*Figure 11*).

Scoring Grid
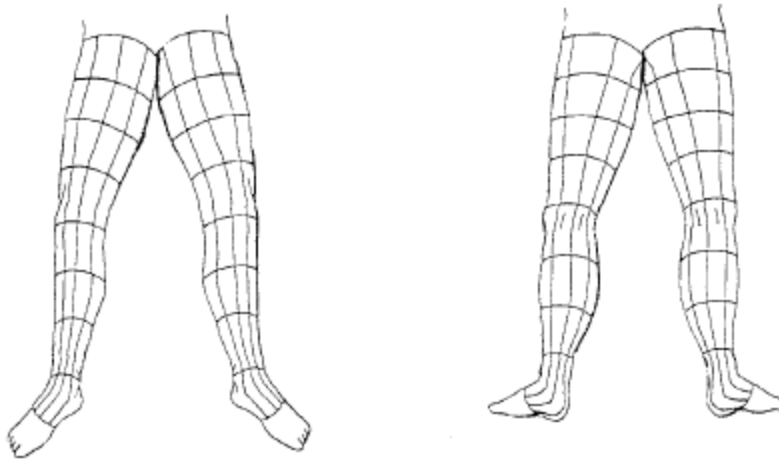
Figure 11: *Scoring grid for question 1 of the Aberdeen varicose vein questionnaire*[47]

The remaining 14 questions are in a tick box format (*Figure 12*).

2 In the past two weeks, for how many days did your varicose veins cause you pain or ache?
(Please tick one box for each leg)

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

3 In the past two weeks at what time of day were your varicose veins usually most painful or aching?
(Please tick one box)

Not painful at all ☐
No particular time ☐
In the morning ☐
In the afternoon and/or evening ☐
At night ☐

4 During the past 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 ☐

5 In the past two weeks, how much ankle swelling have you had?
(Please tick one box)

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

6 In the past two weeks, have you worn support stockings or tights?
(Please tick one box for each leg)

	Right	Left
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	☐	☐

7 Do you take "water tablets" for ankle swelling?
(Please tick one box)

No	☐
Yes	☐

8 In the past two weeks, have you had any itching in association with your varicose veins?
(Please tick one box for each leg)

	Right	Left
No	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Yes, both above and below the knee	☐	☐

9 Do you have purple discoloration caused by areas of tiny blood vessels in the skin, in association with your varicose veins?
(Please tick one box for each leg)

	Right	Left
No	☐	☐
Yes	☐	☐

10 Do you have a rash or eczema in the area of your ankle?
(Please tick one box for each leg)

No	☐	☐
Yes, but does not require any treatment from a doctor or district nurse	☐	☐
Yes, and requires treatment from a doctor or district nurse	☐	☐

11 Do you have a skin ulcer associated with your varicose veins?
(Please tick one box for each leg)

No	☐	☐
Yes	☐	☐

12 Does the appearance of your varicose veins cause you concern?
(Please tick one box)

No	☐
Yes, slight concern	☐
Yes, moderate concern	☐
Yes, a great deal of concern	☐

13 Does the appearance of your varicose veins influence your choice of clothing, including tights?
(Please tick one box)

No	☐
Occasionally	☐
Often	☐
Always	☐

14 During the past two weeks have your varicose veins interfered with your work or 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	☐

15 During the past 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 12: *Questions 2-15 of the Aberdeen varicose veins questionnaire[47]*

For an instrument to be used as a measure of health outcome, it needs to be reliable (reproducible), valid (tests what it purports to measure), responsive (sensitive enough to recognise small but significant differences), and practical (ease of administration)[51,193,194]. An external validation study[48] alongside a further study by the original author[46] confirmed that the AVVQ fulfilled these criteria and as intended; is more responsive than generic instruments. The AVVQ has since become an extremely popular outcome measure, although is not without its criticisms: from the very beginning it was not designed to be patient centred and was developed according to the views of experts rather than patient preferences. Consequently; there appears to be some cross over with the VCSS, including an assessment of clinical severity and the inclusion of compression treatment, both may be questionable features. Despite this, validation studies are favourable and a comparison with subsequent systems involving a more patient-centred approach in development, found similar results[45] and perhaps the performance characteristics of the AVVQ are superior. Furthermore an estimation of clinical severity by the patient themselves is important, irrespective of the actual severity; as it displays that patient's perceptions, as does their decision to comply with compression therapy.

In summary therefore, the AVVQ gives a measure of the patient perceived morbidity in association with their venous disease. It is an outcome measure which is sensitive to small, but meaningful changes in QoL and therefore can be used to show the effectiveness of treatment and the significance of disease recurrence. Other disease specific instruments exist such as the VEINES-Sym[195],

CIVIQ 2[196] and SQOR-V[197], but the AVVQ remains the most popular in the UK and USA and has undergone the most stringent validation to date.

It is recommended that a disease-specific measure should be used in conjunction with a generic instrument[46,51,198-200]; disease-specific measures may be relatively insensitive to the morbidity associated with invasive procedures[48] and are difficult to map on to index utility scores, precluding detailed economic evaluation.

Generic Quality of Life Assessment

Health Profile

The generic SF-36 instrument[201,202] was born of the Medical Outcomes Survey and the RAND health insurance experiment[203,204] (*Figure 13*). The aim was to produce a standardised, comprehensive, psychometrically sound, practical instrument, which could replace long and time consuming health surveys, which prevailed up to this point; reducing the burden of research on both patients and research team. This has become the most widely used generic instrument in the world today[205]. It produces a comprehensive profile of eight domains covering the range of physical and psychological well-being: physical function, role limitation due to physical disability (role – physical), bodily pain, general health perception, vitality, social function, role limitation due to emotional problems (role – emotional) and mental health. Item scores for 36 questions are coded, summed and transformed on to a scale from 0 (worst health) to 100 (best health) in each domain. SF-36 has been extensively shown to be both valid and reliable[46,47,193,206-209], and used in many

patient groups, including those with venous insufficiency. Its global popularity has resulted in its being translated into 130 languages and norm based scores produced for a range of populations based upon population responses, making it a patient centred questionnaire.

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

Excellent	Very good	Good	Fair	Poor
⊙	○	○	○	○

2) Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3) The following questions are about activities you might do during a typical day. Does your health now limit you 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	○	○	○
b. Moderate Activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing several flights of stairs	○	○	○
e. Climbing one flight of stairs	○	○	○
f. Bending, kneeling, or stooping	○	○	○
g. Walking more than a mile	○	○	○
h. Walking several hundred yards	○	○	○
i. Walking one hundred yards	○	○	○
j. Bathing or dressing yourself	○	○	○

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

	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 <u>amount of time</u> you spent on work or other activities	○	○	○	○	○
b. <u>Accomplished less</u> than you would like	○	○	○	○	○
c. Were limited in the <u>kind</u> of work or other activities	○	○	○	○	○
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

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

	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 <u>amount of time</u> you spent on work or other activities	○	○	○	○	○
b. <u>Accomplished less</u> than you would like	○	○	○	○	○
c. Did work or activities <u>less carefully than usual</u>	○	○	○	○	○

6) During the <u>past 4 weeks,</u> to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7) How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very Mild	Mild	Moderate	Severe	Very Severe
○	○	○	○	○	○

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9) These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. **For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...**

	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?	◎	◎	◎	◎	◎
b. Have you been very nervous?	◎	◎	◎	◎	◎
c. Have you felt so down in the dumps that nothing could cheer you up?	◎	◎	◎	◎	◎
d. Have you felt calm and peaceful?	◎	◎	◎	◎	◎
e. Did you have a lot of energy?	◎	◎	◎	◎	◎
f. Have you felt downhearted and depressed?	◎	◎	◎	◎	◎
g. Did you feel worn out?	◎	◎	◎	◎	◎
h. Have you been happy?	◎	◎	◎	◎	◎
i. Did you feel tired?	◎	◎	◎	◎	◎

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 friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
◎	◎	◎	◎	◎

11) How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	◎	◎	◎	◎	◎
b. I am as healthy as anybody I know	◎	◎	◎	◎	◎
c. I expect my health to get worse	◎	◎	◎	◎	◎
d. My health is excellent	◎	◎	◎	◎	◎

Figure 13: *The Short Form 36 Questionnaire (UK V2)*

Index utility

Patient preference or utility scoring allows the production of a single generic index utility score, representing a patient's health status on a continuous interval scale from 0 to 1, where 0 represents dead or unconscious and 1; full health. With some scales; utilities of below 0 are possible for states such as intractable pain and disability, considered "worse than death." This index is used in the calculation of the quality adjusted life year (QALY) and this common currency is the bedrock of health utility analysis. This single common unit potentially allows the meaningful optimisation of the allocation of health resources, ensuring that these resources are invested in such a way as to maximise the health gained from healthcare programmes; addressing the full spectrum of human disease and disability.

In this context, the concept of an interval utility is applied to the measurement of patient or societal preference. That is the measurement of which health states are preferred to others, and by how much. The interval or the numerical difference relates to the magnitude of the difference in preference.

The philosophy of utility in this context was revolutionised in 1941 with the work of von Neumann and Morgenstern on a model of rational decision making under uncertainty; the expected utility theory[210-212], providing the framework of modern decision theory used in business, government, engineering and healthcare.

There are several methods of measuring utility. The most simple is a visual analogue scale, where subjects are invited to place a cross representing their preference for a give state between two defined points; at a distance which

reflects the difference in preference. This technique is rarely used in isolation as it often fails to produce a representative interval scale[213-217]. The optimum methods for evaluating health preference are the time trade off (TTO) and the standard gamble (SG).

The Standard Gamble

The SG is the classical method for measuring utility and does so under conditions of uncertainty (similar to real life situations)[218]. If a health state is preferred to death then a subject is asked to choose between two options. Option 1 is to continue in the health state to be valued and option 2 has two possible outcomes: restoration to full health for life (with a probability p) or instant death (probability 1-p). p is then varied until the subject is indifferent between the two options. The utility estimate is then equivalent to p (*Figure 14*).
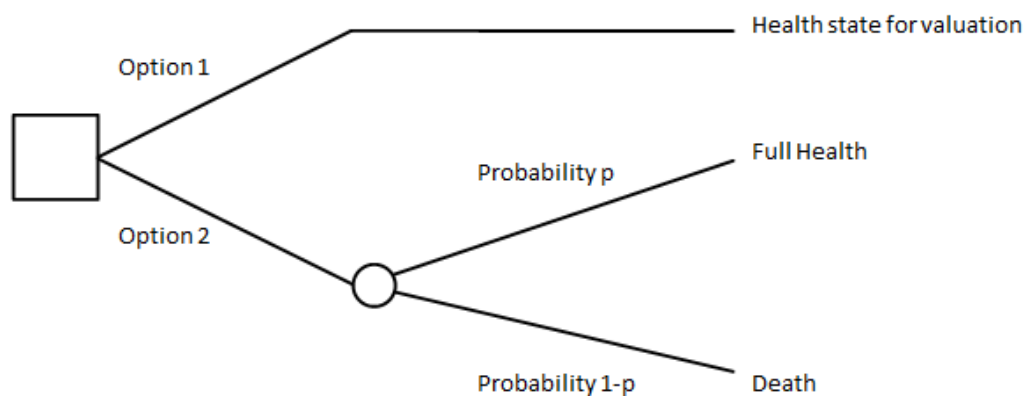
Figure 14: *The Standard Gamble*

The Time Trade Off

A drawback of the SG is that many people struggle to relate to the concept of probabilities. The TTO was designed to be conceptually simple and easy to administer[219]. A subject is asked to choose between option 1 living in the health state to be valued for life or option 2 where they are restored to full health, but with a given reduction in the length of life. The time they are willing to "trade off" is varied until they are indifferent between the two options. The utility estimate is the proportion of life to be traded (*Figure 15*). Some argue that the lack of uncertainty associated with this technique makes it unrealistic.
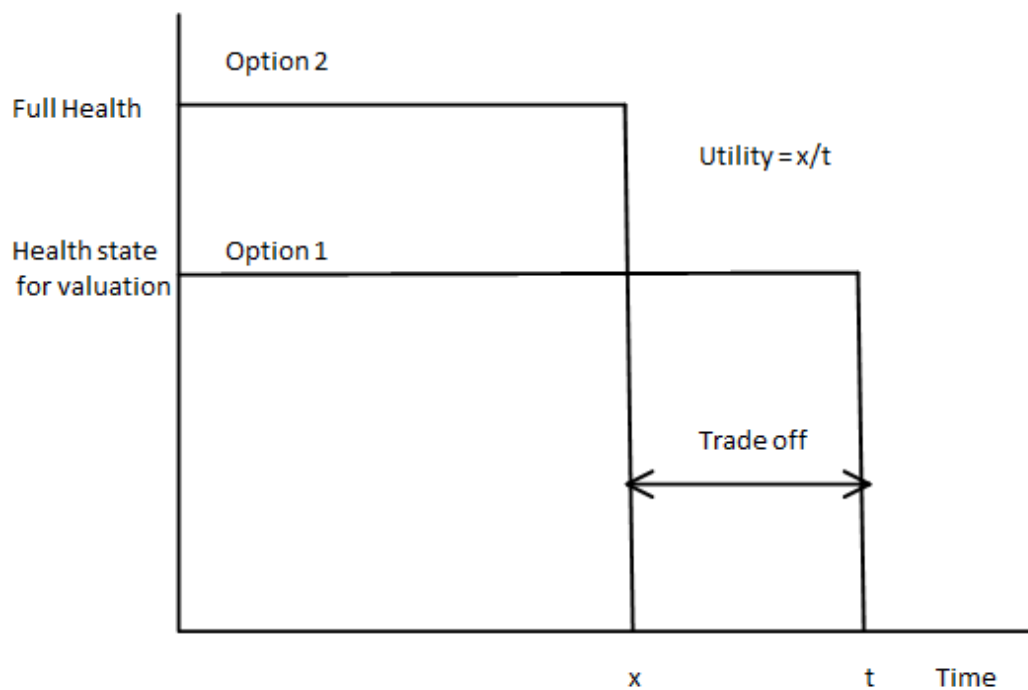
Figure 15: *The Time Trade Off*

Utility Measurement Instruments

Although these methods are the underlying theory behind utility measurement, it is time consuming to employ them and many studies utilise "off the shelf", pre-scored multi-attribute instruments.

The EuroQol (EQ5D™; EuroQol Group, Rotterdam, The Netherlands) was developed by a multidisciplinary group of researchers from five European centres[220] (*Figure 16*). It is an index scale, mapping three available responses to five questions onto a utility scale with 245 possible states. The UK weights were derived from TTO responses from 3000 adults from the general population[221], with statistical modelling. The EQ5D has been shown to be valid[220,222,223] and is the recommended utility measure for cost utility analysis in the UK[190]. It is also a popular system world-wide with 150 languages available. The EQ5D also includes a 100 point visual analogue scale, from "worst imaginable health state" to the "best imaginable health state".

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 16: *The EuroQol Time Trade Off Questionnaire*

Another recently developed index utility score is the SF-6D[224,225]. This can be derived from responses to the SF-36 or the shorter SF-12 health profile. The UK weights were derived from SG responses from 836 adults, again with statistical modelling to produce 18,000 health states. A benefit of this instrument is that it can be calculated from the results of previous studies not featuring dedicated utility assessment. Relatively little is known about the performance characteristics when compared with the EQ5D.

Assessing Anatomical and Haemodynamic Dysfunction

Duplex Ultrasound

Duplex ultrasound (DUS) has become the gold standard investigation of venous disease below the inguinal ligament, giving both morphological and haemodynamic information of the lower limb veins[226]. DUS uses two different principles of ultrasonic interrogation to derive this data.

B-mode – An ultrasound transducer makes use of the unique properties of piezoelectric crystals. As an electric current is passed through a crystal, it changes shape, producing a sound pulse (a short duration sound wave), also; if a sound pulse strikes a crystal, a small electric current is produced. This enables a transducer to emit and detect sound pulses.

Different densities of human tissue resist the transmission of sound waves to different degrees (called acoustic impedance). When a sound pulse is travelling through tissue, as it hits substances of differing acoustic impedance a proportion is

reflected back and a proportion of the sound energy may be transmitted onwards. The proportion which is reflected is proportional to the difference in impedance at the interface. If there is a large discrepancy such as an air-tissue or tissue-bone interface, all of the energy in the sound pulse will be reflected.

Reflected sound pulses are detected by the transducer. The ultrasound device uses the time from emission of the pulse to reception of its echo to calculate the distance from the transducer the reflective interface was, using the assumption that sound travels at the average velocity of $1540ms^{-1}$ in human tissue. This point is plotted in two dimensions on a screen with a dot. The brightness of the dot indicates the magnitude of the energy reflected back in the echo (which is a function of the discrepancy of the acoustic impedance at the interface). These dots are drawn simultaneously in real time to give a moving anatomical image of the tissue undergoing insonation.

Areas where there is little difference in impedance appear black (such as within a homogenous tissue such as fat). Heterogeneous tissue, containing elements of differing density (such as muscle) return occasional low magnitude echoes, which may appear speckled. Interfaces between two tissues of differing density result in bright lines and if the difference in impedance is great; these lines will be very bright and there will be shadows beneath (blackout - as all the sound energy is reflected and none transmitted). *Figure 17* is an example of a B-mode image.
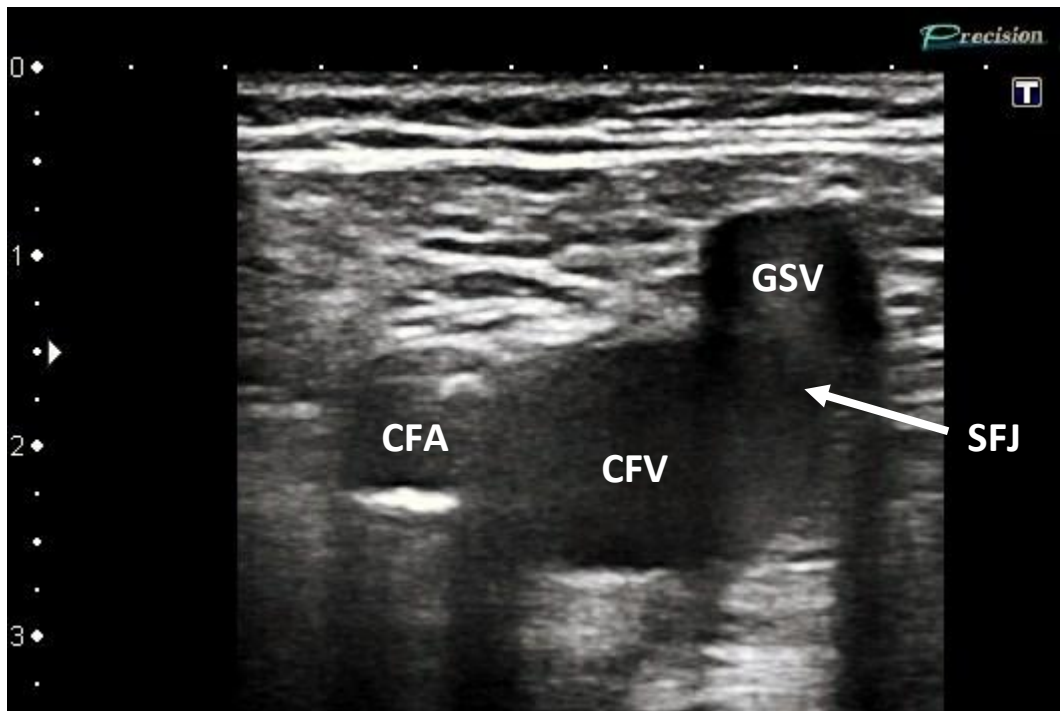
Figure 17: The right saphenofemoral junction (SFJ) in transverse section. CFA – Common femoral artery, CFV – Common femoral vein, GSV – Great saphenous vein

Doppler – B-mode anatomical information can be combined with information gained by Doppler interrogation of the tissues. This scientific principle was described by Christian Doppler in 1842 as an explanation of why light from stars may appear red, even though it is known that the light produced by thermonuclear fusion appears white (as it contains all of the wavelengths of visible light). The theory states that as the distance between an observer and an emitter of a wave increases, the wavelength perceived by the observer will become longer and visa versa. The magnitude of this change in wavelength (the Doppler shift) is proportional to the velocity of the emitter relative to the observer and its effect

can be classically experienced as something loud and fast passes by, such as an ambulance, resulting in a significant change in tone as it drives by.

Using this principle an ultrasound device can superimpose information regarding the velocity and direction of blood flow onto the B-mode image. The direction and the magnitude of the velocity are represented by colours. This is called colour Doppler. Additionally, a more accurate estimation of the velocity and direction of blood flow over time can be charted on a graph. This is called spectral Doppler. This is so accurate that it can detect the range of velocities and directions seen within a unit area, clearly displaying the difference between smooth laminar and turbulent flow. *Figure 18* is an example of a colour duplex image and *Figure 19* is an example of spectral Doppler.
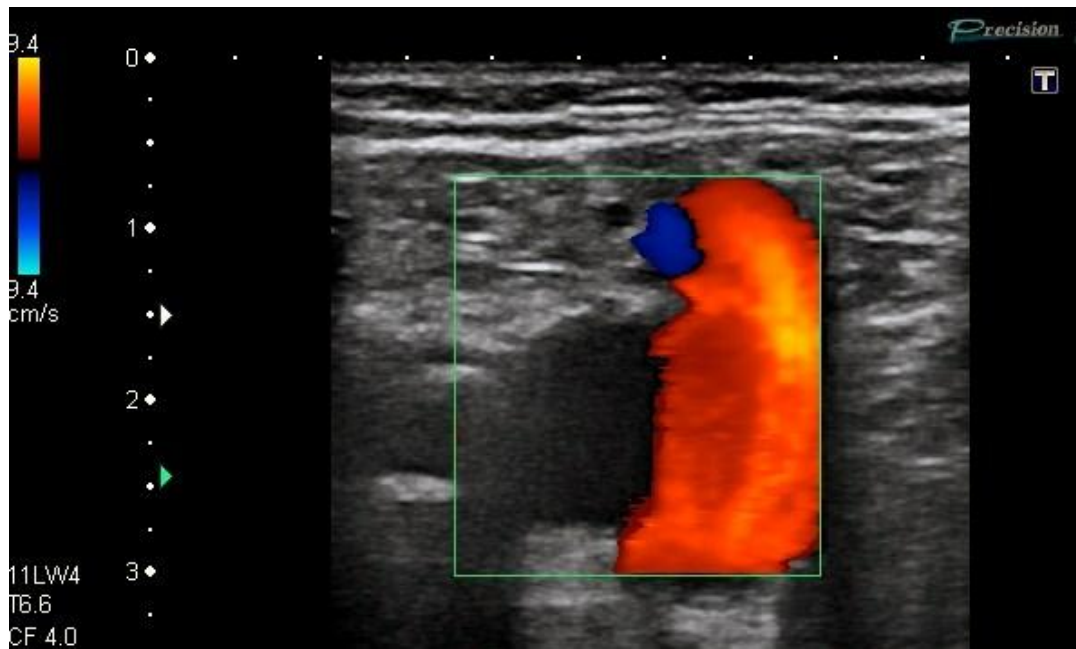
Figure 18: Duplex ultrasound: colour Doppler is superimposed upon the B-mode image. **This demonstrates gross incompetence of the saphenofemoral junction with reverse flow passing towards the transducer (which is aiming slightly antegrade), from the GSV back into the CFV**
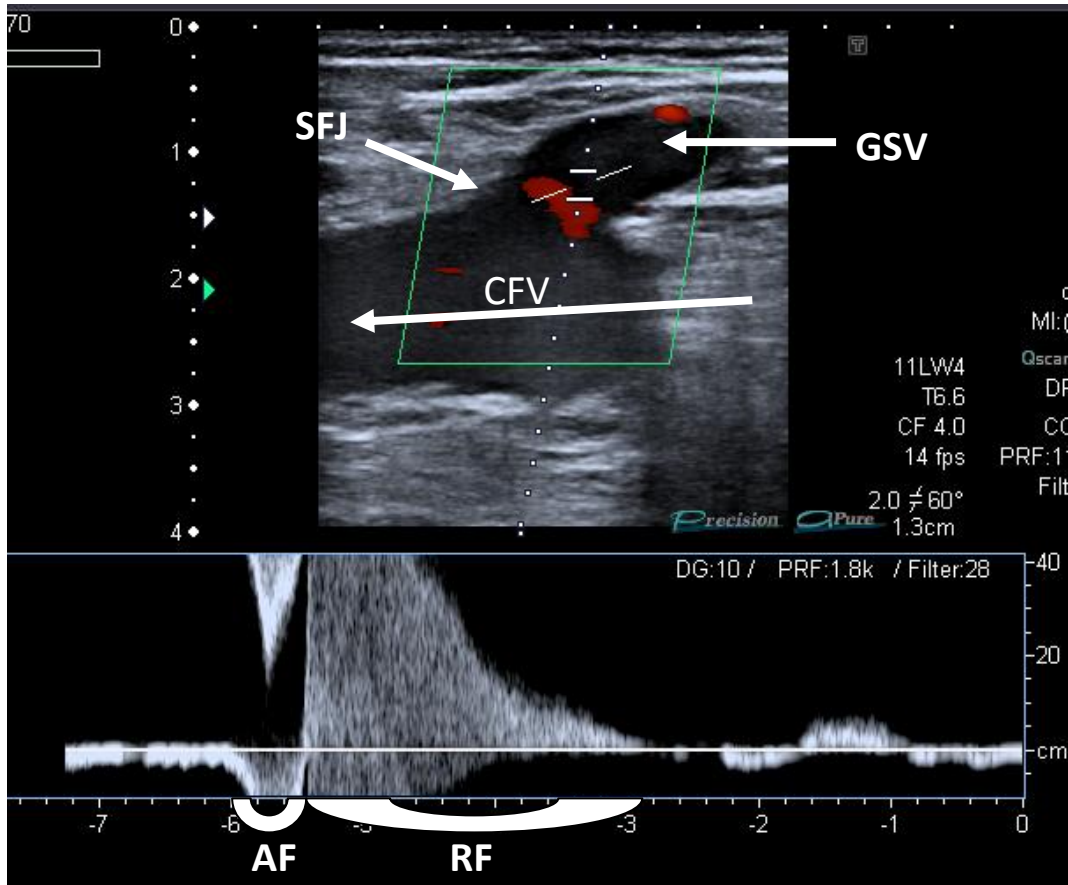
Figure 19: Pulse wave spectral Doppler demonstrating saphenofemoral incompetence (in longitudinal section). Augmentation has resulted in antegrade flow - AF, followed by approximately 2.5 seconds of retrograde flow – RF (reflux)

Together the use of B-mode and Doppler ultrasound gives a detailed assessment of both the anatomy and the physiology of the venous tree and is therefore the most frequently used investigation. DUS results are commonly found as outcomes in the literature and a consensus paper has been published aiming to standardise the technique[227].

One area of controversy within DUS interpretation is the reflux duration required to label a vein segment incompetent. Whilst a cut off of greater than 0.5 seconds may be appropriate for the definition of SVI, such a short duration may overcall insufficiency within the deep veins. Two large studies found that there was little difference in prevalence of SVI using a cut off of 0.5 seconds when compared with a cut off of 1 second[17,18,22]. However the same parameters gave significantly different results for the prevalence of DVI with rates two to four times higher using the threshold of 0.5 seconds. When considering an association with clinically evident venous disease; a reflux duration of 0.5 seconds had a specificity of 87.9% whereas and increase to 1 second improved this to 95.7%[18]. As a result the clinical guidelines of the Society of Vascular Surgery and the American Venous Forum recommend a threshold reflux duration of 1 second in the SFV and PV and 0.5 seconds in all other vein segments in the leg[199].

More traditional methods of evaluation include clinical examination using Trendelenburg tourniquet testing and hand-held continuous wave Doppler (HHD). Given the anatomical and pathophysiological factors discussed above, it is unsurprising that both have been shown to be unreliable[228], and in today's world of image guided minimally invasive interventions; these are inadequate. Even when employing traditional surgical techniques; the use of HHD is associated with a failure to detect 24%-33% of refluxing sites overall[228,229] and only has 44% sensitivity at the SPJ[230]. As a consequence; an RCT demonstrated higher recurrence rates in a group preoperatively assessed clinically and with HHD compared with a group assessed with DUS[231]. DUS is recommended as the first diagnostic test for all patients with suspected CVD[199,227,232].

Plethysmography

Plethysmography is another non-invasive investigation, involving the measurement of a change in leg volume and hence helps to quantify the extent of venous dysfunction in the evaluation of calf muscle pump function, global venous reflux, and venous outflow obstruction[233-236]. This has been used to monitor venous functional changes and assess physiologic outcome of surgical treatments[234]; but its place within the research and clinical landscapes is uncertain. Its use has been suggested in the management of patients with CVD when no reflux or obstruction is determined upon DUS, as it may suggest outflow obstruction or calf muscle pump dysfunction[199].

Venogram and Invasive Investigations

Computed tomography (CT) and magnetic resonance (MR) venography may be used in the investigation of venous disease proximal to the inguinal ligament, or in the evaluation of complex arteriovenous malformations[199]. Significant disease above the leg includes pelvic venous obstruction, iliac vein stenosis, May-Thurner syndrome (compression of the left common iliac vein by the right common iliac artery), nutcracker syndrome (compression of the left renal vein between the aorta and the superior mesenteric artery), gonadal vein incompetence and pelvic venous congestion syndrome. Invasive contrast venography is occasionally used in this role, if the local expertise or availability precludes the use of cross sectional imaging. However, this technique is usually reserved for use during endovenous or open procedures on the deep veins, such as angioplasty and stenting. Intravascular ultrasound may replace this as a diagnostic and surveillance tool in the future and may provide additional information when compared with contrast venography[237].

The Treatment of Venous Insufficiency

Conservative Treatment

The principle conservative treatment measure used for venous insufficiency is the use of compression. Compression seeks to combat the relative venous hypertension and promote the antegrade flow of blood from the leg, improving calf muscle function and decreasing reflux[238,239]. There is little doubt as to the benefits of compression, even in uncomplicated disease, but uncertainty exists around the required degrees of compression and studies of compression are, on the whole, less meticulous than those studying interventions. It does seem that compliance with compression is the key issue dictating benefit and this is higher with lower degrees of compression. Whilst this may bias the results of studies, perhaps the message is that in disease short of ulceration, lower grades of compression may strike the optimal balance between compliance and clinical benefit, offering the best results.

Imaging has shown that compression therapy needs to narrow the veins of patients with venous disorders to achieve a haemodynamic effect; initial narrowing occurs with a median pressure of between 30 and 40 mm Hg in the sitting and standing positions[240] although Grade II compression (18-24 mmHg) appears to have favourable clinical results and higher compliance (as discussed below), suggesting benefits at the tissue level.

A systematic review[241] found the evidence base for the use of compression treatment in uncomplicated varicose veins to be poor quality and in common with

clinical practice, compliance with compression treatment may have attenuated the effect. There is evidence supporting an improvement in symptoms, with maximal relief from Grade II to III (25-35 mmHg) compression[242]. There was no convincing evidence that compression has any effect upon disease progression.

There is further evidence for the benefits of compression for CVI; another meta-analysis looked specifically at the levels of compression and found that patients with varicose veins and CVI see an improvement in symptoms and swelling with compression of 10-20mm Hg over no compression, but there was no evidence found to support a benefit of using higher pressures in this patient group[243]. The authors acknowledge that the evidence is generally poor in quality and it seems unlikely that the benefits from higher compression seen in uncomplicated disease will not be seen in CVI.

There is little doubt that compression has a significant role to play in the treatment of venous ulceration. A Cochrane systematic review found evidence that compression increases healing rates and found multiple component dressings with an elastic layer give the best results[244]. This was confirmed by a European working group, who also found evidence that compression reduces ulcer recurrence[245].

Compression only offers any benefits whilst it is in place[246] and it is therefore not without its problems. The main drawback was alluded to earlier: non-compliance. Non-compliance rates may be very high. For instance 53-63% of patients are non-compliant with compression after one year[247,248]. In a cohort study by Mayberry et

110

al[249], ulcer healing with local care and compression was 97% in compliant patients, but fell to 55% in non-compliant patients. Ulcer recurrence was 16% in compliant patients and 100% in non-compliant patients. Poor compliance may be due to socioeconomic factors (particularly outside of the UK NHS)[247], poor patient education[250], discomfort (with lower compression pressures better tolerated)[251] and concerns regarding cosmesis. This may be compounded in the elderly by difficulties with putting on compression garments. One study found that 15% were unable to apply them and 26% needed considerable help[252].

Care must be taken in the presence of arterial disease and incorrectly measured or applied garments may cause skin and soft tissue damage, which is rare; but has been reported in the literature[253].

Adjuncts to Compression Therapy

There is an absence of evidence supporting lifestyle changes such as weight loss or leg elevation at rest, and a systematic review and meta-analysis has found no supportive evidence for any specific additional dressings on venous ulcers over compression[254], many of which are highly costly. For example Michaels et al[255] demonstrated no evidence of efficacy of silver donating dressings when compared with simple non-adherent dressings. The 3 month healing rate was 59.6% for silver and 56.7% for control dressings. Similarly there was no difference in recurrence rates 11.6% for the silver and 14.4 for the control dressings. These expensive dressings were therefore certainly not cost effective, with an

incremental cost-effectiveness ratio of £489,250, when compared to control dressings, certainly well above the commonly used UK threshold of £20,000 per QALY.

Comparison of Compression Treatment with Surgery

There is clear and compelling evidence of the benefits of interventional treatment for SVI when compared with compression therapy. The REACTIV trial[50] was at the time; the most detailed interventional trial undertaken for the treatment of venous disease, recruiting in total 1009 patients. 246 patients were randomised to receive either conservative management or surgery. Conservative treatment included lifestyle advice relating to exercise, leg elevation, management of weight and diet, and the use of compression hosiery. In the surgical arm, patients received the same lifestyle advice but also underwent high ligation, stripping, and phlebectomies. The surgical group saw an improvement in QoL over 2 years with an estimated QALY gain (95%CI) of 0.083 (0.005-0.160) using SF-6D and 0.130 (0.016-0.250) using EQ5D over those receiving compression alone. The authors then used a Markov economic model to simulate the costs and consequences of the 2 approaches over a 10 year horizon. This estimated the incremental cost effectiveness ratio to be £1936 per QALY, making surgical treatment highly cost effective when compared to conservative measures alone.

The REACTIV study had shown that surgery aiming to address SVI improved the anatomical extent of disease, symptoms and QoL. The ESCHAR study[256] aimed to elicit whether intervention had any favourable effect in the treatment of ulcers. 500 patients with active or recently healed venous ulcers were randomised to compression treatment alone or compression combined with surgical treatment. 75% received high ligation, stripping, and phlebectomies; under a general anaesthetic (GA), but 25% were judged unsuitable for GA and underwent high saphenous vein ligation alone under a local anaesthetic (LA). There was no difference in ulcer healing at 6 months (65% versus 65%), however 1 year recurrence rates were significantly lower in the surgical arm (12% versus 28%, hazard (95% CI) -2.76 (-1.78 to -4.27) and this difference persisted to at least 4 years[257]. Critics of this study suggest that the significant delays prior to surgery and the inclusion of healed ulcers in the analysis (decreasing the power) were responsible for the failure to show a benefit in healing rates. Another study of surgery for venous ulcers, suggests that in the absence of DVI, compression may be unnecessary in the healing of ulcers, demonstrating the power of the correction of SVI[258].

Compression therapy, through reducing venous hypertension; is a powerful tool to combat venous disease, but it cannot replace the benefits of interventions correcting venous insufficiency; hence addressing the underlying pathological cause of venous hypertension itself.

Medical Treatment

Medical treatments for venous insufficiency are not in common use worldwide; however there is emerging evidence that drugs aiming to modulate the pathophysiology of skin changes associated with CVI may offer some benefits.

A range of Cochrane reviews have studied this area. One such review studied 44 trials involving 4413 participants using rutosides, hidrosmine, diosmine, calcium dobesilate, centella asiatica, French maritime pine bark extract, aminaftone and grape seed extract. Overall there was significant heterogeneity within the studies, but there were improvements observed on meta-analysis in oedema RR (95%CI) 0.72 (0.65 - 0.81) and trophic disorders RR 0.88 (0.83 - 0.94)[259]. Horse chestnut seed extract also has some early evidence that it may improve the symptoms, including pain and itching and also the oedema of CVI[260].

Medical treatment may have greater benefits in the treatment of venous ulcers. A meta-analysis of 12 trials involving 864 participants found pentoxifylline with compression is more effective than placebo and compression in ulcer healing RR 1.56 (1.14 - 2.13) and pentoxifylline without compression is more effective than placebo or no treatment RR 2.25 (1.49 - 3.39). However GI side effects were common and this may impact upon compliance and QoL[261]. Micronized purified flavonoid fraction (MPFF) has similarly been shown to be of benefit. The mean ulcer healing time was 16 weeks in patients treated with MPFF plus compression compared with 21 weeks in patients with compression alone, resulting in a 32% increase in the chance of ulcer healing within 6 months 0.32 (0.03-0.70)[262].

Whilst these early results show promise, the evidence base is in its infancy and doesn't support widespread clinical use[259]. Large RCTs are required to confirm the clinical efficacy, QoL improvement and cost effectiveness associated with these treatments.

Interventional Treatment

Surgical intervention for SVI has been clearly shown to offer benefits over conservative management over the spectrum of venous disease and is also highly cost-effective[50,256] (See: *Comparison of Compression Treatment with Surgery, p112*). However there has been a revolution in the management of SVI, with an explosion of new and revised techniques hoping to offer benefits over conventional surgery. These relatively new, minimally invasive endothermal ablative techniques are gaining in popularity. At the time this programme of investigation was initiated, endovenous laser ablation (EVLA) had become the front runner in the endovenous revolution[263]. However, conventional surgery remains the most common intervention for SVI in the UK[264,265], and is widely considered to be the gold standard.

The mainstay of treatment for DVI is compression, however it has been shown that if SVI is addressed, this has favourable haemodynamic consequences on the deep system also; reducing the incidence of DVI[266]. Surgical interventions have been attempted to directly treat DVI and a Cochrane review found three small RCTs detailing the treatment of primary DVI which indicated that there may be

some improvement in ambulatory venous pressure, but pressures remained pathologically high. The quality of evidence is not sufficient to support any positive recommendations at this time[267] and further discussion will concentrate on intervention for SVI.

Open Surgery

Conventional Open Surgery

The classical technique of high ligation of the SFJ, stripping of the GSV and phlebectomy under general anaesthetic has been the standard of care of varicose vein treatment for around a century. The procedure is described in detail below (See *p154*). The benefits of this treatment, particularly the gain in QoL and its cost effectiveness compared to conservative management are well established from large RCTs[50,256] (See: *Comparison of Compression Treatment with Surgery, p112*). These benefits in QoL are significant and even in uncomplicated disease are consistent with those seen after other surgical procedures shown to result in significant QoL improvements such as laparoscopic cholecystectomy[268-270]. Improvements are also durable with benefits lasting until at least 10 years[271].

Some patients however see little benefit and this is likely to be secondary to poor patient selection. "Venous symptoms" are by their very nature vague and may not be secondary to the coincidental existence of venous insufficiency (See: *Quality of Life Impairment p40*). A trial of compression therapy may be helpful as a pre-

operative selection method in cases of doubt over the aetiology of symptoms. Lurie et al found that patients who improved after conservative therapy were more than 15 times more likely to have an improvement in their symptoms at 1 month RR (95% CI) 15.6 (4.3-56.5), and 21 times higher at 1 year after surgery 21.3 (4.7-96.9), compared with those who had no improvement with compression[272].

The Limitations of Conventional Surgery

Short Term

Surgery is not without its drawbacks; in common with all invasive techniques the procedure itself carries some morbidity, resulting in impaired QoL in the early post-operative period. Naturally perioperative complications may exacerbate and extend this phenomenon. Compression therapy post-operatively is thought to promote a more rapid recovery, by reducing haemorrhage, oedema, haematoma and pain, but an RCT of 220 post-surgical patients found no benefit in wearing compression stockings for greater than 1 week with respect to postoperative pain, number of complications, time to return to work, or patient satisfaction for up to 12 weeks after surgery[273].

In good hands, conventional surgery on the whole, is both safe and effective. However, despite this being classified as "clean surgery"; significant rates of wound complications, mostly groin infection are described in 1.5% to 16%[274-278]. Normal wound healing is less likely in current smokers adjusted OR (95% CI) 0.5 (0.3-0.9) and with increasing BMI OR 0.92 (0.87-0.97 per unitary increase)[279].

Mekako et al performed an RCT with 443 patients (600 legs) undergoing groin surgery for varicose veins; the risk of wound infections and wound-related complications was reduced with use of a single dose of perioperative antibiotic prophylaxis from 18.2 to 9.9%. A single dose of co-amoxyclav at induction therefore increases the likelihood of normal wound healing OR 2. 21 (1. 32-3. 60)[279]. Haematomas may also be fairly common and have been described in up to 33%[280], even with the use of post-operative compression.

In the UK, the commonest single cause of litigation following surgery is alleged injury to cutaneous sensory, specifically the saphenous and sural, nerves[281]. These injuries are associated with pain, paraesthesia and anaesthesia. The rate of saphenous nerve injury is partially dependent upon the length of GSV stripping undertaken. The close anatomical relationship between the GSV and the saphenous nerve below the knee[282,283] has been shown to increase the rates of injury if stripping is continued down below the knee. An RCT of full length stripping compared with stripping to the knee found a nerve injury rate of 39% versus 7%[284]. However some have pointed out that as the long term results of stripping to the knee are worse; the length of GSV stripping should be dictated by the length of refluxing vein and not concerns over injury to the saphenous nerve[285-287]. Full-length stripping remains controversial.

Following intervention for SSV reflux, sural nerve injury is described at a rate of 2% to 4%, whereas common peroneal nerve injury occurred in 4.7% in one series and

in 6.7% in another series[288]. It is unclear as to what proportion of these injuries can be ascribed to the popliteal fossa dissection and to the act of stripping[283].

Adjunctive procedures, such as phlebectomy and perforator treatments are associated with nerve injury, but there is little reliable data to quantify this and this is clearly compounded by the extent to which such procedures are required.

Thromboembolic complications were previously thought to be very low[275], however detailed modern follow-up with DUS has found that the incidence of post-operative deep vein thrombosis (DVT) could be as high as 5%, although the majority are asymptomatic and confined to the calf veins with no subsequent propagation or clinical evidence of pulmonary embolism (PE)[289]. The risk of clinically significant PE remains around 0.2–0.5%[275]. Around half of observed DVTs resolved without evidence of DVI at 1 year[289].

Injury to the major vascular structure are very rare (incidence 0.002%-0.300%), but consequences may be disastrous[290].

Long Term

Long-term results following conventional surgical treatment are marred by significant recurrence rates. Quoted rates are as high as 30% at 1 year, 40% at 2 years and up to 66% beyond 10 years[291-297]; this has been linked to poor patient satisfaction[271,298]. Patients requesting re-intervention for symptomatic recurrence are less common, but approximately 15–20% of varicose vein procedures are performed for recurrence[265,299,300].

Recurrence may be due to technically inadequate surgery, the growth of new incompetent vessels within old scar tissue (neovascularisation), significant unaddressed reflux in the below knee GSV or perforators and disease progression.

Innovations in Open Surgical Technique

Many new innovations have been attempted, aiming to re-invent and re-invigorate the technique of open surgery with a hope of addressing its limitations. This evolution has seen diminishing groin incision size and stripping towards a small puncture wound at the knee, made possible by the PIN stripper. The following section covers innovations which have deviated significantly from the principles of what is considered conventional surgery.

Junction Ligation without Stripping

Whether this technique under local anaesthesia minimises peri-procedural morbidity is a moot point, as recurrence rates are inflated when an incompetent GSV is left in situ. An RCT randomising 100 patients to ligation and stripping and ligation alone found that reoperation was required in 6% and 21% respectively (relative risk (95% CI) 0.28 (0.13-0.59)) by 5 years[292].

Techniques Aiming to Reduce Neovascularisation

Neovascularisation has been defined as the presence of multiple new small tortuous veins in anatomic proximity to a previous venous intervention[301]. Neovascularisation is a significant, though poorly understood cause of recurrence at sites which have previously undergone technically adequate surgery[296,302].

Attempts at over-sewing the junction with non-absorbable suture have shown conflicting results, with one RCT in support (31 and 45 patients per group)[303] and another larger study showing no difference (double the sample size) when compared with transfixion with absorbable suture[304] and this has been subsequently confirmed by other studies[305]. Closure of the cribiform fascia however may help, reducing the rates of neovascularisation from 14.8% to 6.7% at 1 year[306].

Conflicting results were also shown for the practice of using prosthetic patches as barriers to neovascularisation, which may also result in an increase in complications[291,306-309].

Loco-regional Anaesthesia

Although not in common use in the UK and USA, European centres have experience in performing open ligation, stripping and avulsions without the use of general anaesthesia[310]. This is a potentially attractive option; potentially reducing the morbidity of the procedure. There are no detailed studies comparing open surgery with and without general anaesthesia. A retrospective study has failed to

see any difference in simple pain scores[311], but there is some evidence of potential benefit seen when comparing this approach with minimally invasive endovenous techniques[312]. The benefits of local anaesthetic surgery may however be attenuated by the frequent requirement of intravenous sedation[313].

Cryostripping

The aim of cryostripping is to reduce the morbidity associated with stripping the GSV. A probe is passed down the GSV from the groin to the level of the knee. Freezing of the vein is then performed at this point using liquid nitrogen and the vein stripped by invagination back towards the groin[314]. This technique is said to reduce the haemorrhage within the saphenous tunnel and avoid a separate incision at the knee, although with modern PIN strippers this is little more than a small stab wound, similar to those for the phlebectomy element of the procedure. An RCT of 160 patients randomised to cryostripping and standard stripping found a reduction in bruising, but no difference was seen in pain or in QoL. This study however was not powered to detect small to medium differences in generic QoL and no peri-procedural QoL analysis was used, only visual analogue pain scores[315]. Cryostripping; when combined with a local anaesthetic procedure may offer the optimum reduction in morbidity possible, whilst retaining the principle of ligation and stripping, though this is yet to be conclusively established.

Preservation of the Great Saphenous Vein

Two techniques are described aiming for conservative surgical management with preservation of the GSV. The underlying premise of this approach is the ascending theory of venous insufficiency (See *The Pathogenesis of Primary Venous Insufficiency p49*) and they rely on the assumption that the interruption of reflux from the distal tributaries will restore competency to the superficial and deep venous trunks.

The first is the ASVAL technique (ambulatory selective vein ablation under local anaesthesia), involving ambulatory phlebectomy of all varicose tributaries, with preservation of the GSV and SSV irrespective of their competence[316]. A case series of patients with very early disease (many asymptomatic) has shown haemodynamic improvement; with 66% of previously refluxing veins (greater than 0.5 seconds) reverting to competence (less than 0.5 seconds reflux) at 4 years. This was accompanied by some symptomatic improvement, but even treating such early disease; 11.5% of patients had suffered recurrence by 4 years[316]. There are no comparative studies to date.

The second approach is the CHIVA technique (conservative haemodynamic ambulatory venous surgery). The principle is to decrease the superficial venous pressure. The actual treatment is tailored to the anatomical pattern of incompetent veins. Venous ligations are then performed in specific locations, maintaining superficial venous drainage, though sometimes using reverse flow[317,318]. For example; a frequently used technique includes proximal ligation of the incompetent saphenous vein; ligation, division, and avulsion of the

incompetent varicose tributaries; and maintaining patency of the saphenous trunk, the competent saphenous tributaries, and saphenous venous drainage to the deep system through the so-called re-entry perforators[319]. Another RCT presented further details of the technique in six different patterns of SVI[320]. Two RCTs have compared CHIVA with conventional ligation and stripping. The first randomised 75 patients per group and found lower recurrence at 10 years following CHIVA (18% and 35%, OR (95% CI) 2.2 (1.0-5.0))[319]. The second randomised 167 patients to CHIVA and 167 patients each, to two ligation and stripping groups (clinical assessment and DUS assessment). Again at 5 years, the CHIVA group had two to two and a half times less recurrence[320]. Other authors have failed to reproduce these results[321]. A final study compares CHIVA to compression treatment in venous ulcer disease with 47 in each group. Ulcer healing was more rapid and recurrence rates were significantly lower following CHIVA (9% compared with 38%)[322]. There is therefore some evidence of efficacy, however the lack of detailed QoL analysis prevents meaningful conclusion over the effectiveness of this treatment to address the QoL impairments associated with the disease, or whether this technique reduces the morbidity of intervention. Furthermore, many doubt whether this complex, operator dependant technique, will offer similar results outside of the hands of a small number of enthusiasts[199] and to date this has not seen widespread adoption.

Minimally Invasive Techniques

Endothermal Ablation

Endothermal ablative techniques involve the percutaneous introduction of a catheter into the target vein under ultrasound guidance. The vein is then surrounded with tumescent local anaesthetic. This results in pain relief, but also performs several other important functions. It compresses the vein onto the catheter allowing the concentrated application of heat via the catheter directly onto the venous endothelium, minimising any blood in between. Blood flow may cool the catheter or clot around it, attenuating its effect upon the vein wall itself. The tumescent also displaces other structures, such as the nerves and deep veins away from the target vein by hydro-dissection, isolating the vein from its surrounding tissue. Finally the tumescent acts as a heat sink; preventing thermal energy from propagating and further protecting the surrounding soft tissues. The use of tumescent anaesthesia therefore results in decreased morbidity[323] and increased efficacy[324-326]. Thermal energy is subsequently delivered to the vein obliterating its structure. The treated vein then heals, leaving behind only a cord like structure of scar tissue.

Thermal energy may be delivered in a range of ways. Endovenous laser ablation (EVLA) uses laser energy, radiofrequency ablation uses electrical current, which may be passes directly through the vein wall itself (direct radiofrequency ablation – RFA) or through a metal coil, which emits thermal energy towards the vein wall

(indirect RFA). Finally a device licensed in continental Europe emits bursts of steam.

Endovenous Laser Ablation

Endovenous Laser Ablation (EVLA) utilises the delivery of laser energy into the vein via an optical fibre. LASER (Light Amplification by the Stimulated Emission of Radiation) produces a collimated (low divergent) "beam" of photons whose waves are coherent (in-phase) allowing a very intense and accurate delivery of energy, which can be mono-chromic (the same "colour" or wavelength) (*Figure 20*).
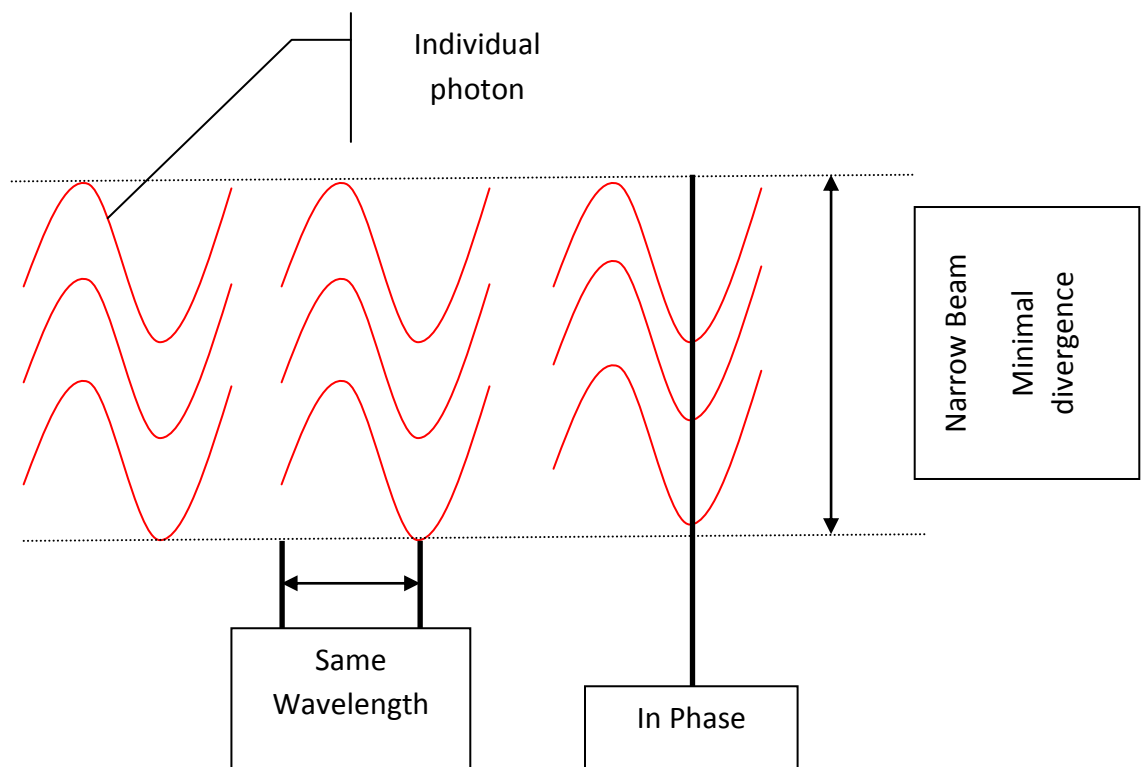
Figure 20: *LASER – A narrow "beam" of photons, emitted "in phase" and of a single wavelength*

This electromagnetic radiation is then absorbed and converted into thermal energy. Shorter wavelengths (810, 940 and 980nm) are absorbed primarily by the haemoglobin in erythrocytes, whereas longer wavelengths (1319, 1320 and 1470nm) by intra and extracellular water[327]. Therefore, rather than hampering the transfer of thermal energy to the vein wall, experimental studies have suggested that it is the blood itself that acts as the transfer medium[328]. Rapid heating of the blood (700-1300°C) creates steam[329]; this alongside some direct heating of the vein wall causes collagen contraction and denudation of endothelium. The result is a non-thrombotic occlusion due to vein wall thickening, luminal contraction and fibrosis of the vein[326].

Laser energy was first used in the treatment of SVI in 1999 by Boné and in 2001, the first case series was published[330,331]. By the time the studies detailed in this thesis were undertaken, the evidence for EVLA comprised of only case series. These confirmed that EVLA had a high initial and medium term technical efficacy. These studies were later subjected to a random effects meta-analysis, estimating that at 3 months 92.9% and at 5 years 95.4% of patients had an absence of reflux on DUS examination[332]. This data however was heterogeneous in many respects and was following an unreported proportion of secondary procedures. None of these early studies attempted to measure QoL following intervention.

EVLA has been shown to have a good safety record, although the procedure is not completely free from morbidity. Inflammation of the sclerosed vein and incisions related to any concomitant treatment are associated with pain and bruising. In a meta-analysis, some bruising was seen in up to 52.2% of cases[333] although the

significance of this is debated. Significant complications are very rare, in meta-analysis and large series, paraesthesia is seen in around 1.7-2.7%, and deep vein thrombosis (DVT) rates are low at 0.3%-0.6%[333-335]. An occasional case of pulmonary embolus (PE) has been described[327,336], along with arteriovenous fistulae[337,338], skin burn[334] and misplaced catheter[339], but these are incredibly rare.

There has been much debate regarding the relative merits of different laser wavelengths. It has been suggested that longer wavelengths may be more "gentle" and associated with fewer adverse effects, however there is little evidence to unequivocally support this and no studies have shown any significant difference in validated QoL measures[324,340-343]. What is clear is that as each wavelength has a different absorption pattern; the evidence base for one wavelength cannot be simply applied to another. The morbidity, complications and efficacy may be very different. For instance; an early study using a 1,064nm laser described skin burns in 5% and a paraesthesia rate of 38%[344]. This was thought to be due to greater tissue penetration at longer wavelengths; but fortunately this has not been seen using other longer wavelengths. Work looking at different wavelengths, frequently varies the energy delivery also. Mathematical modelling suggests that lower energy delivery is required at longer wavelengths in order to induce full thickness venous damage[345] and It is therefore possible that the optimal energy per unit vein required to achieve a durable closure with minimal morbidity may also be different. Studies are required to identify this "sweet spot" for each wavelength utilised, before any conclusions may be made regarding the optimal wavelength.

At least two EVLA device manufacturers have devised fibres designed to evenly distribute the laser energy around the surface of the vein. Biolitec® manufacture the ELVeS® radial fibre and Angiodynamics® have the NeverTouch® gold-tip laser fibre. The theory behind this concept is based on the observation that bare-tip fibres result in multiple vein perforations[346]. This is suggested to result in blood leaking from the vessel; resulting in pain and bruising. To date there is little evidence to support either the theory, or these fibres, which are more expensive that the standard bare tip fibres. There may even be some evidence that they may attenuate the treatment effect[347]. The one obvious benefit is that they are visibly clear on DUS imaging, making fibre placement easier for less experienced surgeons.

Radiofrequency Ablation

Radiofrequency ablation (RFA) was introduced in 1998. This technique is similar conceptually to EVLA. The first device in wide use was the Closure® system. This was a bipolar system; passing a current between two electrodes, with the vein wall closing the circuit. The vein wall was then heated by this current and a temperature of around 85-90°C was used to coagulate the vein wall as in EVLA. However blood between the catheter and the vein wall, attenuated its effect, sometimes even clotting around the catheter tip. This system was later abandoned due to disappointing failure rates and slow withdrawal speeds, compounded by a requirement to occasionally remove the catheter to clean blood clot from the end. Many of the early procedures were performed under a GA

129

without tumescent; which may have been partly to blame for its failings. The manufacturer subsequently developed a more sophisticated indirect RFA system VNUS® ClosureFast®. This catheter has a 7cm long electrically insulated coil at its tip. This is heated by the passage of an electric current through it. The device accurately maintains a temperature of exactly 120°C for a treatment cycle of 20 seconds. This is then withdrawn in a segmental fashion until the entire vein has been treated. This system has similar withdrawal rates as for EVLA[348] and when used with tumescent anaesthesia doesn't become caked with thrombus like the previous catheter.

Early results with the ClosureFast® system appear much better than for the old direct system, with 3 month success rates of 99.6% and 96.9% at 1 year; longer term follow-up is awaited[349].

In the largest series to date (252 veins); complications include painful induration in 32.3% (although reported pain scores were low), paraesthesia in 3.4% and no DVTs[349].

A second RFA system has also been released: the Olympus® Celon RFITT®. This system is similar to the original RFA system, although its manufacturers claim that results are much better. There is little evidence regarding this system. A single small study reported an occlusion rate of 95% at 10 days[350], the results of further studies are awaited.

Steam Ablation

A third technique has recently been introduced in Europe, but is not available in the UK or USA yet. This technique uses superheated steam to apply thermal energy to the vein, hoping to result in the same occlusive changes as seen with the other endothermal techniques. Early experiences appear promising, but there is little evidence to date to allow a clear appraisal of its merits in clinical practise[351].

Sclerotherapy

Sclerotherapy is the use of a chemical agent to occlude incompetent veins by the initiation of a chemical thrombophlebitis, followed by endoluminal fibrosis. This is the oldest of the minimally invasive techniques; having been first described in principle by Chassaignac in 1855. Liquid sclerotherapy is mainly used to obliterate thread veins and telangectasia (for improved cosmesis), but high recanalisation and recurrence rates[352,353] have limited its popularity in main axis or tributary incompetence. Renewed interest has resulted from superior results following the mixture of sclerosant and gas to form a foam and injecting this under DUS guidance[354-356]. The proposed mechanism underlying this improved performance is that the foam displaces the blood inside the vein, allowing a greater concentration of sclerosant to be in contact with the vein wall for a longer time. This improves the likelihood of initiation and the subsequent intensity of induced phlebitis in the target vein. A further benefit is that far less sclerosant is required, reducing the potential for subsequent side effects and complications.

Several different sclerosants have been used including glycerine and hypertonic saline, but it is the detergents, including sodium tetradecyl sulphate and polidocanol, which have become the most popular. These agents dissolve the endothelial cell membrane and denature the surface proteins.

Enthusiasts of foam sclerotherapy have seen good results, with successful occlusion rates around 80% to 5 years[357-359]. A meta-analysis found success rates of 82.1% at 3 months and 73.5% at 5 years[332].

Minor complications such as matting and pigmentation are relatively common, with an incidence of 17.8% in a systematic review[360]. More serious complications including, skin necrosis, neurological complications, anaphylaxis and thromboembolism are rare[360], but potentially catastrophic. A recent systematic review of 10,819 patients found that 0.9% suffered from neurological complications, including 0.3% migraine, 0.1% stroke and 0.1% transient ischaemic attack (TIA)[361]. Half of the strokes and TIAs were in association with a right to left cardiac shunt and it may be that this abnormality is more commonly seen in association with SVI[362].

There is some evidence that using carbon dioxide rather than air in the foam may decrease these adverse events. A cohort study found no difference with visual disturbance (3.1% and 8.2%), but significantly less chest tightness (3.1% and 18%), dry cough (1.6% and 16%) and dizziness (3.1% and 12%) in the carbon dioxide group compared to the air group. Overall the incidence of adverse effects was reduced from 39% to 11%[363].

1.4 Aims and Objectives

When this programme of investigation was embarked upon; evidence for the new minimally invasive techniques was limited to case series, offering general support for the relative safety and efficacy in the improvement of surrogate outcomes, such as reflux on DUS. There were no randomised studies centred on the QoL benefits seen following intervention other than the REACTIV trial[50], which provided compelling evidence for the effectiveness of conventional surgery when compared with conservative management, but gave little insight into the place of sclerotherapy and did not study any other modalities.

Another compounding factor was that the techniques were still to undergo significant evolution and there were considerable variations in techniques and practise, with little evidence of what were the most efficacious approaches. The technique of EVLA was the clear front-runner in this revolution in terms of both popularity and the strength and longevity of its evidence[263,332], and therefore it was EVLA which was adopted as the minimally invasive treatment to go forward in this assessment process.

The primary aim of the treatment of varicose veins is to improve QoL; this must be regarded as the most significant outcome measure, and as such was the key focus of the all three studies.

Study 1; Procedure Refinement – A randomised clinical trial of endovenous laser ablation with concomitant versus selected sequential phlebectomy in the treatment of venous insufficiency

During the planning phase of Study 2; it was noted that the general efficacy of EVLA had been established (See *Endovenous Laser Ablation p126*) but that research was required focusing upon procedure refinement. A fundamental question concerned the management of residual varicosities following truncal laser ablation. Debate existed amongst our research group and other authors regarding the most efficacious management of residual tributaries following truncal laser ablation. Options included sclerotherapy or ambulatory phlebectomy under tumescent local anaesthesia, both of which could be performed as a concomitant or sequential procedure. Review of the literature seemed to support phlebectomy over sclerotherapy due to the complications associated with the latter (See *Sclerotherapy p131*). However, there was no evidence on which to base the timing of the ambulatory phlebectomy, and therefore, following a pilot study which confirmed the feasibility and acceptability of laser therapy with concomitant phlebectomy under tumescent anaesthesia[364], we embarked on a randomised clinical trial to compare concomitant and sequential expectant phlebectomies.

The aim of this randomized clinical trial was to assess the advantages of performing ambulatory phlebectomy as a concomitant procedure to truncal laser ablation, with the primary outcomes based upon patient reported QoL.

Study 2; Technique evaluation – A randomised clinical trial of endovenous laser ablation versus conventional surgery in the treatment of venous insufficiency

Once the optimum procedure had been established, the next study was directed towards a comparison of EVLA with the then current gold standard: conventional surgery; featuring SFJ ligation, above knee stripping and phlebectomy. The aim was to firstly establish whether treatment with EVLA results in the same enviable improvements in patient QoL as seen in the REACTIV trial following surgery [50]. The second and perhaps more important aim was the exploration of whether EVLA could address any of the limitations seen with conventional surgery (See *The Limitations of Conventional Surgery p117*) and challenge the century long dominance of this technique in the management of SVI.

Study 3; Procedure refinement – Energy delivery during 810nm endovenous laser ablation of superficial venous insufficiency and post-procedural morbidity

A meta-analysis suggested that EVLA produces significantly better saphenous ablation rates on DUS up to 5 years than conventional surgery, foam sclerotherapy and RFA[332]. There was however still room for improvement as treatment failure on DUS was still occurring in 1 of 20 saphenous trunks treated. Residual and recurrent disease negates some of the quality of life benefit of treatment and is unpopular with patients. It is known that 71% of patients want full treatment of

their varicose veins in a single visit and over 90% are concerned about the risk of recurrence[365].

During the lifetime of this research programme, several independent research groups established that the magnitude of energy delivery was the most important predictor of success[366-368] and increasing energy delivery has resulted in improved occlusion rates[369,370]. At this time energy deliveries of around 20-40 Jcm^{-1} or equivalent fluence calculations were being used[327], but this new best evidence pointed to improved results at energies higher than this and many providers started to use 60-80 Jcm^{-1}. Despite this, 100% success remained an elusive goal. The reluctance to increase energy delivery further was most likely due to concerns that this may result in increased morbidity and complications from the procedure. There was however, no evidence that this is the case, when EVLA is performed using tumescent anaesthetic solution. Surgeons within this research group were gradually increasing the energy density utilised since the advent of EVLA and deliveries of greater than 100 Jcm^{-1} became common.

The aim of this study was to establish whether there was any evidence that this increase in the energy density has had any effect upon post-procedural pain, quality of life or complication rates.

Chapter 2 – Patients and Methods

Study 1; Procedure Refinement – A randomised clinical trial of endovenous laser ablation with concomitant versus selected sequential phlebectomy in the treatment of venous insufficiency

2.1 Patients

The setting for this non-blinded parallel-group randomised clinical trial was a tertiary referral vascular surgical unit, offering specialist dedicated vascular services to a population of approximately 1.2 million. All consecutive patients presenting to a single consultant vascular surgeon were evaluated for eligibility according to predetermined inclusion and exclusion criteria. Assessment was performed by a consultant vascular surgeon or research registrar with a special interest in the management of venous disease. Clinical assessment included a full history and examination including classification of the clinical severity of disease using the clinical grading element of the CEAP classification[25] and the VCSS system[186]. This was followed by a detailed duplex ultrasound assessment according to a standardised protocol. All ultrasound scans were performed by surgeons who were fully formally accredited in the performance of diagnostic vascular ultrasound. The details of DUS assessment are outlined on *p145*.

Inclusion Criteria

Clinical

- The presence of primary, unilateral, symptomatic venous disease of the lower limb; classifiable as C2-5 on the clinical grading element of the CEAP classification system[25]

- Willingness to accept a local anaesthetic EVLA procedure, including ambulatory phlebectomy (as outlined in Section *2.3 Interventions, p141*)

- Willingness and ability to participate in a clinical trial, including the attendance of additional clinical assessments, completion of questionnaires, duplex follow-up and the analysis and publication of this data

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

Duplex

- Greater than, or equal to 1 second of retrograde flow of blood from the common femoral vein through the SFJ into the GSV on pulse wave spectral Doppler

- Greater than, or equal to 1 second of retrograde flow of blood in the GSV on spectral Doppler in at least the above knee segment

Exclusion Criteria

Clinical

- Age less than 18 years

- Previous intervention aiming to address junction, perforator or superficial axial insufficiency

- Active venous ulceration (C6 classification)

- Inability or unwillingness to give informed consent to trial participation

- Pregnancy

- Symptoms or clinical evidence of arterial disease (including an ankle-brachial pressure index of less than 0.8)

- Previous groin surgery

- Known thrombophilic state

- Known malignancy

- Allergy to local anaesthetic medications

Duplex

- Deep venous disease (including obstruction or insufficiency)

- Sapheno-popliteal insufficiency

- Superficial axis insufficiency other than the GSV (which in the surgeon's view would be optimally treated with ablation or stripping rather than phlebectomy)

- GSV less than 4 millimetre (mm) in antero-posterior diameter at the proposed cannulation point

2.2 Randomisation

Following informed written consent, eligible patients were randomised equally into to one of two parallel groups:

Control Group

Isolated truncal GSV EVLA, with sequential ambulatory phlebectomy of residual varicosities after 6 weeks if required

EVLTAP Group

Truncal GSV EVLA with concomitant ambulatory phlebectomy of varicosities

Randomisation was performed at the screening visit immediately following signing of the consent form. Patients were invited to select any opaque envelope, from those available whilst under supervision. No block randomisation was used.

Sample Size

A sample size calculation was performed, based upon the primary outcome measure. This was informed by data from the literature, giving an estimated AVVQ score of 3.94 in the controls[371] compared with 0.6 in the EVLTAP group[372] (with a standard deviation of 4). For 80% power and a two sided significance of 5%, with a 10% loss to follow up, the estimated sample size was 25 patients per group.

2.3 Interventions

All procedures were performed under local tumescent anaesthesia in a dedicated procedure room within the outpatients department. No sedation was used. Patients were preoperatively marked in the procedure room using a portable MicroMaxx® ultrasound system (Sonosite Ltd, Hichin, UK). The course of the GSV was marked on the skin using a permanent marker pen from the proposed point of cannulation to the SFJ. If ambulatory phlebectomy was to be performed then the sites were also marked preoperatively.

The skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA). In the case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Sterile draping of the leg was performed prior to percutaneous perigenicular cannulation of the GSV with the patient in the reverse Trendelenburg position. A 5 French catheter was introduced into the vein using the Seldinger technique, and its tip accurately positioned at the SFJ using ultrasound. The patient was then put in the Trendelenburg position, and perivenous local anaesthetic (40 millilitres (ml) of 2% Lignocaine with 1:200,000 Adrenaline in 1 litre (l) of 0.9% Sodium chloride solution) was infiltrated along the vein. Total local anaesthetic did not exceed the recommended maximum safe dose per patient. A sterile bare-tipped 600 nanometre (nm) laser fibre was introduced via the catheter for laser ablation of the GSV. Endovenous laser energy was delivered using an 810 nm diode laser generator (Diomed® / Angiodynamics®, Cambridge, UK) at 14 Watts (W) power, continuous mode and withdrawal of the catheter was performed; aiming for a target energy delivery of 60-80 Joules per centimetre (Jcm^{-1}).

In the EVLTAP group, tumescent anaesthetic was also infiltrated around varicose tributaries and stab incisions were made, allowing avulsion of the veins using a Kocherised mosquito clip or vein hook. In both groups, stab incisions were closed with Steri-strips™ (3M, MN, USA), cotton wool, gauze and Panelast® (Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, DE) elastic adhesive bandage was applied to the limb. This remained in situ for 1 week, when it was replaced by a thigh length T.E.D™ anti-embolism stocking (Tyco Healthcare, Gosport, UK),

which patients were advised to wear for a total of 6 weeks. All patients were discharged with Diclofenac 50 milligrams (mg) *ter die sumendus* (tds) to be taken orally regularly for 1 week and Paracetamol 1 gram (g) *quater die sumendus* (qds) orally for breakthrough pain.

All patients were seen immediately pre and post procedure by the same research nurse, who provided the same instructions: elevation of the leg whilst at rest, mobilise as much as possible and return to work as soon as they feel able to do so, avoid driving, returning only when they can safely perform emergency manoeuvres and after discussion with their insurers.   A 24 hour contact number was also given for advice or help.

2.4 Outcomes

Clinical Outcomes

Peri-procedural Outcomes

- **Successful completion of the planned procedure**

- **Technical success** – successful closure of the treated vein segment on DUS at 1 week

- **Procedure duration** – The time in minutes from the commencement of skin preparation until the patient leaves the procedure room

- **Procedural complications**

- **Post-procedural pain scores** – These were recorded by patients in a diary. Diaries contained 7 unmarked 10 cm visual analogue scales, representing day 0 (day of procedure to day 6 post-procedure. One end of the scale is marked "no pain at all" (representing 0.0) the other end is marked "worst imaginable pain" (representing 10.0). Patients were invited to place a cross on each line where they feel that their average pain for that day is best represented. These were collected at 1 week and each cross was measured to the nearest mm using a ruler

- **Recovery** – Time to return to normal activities and work. These were also recorded by patients in a diary and were measured in days

Late Outcomes

- **Objective clinical assessment of venous disease** – The VCSS score was assessed pre-procedurally and at 3 and 12 months by the same vascular research nurse

- **The need for secondary procedures** – The treatment of residual and recurrent disease. These were only offered from 6 weeks to patients with symptomatic perforator reflux, symptomatic or unsightly surface varicosities following a full and frank discussion between the patient and surgeon. These were only undertaken if both parties believed that further treatment would likely benefit the patient.

- **Evidence of recurrence** – on clinical or DUS examination

- **Complications** – assessed at 1 week, 6 weeks, 3 months and 1 year

Health Related Quality of Life Outcomes

All QoL instruments below were measured at baseline and 1 week, 6 weeks, 3 months and 1 year post-procedure. These questionnaires were completed independently by the patients, free from investigator influence and prior to their clinical and duplex assessments. They were then assessed for completeness and in the presence of missing responses; patients were prompted to complete these sections. The following instruments were used:

- **Disease specific QoL** – AVVQ. This was the primary outcome measure used in this study

- **Generic QoL** – SF-36

- **Index utility QoL** - EQ5D

Duplex Assessment

All screening and follow-up duplex assessments were performed using the same device; Toshiba Aplio XV® (Toshiba medical systems Crawley, UK) with a 6 Mega Hertz linear broadband transducer array, using the same initial default settings. The protocol was based upon international consensus, with some minor

modifications[227] and all sonograms were performed by investigators appropriately qualified in the technique.

B-Mode Settings

In order to clearly and accurately demonstrate the venous anatomy in both transverse and longitudinal views; the focal zone was set to the depth of the veins under interrogation. The gain and dynamic gain control were tailored to optimise the image in each case. Tissue harmonic and compound imaging was used to further enhance image quality and allow accurate measurements to be recorded.

Doppler Settings

In both colour duplex and pulse wave spectral Doppler; low flow settings, typically 5-10 centimetres per second (cms^{-1}) were used to capture venous flow data. Filters were reduced and colour gain optimised to enhance sensitivity, whilst avoiding artefact and "colour leaking".

Sonographic Protocol

Patients were assessed whilst standing in a warm room, with the subject leg slightly flexed at the knee and the patients weight transferred onto the other leg. Initially the patient faced the sonographers with the subject leg externally rotated

at the hip. The study commenced with identification of the SFJ in transverse section. Assessment for incompetence was performed using manual flow augmentation with sudden release, greater than 10 cm distal to the region of insonation or the foot; when interrogating the distal calf. Incompetence was defined as retrograde flow greater than or equal to 1 second on spectral Doppler (this criteria was used for both superficial and deep venous systems throughout this study). The groin was then assessed for possible sources of reflux including the SFJ, abdominal or pelvic veins, aberrant groin tributaries and perforators. During detailed mapping, the entire GSV and its tributaries were assessed from groin to ankle, followed by any other incompetent veins emanating from the groin, thigh or calf. Any required antero-posterior measurements were made using the system's electronic calipers positioned at the most anterior echo of the anterior wall and the most posterior echo of the posterior wall of the vein. These were measured to the nearest 0.1 mm. The patency of the superficial system was assessed using colour duplex and compression.

The deep system was then assessed from the groin to the knee, continuous flow, pulsatile flow, obstruction, thrombosis, or incompetence involving the common femoral vein were indications to extend the examination to include the iliac veins and inferior vena cava and lead to consideration of other modalities of imaging (as did the presence of incompetence in the groin emanating from abdominal or pelvic tributaries).

The patient was then repositioned with their back towards the sonographers and their hip was returned to the anatomical position for assessment of the sapheno-

popliteal system and the deep veins of the calf. Initially the SSV was identified at the ankle and then assessed and traced back to the sapheno-popliteal junction. The position of the junction was noted and the examination went on to assess the other proximal and distal tributaries including the Giacomini vein, which, where present; was followed to its termination. Again a search was made for any incompetent perforators, before finally the popliteal and crural veins were assessed for patency and reflux.

Duplex Outcomes

The post-procedural DUS outcomes used in this study were:

- **Technical success** – Successful completion of the planned procedure, i.e. successful initial occlusion of the treated segment of GSV

- **Complications** – Particularly looking for deep vein thrombosis/heat induced thrombosis

- **Recanalisation** – Recurrent flow within a previously occluded GSV

- **Progression of disease** – with further sites of incompetence

Patient Satisfaction

This was assessed at 3 months and 1 year by asking if patients would be happy to undergo the same procedure again, if necessary, or recommend it to a friend.

Data Analysis

This will be detailed in Section *2.12 Data handling and statistical analysis* (*p170*).

Study 2; Technique evaluation – A randomised clinical trial of endovenous laser ablation versus conventional surgery in the treatment of venous insufficiency

2.5 Patients

The setting for this non-blinded parallel-group randomised clinical trial was the same tertiary referral vascular surgical unit featured in Study 1. Larger numbers of patients were required in this study.   In an attempt to make substantial improvements in the convenience and efficiency of the service to patients, clinical and research staff; a dedicated one-stop venous clinic was established.   New patients, referred to the service with venous disorders were given information regarding the trial prior to being their clinic appointment.   They were then assessed clinically by a consultant vascular surgeon or research registrar with a special interest in the management of venous disease.   Clinical assessment included a full history and examination including classification of the clinical severity of disease using the clinical grading element of the CEAP classification[25] and the VCSS system[186]. This was followed immediately by a detailed duplex ultrasound assessment according to a standardised protocol (as outlined in *Duplex Assessment, p145*). All ultrasound scans were performed by surgeons who were formally accredited in the performance of diagnostic vascular ultrasound. Patients

were assessed for eligibility of trial participation according to predetermined inclusion and exclusion criteria. Patients recruited into the trial were randomised and their baseline outcomes measured (as detailed below). Patients were then given a date for their treatment before leaving the clinic.

Inclusion Criteria

Clinical

- The presence of primary, unilateral, symptomatic venous disease of the lower limb classifiable as C2-6 on the clinical grading element of the CEAP classification system[25]

- Willingness to accept a local anaesthetic EVLA procedure, including ambulatory phlebectomy (as outlined in Section *2.7* Interventions*, p154*)

- Willingness to accept a general anaesthetic conventional surgical procedure (as outlined in Section *2.7* Interventions*, p154*)

- Willingness and ability to participate in a clinical trial, including the attendance of additional clinical assessments, completion of questionnaires, duplex follow-up and the analysis and publication of this data

- Both patient and surgeon occupy a position of equipoise over the relative merits of either intervention (including an acceptance that general anaesthesia will not hold significant additional risks for individual patients)

Duplex

- Greater than, or equal to 1 second of retrograde flow of blood from the common femoral vein through the SFJ into the GSV on pulse wave spectral Doppler

- Greater than, or equal to 1 second of retrograde flow of blood in the GSV on spectral Doppler in at least in the above knee segment

Exclusion Criteria

Clinical

- Age less than 18 years

- Previous intervention aiming to address junction, perforator or superficial axial insufficiency

- Inability or unwillingness to give informed consent to trial participation

- Pregnancy

- Symptoms or clinical evidence of arterial disease (including an ankle-brachial pressure index of less than 0.8)

- Previous groin surgery

- Known thrombophilic state

- Known malignancy

- Allergy to local anaesthetic medications

Duplex

- Deep venous disease (including obstruction or insufficiency)

- Sapheno-popliteal insufficiency

- Superficial axis insufficiency other than the GSV (which in the surgeon's view would be optimally treated with ablation or stripping rather than phlebectomy)

- GSV less than 3 mm in antero-posterior diameter at the proposed cannulation point

2.6 Randomisation

Following informed written consent, eligible patients were randomised equally into to one of two parallel groups:

Conventional Surgery Group

SFJ ligation, stripping of the GSV to the perigenicular segment and phlebectomy under general anaesthesia

EVLA Group

Truncal GSV EVLA with concomitant ambulatory phlebectomy using local anaesthesia

Randomisation was performed at the screening visit immediately following signing of the consent form. Patients were invited to select any opaque envelope, from those available, whilst under supervision. No block randomisation was used.

Sample Size

A sample size calculation was performed, based upon the primary outcome measures which were the physical domains of SF-36. Up to 120 patients per group are required to detect a moderate (5-10 point) difference in physical domains between two groups, with a power of 80% and a significance of 5%[51]. Assuming that the differences in the pilot study were reproduced[372], this figure would be sufficient giving a target recruitment of 140 per group allowing for drop out.

2.7 Interventions

Conventional Surgery Group

All procedures were performed under a general anaesthetic in either a day-case or dedicated vascular surgical theatre. Patients received a single dose of preoperative antibiotics according to an RCT based protocol[279]. Placed in the Trendelenburg position, the skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA). In the case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Sterile draping was applied prior to performing an oblique groin crease skin incision, parallel to the inguinal ligament and centred over the SFJ. The dissection was continued through the superficial fascia to identify the groin tributaries and GSV. All tributaries were ligated back to the second junction. A flush ligation of the SFJ was performed, followed by inversion stripping of the GSV to the perigenicular segment. 2-0 uncoated Polyglactin 910 (Vicryl® Ethicon, Cincinnati OH, USA) was the ligature material used. The same suture was used to suture the cribiform fascia and superficial fascia, following evacuation of any blood or thrombus from the GSV strip tract. The skin was closed using subcuticular 3-0 Poliglecaprone 25 (Monocryl® Ethicon, Cincinnati OH, USA) following infiltration of 0.5% Levobupivacaine into the wounds. No additional barrier or over-sewing techniques were employed in an attempt to deter neorevascularisation.

EVLA Group

All procedures were performed under local tumescent anaesthesia in a dedicated procedure room within the outpatients department. No sedation was used. Patients were preoperatively marked in the procedure room using a portable MicroMaxx® ultrasound system (Sonosite Ltd, Hichin, UK). The course of the GSV was marked on the skin using a permanent marker pen from the proposed point of cannulation to the SFJ. If ambulatory phlebectomy was to be performed then the sites were also marked preoperatively.

The skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA). In the case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Sterile draping of the leg was performed prior to percutaneous cannulation of the GSV with the patient in the reverse Trendelenburg position. The initial aim was to cannulate the perigenicular GSV, but the technique evolved during the trial and cannulation was performed at the lowest point of demonstrable reflux above the medial malleolus. A 5 French catheter was introduced into the vein using the Seldinger technique, and its tip accurately positioned at the SFJ using ultrasound. The patient was then put in the Trendelenburg position and perivenous local anaesthetic (20 millilitres of 2% Lignocaine with 1:200,000 Adrenaline and 20 ml of 0.5% Levobupivacaine in 1 l of 0.9% Sodium Chloride solution) was infiltrated along the vein. Total local anaesthetic did not exceed the recommended maximum safe dose per patient. A sterile bare-tipped 600 nm laser fibre was introduced via the catheter for laser ablation of the GSV. Endovenous laser energy

was delivered using an 810 nm diode laser generator (Diomed® / Angiodynamics®, Cambridge, UK) at 14 W power, continuous mode and withdrawal of the catheter was performed; aiming for a specified target energy delivery. Again during the trial this policy evolved. The initial aim was 60-80 Jcm^{-1}, but by the end of the study, 100-120 Jcm^{-1} was the target.

In both groups, surface varicosities and incompetent perforators were marked pre-operatively in the dependant position and concomitant phlebectomies were performed via stab incisions made over varicose tributaries, which were avulsed using a Kocherised mosquito clip or vein hook. Perforators not ablated during the truncal procedure; were divided and ligated through a 1.5 cm incision, which was then closed with a subcuticular monofilament suture. Stab incisions were closed with Steri-strips™ (3M, MN, USA), cotton wool, gauze and elastic compression dressings applied. This was later replaced by a thigh length T.E.D™ anti-embolism stocking (Tyco Healthcare, Gosport, UK), which patients were advised to wear for a total of 6 weeks. All patients were discharged with Diclofenac 50 mg tds to be taken regularly for 1 week and Paracetamol 1 g qds for breakthrough pain.

All patients were seen immediately pre and post procedure by the same research nurse, who provided the same instructions: elevation of the leg whilst at rest, mobilise as much as possible and return to work as soon as they feel able to do so, avoid driving, returning only when they can safely perform emergency

manoeuvres and after discussion with their insurers. A 24 hour contact number was also given for advice or help.

2.8 Outcomes

Clinical Outcomes

Peri-procedural Outcomes

- **Strip length** – During surgical procedures, the length of GSV that was successfully stripped and removed was measured to the nearest cm using a ruler

- **Energy delivery** – During EVLA procedures, the length of ablated vein was measured to the nearest 0.5 cm using the marks on the catheter. This information, along with the total laser energy used was measured to the nearest J, allowing an average laser energy delivery in Jcm^{-1} to be calculated

- **Procedure duration** – The time in minutes from the commencement of skin preparation until the patient leaves the procedure room

- **The need for overnight stay** – post procedure

- **Successful completion of the planned procedure**

- **Technical success** – Successful completion of the planned procedure, i.e. successful disconnection of all groin tributaries and stripping of the GSV to the perigenicular segment in the conventional surgery group and initial occlusion of the treated segment of GSV in the EVLA group (irrespective of the status of the groin tributaries) – established using DUS

- **Post-procedural pain scores** – These were recorded by patients in a diary. Diaries contained 7 unmarked 10 cm visual analogue scales, representing day 0 (day of procedure) to 6. One end of the scale is marked "no pain at all" (representing 0.0) the other end is marked "worst imaginable pain" (representing 10.0). Patients were invited to place a cross on each line where they feel that their average pain for that day is best represented. These were collected at 1 week and each cross was measured to the nearest mm using a ruler

- **Supplementary analgesia** – This was reported by patients in the same diary as the pain scales. For days 0-6, each patient indicated whether they required any supplementary analgesia, for break-through pain

- **Procedural complications**

- **Recovery** – Time to return to normal activities and work. These were also recorded by patients in a diary and were measured in days

Late Outcomes

- **Objective clinical assessment of venous disease** – The VCSS score was assessed pre-procedurally and at 3 and 12 months by the same vascular research nurse

- **Residual varicose veins** – defined as: clinically evident varicose veins greater than or equal to 3 mm in diameter present at week 1 and 6 (irrespective of the existence of reported symptoms)

- **Clinical recurrence** - defined as: clinically evident varicose veins greater than or equal to 3 mm in diameter, not present at week 1 and 6, but becoming apparent during subsequent follow up (irrespective of the existence of reported symptoms)

- **The need for secondary procedures** – The treatment of residual and recurrent disease. This were only offered after 6 weeks post-procedure to patients with symptomatic perforator reflux, symptomatic or unsightly surface varicosities following a full and frank discussion between the patient and surgeon as to the risks and benefits of further intervention. These were only undertaken if both parties believed that further treatment were likely to benefit the patient

- **Late complications**

Health Related Quality of Life Outcomes

All QoL instruments below were measured at baseline and 1 week, 6 weeks, 3 months and 1 year post-procedure. These questionnaires were completed independently by the patients, free from investigator influence and prior to their clinical and duplex assessments. They were then assessed for completeness and in the presence of missing responses; patients were prompted to complete these sections. The following instruments were used:

- **Disease specific QoL** – AVVQ

- **Generic QoL** – SF-36. This was the primary outcome measure used in this study

- **Index utility QoL** – SF6D

- **Index utility QoL** - EQ5D

Duplex Assessment

Duplex assessment was performed according to the same protocol as used in Study 1 (See *Duplex Assessment p145*).

Duplex Outcomes

The post-procedural duplex outcomes used in this study were:

- **Technical success** – as defined above

- **Complications** – Particularly deep vein thrombosis/heat induced thrombosis

- **The patterns of insufficiency associated with clinical recurrence** – including recanalisation (defined as recurrent flow within a previously occluded GSV)

Patient Satisfaction

Patients were invited to place a cross on a 10 cm unmarked visual analogue scale representing satisfaction with the cosmetic outcome of the procedure and satisfaction with the overall treatment, including the process and outcome. One end of the scales was marked "Completely unsatisfied" (representing 0.0) the other end is marked "Completely satisfied" (representing 10.0). These were then measured to the nearest mm using a ruler. This was assessed at 3 months and 1 year.

Data Analysis

This will be detailed in Section *2.12 Data handling and statistical analysis* (*p170*).

Study 3; Procedure refinement – Energy delivery during 810nm endovenous laser ablation of superficial venous insufficiency and post-procedural morbidity

2.9 Patients

The setting for this prospective observational study was the same tertiary referral vascular surgical unit hosting Study 1 and 2. All consecutive patients presenting were evaluated for eligibility in a series of trials according to predetermined inclusion and exclusion criteria. These trials included Study 1 and 2 above, the non-randomised pilot study for Study 2[372] and an RCT of EVLA versus conventional surgery for sapheno-popliteal incompetence (follow-up currently on-going). In addition some patients were suitable for inclusion in these studies, except had a very strong preference for EVLA. In this case, consent was taken to observe their outcomes, using the same follow-up protocol as for Study 2. All available data from patients undergoing EVLA with concomitant phlebectomy was used in this analysis.

Assessment of each patient was performed by a consultant vascular surgeon or research registrar with a special interest in the management of venous disease. Clinical assessment included a full history and examination including classification of the clinical severity of disease using the clinical grading element of the CEAP classification[25] and the VCSS system[186]. This was followed by a detailed duplex ultrasound assessment according to a standardised protocol. All ultrasound scans were performed by surgeons who were formally accredited in the performance of

diagnostic vascular ultrasound. The details of duplex assessment are outlined in Section *Duplex Assessment, p145*.

Inclusion criteria

Clinical

- The presence of primary, unilateral, symptomatic venous disease of the lower limb; classifiable as C2-5 on the clinical grading element of the CEAP classification system[25]

- Willingness to accept a local anaesthetic EVLA procedure, including ambulatory phlebectomy (as outlined in Section *2.10 Interventions, p165*)

- Willingness and ability to participate in a clinical trial, including the attendance of additional clinical assessments, completion of questionnaires, duplex follow-up and the analysis and publication of this data

Duplex

- Greater than, or equal to 1 second of retrograde flow of blood from the common femoral vein through the SFJ into the GSV or from the deep vein through the sapheno-popliteal junction into the SSV on pulse wave spectral Doppler

- Greater than, or equal to 1 second of retrograde flow of blood in the GSV or in the SSV on spectral Doppler

Exclusion Criteria

Clinical

- Age less than 18 years

- Previous intervention aiming to address junction, perforator or superficial axial insufficiency

- Inability or unwillingness to give informed consent to study participation

- Pregnancy

- Symptoms or clinical evidence of arterial disease (including an ankle-brachial pressure index of less than 0.8)

- Known thrombophilic state

- Known malignancy

- Allergy to local anaesthetic medications

Duplex

- Deep venous disease (including obstruction or insufficiency)

- More than 1 superficial axis of insufficiency (which in the surgeon's view would be optimally treated with ablation or stripping rather than phlebectomy)

- GSV or SSV less than 3 millimetres in antero-posterior diameter at the proposed cannulation point

Sample Size

A sample size calculation was performed for the regression analyses planned (See *Section 2.12 Data handling and statistical analysis, p170*). As 11 predictor variables were to be studied, the required sample size to test each individual predictor is 115, whilst the required sample size to test the models is 138[373]. This was regarded as the minimum accepted sample size, in order to reduce the risk of missing any significant relationships.

2.10 Interventions

All procedures were performed under local tumescent anaesthesia in a dedicated procedure room within the outpatients department. No sedation was used. Patients were preoperatively marked in the procedure room using a portable MicroMaxx® ultrasound system (Sonosite Ltd, Hichin, UK). The course of the target vein was marked on the skin using a permanent marker pen from the

proposed point of cannulation to the junction. The sites for ambulatory phlebectomy were also marked preoperatively.

The skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA). In the case of iodine allergy, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Sterile draping of the leg was performed prior to percutaneous cannulation of the target vein with the patient in the reverse Trendelenburg position. A 5 French catheter was introduced into the vein using the Seldinger technique, and its tip accurately positioned at the junction using ultrasound. The patient was then put in the Trendelenburg position, and perivenous local anaesthetic was infiltrated along the vein. Total local anaesthetic did not exceed the recommended maximum safe dose per patient. A sterile bare-tipped 600 nm laser fibre was introduced via the catheter for laser ablation of the GSV. Endovenous laser energy was delivered using an 810 nm diode laser generator (Diomed® / Angiodynamics®, Cambridge, UK) at 14 W power, continuous mode and withdrawal of the catheter was performed.

Tumescent local anaesthetic was also infiltrated around varicose tributaries and stab incisions were made, allowing avulsion of the veins using a Kocherised mosquito clip or vein hook. These incisions were closed with Steri-strips™ (3M, MN, USA), cotton wool, gauze and Panelast® (Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, DE) elastic adhesive bandage was applied to the limb. This remained in situ for 1 week, when it was replaced by a thigh length T.E.D™ anti-embolism stocking (Tyco Healthcare, Gosport, UK), which patients were

advised to wear for a total of 6 weeks. All patients were discharged with Diclofenac 50 mg tds to be taken regularly for 1 week and Paracetamol 1 g qds for breakthrough pain.

All patients were seen immediately pre and post op by the same research nurse, who provided the same instructions: elevation of the leg whilst at rest, mobilise as much as possible and return to work as soon as they feel able to do so, avoid driving, returning only when they can safely perform emergency manoeuvres and after discussion with their insurers.   A 24 hour contact number was also given for advice or help.

2.11 Outcomes

Clinical Outcomes

Peri-procedural Outcomes

- **Energy delivery** – During EVLA procedures, the length of ablated vein was measured to the nearest 0.5 centimetre using the marks on the catheter. This information, along with the total laser energy used was measured to the nearest J, allowing an average laser energy delivery in Jcm^{-1} to be calculated

- **The need for overnight stay** – post procedure

- **Post-procedural pain scores** – These were recorded by patients in a diary. Diaries contained 7 unmarked 10 cm visual analogue scales, representing day 0 (day of procedure) to 6. One end of the scale is marked "no pain at all" (representing 0.0) the other end is marked "worst imaginable pain" (representing 10.0). Patients were invited to place a cross on each line where they feel that their average pain for that day is best represented. These were collected at 1 week and each cross was measured to the nearest mm using a ruler

- **Supplementary analgesia** – This was reported by patients in their pain diary. For days 0-6, each patient indicated whether they took any supplementary analgesia, for break-through pain

- **Time to return to normal activities and work** – These were also recorded by patients in a diary and were measured in days

- **Procedural complications**

Health Related Quality of Life Outcomes

All QoL instruments below were measured at baseline, 1 week and 6 weeks post-procedure. These questionnaires were completed independently by the patients, free from investigator influence and prior to their clinical and DUS assessments. They were then assessed for completeness and in the presence of missing responses; patients were prompted to complete these sections. The following instruments were used:

- **Disease specific QoL** – AVVQ.

- **Generic QoL** – SF36 physical domains

- **Index utility QoL** - EQ5D

Duplex Assessment

Duplex assessment was performed according to the same protocol as used in study 1 (See *Duplex Assessment p145*).

Duplex outcomes

The post-procedural duplex outcomes used in this study were:

- **Complications** – Particularly deep vein thrombosis/heat induced thrombosis

Data Analysis

This will be detailed in Section *2.12 Data handling and statistical analysis*.

2.12 Data handling and statistical analysis

All data was transcribed and recorded into a secure dedicated database (Microsoft Access®, Redmond, WA, USA). All analysis was performed utilising SPSS (Chicago, IL, USA).

The statistical analysis was performed according to a standardised prospectively determined protocol according to the principle of intention to treat.   No assumptions were made at any time as to the direction of any relationships and no imputation of missing data was attempted. Any key assumptions of the statistical techniques used were tested as appropriately.

Continuous data

Description

Normally distributed data was quoted as mean (95% confidence interval) (for dependant variables) or mean (standard deviation) or mean (range) (for independent variables). If data was not normally distributed, it is quoted as median (inter-quartile range).

Continuous data is presented using standard statistical notation in box and whisker plots.   The box indicates the inter-quartile range and the median represented by a line within the box. The whiskers represent the range of data within 1.5 times the inter-quartile range below the 1st quartile and above the 3rd

quartile. Data points outside of this are considered outliers and represented by dots.

Analysis

Prior to any further analysis of continuous data, its distribution was explored using histogram analysis. Any data which appeared to be normally distributed underwent hypothesis testing using the Shapiro-Wilk test (SW)[374] to establish the degree of certainty of this assumption. For the purposes of the following studies; significance values greater than 0.050 were assumed to be normally distributed.

Intragroup comparisons, featured the analysis of paired data (ie before and after in the same patient) and intergroup comparisons used unpaired data (ie from different patients). Hypothesis testing was performed comparing groups according to the data distribution and whether it was paired or unpaired. The quoted "P-value" represents the probability of having observed the data if the null hypothesis were true[375] (ie there is no actual differences between the data). "P-values" are quoted to three decimal places and a value of less than 0.050 was regarded as "significant" and led to rejection of the null hypothesis. These statistically significant differences were then examined to establish whether they represented clinically significant findings in the context of this research and the existing evidence base.

The following hypothesis tests were used according to the nature of the data under interrogation:

Normally distributed data:

- **Paired** – paired Student t-test (t test)[376] (2 samples), ANOVA[377] (multiple related samples)

- **Unpaired** – unpaired Student t-test (t test)[376]

Non-normally distributed data:

- **Paired** – Wilcoxon signed rank test (WSR test)[378] (2 samples), Friedman ANOVA (F-A)[379] (multiple related samples)

- **Unpaired** – Mann-Whitney U test (MWU test)[380]

Categorical data

Description

Simple categorical data is presented as percentages (x/y) where x represents the number of cases in a category and y represents the total number of cases under consideration. When required, relative risk (RR), risk differences (RD) and number needed to treat (NNT) is also quoted along with 95 confidence intervals.

Analysis

The primary hypothesis test used in categorical analysis is Pearson's Chi-square test (χ^2 test)[381]. If greater than 20% of expected frequencies are less than 5 or any are below 1, then Fisher's exact test (FET) [382] was used. In order to account for censored data Kaplan-Meier analysis[383] was conducted featuring intergroup Log Rank significance testing.

Linear regression analysis (Study 3)

In order to test the null hypothesis that increasing linear energy delivery had no effect upon post-procedural pain, QoL and recovery rates in Study 3, linear regression models were used.

Model detail: Predictor variables

The primary predictor variable of interest was the linear energy delivery in Jcm^{-1}. The other independent predictor variables were age, gender, BMI, the radius and length of the treated vein and pre-operative QoL (AVVQ, EQ5D and physical domains of SF-36). These were included within the models, so their effect could be controlled and the effect of the primary predictor studied in isolation.

Some surgeons calculate energy delivery taking into account both length and diameter. Controlling for the radius within these models allows these results to be comparable. Although the QoL outcomes are the change in scores, rather than

the absolute scores post-procedure, baseline scores were entered into the model. This is because it was unknown whether differing scores at baseline would respond with differing magnitudes to treatment. For example would a patient with chronic back pain notice a similar incremental change in their total bodily pain score as someone with no pain at all before EVLA? This effect, where present, was therefore also controlled.

Model detail: Outcome variables

The outcome variables of interest were all independently reported by the patient. They were post-procedural pain (as measured daily for the first week on visual analogue scale), changes in QoL from baseline by week 1 and week 6 (AVVQ, EQ5D and physical domains of SF-36) and recovery rates (the time taken to return to normal activity and the time taken to return to work).

Model detail: Model technique and testing of assumptions

The aim of the models was to test the effect of the primary predictor variable upon the outcome variables, whilst controlling for the other independent predictors. In order to fulfil this aim, linear regression models were produced for these continuous outcomes.

If the continuous outcomes were not normally distributed, they were transformed using standard mathematical techniques. Statistical significance was set at less

than 0.050 (α = 0.05). T-tests of the estimated b values allowed significance level calculation of the contribution of an individual predictor to the model's predictive ability. Effect sizes and the proportion of variance in the outcome due to the energy delivery alone were calculated. The models were produced via the method of "forced entry." This allows the retention of methodological control of the modal and is thought to reduce the effect of random sampling variation within the data and produce replicable results[384].

All predictor variables were continuous, with a variance greater than 0. All outcomes were continuous, independent and not unduly constrained. Correlation statistics were performed and no significant multicollinearity was observed, additionally the variance inflation factor was less than 10 in each model. There are no known important correlations between these predictors and external variables, which will have a significant effect upon the models. Residual values were plotted to establish linearity and homoscedastiscity. Residual value histograms were drawn confirming normal distribution. Finally the independence of errors was established using the Durbin-Watson test. This test statistic was between 1 and 3 in each model; this was taken to confirm the independence of errors.

Logistic regression analysis (Study 3)

In order to test the null hypothesis that increasing linear energy delivery had no effect upon supplementary analgesia for breakthrough pain or the incidence of complications in Study 3, logistic regression models were used.

Model detail: Predictor variables

As for the linear regression models, the primary predictor variable of interest was the linear energy delivery in Jcm^{-1}. The other independent predictor variables were age, gender, body mass index, the radius and length of the treated vein and pre-operative QoL (AVVQ, EQ5D and physical domains of SF-36).

Model detail: Outcome variables

The outcome variables of interest were binary in nature. The first was the patient reported requirement of supplementary analgesia (daily for the first week) the second was the incidence of all patient reported or clinically observed complications (including during standardised duplex assessment).

Model detail: Model technique and testing of assumptions

The aim of the models was to test the effect of the primary predictor variable upon the probability of the outcome variables occurring, whilst controlling for the

other independent predictors. In order to fulfil this aim, logistic regression models were produced for these binary outcomes.

The "forced entry" method was again used in model construction. The individual contribution of the predictors was assessed by Chi square testing of the Wald statistic. Again statistical significance was set at less than 0.050 (α = 0.05). The Odds ratio (95% confidence interval) was calculated for the effect of the primary predictor in isolation upon the outcome.

All predictor variables were continuous, with a variance greater than 0. Correlation statistics were performed and no significant multicollinearity was observed, additionally the variance inflation factor was less than 10 in each model. There are no known significant correlations between these predictors and external variables, which will have a significant effect upon the models. Linearity of the logit and the independence of errors were confirmed. Sufficient data was available for all combinations of variables.

2.13 Ethics

The conduct of these studies, along with dissemination of findings and the drafting of this thesis has been performed with the principles of the declaration of Helsinki at their heart[385]. In particular, the health of each individual patient included and considered for inclusion was seen as the primary concern of each individual involved with this research.

In the context of this research; patients were only offered an intervention if both patient and surgeon felt that on balance this would result in a significant benefit to that individual, with the potential risks being taken into account. Inclusion in randomised studies was only entertained if both surgeon and patient occupied a position of equipoise over the optimal procedure to be undertaken. All patients were made aware of the additional burden of the assessments associated with the research and were aware that they could withdraw at any stage of the research process, without any cost or prejudice to their existing, on-going or future care. Dynamic solutions were sought and found to decrease such burdens, such as the integration of services resulting from the one-stop venous clinics. It was innovations such as this, the institution of routine duplex assessment and tailored treatment in every case, alongside the increased contact and support offered by the research team that led to improvements in patient care and outcomes and very high levels of patient satisfaction.

All interventions were approved for routine use within the context of the NHS, in particular EVLA was accepted as a treatment provided that "the normal arrangements are in place for consent, audit and clinical governance"[386].

The fundamental aim of this body of work was to improve patient care and outcomes by providing reliable information of the risks, benefits and efficacy of these new technologies to the management of superficial venous insufficiency when compared to the gold standard treatment: conventional surgery. Conventional Surgery was established as the gold standard after undergoing rigorous assessment in comparison with conservative management[50].

The design of the studies was intended to conform to what is regarded as gold standard methodology. Protocols were prospectively designed and approval sought and secured from both independent ethics committees and the institutional review board. These trials were then registered in a freely available public registry, as per current recommendations[387]. Where possible, the design was that of a RCT, offering level-1 evidence. The nature of the techniques limited the possibility of blinding in the main part, but every effort was made to be even-handed regarding the surrounding package of information and care, and many of the key outcomes, including the primary outcomes were independently reported by patients themselves using validated instruments. These were completed prior to clinical and duplex assessment, limiting any investigator induced bias and are validated in the role of assessing a patient's quality of life. The fact that quality of life plays such a prominent central role in the evaluation of these technologies, testifies to the great emphasis placed upon patient perspectives and patient-centred end-points, rather than the technical physician-chosen (surrogate) outcomes pervading the literature in this area prior to this work. In order to avoid the wastage and redundancy associated with under-powered, possibly misleading studies; this work was based upon realistic and feasible sample-size calculations, based upon detecting clinically meaningful differences. All statistical analysis was performed using standard, widely accepted techniques, and no imputation of data was performed, reducing unnecessary assumptions having an impact upon the conclusions.

All eligible patients were offered an opportunity to participate, according to their free will. Upon choosing to participate, patients were required to indicate their informed consent by signing a standardised form. Children and vulnerable adults were excluded, to help to ensure that all participants had the true capacity to give, or perhaps later withhold, their consent to participation. All hard copy data is kept in a locked room at the Academic Vascular Surgical Unit (based within Hull Royal Infirmary). All electronic data was held on a secure server hosted jointly by the University of Hull and Hull and East Yorkshire Hospitals NHS Trust. This data has an identified Caldicott guardian, and has not been disseminated in any way, such that individual patient's data or involvement in the studies can be identified.

All investigators had undergone formal training in "Good Clinical Practice" with regards to the undertaking of clinical research and all investigators involved in the delivery of clinical care were appropriately qualified and experienced in the delivery of that care, in particular all duplex assessments were performed by surgeons who had completed (with distinction) a full University-based, post-graduate ultrasound course, designed for the accreditation of full-time vascular sonographers.

The research team did receive some industry support towards research costs; namely Diomed® / Angiodynamics® (Cambridge, UK) provided 50% of a research nurse's salary over a 12 month period to facilitate these studies. The motivation of this support was directed towards the investigators occasionally acting in a teaching / mentoring capacity facilitating uptake of these new technologies. With regard to research; the support was unconditional and this company had no

involvement or influence in the design, data collection, data analysis, or dissemination of this research. In addition the company had no access to any of the documentation, data or analysis that is not available in the public domain. This relationship has been made clear whenever this work has been disseminated.

Chapter 3 – Results

Study 1; Procedure Refinement – A randomised clinical trial of endovenous laser ablation with concomitant versus selected sequential phlebectomy in the treatment of venous insufficiency

3.1 Patient Recruitment and Baseline Analysis

Figure 21 outlines the recruitment and the number of patients involved in analysis at each stage.

Some 50 patients were randomised, as planned; with attention to the inclusion and exclusion criteria specified in the protocol. All patients randomised to EVLTAP received the allocated treatment as per protocol. One patient allocated to the Control group decided that they would prefer concomitant phlebectomy and withdrew from the trial in order to receive their preferred treatment. They declined to continue to participate in follow-up and so were excluded from analysis beyond baseline. Attrition to follow-up was comparable between the two groups and occurred mainly between week 6 and 52. There were no protocol violations.
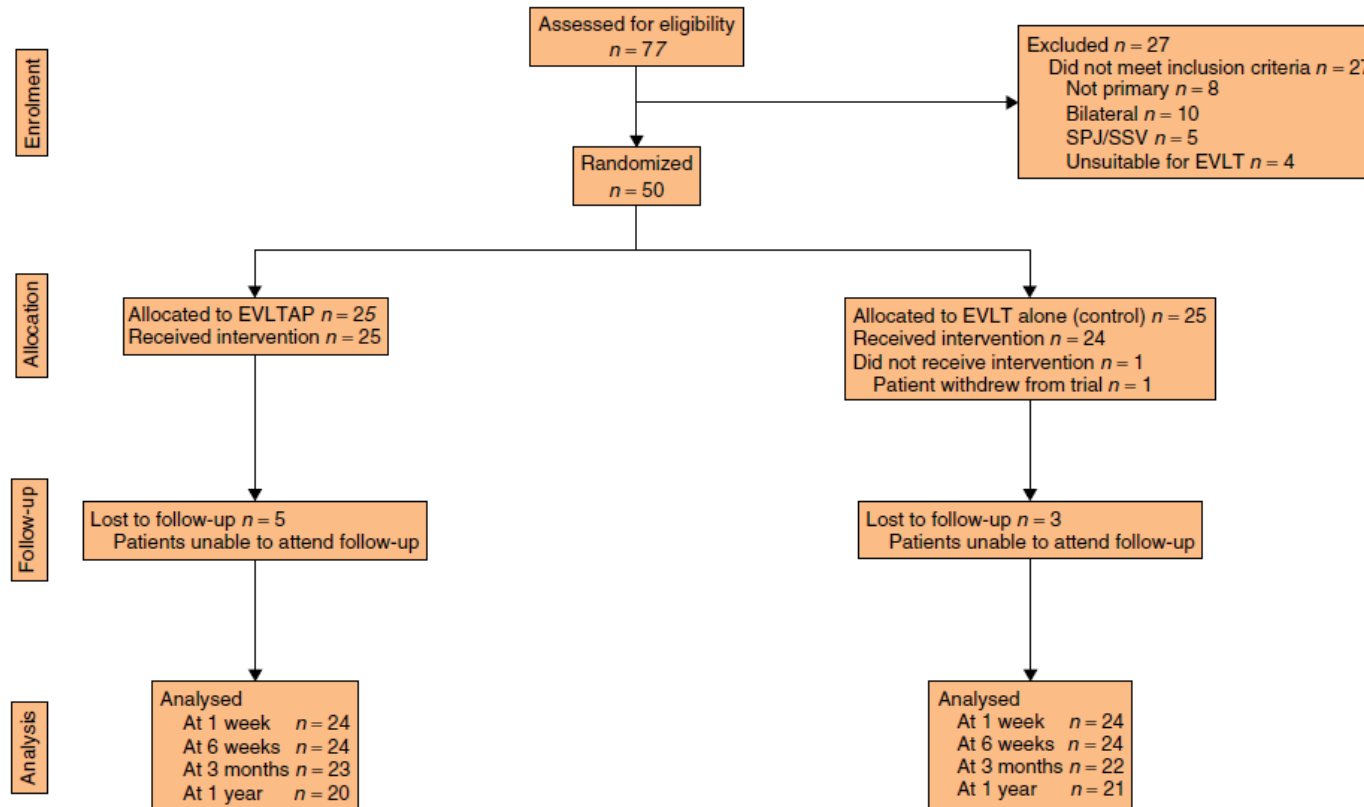
Figure 21: *CONSORT diagram showing flow of patients through the trial (Study 1).* SPJ, saphenopopliteal junction; SSV - short saphenous vein; EVLT - endovenous laser therapy; EVLTAP - EVLT with concomitant ambulatory phlebectomy

The two groups were analysed in terms of age, gender, baseline VCSS and quality of life (*Table 15*). The results for age and AVVQ were found to be normally distributed (P=0.235-0.804 SW) and therefore parametric hypothesis testing was performed to ascertain the significance of any observed differences. The other continuous variables differed significantly from a normal distribution and differences were analysed using non-parametric hypothesis testing. No significant differences were observed as is to be expected from this randomised data.

Table 15 illustrates that the methodology has resulted in the recruitment of a cohort of patients typical of those seen in routine practice. Approximately three quarters are women with a mean age in their early 50s. The median VCSS score is 4, which corresponds to uncomplicated symptomatic varicose veins, which are causing a significant perceived impact upon QoL; as evidenced by a median AVVQ of 13 to 14.

		EVLTAP	EVLT alone (Control)	P Value
Age (yrs): Mean (Standard Deviation)		51 (14)	53 (16)	0.738[*]
Gender: Male : Female		8:17	4:21	0.321[†]
Venous Clinical Severity Score		4 (3-5)	4 (2-5)	0.507
SF-36 Domains	Physical Function	85 (70-99)	93 (80-100)	0.407
	Role – Physical	100 (57-100)	100 (17-100)	0.947
	Bodily Pain	74 (51-84)	79 (55-100)	0.538
	General Health	71 (58-87)	77 (56-91)	0.455
	Vitality	70 (41-75)	68 (60-75)	0.853
	Social Function	100 (63-100)	100 (78-100)	0.517
	Role- Emotional	100	100	0.678
	Mental Health	84 (66-92)	80 (67-88)	0.592
Aberdeen Varicose Vein Questionnaire: Mean (95% Confidence Interval)		13.29 (11.09-15.50)	13.75 (11.67-15.82)	0.728[*]
Euroqol Health Index Score		0.796 (0.769-1.000)	0.796 (0.778-1.000)	0.325

Table 15: *Baseline comparison of the groups (Study 1).* **Figures are quoted as median (inter-quartile range) and the P values are derived from the MWU test unless otherwise stated:** [*] **- t test,** [†] **- χ^2 test**

3.2 Clinical Outcomes

Peri–procedural Outcomes

Procedural success: All attempted procedures were successfully completed as per-protocol. At 1 week all treated vein segments were occluded on examination with DUS, giving an initial technical success rate of 100%.

Procedure duration: The median procedural times were 20 minutes longer for EVLTAP compared to the Control group (65 (50-70) and 45 (40-55) minutes p=0.002 - MWU).

Procedural complications: There were no statistical differences in the complications observed between the two groups. One patient suffered phlebitis of the GSV in the Control group, this settled within 2 weeks following continuing treatment with Diclofenac 50mg tds and topical 0.3% heparinoid gel. One patient developed a small area of pressure necrosis secondary to the dressings, this settled spontaneously. Two patients in the EVLTAP group noticed some pigmentation over the GSV and one patient had neuralgia in their thigh, all of which were self limiting.

Pain: Post procedural pain scores were fairly low in both groups. There was no statistical difference between the groups in terms of perceived pain scores on day 0 to 6 (*Table 16, Figure 22*):

Day	EVLTAP	EVLT Alone (Control)	P Value
0	3.2 (0.2-6.0)	1.9 (0.3 - 4.6)	0.288
1	3.0 (0.1-4.4)	1.6 (0.6 - 3.0)	0.514
2	1.7 (0.0-3.2)	1.5 (0.0 - 3.0)	0.808
3	1.3 (0.0-2.6)	0.6 (0.0 - 1.4)	0.641
4	1.0 (0.0-2.4)	0.5 (0.0 - 1.2)	0.433
5	1.1 (0.0-2.4)	0.2 (0.0 - 2.1)	0.466
6	0.0 (0.0-2.9)	0.3 (0.0 - 1.2)	0.959

Table 16: *Post-procedural pain scores (Study 1).* **Values indicate the med (IQR) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). The P-values are derived from the MWU test**
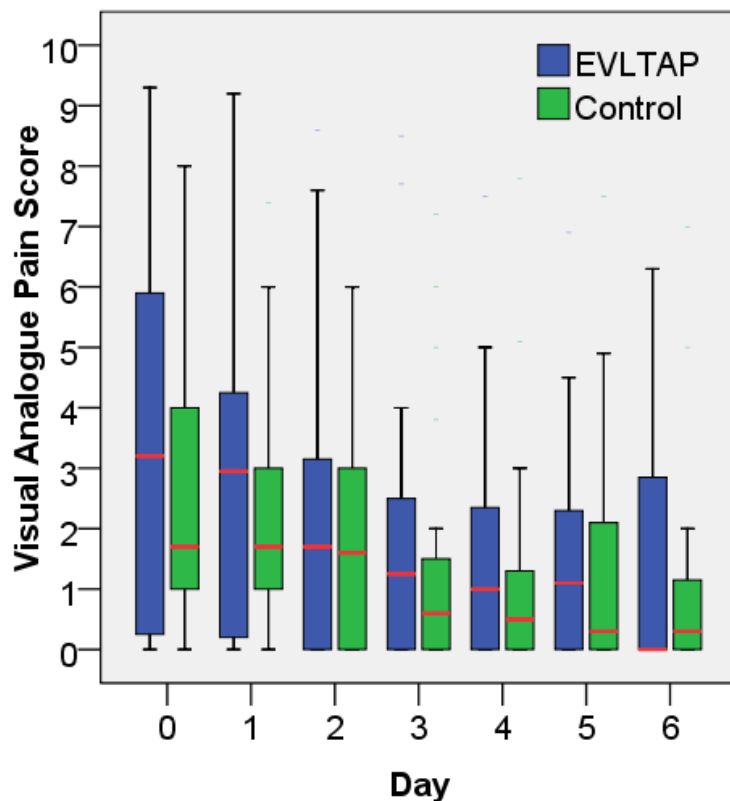

Figure 22: *Post-procedural pain scores from the day of the procedure (day 0) until day 6 (Study 1).* **The visual analogue scale runs from 0 ("no pain at all") to 10 ("worst imaginable pain")**

Recovery: There was no statistically significant difference in the number of days taken to return to work (EVLTAP group – 10 (4-21) days, Control group - 3 (1-14) days P = 0.054 MWU) or return to normal activities (EVLTAP - 8 (1-14) days, Control - 2 (1-5) days p=0.166 MWU).

Late Outcomes

Objective clinical assessment of venous disease*:* Both groups saw a significant decrease (improvement) in VCSS scores over the study period following treatment (p<0.001 – F-A, *Table 17, Figure 23*), however when the groups are compared; there was a significant difference of median 2 points between the groups at 3 months (P<0.001 MWU). The EVLTAP group score significantly lower (better) at this time. By 1 year, this gap had closed again and the groups were once more indistinguishable.

Week	EVLTAP	EVLT Alone (Control)	P-Value
0	4 (3-5)	4 (2-5)	0.817
12	0 (0-1)	2 (0-2)	<0.001
52	0 (0-1) *	0 (0-1) *	0.738

Table 17: *Venous Clinical severity scores, over time by group (Study 1).* **The P-values represent the intergroup comparison at each time point (MWU).** * **- Intragroup comparison over time P<0.001 (F-A).**
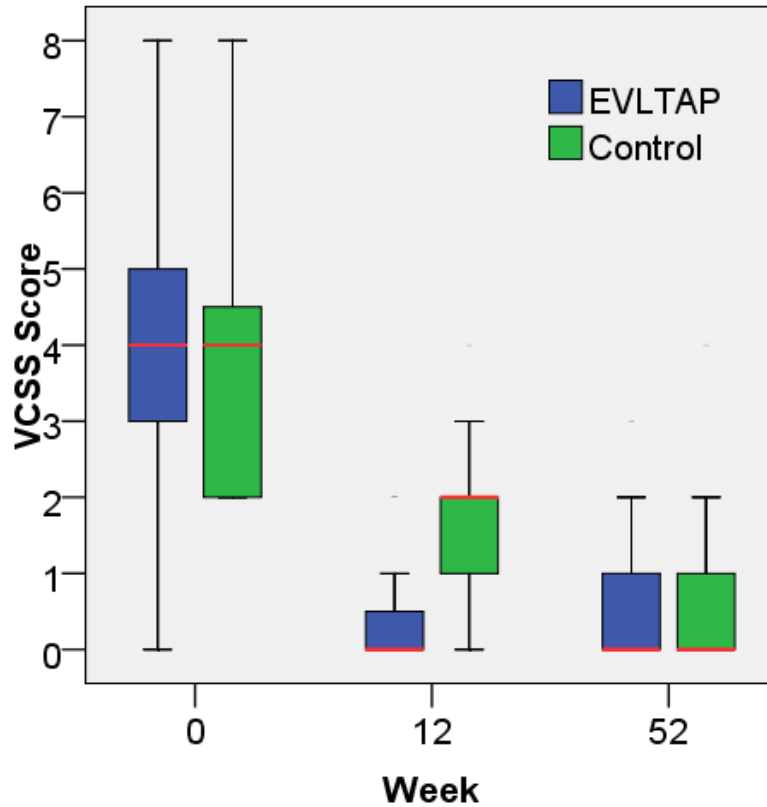
Figure 23: *Clinical Severity of Venous Disease, using the Venous Clinical severity score, over time, by group (Study 1)*

Secondary procedures: In the Control group 16 of 25 patients (64%) required subsequent perforator surgery or ambulatory phlebectomy, compared with only 1 of 25 in the EVLTAP group (4%, $p<0.001$ χ^2). The RR (95% CI) was 0.06 (0.01-0.44) and the NNT (95% CI) with EVLTAP rather than EVLT alone to avoid the requirement for 1 subsequent procedure is 1.7 (1.3-2.5). All were planned and performed close to 6 weeks. No further interventions were required at 3 or 12 months.

Complications: There were no late complications which became apparent during the 1 year follow-up period.

Recurrence: There were no cases of clinical recurrence evident by 1 year in either group. On DUS at 1 year, one SFJ demonstrated reflux in the EVLTAP and two in the Control group. Three patients had a partially re-canalised GSV (two showed reflux) in the EVLTAP group and one in the Control group. No patients required further treatment to the GSV or SFJ.

3.3 Quality of Life Outcomes

Disease Specific Quality of Life

This was the primary outcome for the trial (See *Figure 24*). Both groups saw a significant decrease (improvement) in AVVQ scores over the study period (Control - P=0.031, EVLTAP – P<0.001 – F-A). Detailed analysis using WSR test clearly shows that the EVLTAP group saw a significant improvement from baseline by 6 weeks (P=0.008), but this was not true of the Control group (P=1.000), who did not see an improvement until 3 months post procedure (P=0.018).

When comparing the groups; AVVQ scores were significantly lower (better) in the EVLTAP group at both 6 weeks (P<0.001 MWU) and 3 months (P=0.015 MWU) respectively. However there is no difference at 1 week or 1 year.
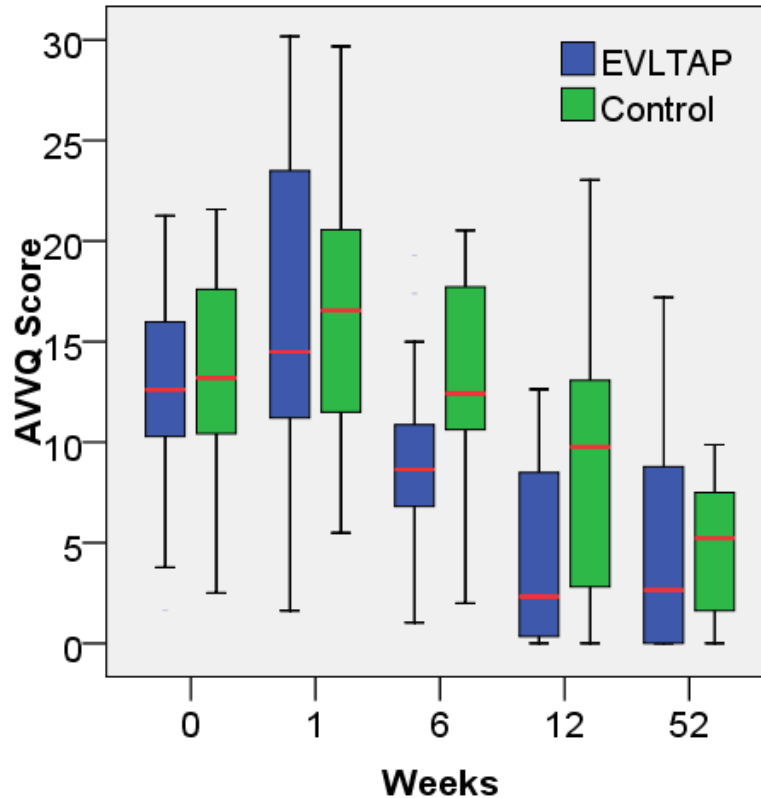
Figure 24: *Disease Specific Quality of Life Impairment using the Aberdeen Varicose Veins Questionnaire, over time, by group (Study 1)*

Generic Quality of Life

There were no statistically significant changes in any of the SF-36 domains over time in either group (*Figure 25 - Figure 32*), however the index utility score increased (improved) over time in the EVLTAP group (P<0.001 – F-A, *Figure 33*) and this improvement was observed from 6 weeks (P=0.002 WSR). This improvement was not demonstrated in the Control group over the study period (P=0.112 F-A).

When comparing the two groups at each time point for each variable, there are no clinically significant differences observed.   There is a statistically significant

difference in MH at 6 weeks; with patients in the Control group scoring lower (worse) (med (IQR) EVLTAP – 88 (76-92), Control – 76 (60-84) (P=0.030 MWU). This difference however is not of a sufficient magnitude to be regarded as a clinically significant difference in this domain[51,388,389]. There were no other statistical differences between the groups across all time points (P>0.050) in generic QoL measures.
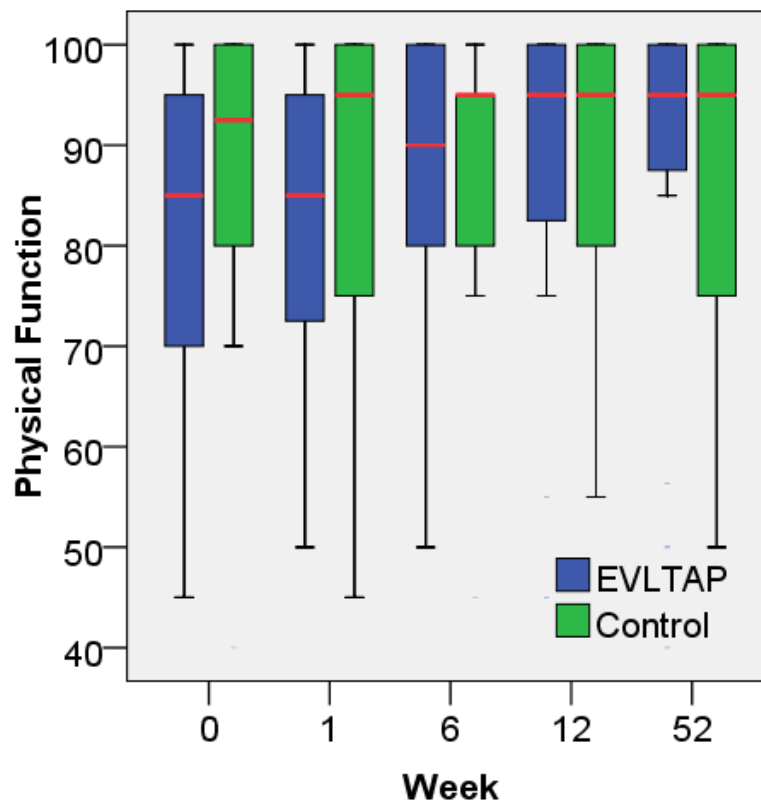
Figure 25: *SF-36 Physical Function, over time, by group (Study 1)*
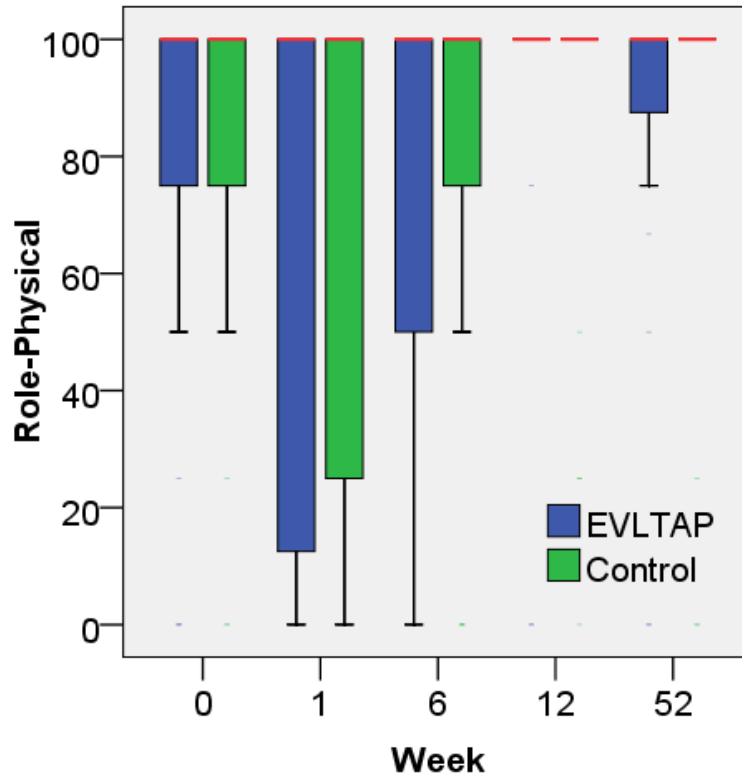
Figure 26: *SF-36 Role Limitation due to Physical Disability, over time, by group (Study 1)*
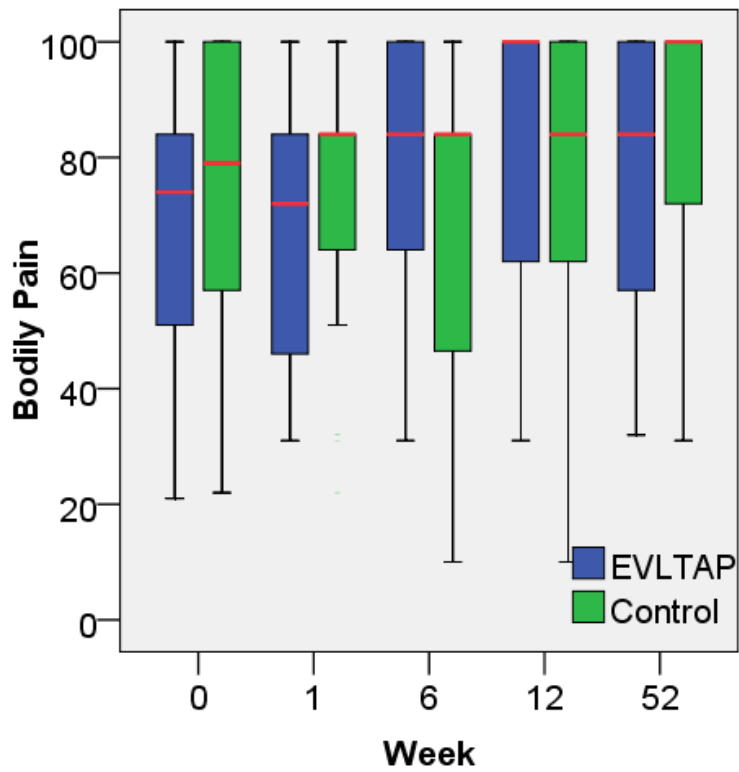
Figure 27: *SF-36 Bodily Pain, over time, by group (Study 1)*
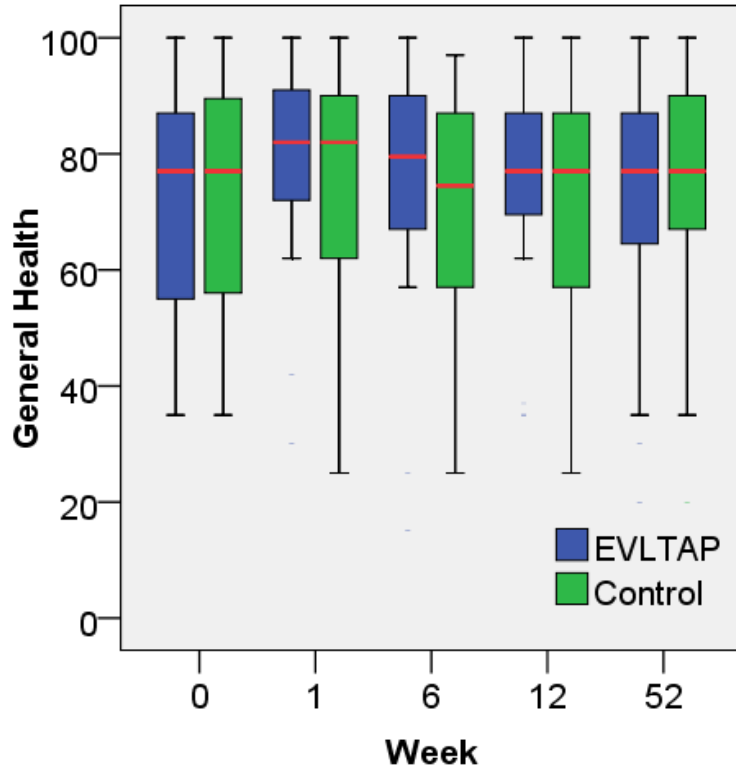
Figure 28: *SF-36 General Health, over time, by group (Study 1)*
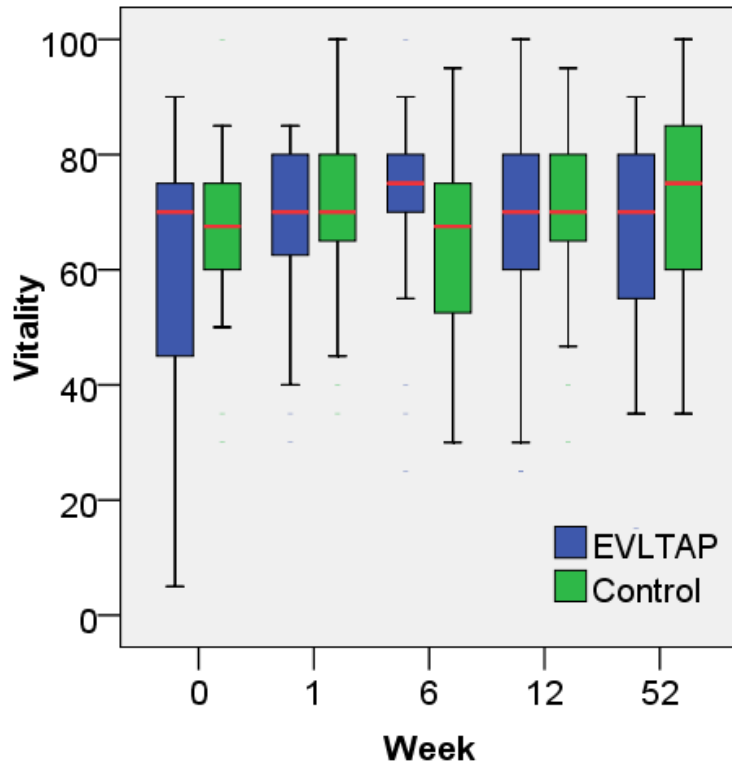
Figure 29: *SF-36 Vitality, over time, by group (Study 1)*
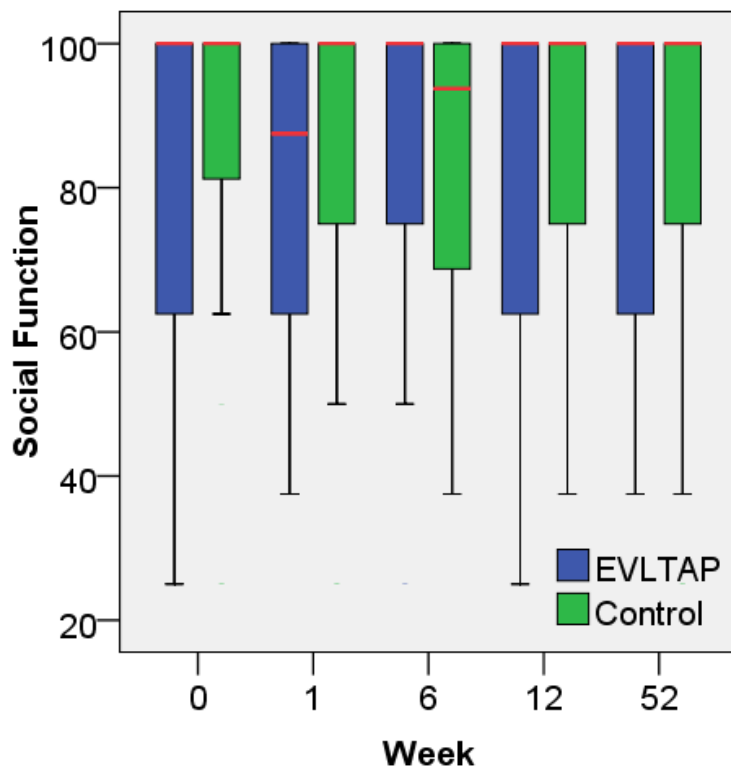
Figure 30: *SF-36 Social Function, over time, by group (Study 1)*
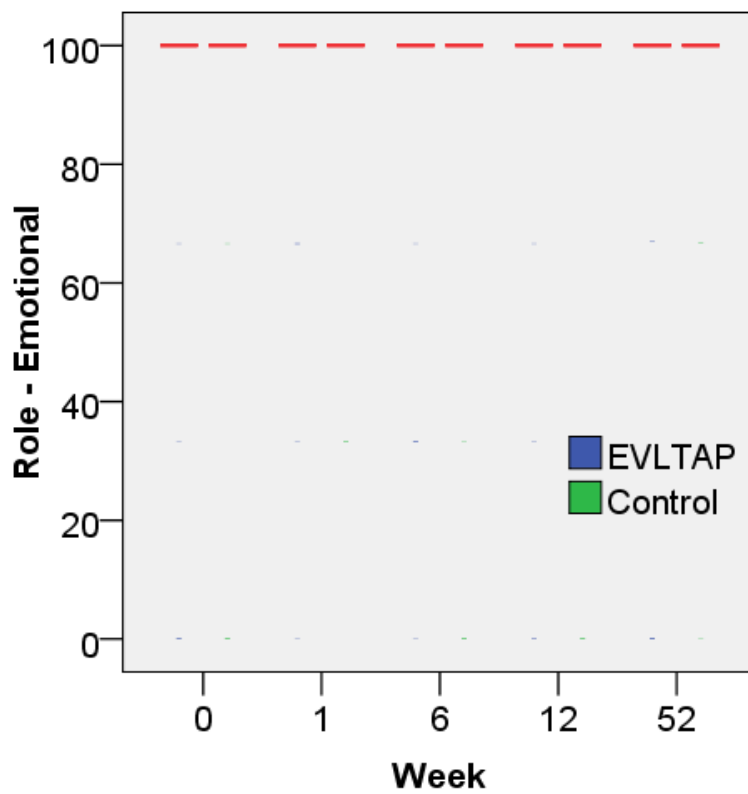
Figure 31: *SF-36 Role Limitation due to Emotional Problems, over time, by group (Study 1)*

195
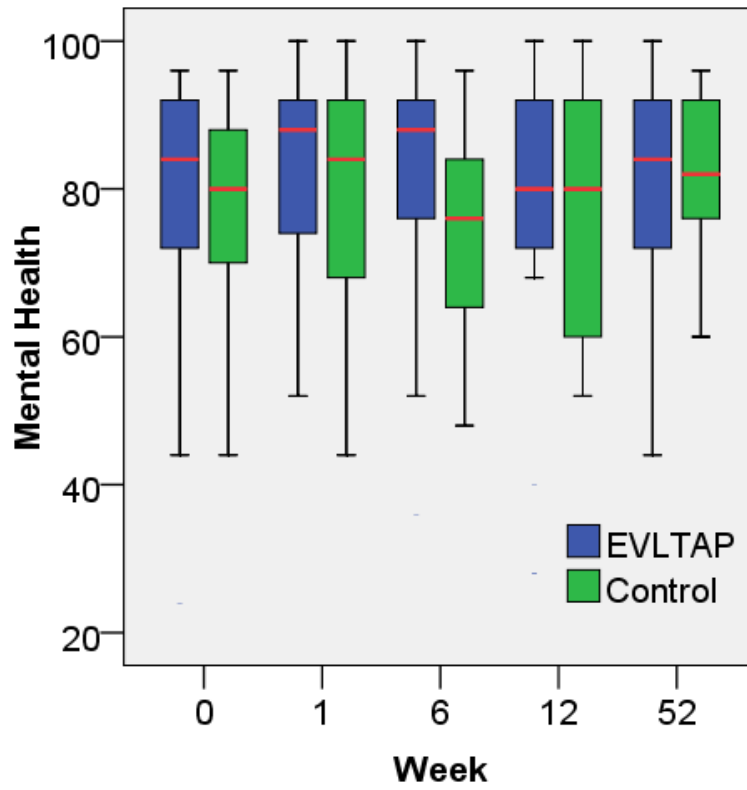
**Figure 32:** *SF-36 Mental Health, over time, by group (Study 1)*
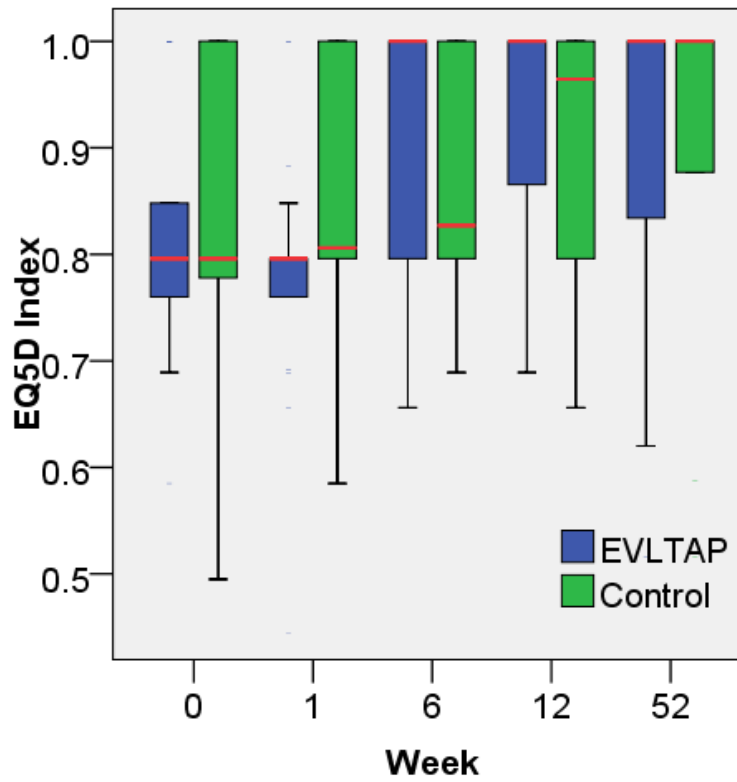
Figure 33: *Euroqol Utility Index Scores, over time, by group (Study 1)*

3.4 Patient Satisfaction

100% (20/20) of EVLTAP patients and 90% (19/21) of Control patients stated that they would have EVLA again if necessary or recommend it to a friend at 1 year (P=0.342 - FET).

Study 2; Technique evaluation – A randomised clinical trial of endovenous laser ablation versus conventional surgery in the treatment of venous insufficiency

3.5 Patient Recruitment and Baseline Analysis

Figure 34 outlines the recruitment and the number of patients involved in analysis at each stage.

Some 280 patients were randomised, as planned; with attention to the inclusion and exclusion criteria specified in the protocol. All but one patient randomised to EVLA received the allocated treatment as per protocol. This single patient decided that they did not wish to undergo any treatment for their venous disease at this time and withdrew from the trial. Three of the patients randomised to surgery withdrew from the trial. They stated that after consideration; they were no longer in a position of equipoise and would prefer endovenous ablative treatment instead, hence withdrawing from the study. These four patients declined to continue to participate in follow-up and so were excluded from analysis beyond

baseline. There was no difference between the groups in terms of the numbers lost or the length of successful follow-up (Log rank p=0.081). Considering the patients who progressed to treatment within the trial, there were no protocol violations.
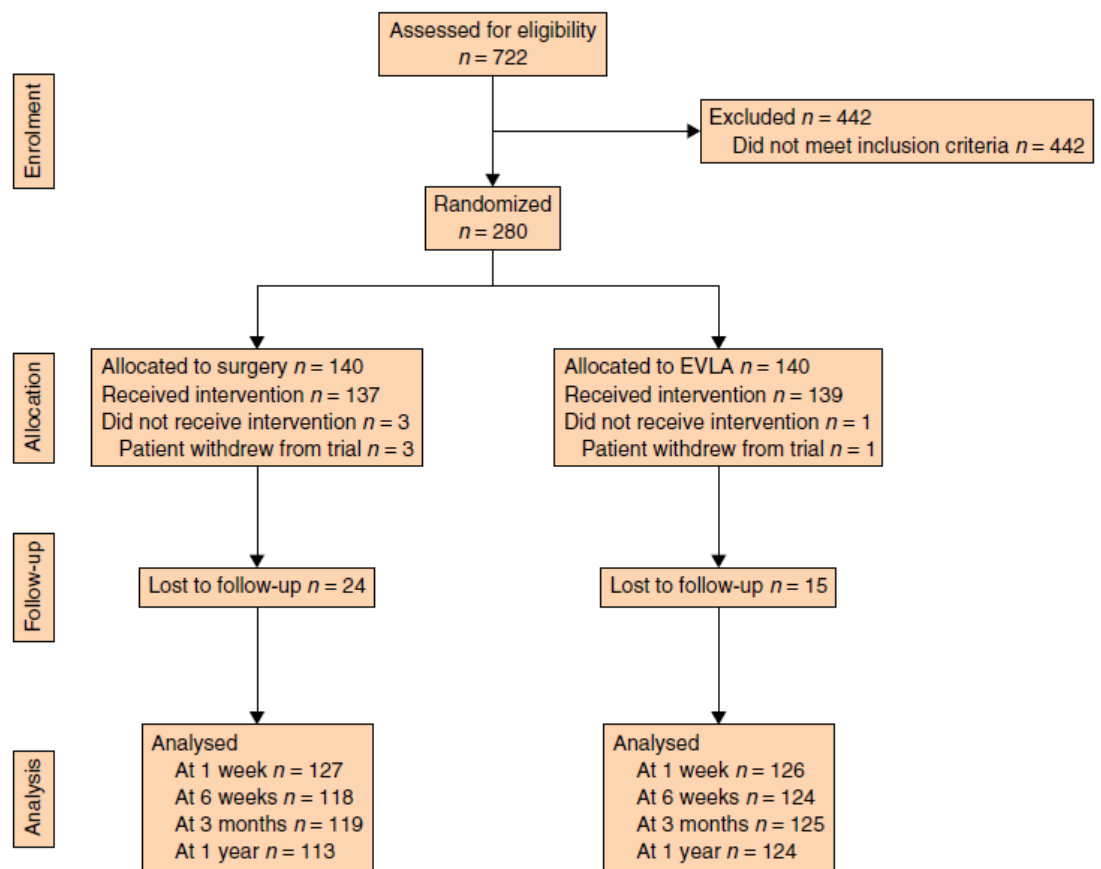
Figure 34: *CONSORT diagram showing flow of patients through the trial (Study 2).* **EVLA - endovenous laser ablation; Surgery – conventional SFJ ligation and GSV stripping**

The two groups were analysed in terms of age, gender, laterality, smoking status, employment status, antiplatelet/anticoagulant usage, height, BMI, baseline vein

diameter, baseline CEAP clinical grade, baseline VCSS and QoL (*Table 18*). No continuous variable was found to be normally distributed for both groups and therefore non-parametric hypothesis testing was performed to ascertain the significance of any observed differences. There was a statistically significant difference in Mental Health, but this is not of a sufficient magnitude to be regarded as a clinically significant difference[51,388,389]. Therefore no significant differences were observed; as is to be expected from this randomised data.

These patients are typical of those presenting with venous disease in this region. Mean age is around 50 years with just over 60% women. 65% are in employment and 50% have a positive smoking history. Approximately 28% are Ex-smokers and 25% are active smokers, compared with a national average of 25% and 22% respectively[390]. The mean height and BMI are comparable to the national average[390]. Around 70% of patients have uncomplicated superficial venous insufficiency, which is causing a significant impairment in QoL, as evidenced by the AVVQ scores. This is typical of such a group and is comparable to that observed in Study 1.

		Surgery	EVLA	P-Value
Age (yrs)		49 (37-58)	51 (39-58)	0.601
Female Gender		65.7%	61.2%	0.433[†]
Left leg		54.0%	52.5%	0.803[†]
Smoking Status	Ex-Smoker	28.5%	26.5%	0.805[†]
	Current Smoker	23.1%	26.5%	
Employed		62.0%	66.9%	0.399[†]
Antiplatelet / Anticoagulant use		8.8%	6.5%	0.474[†]
Height (m)		1.7 (1.6-1.8)	1.7 (1.6-1.8)	0.274
Body Mass Index (kgm^{-2})		25.9 (23.1-28.9)	25.3 (23.1-29.1)	0.583
Diameter GSV (mm):	Groin	7.5 (6.5-9.6)	8.3 (6.9-10.0)	0.101
	Knee	6.4 (5.4-7.5)	6.3 (5.4-7.7)	0.841
Venous Clinical Severity Score		4 (3-5)	4 (3-5)	0.919
CEAP Clinical Grade	C2	70.1%	68.8%	0.824[†]
	C3-C6	29.9%	31.2%	
Aberdeen Varicose Vein Questionnaire		13.7 (9.9-18.2)	12.6 (9.6-17.2)	0.177
SF-36 Domains	Physical Function	90 (80-100)	90 (75-100)	0.644
	Role-Physical	100 (75-100)	100 (50-100)	0.170
	Bodily Pain	74 (52-100)	74 (52-100)	0.609
	General Health	77 (67-87)	77 (62-92)	0.377
	Vitality	70 (53-80)	70 (55-80)	0.616
	Social Function	100 (75-100)	100 (75-100)	0.242
	Role-Emotional	100	100	0.553
	Mental Health	80 (68-90)	84 (68-92)	0.027
Euroqol Health Index Score		0.841 (0.796-1.000)	0.848 (0.796-1.000)	0.954
SF6D Health Index Score		0.795 (0.717-0.847)	0.804 (0.744-0.856)	0.172

Table 18: *Baseline comparison of the groups (Study 2).* SF-36 – UK Short Form-36 V1, Role-Physical – Role limitation due to physical disability, Role- Emotional – Role limitation due to emotional problems, SF6D – Single index utility score derived from SF-36. Figures are quoted as median (inter-quartile range) and the P values are derived from the MWU test unless otherwise stated: [†] - χ^2 test

3.6 Clinical Outcomes

Peri-procedural Outcomes

Procedural details: In the surgical group the mean (SD) strip length was 33 (11) cm. In the EVLA group the mean (SD) energy density was 95 (15) Jcm^{-1}. EVLA had a marginally longer procedural duration than surgery (mean (SD): 67 (16) versus 61 (14) minutes – P=0.002 t test).

Procedural setting: Whilst all EVLA procedures were performed under outpatient conditions, unsuitability for day-case general anaesthetic surgery necessitated in-patient treatment in a proportion of the surgical group and 21% required an overnight in-patient stay (P<0.001 χ^2).

Technical Success: Clinical assessment and DUS data was collected within 6 weeks of intervention for 96.3% (132/137) of patients post Surgery and 98.6% (137/139) post EVLA. Initial technical success was significantly higher following EVLA 99.3% (136/137) versus 92.4% (122/132) (P=0.005 χ^2). The RR of success with EVLA compared to Surgery was 1.07 (1.02-1.07), giving a RD of 0.07 (0.02-0.12). The NNT with EVLA rather than Surgery to avoid one failure to complete the planned procedure was 14.3 (8.3-50.0).

The most common failure in the Surgery group was an inability to fully strip the incompetent GSV in the thigh due to the vein snapping (6/10). One of these

patients required subsequent EVLA to this remnant by 1 year. Two of the 10

Surgery failures were attributable to failed groin dissection secondary to

significant scarring in patients reporting previous intravenous narcotic use. One of

these patients underwent subsequent EVLA. Finally two patients had a single

residual groin tributary emanating from the posterior aspect of the common

femoral vein, this would be difficult to address with a standard surgical approach

and of doubtful significance: none of these patients required further treatment.

The technical failure seen in the EVLA group resulted from an inability to cannulate

the GSV due to spasm. This patient was happy with the results of their

phlebectomy alone and has had no further treatment to date.

Pain scores: EVLA patients reported less post procedural pain than those

following Surgery. This was evident from day 1 and maintained until at least day 6

(P=0.004 - P<0.001 MWU, *Table 19*, *Figure 35*).

Day	Surgery	EVLA	P-Value
0	2.7 (0.9-5.9)	2.0 (0.1-4.9)	0.097
1	2.2 (0.6-5.0)	1.1 (0.0-3.0)	0.004
2	1.7 (0.3-4.0)	0.6 (0.0-2.3)	<0.001
3	1.3 (0.2-3.2)	0.2 (0.0-1.5)	<0.001
4	1.4 (0.0-2.8)	0.3 (0.0-1.4)	0.001
5	1.0 (0.0-2.6)	0.2 (0.0-1.6)	0.001
6	0.9 (0.0-2.4)	0.0 (0.0-1.0)	<0.001

Table 19: *Post-procedural pain scores (Study 2).* **Values indicate the med (IQR) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). The P-values are derived from the MWU test**
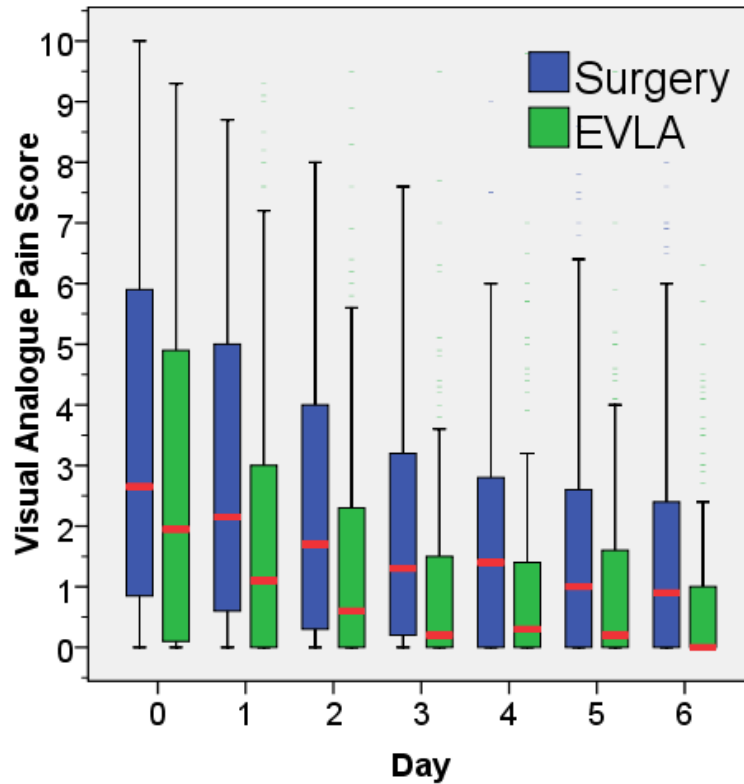
Figure 35: *Post-procedural pain scores from the day of the procedure (day 0) until day 6 (Study 2). The visual analogue scale runs from 0 ("no pain at all") to 10 ("worst imaginable pain")*

Analgesia requirement: As expected from the pain scores; the Surgical group had higher analgesia requirements than the EVLA group over the first week post-procedure, again evident from day 1 until at least day 6 (P=0.012-P=0.001 − χ^2, *Table 20, Figure 36*).

Day	Surgery	EVLA	P-Value
0	68.0%	68.7%	0.904
1	61.1%	45.4%	0.012
2	49.2%	33.1%	0.009
3	41.8%	26.6%	0.011
4	40.2%	23.4%	0.004
5	37.7%	21.3%	0.004
6	35.0%	17.2%	0.001

Table 20: *The percentage of patients requiring supplementary analgesia to control their pain over the first post-procedural week*, **by group** *(Study 2)*. **Significance testing is with** χ^2
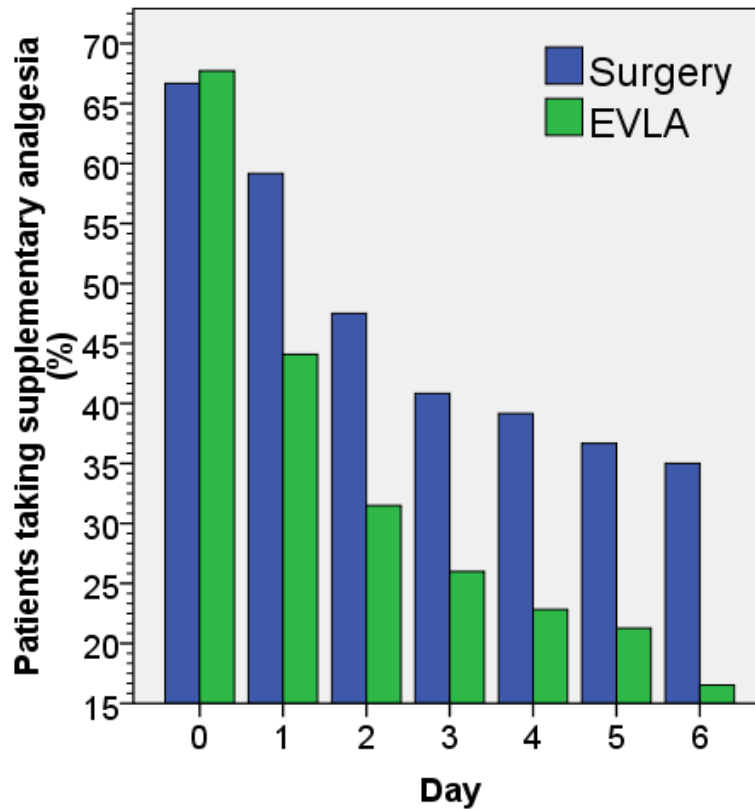
Figure 36: The proportion of patients requiring supplementary analgesia to control their pain in the first post-procedural week *(Study 2)*

Complications: Complications were relatively rare in both groups. However the rates of sensory disturbance, haematoma and infection rates were significantly higher in the Surgical group than the EVLA group (*Table 21*).

	Surgery	EVLA	P-Value
Sensory Disturbance	9.8%	2.9%	0.020
Haematoma	8.3%	0.7%	0.003
Infection	6.0%	1.5%	0.048
Phlebitis	4.5%	2.9%	0.536
Persistent Pain	3.8%	0.7%	0.116
Pigmentation	0.8%	2.9%	0.371
GA complications	2.3%	0.0%	0.118
Persistent Bruising	1.5%	0.7%	0.618
Allergy	0.8%	0.0%	0.493
Thromboembolism	0.0%	0.0%	N/A

Table 21: *Complications following Treatment (Study 2).* Significance testing is with χ^2.

Recovery: The Surgical group also took longer to return to normal activities than the EVLA group; 14 (7-25) versus 3 (1-10) days (P<0.001 MWU). The same pattern was seen in the time taken for employed individuals to return to work 14 (13-28) versus 4 (2-14) days (P<0.001 MWU, *Figure 37*).
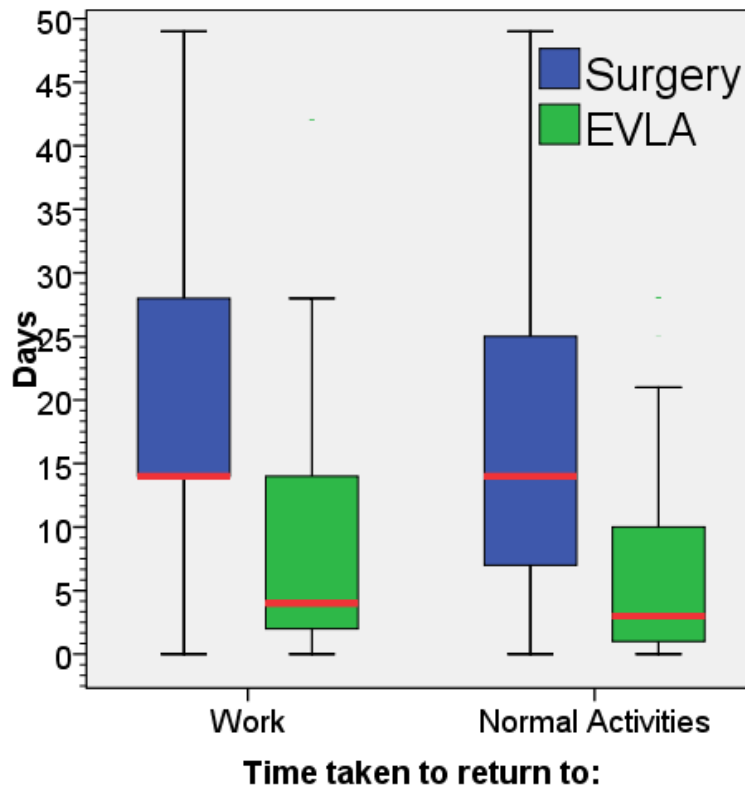
Figure 37: *Time taken to return to work and normal activities post procedure (Study 2)*

Late Outcomes

Objective clinical assessment of venous disease*: Both groups saw the same significant decrease (improvement) in VCSS scores over the study period from med (IQR) 4 (3-5) to 1 (0-1) by 3 months (P<0.001 MWU, *Figure 38*). This was maintained up to 1 year. There was no difference between either group at any time point.
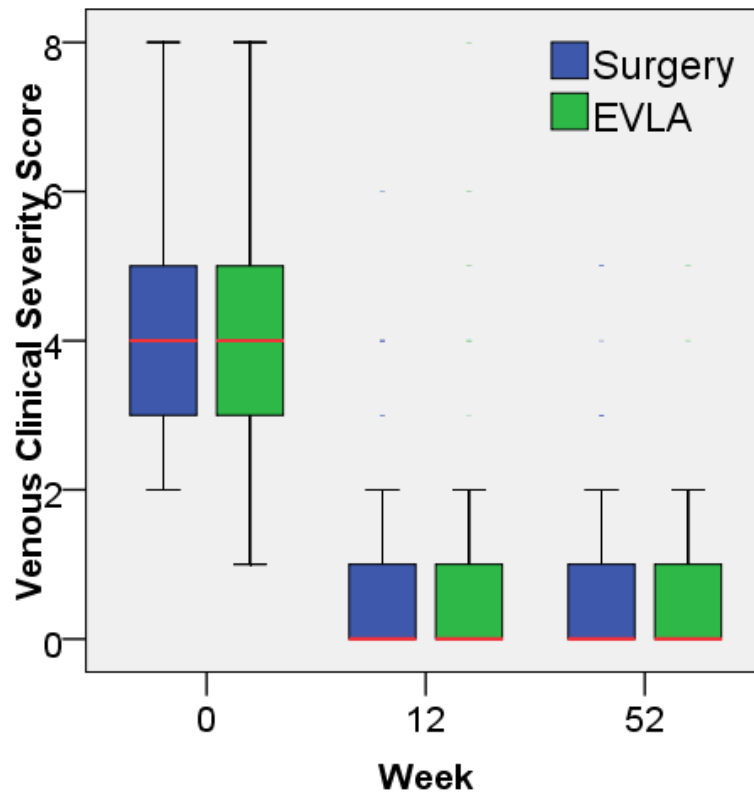
Figure 38: *Clinical Severity of Venous Disease, using the Venous Clinical severity score, over time, by group (Study 2)*

Clinical Recurrence: Clinical recurrence by 1 year was significantly more common in the Surgery group than the EVLA group: 20.4% (23/113) versus 4.0% (5/124) (P<0.001 χ^2, *Table 22*). The NNT with EVLA to avoid one clinical recurrence post Surgery was approximately 6. This analysis is based upon those successfully followed up and undergoing DUS at 1 year. A sensitivity analysis was performed based upon different assumptions regarding the outcomes of those not followed up. With the exception of the assumption that all EVLA patients lost to follow-up underwent clinical recurrence and none of those lost following Surgery did;

recurrence remained significantly higher following Surgery, resulting in an estimated NNT of approximately between 3 and 8.

Group	Proportion of patients with recurrence (%)	P value	RR (95%CI)	RD (95%CI)	NNT (95% CI)
Surgery EVLA	23/113 (20.4) 5/124 (4.0)	<0.001	0.20 (0.08-0.50)	0.16 (0.08-0.25)	6.3 (4.0-12.5)
Assume no lost patients have recurred			0.21 (0.08-0.55)	0.13 (0.06-0.20)	7.7 (5.0-16.7)
Assume all lost patients have recurred			0.42 (0.26-0.67)	0.20 (0.10-0.30)	5.0 (3.3-10.0)
Assume all EVLA lost have recurred but no Surgery lost recurred			0.86 (0.49-1.49)	0.02 (-0.06-0.11)	N/A
Assume all Surgery Lost have recurred but no EVLA lost recurred			0.10 (0.04-0.26)	0.31 (0.22-0.39)	3.2 (2.6-4.5)

Table 22: *The proportion of patients by group with clinical recurrence at 1 year (Study 2).* **The top row represents the actual data collected. The bottom half of the table contains a sensitivity analysis testing the effect of differing extreme assumptions regarding those lost to follow up upon clinical recurrence. The P value relates to the null hypothesis test that there is no significant difference between the groups and is derived using χ^2. RR is relative risk of clinical recurrence following endovenous laser (EVLA) compared to Surgery, RD is risk difference and NNT is the number needed to treat with EVLA to avoid 1 case of clinical recurrence at 1 year following Surgery**

Patterns of recurrence: Up to 1 year, patients regarded as initial technical failures in either group have not been shown to suffer a significantly higher incidence of clinical recurrence than the technical successes (P=0.427 - P=1.000 χ^2); however

technical failure was rare in this study and the power to detect this difference is consequently low (*Table 23*).

Following Surgery, clinical recurrence was most commonly seen in association with an incompetent below knee GSV, followed by recurrence from the groin and new incompetent perforators. Of those with recurrence secondary to an incompetent below knee GSV, 83% (10/12) of these incompetent segments were amenable to EVLA preoperatively and 75% (9/12) were amenable at the time of recurrence; as judged by an experienced endovenous surgeon (in one case the vein became too tortuous to treat with an endothermal ablative technique during follow-up).

Recurrence emanating from the groin following successful Surgery was related to neovascularisation leading to neoreflux (reflux not evident pre or immediately post procedure) in the superficial veins of the thigh, most commonly the ASV. In many cases these incompetent veins were seen to lead back into the perigenicular GSV. Evidence of neovascularisation in the groin was noted from as early as 3 months following Surgery and seen in 15% (17/113) of cases by 1 year. 53% (9/17) of patients with neovascularisation on DUS at 1 year were yet to show evidence of clinical recurrence at this time.

The most common feature associated with clinical recurrence following EVLA was from disease progression at the groin; this was mainly in the form of neoreflux in the ASV. This pattern appears similar to that associated with groin recurrence following Surgery, although no patients demonstrated convincing evidence of

neovascularisation.   Three patients showed some evidence of partial recanalisation of the treated GSV. They had received an energy density of 85, 87 and 112 Jcm^{-1}. This was compared to the overall mean (SD) of 95 (15) Jcm^{-1}. Two of these cases were yet to result in clinical recurrence by 1 year.

There was no convincing evidence of cross groin or supra-inguinal incompetence contributing to any of the observed cases of clinical recurrence.

Group	Source of recurrence on DUS	Proportion of recurrent cases (%)
Surgery	Below knee GSV	12/23 (52.2)
	Groin	10/23 (43.5)
	Perforator	9/23 (39.1)
	Saphenopopliteal junction	3/23 (13.0)
	Non-axial branches alone	3/23 (13.0)
EVLA	Groin	2/5 (40.0)
	Below knee GSV	1/5 (20.0)
	Saphenopopliteal junction	1/5 (20.0)
	Recanalisation	1/5 (20.0)
	Non-axial branches alone	1/5 (20.0)

Table 23: The association of patterns of reflux on DUS with clinical recurrence *(Study 2)*. Some of these patterns (other than "Non-axial branches alone") coexisted, leading to the total incidence of all patterns being higher than the actual number of recurrent cases seen

Secondary procedures: There was no difference between EVLA and Surgery in terms of the number, timing or type of additional procedures performed by 1 year (P=0.357 – P=0.901 LR, χ^2). 18 patients in total had additional procedures. 12 had additional procedures for residual disease or technical failure in the absence of recurrence. A greater proportion of patients with clinical recurrence at 1 year underwent additional procedures than those without 21.4% (6/28) versus 5.7% (12/209, p=0.011 χ^2).

Ten Surgery and seven EVLA patients underwent additional phlebectomy with or without additional perforator ligation under local anaesthetic. Two Surgery patients underwent GSV EVLA. One Surgery patient underwent treatment for saphenopopliteal insufficiency.

Late Complications: No further complications were observed in either group up to 1 year follow-up.

3.7 Quality of Life Outcomes

Generic Quality of Life

SF-36 profile intragroup analysis

At 1 week, the Surgical group demonstrated significant deterioration in five of the eight SF-36 domains: Physical Function (P<0.001 WSR), Role-Physical (P<0.001 WSR), Bodily Pain (P<0.001 WSR), Social Function (P=0.001 WSR) and Role-

Emotional (P=0.029 WSR). EVLA demonstrated significant deterioration in only two of the eight SF-36 domains: Physical Function (P=0.018 WSR) and Role-Physical (P<0.001 WSR), with preservation of pre-operative scores in the domains of Bodily Pain, Social Function and Role-Emotional when compared with Surgery (See *Table 24, Figure 39 - Figure 46*).

After this initial deterioration, both treatments resulted in significant overall improvements in five of the eight domains: Surgery: Physical Function (P<0.001 F-A), Role-Physical (P=0.040 F-A), Bodily Pain (P<0.001 F-A), General Health (P=0.001 F-A) and Vitality (P=0.003 F-A). EVLA: Physical Function (P<0.001 F-A), Role-Physical (P=0.001 F-A), Bodily Pain (P<0.001 F-A), General Health (P=0.030 F-A) and Vitality (P<0.001 F-A).

SF-36 profile intergroup analysis

The relative preservation of QoL seen in the EVLA group at 1 week resulted in significantly higher (better) scores in six of the eight domains than those observed in the Surgical group: Physical Function (P=0.012 MWU), Role-Physical (P=0.005 MWU), Bodily Pain (P=0.031 MWU), Vitality (P=0.049 MWU), Social Function (P=0.004 MWU) and Role-Emotional (P=0.027 MWU). From 6 weeks onwards there were no differences between the groups (See *Table 24, Figure 39 - Figure 46*).
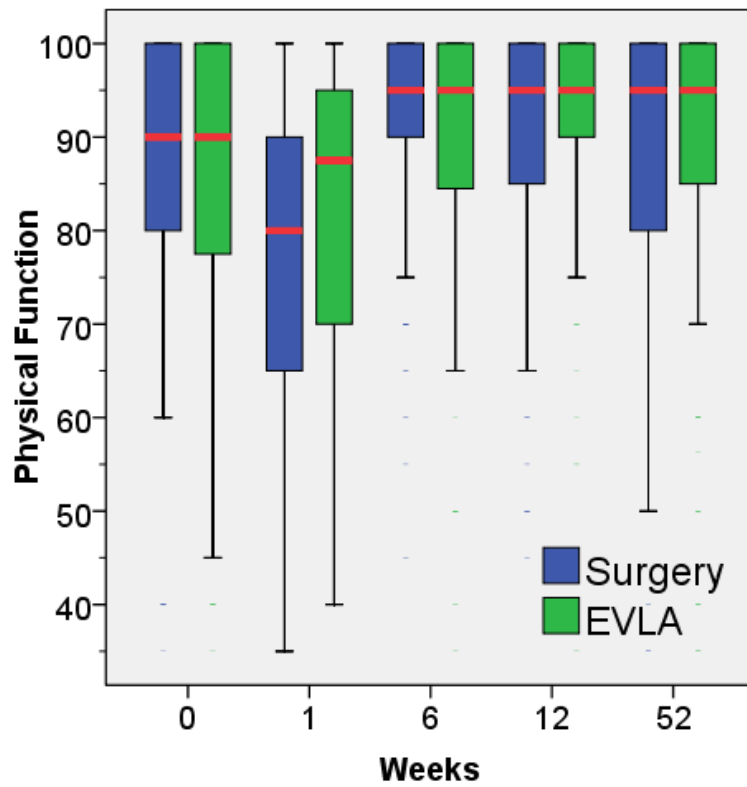
Figure 39: *SF-36 Physical Function, over time, by group (Study 2)*
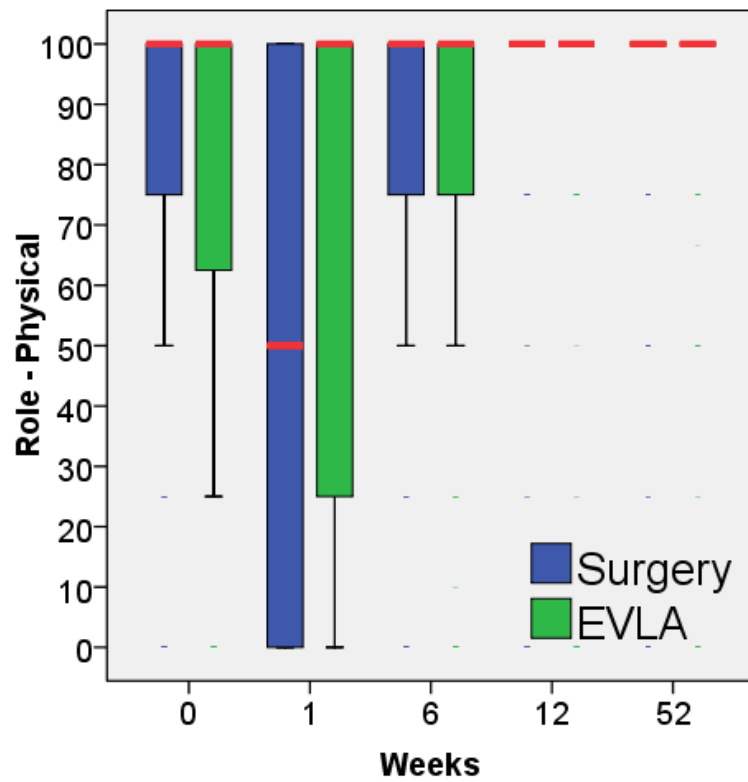
Figure 40: *SF-36 Role Limitation due to Physical Disability, over time, by group (Study 2)*

213
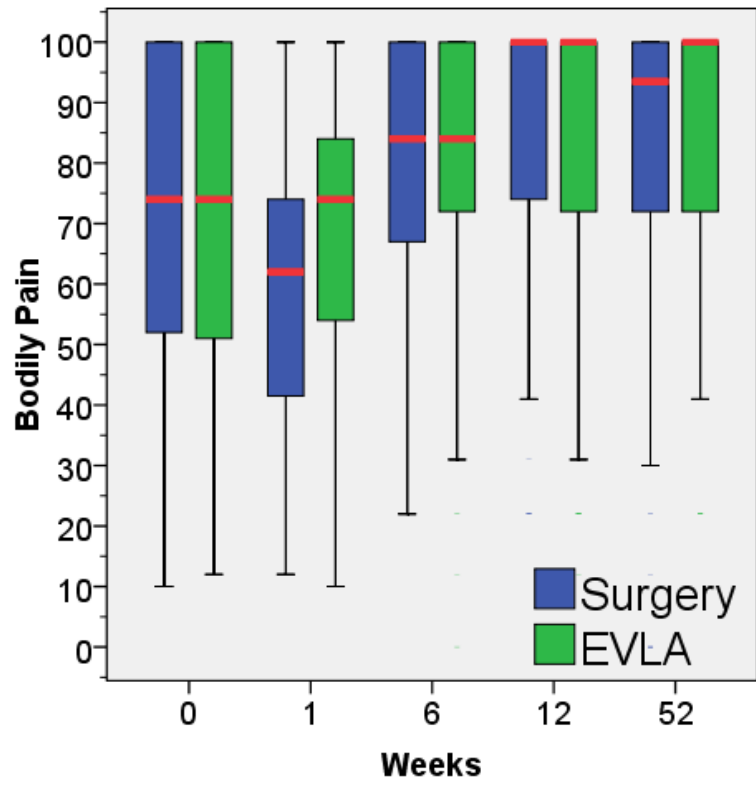
Figure 41: *SF-36 Bodily Pain, over time, by group (Study 2)*
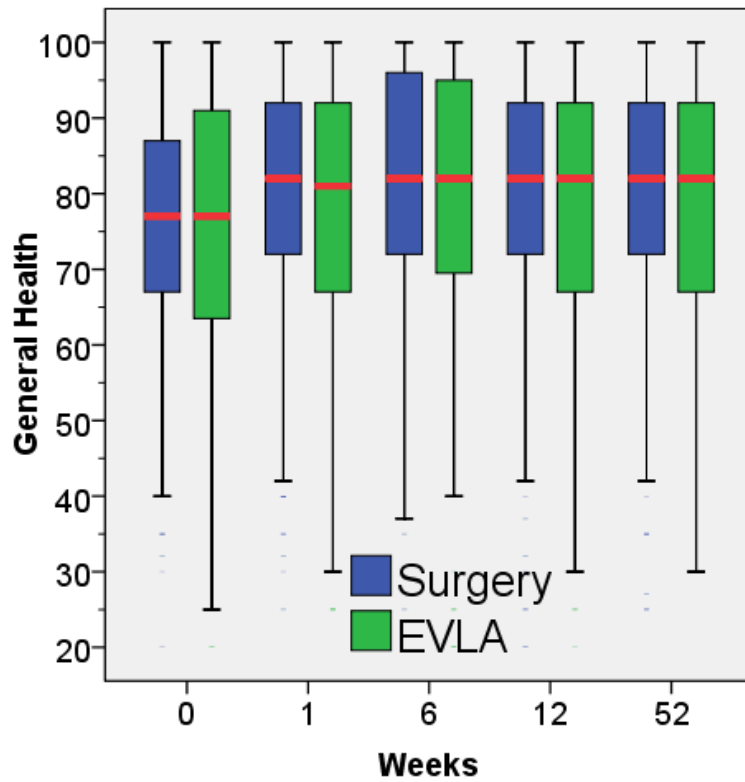
Figure 42: *SF-36 General Health, over time, by group (Study 2)*
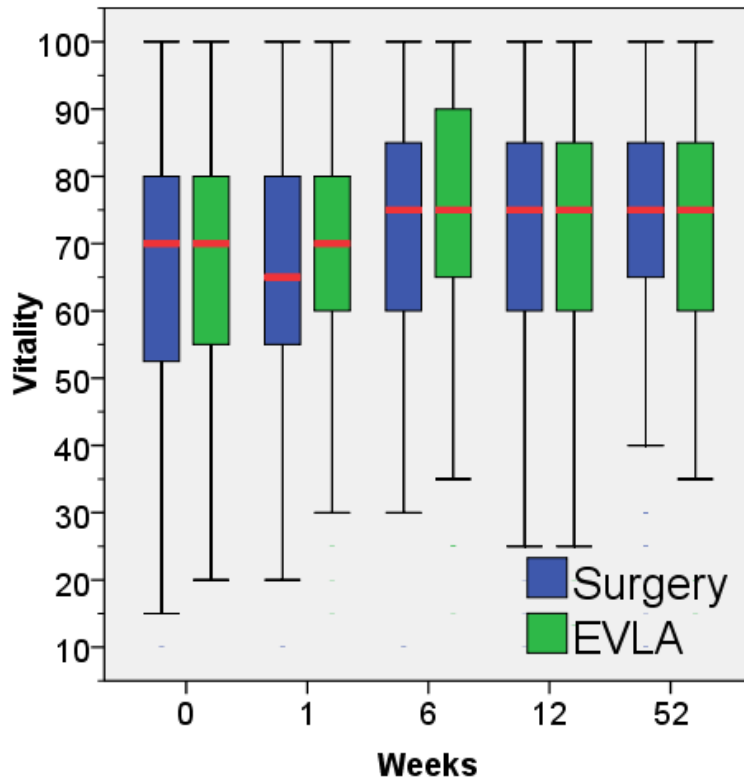
Figure 43: *SF-36 Vitality, over time, by group (Study 2)*
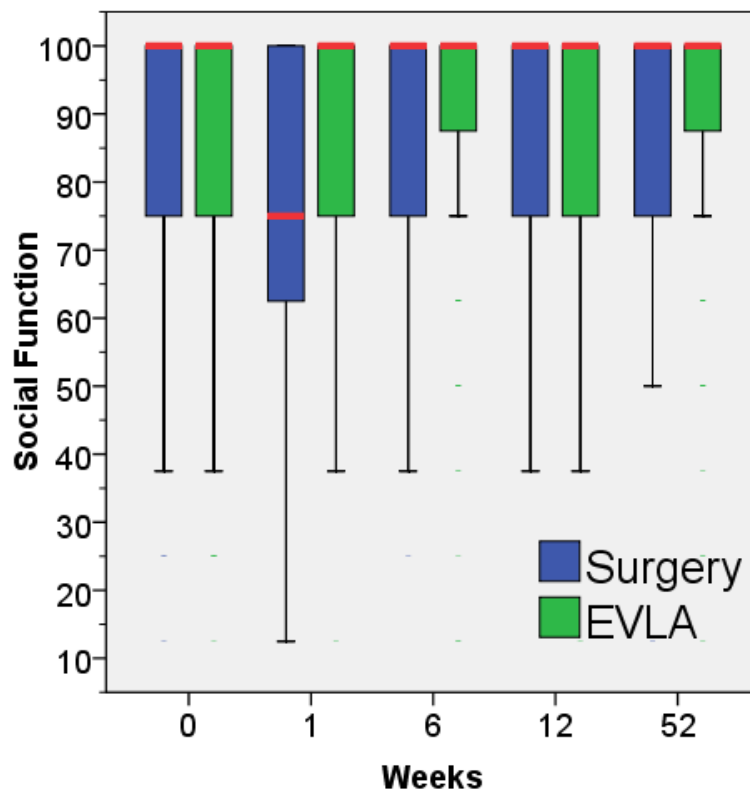
Figure 44: *SF-36 Social Function, over time, by group (Study 2)*
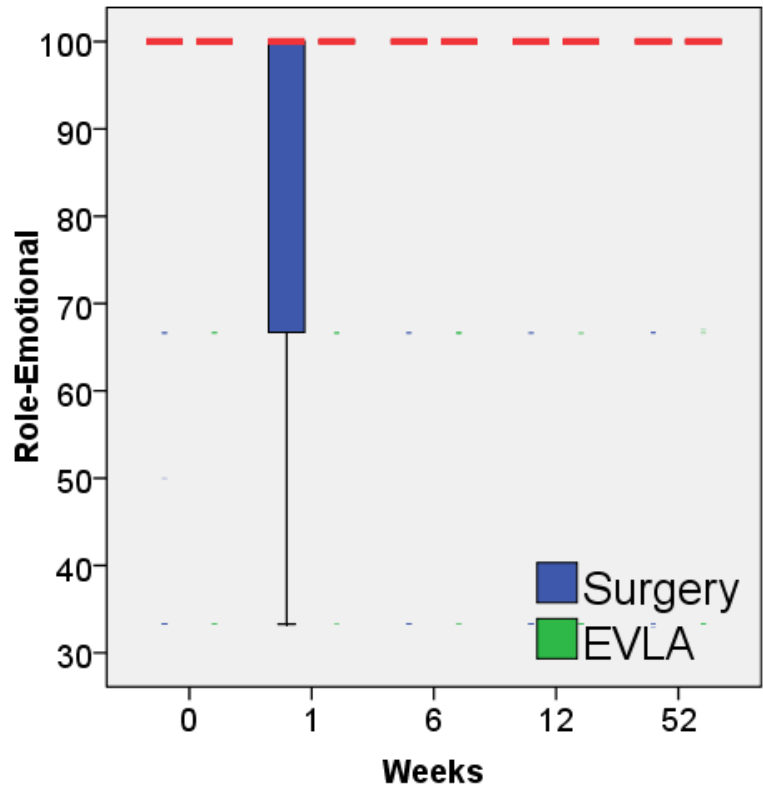
**Figure 45:** *SF-36 Role Limitation due to Emotional Problems, over time, by group (Study 2)*
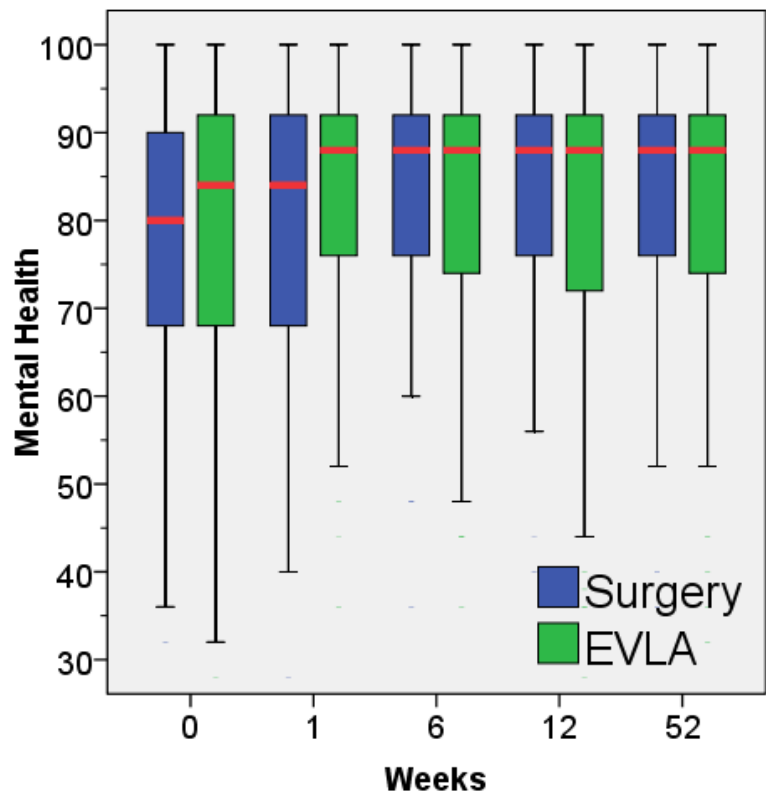
Figure 46: *SF-36 Mental Health, over time, by group (Study 2)*

		Week	Surgery	EVLA
SF-36 Domains	Physical Function	0	90 (80-100)	90 (75-100)
		1	80 (65-90)	88 (70-95)
		52	95 (80-100)	95 (85-100)
	Role-Physical	0	100 (75-100)	100 (50-100)
		1	50 (0-100)	100 (25-100)
		52	100	100
	Bodily Pain	0	74 (52-100)	74 (52-100)
		1	62 (41-74)	74 (54-84)
		52	94 (72-100)	100 (72-100)
	General Health	0	77 (67-87)	77 (62-92)
		1	82 (72-92)	81 (67-92)
		52	82 (72-92)	82 (67-92)
	Vitality	0	70 (53-80)	70 (55-80)
		1	65 (55-80)	70 (60-80)
		52	75 (65-85)	75 (60-85)
	Social Function	0	100 (75-100)	100 (75-100)
		1	75 (63-100)	100 (75-100)
		52	100 (75-100)	100 (88-100)
	Role-Emotional	0	100	100
		1	100 (67-100)	100
		52	100	100
	Mental Health	0	80 (68-90)	84 (68-92)
		1	84 (68-92)	88 (76-92)
		52	88 (76-92)	88 (74-92)
Aberdeen Varicose Veins Questionnaire		0	13.7 (9.9-18.2)	12.6 (9.6-17.2)
		1	16.5 (12.2-22.7)	16.6 (12.4-21.1)
		52	2.0 (0-5.3)	2.0 (0-5.3)
Euroqol Health Index Score		0	0.841 (0.796-1.000)	0.848 (0.796-1.000)
		1	0.801 (0.691-0.895)	0.796 (0.760-1.000)
		52	1.000 (0.841-1.000)	1.000 (0.877-1.000)
SF6D Health Index Score		0	0.795 (0.717-0.847)	0.804 (0.744-0.856)
		1	0.759 (0.672-0.830)	0.796 (0.735-0.838)
		52	0.835 (0.777-0.878)	0.843 (0.773-0.876)

Table 24: *Observed health related quality of life (Study 2).* SF-36 – UK Short Form-36 V1, Role-Physical – Role limitation due to physical disability, Role- Emotional – Role limitation due to emotional problems, SF6D – Single index utility score derived from SF-36. Figures are quoted as median (inter-quartile range)

EQ5D index scores

Both groups saw a significant decrease (worsening) of EQ5D scores at 1 week (Surgery P=0.003 WSR, EVLA P=0.024 WSR). Again following this there was an increase (improvement) in scores over the study period (P<0.001 F-A). There was no significant difference between the groups at any time (See *Table 24, Figure 47*).
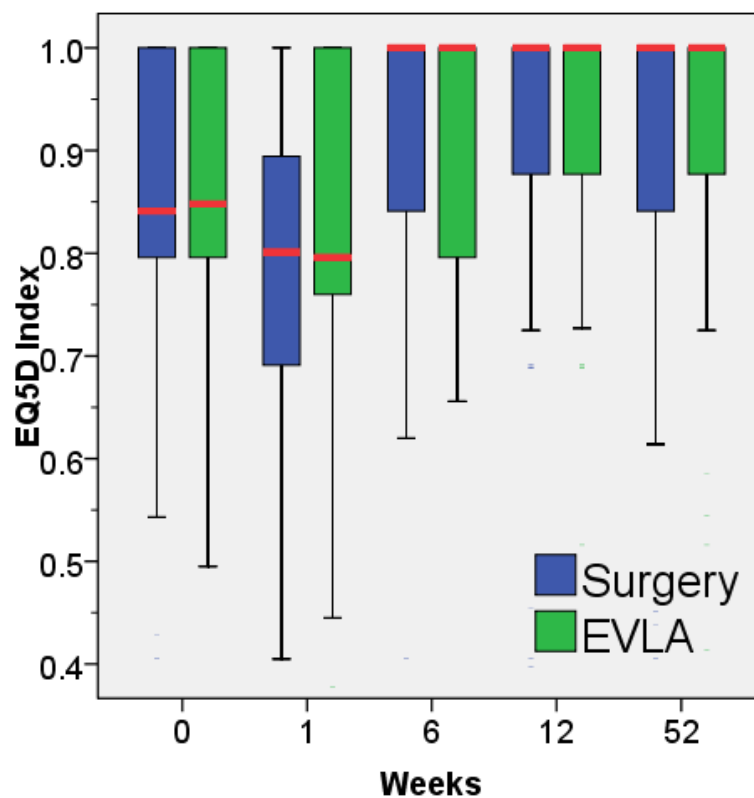
Figure 47: *Euroqol Utility Index Scores, over time, by group (Study 2)*

SF6D index scores

A different story was seen with SF6D scores, where deterioration was only evident in the Surgical group at 1 week (P<0.001 WSR); scores were preserved in the EVLA

group, with no difference from baseline (P=0.141 WSR). As with EQ5D both groups saw significant improvements overall (P<0.001 F-A). This lack of deterioration from pre-operative health status at 1 week in the EVLA group resulted in significantly higher (better) scores when compared to patients receiving Surgery (P=0.003 MWU) (See *Table 24, Figure 48*).
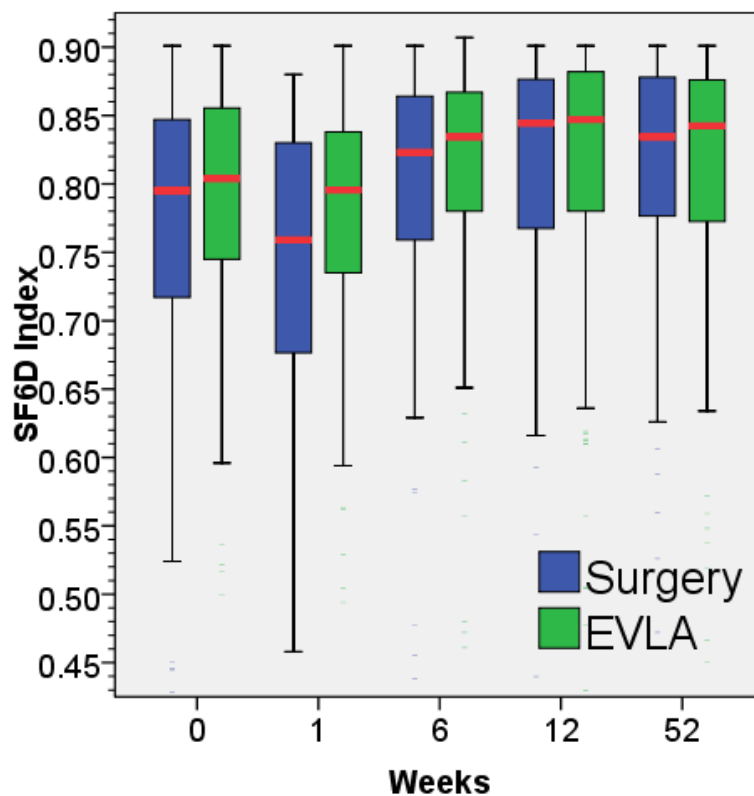
Figure 48: *SF6D Utility Index Scores, over time, by group (Study 2)*

Disease Specific Quality of Life

Both groups saw the same significant increase (worsening) in AVVQ scores at 1 week (P<0.001 WSR). This in turn was followed by a decrease (improvement) in AVVQ scores over the study period from baseline (P<0.001 F-A). There was no

significant difference in AVVQ scores between the groups at any time point (*Table 24, Figure 49*).

Patients with clinical recurrence at 1 year reported significantly higher (worse) AVVQ scores than those who did not - 4.6 (1.7-9.4) versus 2.0 (0.0-4.9) (P<0.001 MWU, *Figure 50*); demonstrating that although this recurrence is early and relatively minor at this stage, there is some early impact upon QoL.
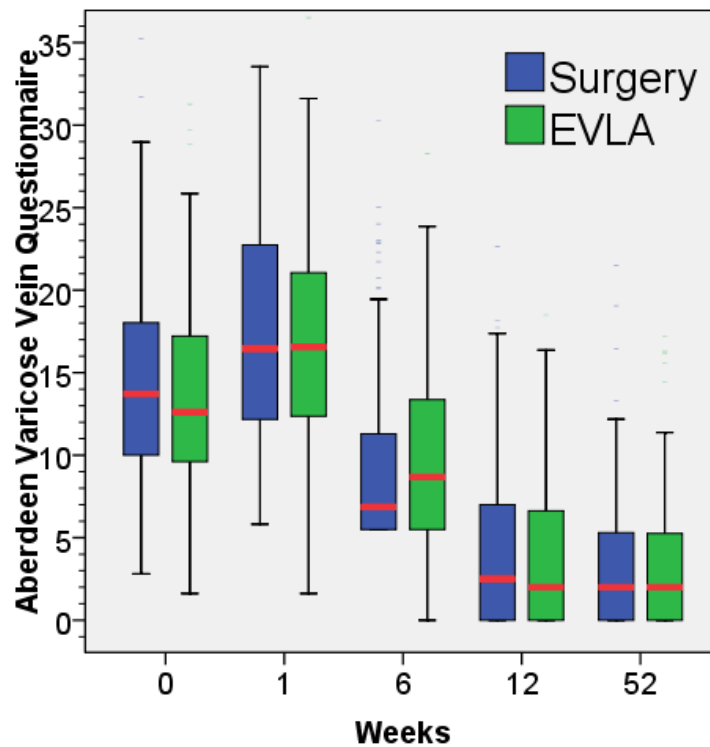
Figure 49: *Disease Specific Quality of Life Impairment using the Aberdeen Varicose Veins Questionnaire, over time, by group (Study 2)*
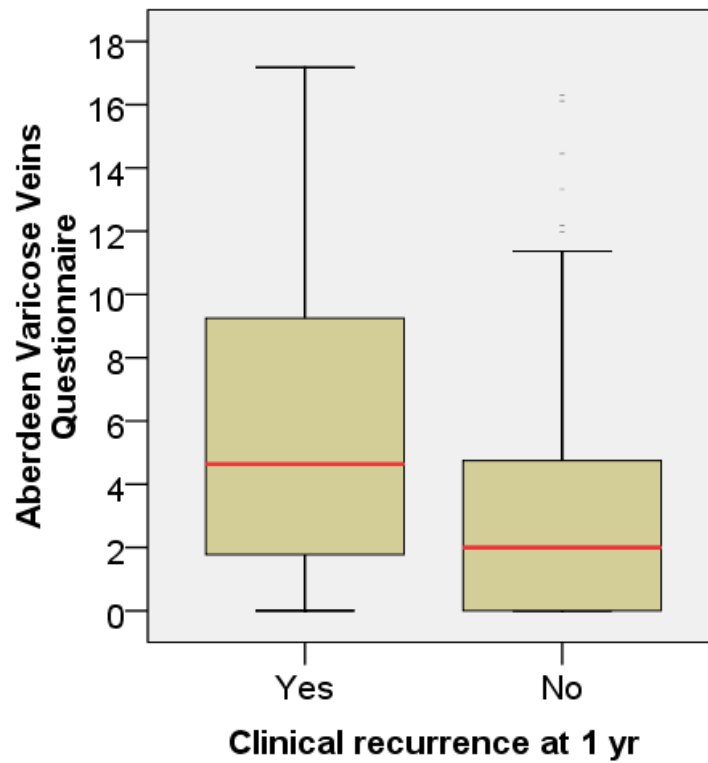
Figure 50: *Aberdeen Varicose veins Questionnaire results at 1 year for patients with and without clinical recurrence at 1 year (Study 2)*

All of the observed longitudinal and cross sectional changes in QoL instrument scores reaching statistical significance in this trial are independently accepted as being clinically significant and of a meaningful magnitude (unless otherwise stated)[49,51,388,389,391].

3.8 Patient Satisfaction

EVLA patients reported slightly higher satisfaction with the cosmetic outcome of the procedure at 1 year (P=0.034 MWU), however there was no significant difference in satisfaction with the overall treatment (*Figure 51*).

Patients with early evidence of clinical recurrence reported lower satisfaction in terms of cosmesis - 8.0 (7.0-9.7) versus 9.8 (9.0-10.0) (P<0.001 MWU) and overall satisfaction - 9.9 (8.2-10) versus 10 (9.5-10) (P=0.016 MWU, *Figure 52*).
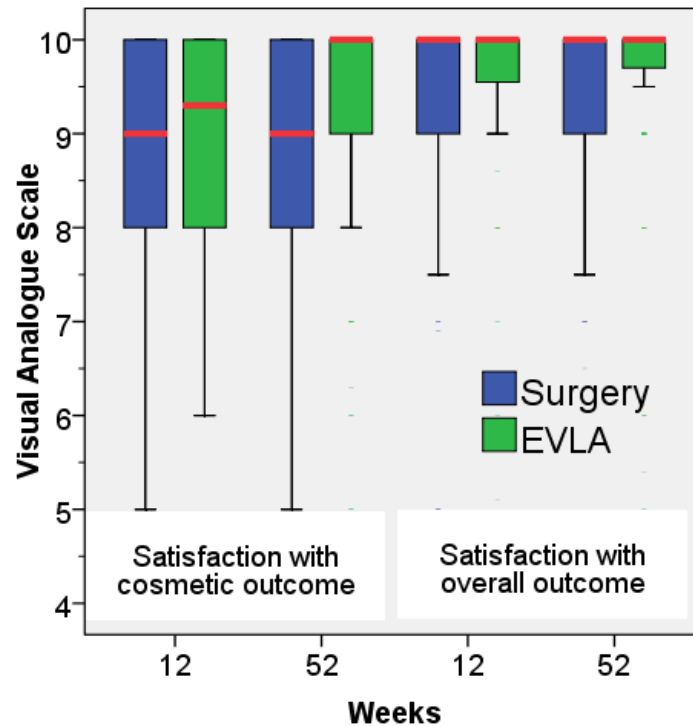
Figure 51: *Patient reported satisfaction with the cosmetic outcome and the overall treatment by treatment group (Study 2).* **Values indicate the reported on an unmarked visual analogue scale from 0 ("Completely unsatisfied") to 10 ("Completely satisfied")**
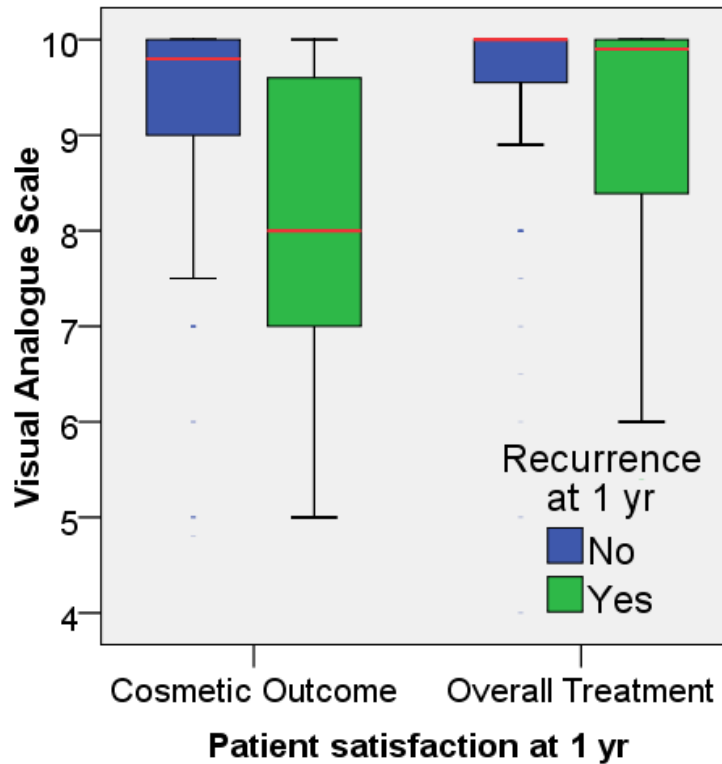
Figure 52: *Patient reported satisfaction with the cosmetic outcome and the overall treatment in those with and without clinical recurrence at 1 year (Study 2).* Values indicate the reported on an unmarked visual analogue scale from 0 ("Completely unsatisfied") to 10 ("Completely satisfied")

Study 3; Procedure refinement – Energy delivery during 810nm endovenous laser ablation of superficial venous insufficiency and post-procedural morbidity

3.9 Patient Recruitment and Baseline Analysis

Some 232 patients were included in this analysis with attention to the inclusion and exclusion criteria outlined for the study. The mean (range) age was 50 (18-83) years. 63% were women. The mean diameter for each treated vein was calculated by dividing the sum of the diameter 1cm distal to the junction and the diameter at the point of cannulation by 2. The mean (range) diameter of the vein

223

segments treated was therefore 7.4 (3.0-16.4) mm (assuming uniformity). There was no statistical difference between the energy given to men or women (P=0.404 t test) and therefore no further gender-specific analysis was performed. Baseline clinical severity scores and quality of life are shown in *Table 25*. No further analysis was performed of baseline data as its inclusion in the models themselves controls for any variation, precluding the necessity.

		Baseline	1 Week	6 Weeks
Venous Clinical Severity Score		4 (3-5)	N/A	N/A
Aberdeen Varicose Vein Questionnaire		12.9 (9.9-17.8)	16.8 (12.8-21.8)	8.1 (4.7-12.9)
Euroqol Health Index Score		0.796 (0.760-1.000)	0.796 (0.708-1.000)	1.000 (0.796-1.000)
SF-36 Domains	Physical Function	90 (75-100)	85 (70-95)	95 (80-100)
	Role- Physical	100 (50-100)	75 (0-100)	100 (75-100)
	Bodily Pain	74 (51-84)	74 (51-84)	84 (62-100)
	General Health	77 (60-90)	77 (67-92)	82 (67-92

Table 25: *Clinical and quality of life measures at baseline, 1 week and 6 weeks post-procedure (Study 3).* **SF-36 – UK Short Form-36 V1, Role-Physical – Role limitation due to physical disability. Figures are quoted as median (inter-quartile range)**

3.10 Clinical Outcomes

Energy delivery: The mean (range) energy delivery used was 89.8 (44.5-158.4) Jcm^{-1}.

Setting: All procedures were performed under local anaesthetic in an outpatient setting. No patients required sedation or an overnight stay.

Pain scores: There was no statistically significant relationship between the energy delivered and the magnitude of post-procedural pain reported by patients (*Table 26*).

Day	Pain Score	Effect size	Proportion of Variance (R^2)	P-Value
0	1.7 (0.3-4.9)	-0.16	2.7%	0.087
1	1.2 (0.0-3.0)	-0.15	2.2%	0.154
2	0.6 (0.0-2.1)	0.06	0.4%	0.570
3	0.2 (0.0-1.5)	0.05	0.3%	0.649
4	0.3 (0.0-1.3)	0.03	0.1%	0.821
5	0.2 (0.0-1.5)	0.07	0.5%	0.559
6	0.0 (0.0-1.0)	0.08	0.6%	0.562

Table 26: *Results of a linear regression model analysing the effect of linear energy delivery (Jcm^{-1}) on patient reported post-procedural pain scores (Study 3).* **Pain score values indicate the med (IQR) scores reported on an unmarked visual analogue scale from 0 ("no pain at all") to 10 ("worst imaginable pain"). The effects of age, gender, body mass index, vein dimensions and pre-procedural quality of life are controlled**

Analgesia requirement: There was no statistically significant relationship between the energy delivered and the requirement for supplementary analgesia during the first post-procedural week (*Table 27*).

Day	Percentage of Patients	Odds Ratio (95% CI)	P-Value
0	64.6	1.002 (0.995-1.031)	0.154
1	45.5	1.016 (0.998-1.033)	0.078
2	32.1	1.002 (0.984-1.021)	0.805
3	21.5	1.009 (0.986-1.032)	0.461
4	17.2	1.005 (0.981-1.030)	0.669
5	18.7	1.010 (0.987-1.034)	0.405
6	14.4	1.005 (0.979-1.032)	0.693

Table 27: *Results of a logistic regression model analysing the effect of linear energy delivery (Jcm^{-1}) on the proportion of patients requiring supplementary analgesia to control their pain (Study 3). The effects of age, gender, body mass index, vein dimensions and pre-procedural quality of life are controlled*

Recovery: Increasing energy delivery also had no demonstrable effect upon the number of days taken to return to work or to other activities (*Table 28*).

	Recovery Time in Days	Effect size	Proportion of Variance (R^2)	P-Value
Work	4 (1-11)	-0.18	3.4%	0.088
Normal activity	3 (1-14)	-0.11	1.2%	0.210

Table 28: *Results of a linear regression model analysing the effect of linear energy delivery (Jcm^{-1}) on the time taken by patients to return to work and return to normal activities (Study 3). Recovery time values indicate the med (IQR) number of days reported. The effects of age, gender, body mass index, vein dimensions and pre-procedural quality of life are controlled*

Complications: Complications were uncommon and therefore were insufficient to allow meaningful further detailed analysis (*Table 29*).

Sensory Disturbance	3.7%
Phlebitis	2.1%
Pigmentation	1.7%
Infection	1.2%
Haematoma	0.4%
DVT	0.0%

Table 29: *Percentage of patients with complications (Study 3)*

3.11 Health Related Quality of Life Outcomes

The QoL data at each time point is summarized in *Table 25*. Increasing energy delivery had no statistically significant effect upon generic QoL outcomes or disease specific AVVQ scores at 1 week (*Table 30*). At 6 weeks, there was a weak association between increasing energy delivery and higher (worse) AVVQ scores. This was of borderline statistical significance and accounted for only 3.1% of the variance at this time point. This brings into doubt the clinical significance of this finding.

		Week	Effect Size	Proportion of Variance (R^2)	P-Value
SF-36 Domains	Physical Function	1	0.06	0.4%	0.451
	Role-Physical		0.05	0.3%	0.536
	Bodily Pain		0.08	0.6%	0.344
	General Health		0.13	1.8%	0.111
	Physical Function	6	0.16	2.6%	0.072
	Role-Physical		0.16	2.6%	0.073
	Bodily Pain		0.13	1.6%	0.162
	General Health		0.12	1.4%	0.203
Aberdeen Varicose Vein Questionnaire		1	0.06	0.4%	0.464
		6	-0.18	3.1%	0.050
Euroqol Health Index Score		1	0.06	0.4%	0.484
		6	0.08	0.6%	0.402

Table 30: *Results of the linear regression model charting the effect of linear energy delivery (Jcm^{-1}) on post-procedural quality of life (Study 3).* **SF-36 – UK Short Form-36 V1, Role-Physical – Role limitation due to physical disability. The effects of age, gender, body mass index, vein dimensions and pre-procedural quality of life are controlled**

Chapter 4 - Discussion

These three studies all provide a significant contribution to the evolving literature focused upon the use of minimally invasive interventions for the treatment of SVI.

Study 1 was the first trial designed to explore the impact of different treatment approaches in the management of tributaries aiming to establish the optimal treatment of non axial SVI.

Study 2 was not the first randomised trial to present its findings of a comparison of minimally invasive treatment with the gold standard of conventional surgery. However, it was the first to focus upon the true outcome of interest in venous intervention; namely health related quality of life. It was the first trial with sufficient power to allow in-depth analysis of health-related quality of life; powered to detect small, but significant differences in quality of life and the first to clearly elicit the benefits of this new technology.

Finally Study 3 was the first to explore the link between the safety and morbidity of the EVLA procedure with the magnitude of energy applied to the target vein; aiming to shed light onto the debate regarding the optimum energy delivery to balance recanalisation and potential harm.

Previous studies have centred on technical and safety outcomes, and have shown new endothermal ablative techniques in particular to be safe[336] and result in better duplex derived outcomes than conventional surgery[332]. The hope is that recurrence rates will be reduced in the long term, although a clear understanding

of the impact of the milder degrees of recurrent veins on QoL has yet to be ascertained. Until now, there has been little hard evidence to show that EVLA, or the other technologies, demonstrates measurable QoL benefits over conventional surgery.

What has been shown clearly is that successful treatment of venous insufficiency results in significant QoL improvements[50]. Minimally invasive techniques have been demonstrated to result in less post-procedural pain than surgery[312,372,392-394], and allow an earlier return to work and normal activities[392-395], although this has not been a unanimous finding[312,396].

4.1 Effectiveness

Study 1 illustrates that EVLA with or without concomitant phlebectomy is a popular, effective and well tolerated procedure. EVLA improves objective clinical venous severity, resulting in significant benefits in QoL. Study 2 confirms that both surgery and EVLA are popular and equally highly efficacious interventions. Both treatments result in significant improvements in the objective severity of venous disease, with lower VCSS values after treatment. This subsequently produced a decrease in AVVQ scores, signifying a reduction in the impact of venous disease on QoL, which in turn had a positive effect on generic QoL. Primarily the physical, rather than emotional and psychological, attributes of health were improved, enhancing overall QoL, as evidenced by QALY gains. This is in agreement with the

findings of a study modelling the quality of life impairment seen in association with SVI, where the reported morbidity was centred on physical domains[44]. It has been shown that cosmetic concern is most closely associated with mental health[46], highlighting the dominance of physical rather than cosmetic concerns of sufferers.

Patient satisfaction is known to be low following venous surgery[298] and it is reassuring to see such high rates following either treatment. There is a trend that fewer patients are being referred for treatment of varicose veins in the UK[265]. The data from this and other studies[43,50,268,397] suggest that treatment results in significant, durable improvement in QoL.

Study 1 indicates that concomitant ambulatory phlebectomy alongside EVLA is feasible under local anaesthetic as an outpatient procedure. It is well tolerated, with no significant increase in postoperative pain detected. There was a trend towards faster recovery in those who had EVLA alone, but this did not reach statistical significance owing to the small sample size and the additional recovery period following any subsequent procedures was not accounted for in this comparison. EVLTAP took a median of 20 minutes longer to perform, but to counter this; two-thirds of patients in the Control group returned for subsequent phlebectomy, which was reflected in significantly worse VCSS values at 3 months. This inconvenience and morbidity of subsequent procedures resulted in a demonstrably poorer disease specific QoL at 6 weeks and 3 months. If patients do not undergo phlebectomy at the time of initial treatment, it takes up to a year to see the same QoL benefit as in those who have EVLTAP.

One question that cannot be answered is whether the patients who had not undergone phlebectomy by 1 year would have benefited from it, or whether it would have been an unnecessary procedure. The Control group continued to have higher AVVQ scores at 1 year, although this did not reach statistical significance. It seems unlikely that patients undergoing phlebectomy after 6 weeks would have been significantly worse than those in the EVLTAP group at 1 year. It is therefore possible that that those who did not have phlebectomy account for this difference at 1 year, although this involved only eight patients. The lack of significant difference in any of the psychological domains of SF-36 suggests that the observed differences in AVVQ scores were due to the specific venous symptoms and not to the negative psychological effect of having residual veins.

Although the EVLTAP group showed a significant improvement in EQ-5D scores from 6 weeks, there was no improvement in the Control group. This would suggest a generic QoL benefit in favour of EVLTAP, but this was not proven on intergroup analysis. It is possible that this represents a type II error, as the sensitivity of the EQ-5D is relatively low and the study was not powered to analyse intragroup EQ-5D scores.

Comparison of studies which utilise laser therapy alone, or in combination with concomitant phlebectomy, but do not directly compare the two approaches, is difficult due to variation in study design. However, we can be certain that combining laser therapy with concomitant phlebectomy significantly reduces the requirement for subsequent interventions in this randomised clinical trial from 67% to 4%. In other studies the requirement for secondary procedures following

isolated laser therapy varies considerably from 17% to 95%[393,398,399]. Secondary procedures are unpopular with patients; with 71% wanting full treatment of their varicose veins in a single visit[365]. This one stop, single treatment seems attractive to both patients and surgeons who appear to be voting with their feet[400-402].

On the basis of the Study 1 findings; it was decided that the EVLA group in Study 2 should receive concomitant ambulatory phlebectomy. As discussed above; Study 2 confirmed equivalent improvements in objective disease severity and quality of life up to 1 year following both EVLA and surgery. In a trial with the power of Study 2 and given the differences observed in Study 1; if concomitant phlebectomy had not been employed in the EVLA arm, it seems likely that there would have been a significant deficit in clinical and symptomatic improvement when compared with surgery.

The next issue to explore was whether EVLA addresses any of the limitations of conventional surgery (See p117).

4.2 Post-procedural Morbidity

Any invasive procedure will have some negative short-term impact on QoL, but this was minimized in the group receiving EVLA. The surgery group had a significant deterioration in early QoL, whereas QoL was relatively preserved following EVLA. Patients who had EVLA saw less disruption in their activities of daily living, and returned to normal within less time. The time taken to return to work is known to be influenced by multiple factors[403,404]. However, the groups in this study were well matched at baseline, and efforts were made to give the same advice regarding the expected convalescence. Thus the difference of 10 days reported here is likely to be real.

It is important to note that despite any concerns regarding additional pain and prolonged healing following concomitant phlebectomy; this study clearly shows that EVLA with concomitant phlebectomy is superior to what was widely regarded as current best practice.

4.3 Recurrence

Analysis of 64 prospective studies of endovenous treatments for varicose veins suggested that freedom from incompetence on duplex ultrasound examination was more likely at 5 years after EVLA than following surgery (95.4 versus 75.7%)[332]. However this paper was criticised for compiling data from hetrogenous case series with hetrogenous outcomes. Study 2 has clearly confirmed the higher rates of early clinical recurrence following surgery compared with EVLA. The fear of recurrence is significantly high amongst patients (90%)[365] making this a significant issue irrespective of the uncertainty surrounding the degree of associated quality of life impairment. It has been claimed that the observed high recurrence rates following surgery for varicose veins are related to the technical inadequacy of the initial procedure[299,405-407]. This has been challenged; recurrence after surgery is progressive from as early as 3 months, at sites that had undergone proven technically adequate surgery[296]. This was shown again here, as postoperative duplex imaging confirmed the adequacy of standard groin surgery in all but two patients; yet almost half of recurrences were related to recurrent groin incompetence and 15.0% overall had convincing evidence of neovascularisation by 1 year. Another large duplex ultrasound study of 264 legs with symptomatic recurrent veins found that 70.8% had groin recurrence (20.4% due to an intact SFJ, leaving 50.4% due to neovascularisation) and 57.2% had residual incompetent GSVs[408]. About half of the patients in Study 2 with neovascularisation have not yet suffered a clinical recurrence. Given the evidence to date, if they do; the gap

between EVLA and surgery may be widened further, even in the absence of the development of more sources of neoreflux.

Neovascularisation has been implicated as the leading cause of surgical recurrence in several studies[294,302,408-410] with rates as high as 52% at 2 years[294,305] and 79% at 5 years[291,296]; evidence of neovascularisation on duplex imaging at 1 year has shown a positive predictive value for clinical recurrence of 70–100%[411]. This is ultimately linked to the need for reintervention[297]. Barrier techniques aiming to reduce the rates of neovascularisation have shown mixed results[291,304-309,412] and are not in widespread routine use. Neovascularisation is thought to be the result of angiogenesis following the tissue trauma of surgical dissection[410], whereas it is speculated that extra venous inflammation does not occur following EVLA. It has also been suggested that the preservation of groin tributaries during EVLA avoids the stimulus for angiogenesis[348]; some surgeons even preserve groin tributaries during saphenofemoral ligation on this basis[413]. It seems naive to believe that EVLA causes no extra venous inflammation. Anecdotally groin dissections following EVLA recurrence secondary to groin tributaries has found evidence of fibrosis. Irrespective of these arguments, neovascularisation appears rare following EVLA.

This trial also demonstrated a flaw in the widely practised principle of only stripping the GSV to the knee. Below knee GSV reflux is especially significant, due to its association with CVI (See *Table 3, p39*) and therefore it can be argued that this mandates particular attention during treatment. The largest number of recurrences were also associated with incompetence in the below-knee GSV[408,409]

and on detailed analysis there is some suggestion that the occurrence of above-knee neoreflux may be associated with residual below knee disease. If proven definitively, this would clearly lend some support to the ascending theory of venous insufficiency (See *The Pathogenesis of Primary Venous Insufficiency p49*). It has been argued that the length of GSV stripping should be dictated by the length of refluxing vein and not concerns over injury to the saphenous nerve[285-287]; full-length stripping remains controversial. Below-knee EVLA, in contrast, is safe and effective as shown in this study and others[399,414] and many of the incompetent below knee segments in the surgical arm would have been amenable to treatment with EVLA initially.

Several independent research groups have established that the magnitude of energy delivery during EVLA is the most important predictor of success[366-368] and increasing energy delivery has resulted in improved occlusion rates[369,370]. Commonly energy deliveries of around 20-40 Jcm^{-1} or equivalent fluence calculations have been used, but the current best evidence points to improved results at energies higher than this and many providers now use 80-100 Jcm^{-1}. Despite this, 100% success remains an elusive goal. The reluctance to increase energy delivery further is most likely due to concerns that this may result in increased morbidity and complications from the procedure. There is however, no evidence that this is the case, when EVLA is performed using tumescent anaesthetic solution.

Early recurrence is uncommon following EVLA in Study 2 and all but one of those observed were associated with the development of new incompetence, including

in the groin tributaries, which occurs despite a policy of placing the fibre tip at the SFJ. This has been observed previously[415], although some claim that such tributaries are insignificant[416]. It is difficult to suggest how this can be prevented and it seems likely that, alongside neoreflux in the saphenopopliteal junction, perforators and non-axial branches, it represents natural background disease progression. All three patients who had recanalisation after EVLA in this trial were treated above the previously recommended 810nm energy density threshold of 60 Jcm^{-1} [367], suggesting that this threshold may be too low. No recanalisation was seen when energy densities above 115 Jcm^{-1} were used.

One would expect that increasing the magnitude of energy delivery to the vein would increase the magnitude of tissue damage created, increasing both pain and swelling, alongside analgesia requirement. This should then have a detectable impact upon quality of life, reducing mobility and general health perception. Patients would take longer to recover. Moreover, transmission of thermal energy beyond the vein should, in theory damage surrounding structures resulting in higher complication rates. Study 3 does not support this proposed theorem (within the range of energy utilized). Increasing energy had no effect upon pain or analgesia requirements. The effect of energy upon AVVQ scores at 6 weeks is of borderline statistical significance and doubtful clinical significance; energy accounts for just 3.1% of the variation. It has been previously found that generic QoL analysis is more sensitive to the QoL changes associated with periprocedural morbidity than AVVQ[417] and yet there was no difference seen in either of the instruments analysed. It follows therefore that there was no effect upon recovery

times and complication rates were low, adding further support to the evidence that EVLA is a very safe procedure[332,333,336]. The sample size used in this analysis is double that required for testing the significance of an individual predictor, and so it is unlikely that any significant relationship has been missed.

It seems likely that these results are explained by the use of tumescent local anaesthetic. Accurate and meticulous infiltration of local anaesthetic around the vein causes hydro-dissection of the surrounding tissues away from the vein and the laser fibre. This fluid collapses the vein around the fibre and acts as a heat sink, reducing the transmission of thermal energy by convection and conduction beyond the vein wall. The 810nm photons from this laser are primarily absorbed by haemoglobin within the blood[327], minimizing the transmission of radiant energy beyond the vein, also trapping the heat where it is needed: inside the vein. This may not be the case with longer wavelengths, which are primarily absorbed by water, and may therefore be transmitted to the heat sink and possibly beyond.

The early benefits of concomitant phlebectomy and treatment of incompetent perforators upon effectiveness has been discussed above, however it is possible that they could have a favourable impact upon disease recurrence also. The ascending theory of venous insufficiency (See *The Pathogenesis of Primary Venous Insufficiency p49*) would suggest that unaddressed tributary incompetence will gradually result in the development of further disease more proximally. It is therefore uncertain whether these results can be applied to the simple treatment of isolated superficial axes with EVLA alone, either in terms of early efficacy or later recurrence. These studies do not at present provide clear evidence on this

issue and Study 1 is clearly not powered to look at recurrence; only a handful of patients got to 1 year without requesting further intervention.

4.4 Additional Findings

Cost utility analysis in economic evaluation requires the use of utility scoring systems to estimate the QALY value associated with differing health states. The different utility scoring systems, lead to different results, therefore standardisation is required. In the UK, NICE recommends that cost utility analysis should utilise EQ5D[190] and it is also the chosen generic instrument for the routine collection of patient-reported outcome measures in the UK[191]. However the newer SF6D has shown some relative advantages. Firstly it can be derived from previous studies using SF36 or SF12, when no dedicated utility scoring system was utilised. Additionally, the theoretical basis at the heart of SF6D is the standard gamble and the principle of decision making with uncertainty. This is felt by purists to be the optimum method for valuing health states (See *Index utility p95*). Finally Study 2 highlights the increased sensitivity of SF6D, allowing it to detect differences missed by EQ5D.

It has been noted previously that EQ-5D is a relatively insensitive instrument, particularly when used in situations such as Study 2[50,222,418]. These findings challenge the place of EQ5D in this context; however despite the drawbacks of

QALY league tables when comparing different healthcare programmes[212], analyses must be made using broadly similar units. This is because the principle of rational economic decision making under a fixed budgetary constraint relies upon the adoption of an economically favourable programme by the sacrifice of the least favourable programme(s), thus freeing the required resources. This process clearly cannot be undertaken with any certainty if programmes are not valued in the same units. The adoption of a new index system would therefore require a "currency exchange" across the entire healthcare landscape.

4.5 Critique

In common with most comparative trials of SVI treatment, neither the patients nor the assessors could be blinded to the techniques used. The risk of observer bias was reduced, however, as the majority of key outcomes reported (including the primary outcomes) were reported independently by the patient. Those observed by an assessor were registered using objective and validated instruments. Furthermore specific imaging protocols and definitions were also used to minimize the possibility of bias.

As with all trials of venous interventions; continued and complete follow-up is challenging. This did not have a critical effect on the power of the trials for example, in Study 2; a sensitivity analysis explored the confidence of the results

given extreme assumptions regarding those lost to follow-up. EVLA reliably had lower recurrence rates at all sensible assumptions. Follow-up on the whole was relatively short following venous intervention and data acquisition must continue.

The inclusion and exclusion criteria were fairly specific. In designing these trials, the aim was to produce studies which gave clarity in the outcome and interpretation, while being a true reflection of clinical practice in the UK. QoL data are subject to significant degrees of unsystematic variation, leading to problems with statistical interpretation. Therefore, it was felt important to minimize variation and allow meaningful differences to be uncovered.

A criticism of Study 2 is that patients in the surgery arm underwent conventional inversion stripping under general anaesthesia. This reflects the predominant practice in the UK. Newer techniques such as cryostripping, or the use of tumescent anaesthesia for surgical stripping are described, but there is little convincing evidence to date that these will significantly improve short-term outcomes following surgery[312,315,393].

A criticism of Study 3 is that although all patients underwent some concomitant treatment (phlebectomy and/or perforator ligation), the extent of these procedures could not be controlled between individuals. However; these procedures maximize the quality of life benefits of treatment (as per the findings of Study 1) and achieve the much desired aim of one-stop treatment[419-421]. This study therefore aimed to reflect true clinical practice with the aim of allowing the results to be generalized.

4.6 Further Avenues of Research

The popularity of minimally invasive techniques for the treatment of superficial venous insufficiency has led to a series of studies aiming to establish which is optimal. A large industry has developed centred around these technologies, and with a market of such considerable size, financial backing has found its way in the form of industry sponsored studies. Some question the quality and validity of some of the resultant findings and it is difficult to make any firm conclusions at present. A detailed discussion of the evidence to date is beyond the scope of this thesis, which was designed to establish the relationship of one of these technologies with the gold standard. There is little conclusive evidence to date that one approach is an obvious leader, but each has its advocates and each has comparative strengths and weaknesses in different situations. This has led to a number of surgeons using differing techniques in different situations and the mixed use of technology in the same patient, particularly in the treatment of recurrence is not uncommon.

Presently there is much debate around the use of higher wavelength lasers and specialised fibre-tips. To date there is no conclusive evidence supporting improved results and care must be taken in this area. The thermodynamic and absorption profile of different wavelengths of laser are different. The hope is that this will lead to improved morbidity and side-effect profiles, but this could go the other way[344] and using water specific wavelengths could see greater quantities of energy being transferred to the tumescent anaesthetic attenuating its effect as a "heat shield". It is also incorrect to assume that the recanalisation rates for short

wavelength lasers at specific energy densities can simply be applied to the new wavelengths or fibre tips altering the density of laser delivery, in the same way that the long term results of direct RFA cannot be applied to the ClosureFAST® device.

Economic analysis is a critical component of health technology assessment, more so now than ever. Economic modelling is an established technique, but the validity of its findings is entirely dependant upon the credible valuation of the QALY associated with each health state and the probability of transition between states. This process has clearly established the superiority of conventional surgery when compared with conservative management in the REACTIV trial[50]. To date there has been only one detailed attempt at this for the modern management of SVI[422]. This was a high quality Markov model analysis, finding EVLA under tumescent anaesthetic to have the highest probability of all treatments of being cost effective at the commonly quoted UK NHS threshold of £20 000 per QALY. Below this came day-case surgery (under GA) and then RFA (under tumescent anaesthetic). Foam sclerotherapy was dominated due to the assumption of high recurrence and re-intervention rates. An additional finding was that EVLA and RFA with concomitant phlebectomy under a GA was less likely to be cost effective than simple day-case surgery under GA. There were however flaws in the analysis: QoL following successful intervention was assumed to be the same for all groups (Study 2 disproves this). It was assumed that a GA would be required to perform concomitant phlebectomy (Study 1 disproves this). Some authors would also object to the high levels of recurrence assumed following foam

sclerotherapy[358,359]. This paper therefore highlighted some of the issues with the current literature which need addressing to take such an analysis forward. Another such issue is the nature of recurrence. Little is known of the QoL impact of early recurrence. There is no doubt that by the time such cases present in clinic requesting treatment, there is little difference between them and those with no history of intervention, however it is impossible to draw firm conclusions regarding the significance and natural history of early recurrence seen on intensive follow-up such as that seen in Study 2. Further work in this area and upon the natural history of venous disease in general, will improve patient selection and inform economic models, allowing the extrapolation of such analyses over the appropriate time frame: a patient's lifetime. This area of economic analysis also highlights a methodological debate. Conventionally health economic analysis is performed from the perspective of the healthcare system; often (possibly erroneously) labelled as the "third party payer". Whilst from an international perspective this allows information transfer between differing models of healthcare provision, in the UK (where society is the third party payer); a societal perspective is arguably a more appropriate viewpoint. This would then consider the impact of minimally invasive treatments upon lost productivity and time spent away from employment.

A further area requiring additional study is the treatment of venous ulceration. Most cases of venous ulceration involve SVI (See *Patterns of Reflux, p36*) and the degree of venous hypertension is therefore amenable to reduction by the treatment of SVI. Whilst surgery for SVI is yet to be shown to improve ulcer

246

healing, it does decrease recurrence[256,257]. A significant proportion of patients with venous ulcers are elderly, with significant co-morbidities making them less suitable for treatment under GA. In addition around 25% of patients refuse conventional surgery, when offered[256,423]. The potential advantages of minimally invasive intervention are clear and research in this area is required.

4.7 Conclusions

SVI is a very common disease and results in significant impairment in health related QoL. The treatment of SVI has been demonstrated to be highly effective; improving QoL with an extremely competitive economic profile.

Endothermal ablation with EVLA of SVI is a popular, safe and effective treatment resulting in equivalent health benefits over time to those seen following conventional open surgery. Additionally EVLA addresses the limitations of conventional surgery; minimising the disruption in sufferer's lives and careers; resulting in superior post-procedural QoL and reducing early recurrence rates.

Concomitant phlebectomy with EVLA is feasible and acceptable to patients under local anaesthetic. The use of general anaesthesia negates some of the benefits and in particular has been shown to be economically non-viable. The application of concomitant phlebectomy virtually eliminates the need for any subsequent interventions and results in superior QoL benefits for at least the first year. There is no clear associated increase in post-procedural pain or time to recovery and patient satisfaction is very high. The only discernable disadvantage seems to be a small increase in operative time and the vast reduction in secondary procedures more than compensates for this.

In experienced hands 810 nm EVLA is safe and effective, with no evidence of increased complications or morbidity associated with increasing energy delivery in the range studied. This confidence in the safety of EVLA has allowed the increase in applied energy density to result in enviably low recanalisation rates, but the

optimal energy required to result in 100% closure rates is yet unknown. It is likely that the aim of durable one-stop treatment, first time, and every time is possible.

The benefits of minimally invasive intervention with EVLA and concomitant phlebectomy mandate the consideration of adoption of this technology as the gold standard treatment for SVI.

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