Long Term Outcome of Minimally Invasive Treatment for Superficial Venous Insufficiency of the Lower Limb

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Abstract

Background

Venous insufficiency is estimated to affect up to half of the adult population and is associated with significant quality of life (QoL) impairment. Minimally invasive techniques, such as Endovenous Laser Ablation (EVLA) aim to treat superficial venous insufficiency (SVI) by using thermal energy to destroy the incompetent venous axis. Numerous studies have reported that the EVLA method is superior to Conventional surgery, a previously standard technique, which uses ligation and stripping of the incompetent axis to remove venous reflux associated with SVI. In the short term, EVLA is associated with fewer complications and enhanced QoL recovery compared to conventional surgery, but the long term outcomes remain uncertain.

Objectives

The aim of this study was to investigate the five year outcomes of EVLA and conventional surgery in the treatment of SVI. The HELP-1 trial directly compared the clinical and technical outcomes of conventional surgery and EVLA. The EVLTAP trial compared the long term consequences of a policy of concomitant or sequential phlebectomy with EVLA. Due to advantageous size of the HELP-1 study, a comparison of the long term outcomes of patients with different severities of SVI was also explored. A cost effective analysis was also undertaken. Finally, investigation of the importance of different EVLA settings and techniques was investigated.

Methods

The HELP-1 and EVLTAP studies were both randomised clinical trials. All patients had primary, symptomatic, unilateral venous insufficiency, with isolated Sapheno-femoral junction (SFJ) incompetence, leading to reflux into the great saphenous vein (GSV). In the HELP-1 study, 280 patients were equally randomised into two groups of either conventional surgery or EVLA. In the EVLAP trial, 50 patients were equally randomised into two groups of either concomitant phlebectomy or sequential phlebectomy. Both groups were offered sequential phlebectomy of any symptomatic residual venous tributaries present after six weeks. Outcomes were generic QoL (Short form 36 (SF-36), EuroQoL 5 Dimension (EQ5D), Disease specific QoL (Aberdeen Varicose Vein Questionnaire AVVQ), Utility Index QoL (SF6D), Objective clinical assessment of venous disease (VCSS), Cosmetic and overall satisfaction, clinical recurrence, symptomatic recurrence and requirement of additional procedures. Assessments were at 1, 6, 12, 52, 104, 260 weeks.

The further study of EVLA settings and technique used linear and logistic regression modelling to investigate the effects of Watt power (12W or 14W) and concomitant phlebectomy on QoL (SF-36, EQ5D and AVVQ), clinical outcomes and recurrence. For the economic analysis, costs were calculated using prospective data estimated from the actual resource requirement in each case over five years. Health utility index from the EQ5D or SF6D was used to calculate quality adjusted life years (QALYs) over five years using Area under the Curve (AUC). The Cost per QALY increase was calculated to produce a cost effective ratio (ICER) to determine cost effectiveness at various economic limits. Sensitivity analysis explored parameter uncertainty. For EVLTAP a Monte Carlo simulation was developed to explore the additional costs of various thresholds for sequential phlebectomy.

Results

Over five years, the HELP-1 trial detected early deterioration in the SF-36 QoL domains of Physical function (PF), Role physical (RF), Bodily pain (BP), Social function (SF) and Role emotional (RE) after conventional surgery After EVLA only the domains of PF and RP were impacted. Beyond one year, improvement in the domains of PF, BP and Mental health (MH) were maintained after conventional surgery, as were the domains of PF and BP after EVLA. At five years, all SF-36 domains in both groups had returned to baseline, aside from Social Function (SF) which was worse in both groups. Beyond one year, no differences in SF-36 domains were detected between the groups at any time point. Improvement in AVVQ and EQ5D was sustained in both groups, as was objective measure of venous disease (VCSS), with no differences detected between the two treatments. Overall satisfaction and cosmesis remained high. Over five years, clinical recurrence was detected in 56.4% and 44.4% of conventional surgery and EVLA patients respectively (P=0.078). Estimated freedom from clinical recurrence was higher after EVLA (P=0.031). Over five years, symptomatic recurrence was detected in 18 and 19 conventional surgery and EVLA patients respectively (P=0.862) and likelihood of symptomatic recurrence development was similar between both groups (P=0.983). The proportion of those requiring additional procedures were similar between both groups over five years (P=1.000)

Over five years, the EVLTAP trial detected an early improvement in AVVQ at six weeks among those receiving concomitant phlebectomy (P=0.008). At 12 weeks both groups reported an improvement in AVVQ (EVLA alone P=0.018, EVLTAP P<0.001). Compared to sequential phlebectomy, concomitant phlebectomy had lower (better) AVVQ scores at 6 weeks (P=0.008) and 12 weeks (P=0.015). Beyond

one year both groups reported significantly improved with no intergroup differences detected. Sequential phlebectomy was required in 66.7% of those in the EVLA alone group, and 4% of those in the EVLTAP group. The requirement for additional intervention after one year was however similar between the two groups.

From the HELP-1 trial data, more severe baseline disease (CEAP 3-4) was associated with worse long term outcomes compared to those with uncomplicated venous disease (C2). Clinical recurrence arose in 70% of those with C3-4 disease and 43% of those with C2 disease. Symptomatic recurrence was also higher in those with complicated disease, at 27% and 12% in C3-4 and C2 groups respectively. Whereas QoL improvement was maintained to five years in the domains of RP, RP, Vit and RE among those with C2 disease, those with C3-4 disease did not manage to sustain any improvement in any SF-36 QoL domain. However, over five years both groups did improve in disease specific measures of VCSS and AVVQ. Additional treatments were also more prevalent amongst those with C3-4 disease

Economic analysis suggested that the initial treatment costs of EVLA were less than conventional surgery, but after one year costs were broadly the same. QALYs were also similar between both treatments. Cost effectiveness over five years was similar between both treatments, with marginal improvement of QALY but more cost among conventional surgery. Significant costs associated with the long term treatment of those with C3-4 disease and worse QoL outcomes suggested that treatment of C2 disease was much more cost effective overall. Performing EVLA without concomitant phlebectomy is both quicker and cheaper, but additional costs of sequential phlebectomy by one year inflate the overall costs to beyond that of the concomitant group. Costs beyond one year are similar. Monte Carlo modelling

suggests that sequential phlebectomy is highly unlikely to be more cost effective at any threshold of further intervention.

Investigation into the effects of EVLA setting and technique found that at 12 weeks, PF, Vit and MH were enhanced in those receiving the 14W continuously delivered EVLA versus those receiving the 12W pulse delivered EVLA. Early benefit in PF and AVVQ was also detected in those receiving concomitant phlebectomy. Beyond 12 weeks there was no significant difference in QoL detected, nor did the treatment ultimately effect the clinical outcomes or recurrence.

Conclusion

EVLA and conventional surgery are both highly effective long term treatments for SVI. In considering the early benefits, this study supports the recent NICE guidance that EVLA should be preferred over conventional surgery. Concomitant phlebectomy during EVLA appears to be the optimum treatment, and treating those with SVI earlier, appears to produce better long term outcomes.

Contents

List of Figures

List of Tables

Glossary of Abbreviations

95% CI	95 % Confidence Interval
AASV	Anterior Accessory Saphenous Vein
AUC	Area under curve
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	Body Mass Index
BP	Body Pain
CEAP	Clinical aEtiologic Anatomic Pathophysiologic Score
CT	Computed Tomography
CVA	Cerebrovascular accident
CVI	Chronic Venous Insufficiency
DUS	Duplex Ultrasound
DVT	Deep Vein Thrombosis
EBM	Evidence based medicine
EQ5D	EuroQol 5 dimension
EVLA	Endovenous laser ablation
EVLAP	Endovenous laser ablation with phlebectomy
EVTA	Endovenous thermal ablation
FT	Friedman ANOVA test
g	Gram (weight)
GA	General Anaesthetic
GH	General Health
GP	General Practitioner
GSV	Great Saphenous Vein
HR	Hazard ratio
IQR	Interquartile range
J	Joules (unit of energy)
L	Litre
LA	Local Anaesthetic
LR	Log rank test
m	Meter
MCID	Minimal clinically important difference
MH	Mental Health
MRI	Magnetic resonance imaging

NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PE	Pulmonary Embolism
PF	Physical Function
QoL	Quality of Life
RCT	Randomised Clinical Trial
RE	Role Emotional
RFA	Radiofrequency ablation
RP	Role Physical
RR	Relative risk
SD	Standard deviation
SF	Social Function
SF-36	Short Form -36
SFJ	Sapheno-Femoral Junction
SPJ	Sapheno-Popliteal Junction
SSI	Surgical Site Infection
SVI	Superficial Venous Insufficiency
UGFS	Ultrasound guided foam sclerotherapy
VAS	Visual analogue score
VCSS	Varicose Clinical Severity Score
Vit	Vitality

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“Time is the longest distance between two places”

Tennessee Williams, The Glass Menagerie

Author Declaration

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Chapter 1 – Introduction

1.1 History of venous disease

Venous disease has long afflicted humanity and remains a serious medical problem today. A common and highly visible manifestation of venous disease can be the development of varicose veins, a term itself derived from the ancient Latin "varus" meaning "bent or crooked"[1]. While it is plausible that venous disease has been present in mankind for thousands of years, its earliest mention was first found in the ancient Egyptian medical text the *Ebers Papyrus* (~1550 BC), in which a patient with "serpentine windings" is warned against intervention lest they suffer significant blood loss, an often fatal complication in ancient surgery[2]. Indeed, for much of human history venous disease was primarily treated by a combination of bandages or strapping, a practice advocated by legendary physicians, such as Hippocrates (460–370 BC)[3], and a treatment which remained popular for hundreds of years. It was several centuries until surgical techniques began to be tentatively developed, first by the Roman physician Celcus (25 BC–14 AD)[3] and later improved by Galen (130-200 AD). While it was Celcus in his *De Medicina* who first described venous avulsions, it was not until the great Moorish surgeon Al-Zahrawi (936–1013 AD) (also known more commonly in the west as Albucasis) that the more advanced surgical techniques, such as ligation, venous stripping and cautery became to be first described[4]. Over the following centuries these operations were further improved by a series great surgeons, notably Trendelenburg (1844–1924 AD), and other innovative techniques such as injection sclerotherapy were also introduced. Unfortunately, while sclerotherapy was initially developed to avoid the risks of surgery, it was often

based on a highly irritative formulations of iron or perchloride, which were frequently uncomfortable and often plagued with complications. Regardless, the appeal of a highly effective treatment with few risks remained and it is only perhaps in the past few decades that this ideal can be reached. Following a series of technological advancements, recently developed minimally invasive surgical techniques have been designed to direct treatment into a specific vein, thereby controlling the treatment area and also reducing the risks of treatment. While the short term results of minimally invasive treatments are very encouraging the long term outcomes of such treatments are less clear and it is this question which this study aims to elucidate.

Lower limb venous anatomy & physiology

Venous anatomy

The peripheral venous system of the body has two key functions; to provide a method of venous return to the heart and to act as a venous reservoir of blood[5]. The peripheral venous system is divided into two main components; the deep venous system and superficial venous system, both interconnected via various anatomical junctions and a multitude of perforating veins[6]. Whilst venous anatomy is highly variable (and has historically been beset with inconsistent nomenclature), the terminology and description of the venous system detailed below conforms to standard international consensus[7].

Distal venous system

The distal aspect of the lower limb venous system commences at the sole of the foot and starts as a fine venous plexus called the plantar cutaneous venous arch. This plexus drains the plantar digital veins of the toes and is continuous with the medial

and lateral plantar veins located at either side of the foot. These both drain into the posterior tibial vein and also function as a venous reservoir for the plantar venous pump. The dorsal venous arch lies within the dorsum of the foot and drains the dorsal digital veins of the toes. It is continuous with the marginal veins of the foot, importantly, the medial marginal vein (the origin of the great saphenous vein (GSV) and the lateral marginal vein (the origin of the small saphenous vein (SSV). Both plantar and dorsal arches are in continuous communication with each other through numerous intercapitular veins, with blood often pushed into the dorsal arch once pressure is placed on the sole, thereby compressing the plantar arch of the foot.

Great saphenous vein (GSV)

The GSV is the longest vein in the human body and the most common vein to develop venous insufficiency. At the ankle the GSV begins anterior to the medial malleolus and courses superiorly along the medial aspect of the limb with the saphenous nerve towards the groin[8, 9]. Approximately 3 to 4 cm below the pubic tubercle the GSV pierces the cribriform facia and through the Sapheno-femoral junction (SFJ) joins the common femoral vein (CFV). The SFJ also drains other venous axes[10]. One of the most important, the anterior accessory saphenous vein (AASV), also drains into the SFJ although it is not uncommon to see the AASV join the CFV at other points. The AASV typically has its origin at the lateral level of the knee and usually ascends across the thigh towards the groin. However, it is also possible for the AASV to originate further down the limb and to even course along the medial side of the thigh, sometimes mimicking the GSV and giving an appearance of a “duplex” GSV. Rather, a true duplication of the GSV is uncommon and estimated to have a prevalence of 1.6% to 2%[11]. Numerous tributaries also drain

into the SFJ but they are often quite variable in their nature and their patterns are described in detail in most dedicated anatomical textbooks.

Small saphenous vein (SSV)

At the ankle the SSV begins posterior to the lateral malleolus and courses superiorly along the posterior aspect of the calf towards the popliteal fossa. At approximately the level of the knee the SSV pierces the popliteal facia and connects via the Sapheno-popliteal junction (SPJ) into the popliteal vein. The location of the SPJ is often variable and the SSV may even extend above the typical location of the SPJ, termed “cranial extension of the SSV”, piercing the posterior thigh facia to connect into the deep system directly or to connect to the GSV or SFJ as an ascending superficial vein tributary, commonly termed a Giacomini vein.

Deep venous system

The majority of venous return (approximately 90%) occurs through the deep venous system. The posterior and anterior tibial veins ascend and unite to form the popliteal vein at the level of the knee. The popliteal vein continues caudally and traverses the adductor canal to become the femoral vein (used in preference to its former name superficial femoral vein to avoid clinical confusion regarding its importance[12, 13]. At the level of the mid-thigh the profunda femoris vein connects to the femoral vein to form the CFV and, once it passes the inguinal ligament, becomes known as the external iliac vein. The internal iliac vein unites with the external iliac vein to become the inferior vena cava (IVC) which itself enters the chest cavity to drain directly into the right atrium of the heart.

Vein perforators

Numerous vein perforators exist to help drain blood from the superficial to the deep venous system. While the exact location of individual perforators often varies from person to person, certain groups of perforators exist in predictable patterns and locations. Perforators are often categorised according to their general area, with those in the lower third of the calf named Cockett's perforators, those of the middle third named medial gastrocnemius perforators and those of the upper third named Boyd's perforators. Above the knee, perforators of the distal thigh are named Dodd's perforators and those of the middle thigh named Hunterian perforators. To maintain direction of flow from the superficial to the deep system these perforators also have specialised valves to prevent any venous reflux.

Venous physiology

The vein wall consists of three main layers; an outer layer of connective tissue (tunica adventitia), a middle layer of smooth muscle (tunica media) and an inner layer of endothelium (tunica intima). To help venous return a vein usually contains a series of bicuspid valves along its course. This helps prevent retrograde blood flow, which is especially important in the lower limb venous system because blood will often have to return against gravity[14]. While the overall systemic venous circulation is estimated to have an average pressure of 5-10 mmHg, once upright the effect of gravity greatly elevates the pressure in the lower venous circulation by approximately 0.77 mmHg for each centimetre below the level of the heart[15]. The pressure within the in the distal portion of the limb can be substantial making valves a crucial aspect of venous return. However, venous return does not just rely on valves alone. A significant amount of venous blood is moved by the action of

muscles, especially those of the calf (gastrocnemius and soleus) as well as those in the foot and thigh. As the muscles contract substantial pressures can be generated within the muscle and the enveloping facial compartments. This has the overall effect of producing a large pressure gradient, with deep veins of the calf estimated to experience pressures in excess of 200 mmHg and those of the thigh around 100 mmHg, with the valves ensuring a sustained elevation of a column of blood. Once this pressure subsides the relatively low pressures found in the deep system encourages movement of blood from the superficial to the deep system, with the valves of the superficial system and connecting perforators preventing reflux back into the superficial system.

Venous valves

Venous valves are primarily dynamic structures which open and close multiple times per minute. Their mechanism of action is as follows; during contraction, pressure builds within the column of blood located between valves. The elevated pressure forces the valve leaflets apart with a small space remaining between the vein wall and the valve cusp. Within this space a vortex of blood forms which prevents venous stasis and supports the valve from significant shearing forces. Once the vortex becomes more powerful than the flow of blood, the leaflets collapse and shut, thereby preventing venous reflux and ultimately maintaining a linear direction of blood flow.

Numerous valves exist within the venous system and they often vary in both number and location. The GSV itself usually has a median of 6 valves, although it has been documented that up to 25 have been found in some patients[16-18]. It is also common to find a specific valve located in the GSV 2 to 3 cm distal to the SFJ, presumably to

help prevent junctional reflux. The SSV usually has a median of 7 valves, although this can also range in number, normally between 4 and 13[19]. The number of valves in the deep system, while typically fewer in total number when compared to the superficial system, can also be highly variable[20]. For example, while approximately half of people will have only one valve in the CFV or external iliac, one third of people will have none[21].

Venous Insufficiency

Superficial venous insufficiency (SVI) of the leg is defined as retrograde blood flow in a superficial vein which is greater than 0.5 seconds in duration[22]. Failure of the venous system results in the development of venous hypertension, potentially leading to damage within the vein intima and surrounding tissues. Damage associated with venous insufficiency can be severe, progressing from oedema, pigmentation, extensive tissue changes and, in extremis, venous ulceration. This spectrum of disease can be termed chronic venous insufficiency (CVI)[23]. Taken together, SVI and CVI can be considered under the umbrella term chronic venous disease (CVD), in which the full spectrum of morphologic and functional abnormalities of the venous system can be accommodated[24].

Several physical manifestations of SVI exist, with perhaps its most classical clinical presentation being the development of varicose veins. These are defined as "subcutaneous dilated veins greater than 3 mm in diameter, once measured in an upright position"[24]. However, while varicose veins are easily recognised and a common complaint, the first indication of SVI may actually be the development of small dilated intradermal venules called telangiectasia. These are typically less than 1 mm and often present as small blue lines, commonly called spider or thread veins,

and may collect into organised structures called hyphen webs. In between the telangiectasia and varicose veins are reticular veins. These are subdermal veins measuring between 1 and 2.9 mm, are often blue in colour, and display similar characteristic dilation and tortuosity expected of venous disease.

Pathophysiology of superficial venous insufficiency (SVI)

The majority of cases of primary SVI are idiopathic with no identifiable cause[25]. Congenital or obstructive pathologies are less common than primary SVI (typically less than 20% of all cases) but are clinically important. Rare congenital conditions such as Klippel–Trénaunay or Parkes-Weber are associated with varicose veins but commonly present with other venous abnormalities, such as venous aneurysms and limb hypertrophy[26, 27]. Obstructive pathologies can be mechanical or functional in nature. A classic example of venous obstruction would be a deep vein thrombosis (DVT), but extrinsic luminal compression can also cause obstruction, such as in May-Thurner and Nutcracker syndrome. Mechanical failure is unusual but can be caused by impairment to the musculovenous pump mechanism. Any lack of muscle contractility or neurological innervation may significantly impair venous return[28, 29].

Primary superficial venous insufficiency

Primary SVI is characterised by venous dilation, valve failure and venous hypertension[30]. One of the first theories of SVI, the "descending theory", suggested that incompetence at the saphenous junction was the primary cause of SVI[31]. This theory in essence states that, once the proximal saphenous valve begins to fail, a "domino effect" occurs down the vein, whereby the column of blood previously held

above the working valve becomes unsupported and falls into the preceding vein segment. This raises intraluminal pressure and the venous hypertension begins to damage the vein wall and valve. Eventually, another valve also begins to weaken and the process repeats down the limb until the entire axis is affected.

However, as venous disease became better understood it soon became acknowledged that the descending theory was unable to explain some of the unusual but common clinical presentations seen in certain patients. For example, it was known as early as the nineteenth century that some patients with venous disease had otherwise normal saphenous junctional anatomy[31]. The failure of the descending theory to explain such a situation led to the promotion of an alternative theory, the "ascending theory", which counterintuitively suggested that venous disease in fact progresses in a retrograde fashion from a distal site of disease[32]. Still, for both theories to work they both had to overlook the role of vein perforators and any patients with venous disease but healthy venous valves[33, 34]. It is now thought that venous disease is instead a focal, or perhaps multifocal, process which can occur at any point along a vein and can spread both proximally as well as distally and may not necessarily involve the valves or cause valvular dysfunction [35, 36]. Exactly what initiates the disease process still remains to be elucidated, however, histological analysis of diseased veins indicates that it might be a process of inflammation which confers most of the damage to the venous tissue[37-39]. Venous valves are themselves an embryonic extension of the vein wall endothelium and both venous tissues receive oxygen and nutrition from the transported blood[40]. Any disruption to the normal flow within varicose veins may cause venous stasis, which could impair cellular respiration and eventually result in hypoxia within the venous tissue[41-43]. The

cyclical nature of such a disease process has been described as “a vicious cycle” and could be potentially initiated at any point around it[15] (Figure 1).

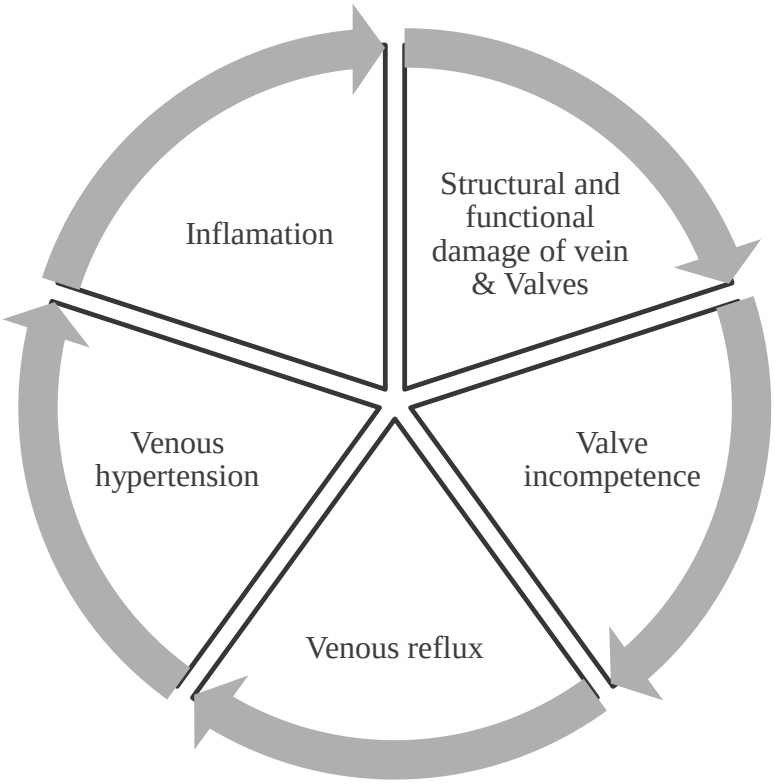


Figure 1. The vicious cycle of the pathophysiology of primary venous insufficiency

Vein inflammation and vein repair

Venous tissue is constantly undergoing a process of repair and remodelling as it experiences the natural strain and deformation typical of normal venous physiological processes[44]. In varicose tissue it appears that the underlying process of repair is either altered or impaired[45]. In normal conditions a careful balance between matrix metalloproteinase enzymes (MMPs) and tissue inhibitors of MMPs (TIMPs) is maintained to ensure structural integrity of the venous architecture[45-48]. However, in varicose veins the structural damage often appears irregularly and can affect any

layer of the vein wall or valve[41]. Disruption of the MMPs and TIMPs equilibrium can therefore result in a significant alteration of the venous structure with significant loss of control of the extracellular matrix and potential atrophy or hypertrophy of the vein layers, depending on which side the balance is tilted[49-51]. Inflammatory processes are likely to play a role in this change, with inflammation a response to excessive levels of stress on the vein endothelium due to venous hypertension[41, 43, 47, 52]. Release of inflammatory mediators compels inward migration of macrophages, leukocytes, granulocytes and mast cells to the area of strain[58, 59], where proteases and growth factors are released to modify the extracellular matrix[53, 54]. Under this process the vein wall is stiffened as smooth muscle and elastin levels are reinforced and type 1 collagen is chosen over the more flexible type 3 collagen[41, 43, 55]. A release of MMPs by macrophages adds to this process, with collagen and elastin in the vein further degraded[45, 48]. Unfortunately this repair process is not consistent and leads to an alternating pattern of either weakened or stiff inelastic tissue along the vein media, adding to the disordered nature of the varicosity[56, 57].

This cycle of venous hypertension and inflammation has been demonstrated in a rat model. In vivo experiments have shown that consistently elevated femoral vein pressures are associated with an increased number of inflammatory cells within the vein wall and valves[58-60]. However, while valves were noted to stretch almost immediately the development of venous reflux actually took several days to develop. Histological examination of patients with varicose disease appears to support this observation, with the deformed varicose valves often infiltrated with significant numbers of inflammatory cells and processes[61]

Chronic venous insufficiency

Once the vicious cycle of SVI has commenced there is a risk that it may evolve into a more obstinate disease state termed chronic venous insufficiency (CVI), typically characterised by oedema, skin changes, pigmentation and even tissue ulceration. Although it is common for patients with CVI to also have underlying SVI, it remains unclear as to the causal reasons for this disease progression. It is likely that venous hypertension and inflammation also play a significant role in the development of CVI, as is understood to occur in SVI, with evidence suggesting that patients with elevated post ambulatory venous pressures (AVP) are more likely to develop tissue damage and ulceration compared to those with a low AVP. Evidence which supports this theory comes from the observation that tissue ulceration is typical in patients with an AVP above 90 mmHg, whereas it is comparatively rare in patients with an AVP less than 30 mmHg[62, 63]. The mechanism behind this process remains uncertain, but is presumed to be due to trapping of leukocytes in the tissues with attendant inflammation, and is discussed below.

Leukocyte trapping

Experiments have shown that venous blood returning from a leg, especially from one with CVI, is often depleted of leucocytes after being held in the dependent position over a period of time[64, 65]. The cause of this phenomenon is not yet well understood but is thought to relate to an increased leucocyte adhesion to the capillary endothelium due to a combination of reduced shear forces and increased numbers of adhesion-molecules within the hypertensive environment[66-68]. Once trapped, the leucocytes begin to migrate into the soft tissues and subsequently become activated, producing an inflammatory response and eventually tissue changes[69, 70]. A pattern of

inflammation has been confirmed in such diseased limbs, with immunohistological staining of lipodermatosclerotic skin recording greater numbers of macrophages and T-lymphocytes than expected[61]. CVI may also result in up regulation of MMPs and down regulation of TIMPs, further adding to disorganisation in the extracellular matrix, reducing healing and increasing the risk of ulcer formation[71-73]. Other processes, such as elevated levels of ferritin and ferric iron in the skin, may arise due to extravasation of erythrocytes caused by increased venous pressure and capillary permeability[74, 75]. These cells, once consumed and broken down by phagocytes, may add to oxidative stress and MMP activation, further delaying healing[76].

Proximal venous obstruction

As mentioned briefly above, pathology which affects the proximal deep venous system can also affect the distal superficial system. This can be related to an acute process, such as an obstruction (i.e. DVT), a later post thrombotic syndrome (PTS) or a non-thrombotic cause, such as a non-thrombotic iliac vein lesion (NIVL). One of the most significant complications associated with a DVT is a venous thromboembolism (VTE). A deep vein thrombosis may not only have local effects such as pain and swelling, but if parts of the clot break off they can cause a VTE and travel via the blood stream and block important blood vessels, especially those in the lung. This is termed a pulmonary embolism (PE) and can cause significant respiratory and cardiovascular problems. A VTE is a serious complication and can lead to death. It has been reported by NICE that approximately 25,000 people die per year from a preventable hospital acquired venous thromboembolism (VTE)[77].

The prevalence of NIVL is reportedly high with cadaveric studies performed as early as 1908 reporting that intrinsic intraluminal lesions were observed in 33% of

randomly selected bodies[78], a finding supported in several later studies[79, 80], perhaps most eponymously by Dr May and Dr Thurner[81] . The cause for such lesions is still unclear. It may be related to embryonic development of the venous fusion sites or perhaps repeated trauma due to adjacent vascular pulsations[82]. While such a lesion is unlikely to be caused by thrombosis[81], the presence of NIVL is a known risk for a secondary thrombosis[83]. Imaging studies suggest that extrinsic compression at the arterial cross over point may be present in up to two thirds of all patients, with often no venous symptoms[84].

The importance of proximal venous obstruction in SVI is not yet currently well understood and is likely to develop into a large avenue of research in the next few decades. Tentative signs of its potential significance can be found in pelvic venous congestion, whereby venous stenting of common iliac or IVC veins has been found to improve symptoms in females with chronic pelvic pain and dyspareunia[85]. Some studies have found encouraging results in venous stenting in patients with CVI and venous ulcers[86]. A systematic review performed by Seager et al[87] suggested that, while the evidence for deep venous stenting was weak, the outcomes of studies collated consistently reported an improvements in venous haemodynamics and symptoms in patients with obstructive CVD. The role of deep venous stenting and angioplasty in SVI has yet to be fully investigated, especially in its role after treatment and its potential role in recurrence after treatment.

1.4 Epidemiology

SVI is a common disease with up to half of the world's population estimated to have at least minor stigmata of venous disease and up to quarter of all adults estimated to have visible varicose veins[88]. As detailed in Table 1, the reported prevalence of

venous disease can vary widely across the world, possibly a reflection in differences in both study methodology as well as actual prevalence[89]. Fortunately several high quality studies, namely the Edinburgh vein study[90], the France study[91], the Bonn vein study[92, 93] and the Belgium-Luxembourg study[94], have allowed an important insight into the burden of venous disease in the western European population

One of the earlier studies, the Edinburgh vein study[90], reported that the prevalence of venous disease was much higher in women aged up to 45 years old, but in those aged between 55 to 65 years old it was twice as prevalent amongst men (25.3% versus 12.3%). A population study in the south of France reported that varicose veins were present in 50.5% of women and 30.1% of men, with venous symptoms affecting 5.4% of women and 2.8% of men[91]. The Bonn vein study[92] revealed that the diagnostic criteria for SVI (reflux longer than 0.5 seconds in a superficial vein) was met in 17.7% of men and 23.5% of women, with the GSV implicated in 11.8% of men and 16.4% of women screened. A study across Belgium and Luxembourg reported that venous disease was evident in 61.3% of adults, with 25.9% showing clinical signs of CVI and 0.9% an active venous ulcer[94].

The incidence of venous disease is less reported but has been researched in several studies. One of the longest follow-up studies lasted for 16 years in Framingham, USA[95], and suggested that the incidence rate was on average 51.9 per 1000 for females and 39.4 per 1000 for males over two years. A follow-up of the first Bonn vein study [96] reported that the incidence rate of uncomplicated varicose veins was 13.7% over six years. In Bochum[97], a study of young adolescents aged 10 to 12 years old reported that, while no child had visible varicosities at the start of the study, the prevalence of SVI was 2.5% despite their young age. However, when the group were

examined again between 18 and 20 years old the prevalence of SVI had increased to 19.8%, with up to 5% now displaying visible surface varicose tributaries.

Year	Author	Location	Sample size	Prevalence (%)	
				Male	Female
1942	Lake[98]	United States	536	40.7	73.2
1958	Arnoldi[99]	Denmark	1684	18.4	38.0
1966	Bobek[100]	Bohemia	15060	6.6	14.1
1966	Weddell[101]	United Kingdom	289	31.0	36.0
1969	Mekky[102]	Egypt	504	-	32.1
		England	467	-	5.8
1970	Prior[103]	New Zealand	232	25	42
1972	Malhotra[104]	India (North)	354	6.8	-
		India (South)	323	25.1	-
1973	Coon[105]	United States	6389	12.9	25.9
1973	Guberan[106]	Switzerland	610	-	29
1974	Da Silva[107]	Switzerland	4376	57.0	68.0
1975	Beaglehole [108]	Cook Island (Rarotonga)	417	15.6	14.9
		Cook Island (Pukapuka)	377	2.1	2.0
		New Zealand (Maori)	721	33.4	43.7
		New Zealand (Pakeha)	356	19.6	37.8

		Tokelau	786	2.9	0.8
1975	Stanhope[109]	New Guinea	728	5.1	0.1
1977	Richardson[110]	Tanzania	1259	6.1	5.0
1981	Abramson[111]	Israel	4802	10.4	29.5
1981	Ducimetiere[112]	France	7425	26.2	-
1986	Maffei[113]	Brazil	1755	37.9	50.9
1988	Novo[114]	Italy	1122	19.3	46.2
1989	Leipnitz [115]	Germany	2821	14.5	29.0
1990	Hirai [116]	Japan	541	-	45
1991	Stvrtinova [117]	Slovakia	696	-	60.5
1992	Franks [118]	England	1338	17.4	31.6
1993	Laurikka [119]	Finland	5568	18.4	41.7
1994	Komsuoglo [120]	Turkey	856	34.5	38.3
1995	Sisto [121]	Finland	8000	6.8	24.6
1997	Krijnen [122]	Netherlands	387	58.0	-
1998	Canonico[123]	Italy	1319	17.0	35.2
1999	Evans[90]	Scotland	1566	39.7	32.2
1999	Preziosi[124]	France	3065	10.8	18.1
2000	Kontosic [125]	Croatia	1324	18.9	34.6
2003	Criqui[126]	Unites States	2211	15.0	27.7
2003	Rabe [93]	Germany	3072	12.4	15.8
2003	Jawien[127]	Poland	40095	28.0	35.0
2004	Carpentier[91]	France	8000	30.0	51.0
2007	Sam [128]	United Kingdom	100	33.0	-

2008	Pospisilova [129]	Czech Republic	319	36.0	54.0
2008	Maurins [92]	Germany	3072	-	31.4

Table 1 Reported prevalence estimates of varicose veins comparing gender across the world

Associations and risk factors

It remains unclear if genetic or environmental risk factors can predispose someone to venous disease. Regardless, it is a common preconception amongst the general public that certain risk factors do indeed exist; with pregnancy, frequent standing and family history all commonly cited. Unfortunately, epidemiological evidence is limited in its illumination for such influences, often due to a lack of standardised protocols, diverse reporting and limited patient selections. Other issues, such as patient self-selection, are a particular problem in epidemiological studies of this type because this may overestimate the true significance of certain risk factors. It must also be recognised that older studies may also lack some sophisticated statistical techniques which are now commonplace in epidemiological research, which often allow for adjustments for confounding factors, such as age and gender. Still, some studies have suggested that there are some influences on venous disease and these are discussed below.

Gender

Numerous studies have reported a higher prevalence of venous disease in females[91, 93, 99, 101, 105, 108, 111, 113, 114, 118, 119, 121, 123, 124, 127, 130] with only a minority of studies reporting a higher prevalence amongst men[109, 131]. However, it is difficult to estimate how much of this a true reflection of disease prevalence and how much is due to selection bias in inadequately conceived studies. For instance, females are both more

likely to volunteer for medical research and more likely to notice the appearance of early venous disease. Perhaps more importantly, in retrospective studies females with venous disease are also more likely to be correctly diagnosed by their doctor compared to men with venous disease[90]. It is also important to note that it was one of the higher quality epidemiological surveys, the Edinburgh vein study, which actually reported a higher prevalence of axial varices in men compared to women (after both groups were adjusted for age) suggesting that the conventional view that women are more affected may not necessarily be the full picture[90].

Age

Many studies consistently report an association between increasing age and burden of venous disease [90, 91, 99, 101, 102, 104-106, 111, 114, 116-118, 121, 123, 124, 130-133]. The Edinburgh vein study[90] reported that the prevalence increases from 11.5% among 18 to 24 year olds to 55.7% among 55 to 64 year olds. The Tampere vein study[132] found that, compared to those aged 40 years old, the odds of developing venous disease doubled among those aged 50 years old and almost trebles among those aged 60 years old. The San Diego vein study[134] reported that the prevalence of venous disease was 16.9% among those aged below 50 but was 29.9% in those aged over 70.

Hereditary factors

It is a common perception amongst patients is that there is a hereditary component to venous disease, with risk thought to be conferred by family history reflected in some published literature[91, 97, 101, 102, 116, 117, 119, 132, 134-136]. To investigate this issue, a study by Cornu-Thenard et al[135] examined both patients and their families to clinically elicit if there was indeed a hereditary association. After examining 134 separate families it was reported that if both parents had venous disease the prevalence was approximately 90% in their children, if one parent had venous disease the prevalence

was around 60% in a daughter and around 25% in a son, and if there was no family history the usual prevalence was only 20%.

Pregnancy

The physiological changes experienced during pregnancy are considerable, as are the changes in the circulating hormones, but while varicose veins in pregnancy are a common concern among expectant mothers it is unclear if there is a relationship between venous disease and pregnancy, with some studies supporting the assertion [88, 91, 111, 116, 117, 132, 137] but others discounting it[101, 105, 106, 138]. It has also been observed in some studies that multiple pregnancies may increase the risk of developing varicose veins, but this is by no means confirmed[121, 131, 132]. The original (and now discredited) hypothesis was that an increase in abdominal pressure due to a gravid uterus would impair venous return and therefore cause varicose veins as venous hypertension develops[139]. But this could not explain the observation that varicosities typically develop during the first three months of pregnancy (before any significant increase in uterine volume) and that they also have the tendency to regress after birth, suggesting that it is more a physiologic rather than an obstructive process[140, 141] Instead it appears more likely that circulating hormones and chemical mediators have an important role and hormone receptors have been identified on venous valves signifying a potential interaction[142, 143]. As such, under conditions of pregnancy veins have been observed to increase in laxity and dilate, whereas in the absence of such conditions (i.e. the postpartum period) veins often return to their original size[144, 145].

Body mass index (BMI)

There appears to be a link between BMI and venous disease, but the exact nature of the relationship remains unclear. While the Bonn vein study[92] reported that venous disease was more likely in those with a BMI greater than 30, several studies have

suggested that this association may be only be in women[90, 95, 111, 123]. Evidence suggests that adipose tissue may elevate the levels of circulating oestrogen, thereby causing a similar dilating effect on veins as seen in pregnancy[146]. It has also been proposed that the mass effect of obesity on veins may itself impair normal venous return[147]. It has been noticed that height is an independent risk factor for developing SVI, even when controlling for BMI.[91, 121, 132, 148].

Lifestyle and physical activity

In keeping with the vicious cycle hypothesis it is logical to suppose that any additional stress on the venous system would increase the risk of developing venous disease. One such stressor hypothesised is vigorous physical activity and, indeed, one case control study has suggested that regular exercise may increase the risk of SVI, although this association is believed to weaken as age increases[149]. Conversely, some studies have suggested that SVI is greater among those who barely exercise[95 91, 117]. A possible explanation for this contradiction may be in that SVI is associated with worsening leg symptoms, putting those with SVI off any form of exertion and giving the appearance of a negative relationship. Other forms of physical activity, such as heavy lifting[101] or frequent standing have also been suggested as risk factors[95, 111, 121, 150]. However, most studies have failed to find evidence of any relationship[113, 148]

Nutrition and diet

Studies have suggested that a low fibre diet is associated with varicose veins[111, 114]. Rather than a direct nutritional deficiency, it has been proposed that increased intra-abdominal pressure during defecation (i.e. constipation) could result in impaired venous return. Such an association between straining while defecating and moderate to severe truncal varicosities in men has actually been identified in the Edinburgh

vein study[151]. Other studies have failed to confirm this association and it is likely that numerous confounding factors will make it difficult to establish if there is an actual relationship[102, 123].

1.5 Clinical assessment

A careful medical history and examination are essential elements in the clinical assessment of a patient with suspected venous disease. Non-specific leg symptoms are common among the general population and it is therefore important to ensure that the presenting symptoms are indeed directly related to underlying SVI, otherwise any intervention may be ineffective and unnecessary. It is important to note that some chronic leg conditions and arterial pathologies can present in a similar fashion to venous disease, so early diagnosis and prompt specialist input is essential to avoid any preventable morbidity or complications. In the UK, most patients are referred to a specialist unit after they have been consulted by their General Practitioner (GP). The National Institute for Health and Clinical Excellence (NICE) guidelines for referral to a specialist doctor[152] are outlined in Table 2.

Section	Recommendation	Note
1.2.1	• Refer people with bleeding varicose veins to a vascular service* immediately	* A team of healthcare professionals who have the skills to undertake a full clinical and duplex ultrasound assessment and provide a full range of treatment
1.2.2.	Refer people to a vascular service if they have any of the following.	** Veins found in association with troublesome lower limb symptoms (typically pain, aching,

	• Symptomatic** primary or symptomatic recurrent varicose veins. • Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency. • Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence. • A venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks). • A healed venous leg ulcer.	discomfort, swelling, heaviness and itching)

Table 2 National Institute for Health and Clinical Excellence (NICE) Referral guidelines for varicose veins[152]

Medical history

In the UK most patients who are referred by their GP to a vascular surgeon are seen in a dedicated vascular clinic[153]. At this appointment a medical history is undertaken and the patients' symptoms are described and documented. Common complaints can range from leg aches or cramps, frequent itching, limb swelling to a leg which often feels heavy and uncomfortable[154]. Some patients may also complain that their symptoms worsen after a long period of standing, possibly relating to prolonged

distention of the veins which stretches the subcutaneous nerve fibres[155]. In addition to their symptoms it is also important to review their medical and surgical history, especially regarding any previous venous treatments, presence of deep vein insufficiency, leg or groin traumas, pregnancies, hormone use, heart conditions (especially a patent foramen ovale), anti-coagulant medication and any coagulation disorders. Family history and social history, with smoking and alcohol consumption quantified, should also be undertaken at this point.

Clinical Examination

The physical examination should be undertaken in a warm, well-lit environment with patient privacy safeguarded and, if desired, a chaperone in attendance. With the patient exposed from the umbilicus down, the examination often starts with the patient standing. First, visual inspection of both groins and legs is performed, with any atypical location of varicosities, such vulvar or abdominal wall tributaries, noted as these may indicate complex proximal disease or obstruction[156]. Second, stigmata and extent of venous disease is recorded and the limb classified as per international standards (see CEAP classification (see page 60) and VCCS classification (see page 63). Several eponymous techniques can also be performed, such as the Trendelenburg, Fegan and Perthes tests, but these are now generally regarded as antiquated test, unlikely to alter the patients management and are as a consequence seldom performed today[157].

Investigations

Duplex Ultrasound Scan (DUS)

Duplex ultrasound (DUS) is recommended by NICE and other international bodies as the primary, "gold-standard" diagnostic investigation for patients with suspected

venous disease[10, 152, 158, 159]. It is a non-invasive test which is accurate, safe and cost-effective and is widely available and, due to its clinical usefulness and ubiquity, can be used before, during and after treatment to evaluate outcomes and help detect complications[160, 161 162]. Before the widespread introduction of DUS continuous hand-held Doppler ultrasound machines were often used in outpatient clinics to try to help deduce the underlying pathology (i.e. the presence or absence of junctional reflux). However, because of its inherent inaccuracy and inability to provide detailed anatomy information the hand-held Doppler device was quickly superseded by DUS in most venous referral centres[152, 163, 164]. Today, even when a continuous hand held Doppler is performed in clinic, most patients will undergo a formal DUS examination as a matter of course[153].

One of the reasons by DUS has become so popular is because it is a technique which can display both anatomy and blood flow within a limb. Using three standardised modes; B-Mode, Colour Doppler and spectral Doppler mode; a DUS machine can provide significant amounts of haemodynamic information to help diagnose and guide treatment[165]. The first mode, B-Mode, displays the “classical” black and white picture expected of an ultrasound scan, the principles of which are as follows.

A piezoelectric crystal located at the tip of an ultrasound probe receives specially generated electrical impulses which are controlled by a computer. The crystal is deformed as the electric charge induces the Piezoelectric effect, causing the generation of sound waves which pass back and forth throughout the tissue. Conversely, when these sound waves return to the tip of the probe the piezoelectric crystal undergoes mechanical stress, generating its own electric charge. The ultrasound machine computer can therefore analyse this process and calculate the

spatial location of the reflector and generate an image of the anatomy beneath the skin[166].

Over the past few decades numerous advances in ultrasound technology have led to the development of ultrasound machines which can measure and interpret ultrasound signals associated with movement and blood flow. By utilising the "Doppler shift" phenomenon, a computer is able to detect and analyse signals which return from moving objects and liquids[167]. The ultrasound machine can then represent this information as a velocity measurement (typically cm/s in medical settings) or visually (with pixels representing velocity on a colour scale) with an overlay image of all these pixels creating a visual impression of the flow detected. This technique can also allow the ultrasound operator to place a Doppler sample gate (a special function in most modern ultrasound machine computers) over the area of blood flow to record the Doppler frequency signals which can be captured as a Doppler waveform and presented as a blood velocity over time[168]. This function is important because when a vein is under DUS examination any significant venous reflux is defined as reflux lasting 0.5 seconds or longer in a superficial vein and 1 second or more in a deep vein. Using a combination of these three modes the DUS technique has been shown to be an effective method in producing detailed anatomical and haematological medical reports, vital in the diagnosis and treatment of venous disease[10, 158, 161].

Plethysmography

Plethysmography is a non-invasive investigation which can measure the change in volume of a limb or organ. In investigating venous disease it is often used as a dynamic test which can assesses the function of the musculo-venous pump mechanism of the leg and potentially detect the presence of venous reflux and

outflow obstruction[169, 170]. Various Plethysmography techniques exist, such as air-plethysmography, photo-plethysmography and strain-gauge plethysmography[171, 172]. The general principle behind plethysmography is that, over a series of calf exercises, it is possible to measure the reservoir and ejection volume of a limb. After the test is completed, the reservoir, ejection and residual volumes are all measured and can be used to calculate a venous filling index which, if abnormal, could suggest venous insufficiency[173]. While plethysmography has found a role in venous research and compares well diagnostically to DUS, in most healthcare centres it is mainly reserved a test reserved for complex cases, such as patients with advanced CVD and those with inconclusive DUS results (often when axial reflux or obstruction is inconclusive[174-176]). Despite its usefulness, plethysmography does have the limitation that, unlike DUS, it can only provide an assessment of the physiological function of the limb and cannot provide any anatomical information.

Venography

Invasive and non-invasive venographic techniques are often reserved for complicated venous patients, such as those with rare genetic diseases or proximal and obstructive conditions. Invasive contrast venography used to be commonplace but in most centres today CT and MRI are now generally preferred due to their non-invasive nature and high degree of detail[177]. However, while the images obtained will delineate the anatomy, they cannot show the underlying vein haemodynamics which is often invaluable information when planning complicated open or endovenous procedures[178].

Classification of venous disease

The spectrum of CVD is broad and encompasses a wide variety of disease manifestations. Unfortunately, the long history of venous disease has led to the legacy of several competing definitions and classifications, with the overall effect confusing and dividing the literature. Thus, the American Venous Foundation in 1994 convened a committee of international experts to establish the first internationally recognised classification system for venous disease, the Clinical, aEtiologic, Anatomic and Pathophysiologic (CEAP) system[24, 179, 180].

CEAP classification

The CEAP is regarded as the authoritative international classification system for venous disease[160] (Table 3). Divided into four parts, the CEAP system aims to logically classify the severity of venous disease and its underlying pathology into a straightforward and logical system. Unfortunately, this comes at a cost and some clinical limitations with the CEAP system have been noted. Firstly, CEAP is relatively insensitive to detail when describing the extent of disease[181-184]. For example, a CEAP of C2 does not discriminate between a limb with a single venous tributary to one with large numbers of venous tributaries. Secondly, the system is unable to measure the extent of a patients symptoms. Thirdly, the CEAP is relatively insensitive to change. For example, a limb with a healed venous ulcer can never be classified below C5 and, realistically, a limb with C4 disease is unlikely to ever be downgraded due to near permanence of the tissue changes. Fourthly, CEAP is incapable at measuring improvement after treatment, especially with the more severe disease states, limiting its usefulness for research and audit[160, 185]..

Venous Clinical Severity Score (VCSS)

The Venous Clinical Severity Score (VCSS) was first introduced in the year 2000 and complements the CEAP system considerably, especially in the characterisation of symptoms and extent of venous disease[160, 186, 187] (Table 4). The VCSS consists of ten questions scored out of three and it compares well with both CEAP and DUS results as well as being a highly responsive questionnaire to changes after treatment[187-191]. As such, the VCSS tool is often used both before and after treatment for assessment and to measure patient outcomes. However, while the VCSS is useful in this regard one question (Compression Therapy) has attracted some criticism. The value of compression has yet to be established and compliance with stockings is can often be poor[192]. It is not uncommon for patients to find compression uncomfortable or painful, especially after treatment, and some elderly patients may be physically unable to apply compression without assistance[193]. Two patients with the exact same level of disease can therefore have vastly different VCSS scores simply because one has the ability to ability to apply compression while the other does not.

	CEAP	Description
Clinical classification	**C_0**	No visible or palpable signs of venous disease
	C_1	Telangiectasia or reticular veins
	C_2	Varicose veins
	C_3	Oedema
	C_{4a}	Pigmentation and / or eczema
	C_{4b}	Lipodermatosclerosis and / or atrophie blanche
	C_5	Healed venous ulcer
	C_6	Active venous ulcer
aEtiologic classification	**E_c**	Congenital
	E_p	Primary
	E_s	Secondary
	E_n	No venous aetiology identified
Anatomic classification	**A_s**	Superficial veins
	A_p	Perforator veins
	A_d	Deep veins
	A_n	No venous location identified
Pathophysiologic classification	**P_r**	Reflux
	P_o	Obstruction
	$P_{r,o}$	Reflux and obstruction
	P_n	No venous pathophysiology identified

Table 3 CEAP classification [24] (Each clinical classification can be given a suffix of "S" or "A" for symptomatic or asymptomatic respectively

Attribute	Score			
	None: 0	**Mild: 1**	**Moderate: 2**	**Severe: 3**
Pain	None	Occasional. Not restricting daily activity	Daily. Interfering with, but not preventing regular daily activities	Daily. Limits most regular daily activities
Varicose veins	None	Few: scattered	Confined to either calf or thigh	Involve calf and thigh
Oedema	None	Limited to foot and ankle area	Extends above ankle, but below knee	Extends to knee and above
Skin pigmentation	None or focal	Limited to perimalleolar area	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 of calf
Inflammation	None	Limited to perimalleolar area	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 of calf
Induration	None	Limited to perimalleolar area	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 of calf
No. of active ulcers	0	1	2	≥3
Duration of longest active ulcer	-	<3mths	>3mths but <1yr	>1yr
Diameter of largest active ulcer	-	<2cm	2-6cm	>6cm
Compression therapy	Not used	Intermittently used	Worn most days	Full compliance

Table 4 Varicose Clinical Severity Score (VCSS) [187]

Assessment of Quality of life (QoL)

The era of evidence based medicine (EBM) has led to the development of several health related Quality of Life (QoL) tools which aim to objectively measure the physical and psychological changes on a person's well-being associated with illness and disease. The impact of SVI on a patient's QoL can be quite significant and cannot be simply predicted by the disease severity alone[194-196]. Improvement in QoL is now regarded as one of the most important measures of treatment success and NICE often uses QoL measurements in their treatment recommendation and cost effectiveness calculations[197]. As such, treatments which do not improve QoL are unlikely to be supported by NICE and, by extension, unlikely to become adopted on any significant scale.

Short Form 36 (SF-36)

The Short Form 36 (QualityMetric, Lincoln, Rhode Island, USA) is one of the most comprehensive and well-known generic QoL measurement tools available today[198-204]. Prior to its introduction any assessment of an individual's QoL would often require a long and arduous interview with a trained interviewer, sometimes needing to ask over a hundred questions to generate any meaningful result. Fortunately, the SF-36 consists of only 36 questions and is essentially a refinement of two earlier and much larger QoL projects; the Medical Outcomes Study[200] and the RAND health insurance study[205]. Compared to its predecessors the SF-36 has fewer and more focused questions (all but the most pertinent questions were removed) and has been shown to be a valid, sensitive and accurate method of measuring QoL across a wide range of diseases[195, 198, 199, 201, 202, 206]. The utility of the SF-36 in venous disease has long been established[195, 196]. The instrument itself measures eight psychometric

domains and is graded on a scale from 0 (worst health) to 100 (best health) (Table 5). While the SF-36 is a useful tool it is important to be cautious in interpreting the information collected, especially in regards to a minimal clinically important difference (MCID). In short, the MCID is smallest change in score which can be associated with a significant improvement in health. The authors of the SF-36 state that a 5 point (out of 100) change should be the minimum amount required to produce a "clinically and socially relevant" change in any individual[199]. While this is generally true, some studies have found that the MCID can actually vary in certain domains. For example, Angst et al [207] reported that in patients with osteoarthritis of the hip or knee the MCID could range from 3.3 to 5.3 points in the physical function domain and 7.2 to 7.8 points in the body pain domain. As such the developers consider the MCID to be "typically in the range of 3 to 5 points" but also recommend caution when interpreting results which fall into this range[208].

SF-36	**Physical Domains**	**Physical Function (PF)**
		Role Physical (RP)
		Body Pain (BP)
		General Health (GH)
	Mental Domains	Vitality (Vit)
		Social Function (SF)
		Role Emotional (RE)
		Mental Health (MH)

Table 5 Domains of the SF-36

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

B1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

B2. 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
☐	☐	☐	☐	☐

B3. 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 sport	☐	☐	☐
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 one mile**	☐	☐	☐
h) Walking **several hundred yards**	☐	☐	☐
i) Walking **one hundred yards**	☐	☐	☐
j) Bathing and dressing yourself	☐	☐	☐

B4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐
b) **Accomplished less** than you would like	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐
d) Had **difficulty** performing the work or other activities (for example it took extra effort)	☐	☐

B5. During the past 4 weeks, have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐
b) **Accomplished less** than you would like	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐

B6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

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

B7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

B8. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

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

B9. These questions are about how you feel and how things have been with you during the past 4 weeks. 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 past 4 weeks…

	All of the time	Most of the time	A Good bit of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
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?	☐	☐	☐	☐	☐	☐

B10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

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

B11. How TRUE or FALSE is each 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 anyone I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

EuroQol 5 Dimension (EQ5D)

The EQ5D™ (EuroQol Group, Rotterdam, NL) is a valid, accurate and popular generic index QoL measure which can be used to calculate Quality Adjusted Life Years (QALY's), a fundamental unit in health economics[197, 204, 209-211]. The EQ5D consists of five questions on a three level scale and has a visual analogue scale (VAS) to measure a global health state. The EQ5D calculates a single "index-utility score", a unit of health which can be used to compare between patients and different diseases. On an index scale between 1 and 0, a health state of 1 would be considered the best imaginable health state whereas an index of 0 would be considered a state of complete absence of health (i.e. terrible health or death). In some cases the index score may be negative, essentially representing a health state worse than death[212]. But the EQ5D does have some limitations. Despite its international popularity (especially in Europe) and widespread adoption, the EQ5D is relatively unresponsive to diseases with mild to moderate QoL impairments[213, 214]. A typical MCID for the EQ5D has been estimated to be around 0.125[215], which is quite a significant proportion of the overall index score of 1. In recognition of this limitation a modified questionnaire called the EQ5D-5L (which uses a five level scale) has been recently developed in the hope that it may prove to be more responsive to milder disease states, improving its effectiveness and overall value[216]. Regardless, the current EQ5D remains popular and a significant body of medical research has used it successfully over several decades and will likely continue to do so in the near future.

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

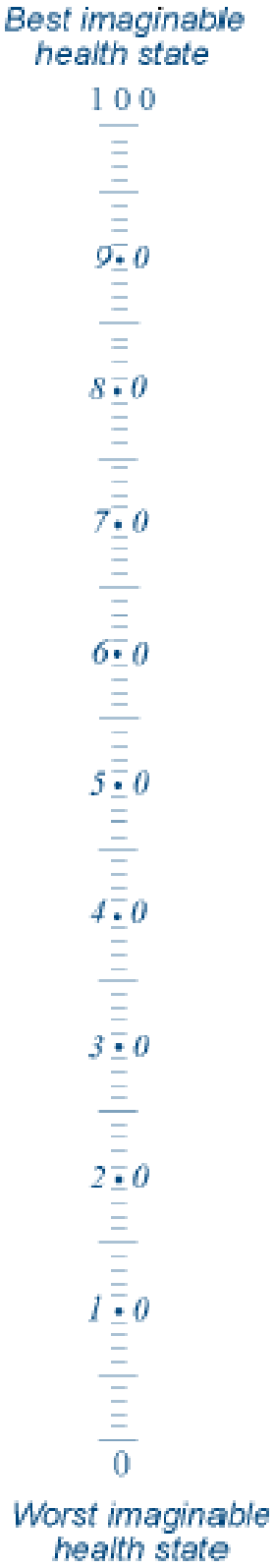
A1.	**Mobility**	I have no problems in walking about	☐
		I have some problems in walking about	☐
		I am confined to bed	☐
A2.	**Self-care**	I have no problems with self-care	☐
		I have some problems washing or dressing myself	☐
		I am unable to wash or dress myself	☐
A3.	**Usual Activities** *(e.g. work, 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	☐
A4.	**Pain/Discomfort**	I have no pain or discomfort	☐
		I have moderate pain or discomfort	☐
		I have extreme pain or discomfort	☐
A5.	**Anxiety/Depression**	I am not anxious or depressed	☐
		I am moderately anxious or depressed	☐
		I am extremely anxious or depressed	☐

A6. **Please indicate on this scale how good or bad your own health state is today.**

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today

Your health state today



SF-6D

Derived from the SF-36 and SF-12 QoL questionnaires, the SF-6D is an alternative index utility score to the EQ5D[210, 213, 217-219]. As with the EQ5D, the SF-6D also determines health index scores between 1 and 0 and can be used to generate QALYs for health economic calculations but, while the SF-6D is regarded as useful, the EQ5D remains the index utility score recommended by NICE and as such remains more dominant in UK research[220-222]. Despite this, the SF-6D does have the advantage over the EQ5D in that its MCID is considerably smaller at around 0.010 to 0.048 points[223].

Recently, some questions have arisen regarding the comparability of the EQ5D and SF-6D in health economic studies. While it is not unsurprising that there will be some differences between both scoring tools in some patients, there is the potential that these differences could magnify over different populations and diseases and hence give significantly different outcomes. In some studies these differences only produce a negligible difference in the end product of a cost economic analysis but, in others studies, significant differences in index scores and their subsequent results have been found[224-226]. The implications of this discrepancy in medical research have yet to be ascertained but it is clear that both tools should be considered distinct and used carefully in their analysis[227].

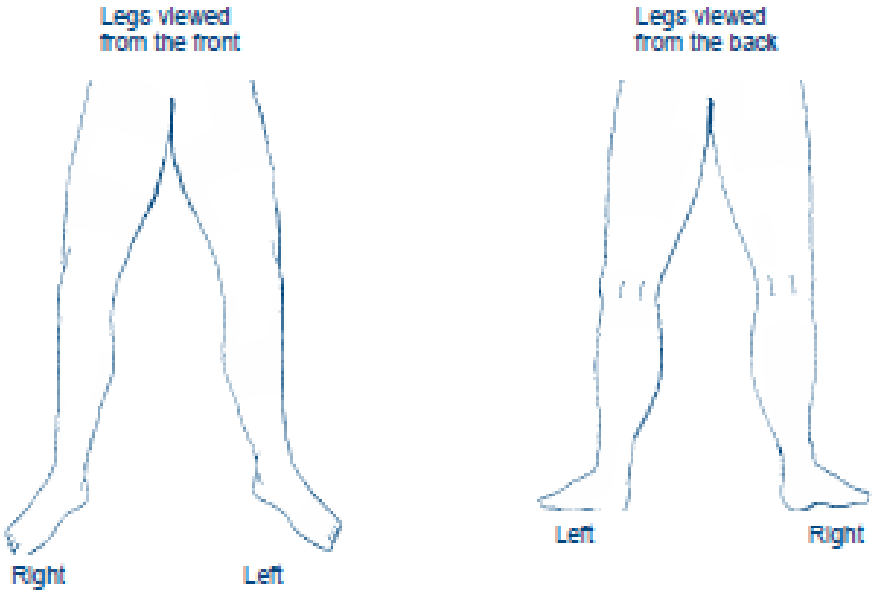
Aberdeen Varicose Vein Questionnaire (AVVQ)

The Aberdeen Varicose Vein Questionnaire (AVVQ) is a disease specific measure of QoL and one of the best measures of QoL impairment associated with SVI available[195, 228184, 185, 209]. The AVVQ consists of two parts; the first section asks the patient to draw a visual representation of their venous disease on diagram (which is later scored using a transparent grid) and the second section asks 13 questions which

measure the impact of SVI on mental and physical well-being[229]. The AVVQ is scored out of 100 but very high scores are uncommon. Those with uncomplicated SVI usually score between 10 to 30 points and those with venous ulcers typically score between 30 to 60 points[230].

It has several advantages over the other generic QoL tools such as the SF-36 and EQ5D. Firstly, the AVVQ is specific to patient's complaints regarding SVI and therefore patients may find the AVVQ more relevant and relatable to their current health state[228]. Secondly, the AVVQ is also more likely to discriminate between patients, especially at the milder end of the disease spectrum, and this has proven to be a useful measure of improvement after venous intervention[231]. Thirdly, the ease and usefulness of the AVVQ has even led to some specialists suggesting that the AVVQ could be completed by patients at home or online, helping speed up referrals and appointments[232, 233]. The limitation with the AVVQ is that despite its pedigree its MCID has yet to be formally established. Fortunately, due to the inherent sensitivity of the AVVQ and its detailed questions it is likely to be small, on the order of 1 to 2 points[234]

C1. Please draw in your varicose veins in the diagram(s) below:-



C2. In the last two weeks, for how many days did your varicose veins cause you pain or ache? *(Please cross one box for each leg)*

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

C3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins? *(Please cross one box)*

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

C4. In the last two weeks, how much ankle swelling have you had? *(Please cross one box)*

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

C5. In the last two weeks, have you worn support stockings or tights? *(Please cross one box for each leg)*

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

C6. In the last two weeks, have you had any itching in association with your varicose veins? (*Please cross one box for each leg*)

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

C7. Do you have any purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C8. Do you have a rash or eczema in the area of your ankle? (*Please cross one box for each leg*)

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

C9. Do you have a skin ulcer associated with your varicose veins? (*Please cross one box for each leg*)

	Right Leg	Left Leg
No	☐	☐
Yes	☐	☐

C10. Does the appearance of your varicose veins cause you concern? (*Please cross one box*)

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

C11. Does the appearance of your varicose veins influence your choice of clothing including tights? (*Please cross one box*)

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

C12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities? (*Please cross 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 ☐

C13. During the last two weeks have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)? (*Please cross 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 ☐

1.6 Management of venous insufficiency

Compression bandages and hosiery

Compression is a widespread and well-established conservative treatment option for venous disease and has several clinical benefits, not least an improvement in symptoms[235-237] and underlying venous haemodynamics[238-240]. The principle behind compression is that by applying a source of extrinsic pressure the incompetent venous system can be temporarily supported, which should reduce venous reflux and, by extension, venous hypertension[241-243]. High levels of compression will occlude most superficial veins and prevent most blood flow (including reflux), but it has been reported that a moderate level of compression may be able improve the haemodynamics inside the varicose vein while maintaining its patency[240, 244, 245]. One theory is that that by compressing a vein back to a relatively normal diameter the functionality of the venous wall and valves can be restored, increasing venous return and preventing venous stasis, reflux and, potentially, averting venous hypertension and the vicious cycle (see page 40) [243, 246, 247]. Clinical studies suggest that a compression pressure greater than 60 mmHg should occlude most superficial leg veins completely, whereas a median compression pressure between 30 to 40 mmHg should provide a hemodynamic benefit in legs which are both supine and standing[248]. Venous return can be further assisted if, as per the law of Laplace (pressure = tension/radius), application of compression forms a pressure gradient up the limb towards the groin[243].

A multitude of compression products and techniques are now available to both healthcare professionals and patients directly. Compression can generally be divided into two forms, compressive bandages or compression hosiery, and there is a wide

variety of compression application options. Products also often differ in their material composition, such as elasticity or antimicrobial qualities[249-251]. Compression hosiery, such as graduated elasticated stockings, are graded according to their strength of compression (Table 6), although small differences exist between the leading international standards.

Class	USA standard	German standard (RAL)	French standard (AFNOR)	British standard (BSI)
1	15 – 20	18 – 21	10 – 15	14 – 17
2	20 – 30	23 -32	15 – 20	18 – 24
3	30 – 40	34 – 46	20 – 36	25 – 35
4	40 – 50	>49	>36	-

Table 6 Standard compression range versus compression class (range in mmHg)

Today, various compression regimes exist but the eventual choice will often be tailored to the patient's own specific individual requirements. The key objective behind compression is to achieve a comfortable application at the highest possible pressure. Evidence suggests that pressures below than 30 mmHg are less likely to alleviate leg symptoms and stigmata of venous disease, such as limb oedema, but compression levels which are too high will become uncomfortable or painful[246, 252-254]. Indeed, a major limitation to any compression regime is that the beneficial effects are only present during its use[255]. Some patients may struggle wear compression because of problems related to sweating, itching, issues with exudate, staining, cosmetic concerns and, especially if elderly or infirm, difficulty in applying the compression garment itself[256-258]. The true rate of compliance is unknown, but some studies estimate that up to a third of patients are unable to tolerate compression stockings at all[259]. Even for those who are compliant the compressive effect of

stockings may weaken relatively quickly as they become worn necessitating frequent replacement to achieve continuous benefit[260]. It has even been reported that poorly applied compression can damage the skin and underlying tissues and can even, in rare cases, compromise the arterial blood supply to the limb[160, 261-263].

There is currently little evidence supporting the use of compression as a long term treatment or as a method to delay disease progression and, as such, compression is currently only recommended by NICE for those unable or unwilling to receive treatment for SVI[152]. Several systematic reviews of the published literature have found that much of the evidence is of poor quality, heterogeneous, potentially biased and severely lacking in supportive data[254, 264-267]. However, in one of the few high quality randomised clinical trials designed to investigate compression as a treatment option for SVI, the REACTIV trial[268] found that conventional surgery was associated with a greater QoL improvement, better symptomatic relief and higher patient satisfaction compared to compression or sclerotherapy treatments. The long term outcomes of compression were also relatively poor, with half of those randomised to compression dissatisfied with their treatment at one year. Tellingly, it later appeared that a large number potential patients had declined to participate in the study in case they were randomise to a non-surgical group. Accordingly, a later follow up of the study found that over half of those who declined to participate had undergone surgery[268]. It seems that while most patients were prepared to use compression as a temporary measure, such as while awaiting treatment, most could not accept compression as a long term treatment itself[269].

For venous ulcers there is a convincing body of evidence that suggests compression can reduce healing time and chance of ulcer recurrence[264, 270-273]. Compliance is, however, crucial. For example, a study by Mayberry et al[270] found that patients with

a treated venous ulcer had an ulcer recurrence rate of 16% among those compliant with compression but a recurrence rate of 100% amongst those who were non-compliant with compression. As venous ulcers are more common in the elderly it is vital to ensure that they can apply the compression prescribed and, if not, that there are measures available to help them apply it[274].

The optimum type of compression and required duration for venous ulcers remains uncertain[275]. Bandages tend to be preferred by most experts[273], but the VenUS IV trial[276] reported similar clinical outcomes between four layer bandages and two layer compression hosiery. Treating the underlying venous pathology has also been proposed as a potential adjunct to compression, but the ESCHAR trial[277, 278] reported that ulcer healing rates were similar between those undergoing conventional surgery and compression to those treated with compression alone. Interestingly, the ESCHAR trail also reported that the rate of recurrence was much lower at one year among those who had undergone surgery compared to those allocated to just compression. Again, a similar recruitment problem arose in this study, whereby patients were reluctant to enrol because of the prospect of open surgery (endovenous treatments had recently become introduced) and the risks it would entail. It is hoped that the option of minimally invasive techniques at the outset may improve recruitment to a study to test such a hypothesis, and as such the results of the EVRA trial (ISRCTN02335796), a study investigating endovenous treatments with compression, are eagerly awaited.

Pharmacological treatment

Medications used to treat venous disease, also known as phlebotonics, have a long history and are often based on traditional natural remedies. Their role in the

management of SVI is currently uncertain, but there appears to be some indication that phlebotonics may help improve the more severe manifestations of venous disease such as venous ulcers[279]. A large Cochrane meta-analysis review looked at the efficacy of several phlebotonics, namely rutosides, hidrosmine, diosmine, calcium dobesilate, centella asiatica, French maritime pine bark extract, aminaftone and grape seed extract[280]. While the results were far from conclusive it did appear that some beneficial effect was noted in SVI associated limb oedema. A meta-analysis performed by Pittler[281] specifically looking at escin, the main active constituent of horse chestnut seed extract, found it to be an effective treatment for leg symptoms associated with SVI and, in some studies, as effective a compression stockings. Another Cochrane meta-analysis by Jull et al[282] reported that Pentoxifylline, a phosophodiesterase inhibitor, appeared to accelerate venous ulcer healing when compared to a placebo. The exact mechanism of action behind this and many other phlebotonics remains elusive but it has been suggested that there is some underlying modification of the inflammatory process, thereby lessening leucocyte activity, cytokine synthesis and free radial production[23, 283]. However, until their efficacy and cost effectiveness is established in a large randomised clinical trial it is unlikely that phlebotonics will ever be recommended by a body such as NICE. But even so, the current market for phlebotonics is sizeable and is already in excess of tens of millions of Euros per annum in Western Europe alone.

Conventional open surgery

Pioneered by distinguished surgeons such as Friedrich Trendelenburg (1844-1924), Georg Perthes (1869-1927) and Charles Mayo (1865-1939), amongst others, conventional open surgery has been the dominant treatment for venous insufficiency for well over a century[284]. , While the popularity of conventional surgery has begun

to wane since the arrival of minimally invasive surgery, it still remains one of the most common venous interventions worldwide[285]. The standard procedure is discussed in detail below (see page 119) but the ultimate aim of treatment is to remove the axial incompetence and venous hypertension. Conventional surgery typically requires ligation of the SFJ and stripping of the diseased axial trunk with concomitant avulsion of any symptomatic superficial varicose tributaries if required[286]. Compared to conservative measures this technique is associated with a significant increase in QoL, improvement in cosmetic appearance and a reduction of venous symptoms[268, 287-289]. It also appears that surgical treatment can improve the underlying haemodynamics of the entire limb, effectively acting like a "permanent" application of compression[288-290]. The QoL gain seen after venous surgery is substantial and comparable to other established elective treatments such as laparoscopic cholecystectomy[291]. Unfortunately, conventional surgery is not free of complications and, as such, several modifications to the conventional procedure have been attempted with varying levels of success

Complications of conventional surgery

One of the most significant complications with conventional open surgery is the risk of nerve damage, especially the saphenous and sural nerves (see page 35). The effects of nerve injury can be profound and it is one of the most common causes of litigation in venous surgery[292, 293]. Great care is often taken during surgery to avoid damaging any nerves and it is often now unusual to see full length vein stripping because the reported rates of nerve injury were unacceptably high at 39%, compared to only 7% when stripping was limited to above the knee only[294-296].

Another common complication after surgery is the risk of developing a surgical site infection (SSI). Venous surgery is regarded as a "clean surgery" and therefore

expected to have a nosocomial infection rate of less than 5%[297]. However, SSI's are often under reported and some studies suggest that the actual rate of infection in the groin after venous surgery can be as high as 16%[298-303]. Prophylactic antibiotics are now routinely given prior to surgery, with evidence from the HARVEST trial[304] reporting that the SSI rate can be halved from 18.2% to 9.9% with a single preoperative dose of Co-amoxyclav[305].

While it is common for most patients to experience bruising or skin discolouration after surgery, it is estimated that up to a third of patients may develop a haematoma. Once arisen this can delay recovery, increase pain and impair recovery of QoL[306 307]. It has also been suggested that a haematoma may induce groin neovascularisation, itself linked to clinical recurrence[308, 309]. Various modifications of the surgical technique to try to reduce haematoma formation have been attempted, such as stripping with suction[310] or cryostripping[311-313], but it appears that good quality postoperative compression may be the most effective method[306, 314-316].

One of the most serious complications after surgery is the risk of a thrombotic event. The rates of DVT and pulmonary embolism (PE) are low, estimated to be much less than 1% for DVT and 0.5% for PE[317, 318]. Some studies suggest that the true rate of deep venous thrombosis might be ten times higher, albeit limited to the distal crural vessels and of doubtful clinical significance[319, 320]. Another serious complication is iatrogenic injury to important nearby blood vessels. This is rare and estimated to be less than 0.3%[321].

Improvement in QoL after surgery has been reported to last for up to ten years, but a particular worry for patients over this time period is that they may develop a recurrence[322-326]. It has been shown that recurrence can significantly impair QoL improvement after treatment[327]. There are three main reasons for clinical recurrence,

namely progression of the underlying venous disease, inadequate primary treatment, and neovascularisation[328]. Inability to ligate the junction or incomplete stripping of the axial vein are both associated with excessively high rates of recurrence[289, 329-332]. Conversely, flush ligation does not appear to improve outcomes over the conventional approach[333, 334]. Various technique modification have been attempted to try to reduce the chance of neovascularisation, from suturing the cribriform fascia to biological or synthetic barrier grafts[335-341]. While the rates of neovascularisation may have reduced, this did not appear to ultimately affect the overall recurrence rate and instead just added risks associated with prosthetic material.

GSV Preservation Surgery

An alternative to removal of the main axial trunk by conventional surgery are two GSV preservation surgical techniques; namely the "Conservatrice et Hemodynamique de l'Insufficience Veineuse en Ambulatoire" (CHIVA) technique[342] and the "Ambulatory Selective Vein Ablation under Local anaesthesia" (AVSAL) technique[343, 344]. Both these treatments work on the principle of the ascending theory in that, by treating peripheral disease, is it possible to delay or prevent disease spread to the main axial trunk and, if sufficient, will return normal haemodynamic blood flow to the limb[345]. While these techniques will be ineffective against multifocal disease they do have the advantage that they will preserve the GSV for possible future surgery as a bypass conduit. These techniques are less prevalent in the UK but have found several proponents in Europe, especially in France, Italy and Spain, although it appears that minimally invasive treatments have also started to erode their popularity, as has occurred with conventional surgery generally.

CHIVA

The CHIVA technique starts with a careful preoperative DUS planning stage which aims to characterise the retrograde blood flow and identify any venous-venous shunts, which are effectively points of ejected retrograde proximal reflux blood flow into the superficial venous system which returns to the deep venous system. It is thought that such a closed circuit would not only cause local vein wall distension and venous valve dysfunction but that it will also raise the hydrostatic pressure inside the vein, potentially initiating the vicious cycle of venous dysfunction[346]. The CHIVA technique aims to disconnect these escape points with the following underlying principles; fragmentation of the venous pressure column, disconnection of venous-venous shunts, preservation of the re-entry perforators and abolition of any undrained superficial varicose veins[347, 348]. The procedure is usually performed by open surgery under local anaesthesia although minimally invasive techniques have been proposed as an alternative[349]. A Cochrane systematic review of the CHIVA technique found that recurrence of varicose veins was significantly fewer amongst those receiving CHIVA compared to those undergoing conventional surgery with axial stripping (RR 0.63; 95% CI 0.51 to 0.78) [347, 350-352] . However, the review authors also stressed caution because all the studies included for analysis were at risk of significant levels of bias. For example, no study attempted any blinding, inclusion criteria was often very strict (potentially favouring CHIVA patients), power calculations were ignored and follow up numbers were often inadequate. Regardless, the Cochrane study group felt that the CHIVA technique was associated with fewer recurrences, improved QoL and was less likely to cause bruising or nerve damage. Conversely, no difference in clinical improvement or cosmesis was detected. The disadvantages of CHIVA are that it has yet to be formally tested in a randomised

clinical trial against minimally invasive surgical techniques, almost certainly its main modern rival, and that the open technique is relatively complicated to perform compared to conventional surgery, limiting its practicality[353].

ASVAL

The ASVAL technique is a relatively recent concept in venous surgery and proposes the removal of the superficial tributary reservoir while preserving the GSV as a method of returning competence to the axis. Early haemodynamic studies have suggested that the GSV diameter can be reduced by the removal of a single incompetent tributary[354] and Zamboni et al[355] later reported that it was even possible to abolish GSV reflux entirely by removing all incompetent perforators and venous tributaries. While ASVAL has yet to be properly investigated in a randomised clinical trial, two retrospective studies have explored its potential in treating SVI. Pittaluga et al[344] reviewed the clinical and haemodynamic outcomes of 811 limbs in 599 patients following ASVAL and conventional surgery. Of 303 limbs undergoing AVSAL, GSV reflux was significantly reduced in 92.1% of limbs by 6 months and 90.7% of limbs by 4 years. There were also significant improvements in symptoms and cosmetic appearance. Long term results found that after 4 years 66.3% of limbs managed to maintain axial competence and 88.5% of limbs were free from recurrence. Unfortunately, the study was limited by significant flaws in its composition. For example, the AVSAL group were typically younger, more female, less BMI and had typically less severe disease. In addition 33.7% of the ASVAL group were preoperatively asymptomatic. But a recent small study by Atasoy et al[356] found that in 41 patients, AVSAL delivered by endovenous laser ablation and ultrasound guided foam sclerotherapy was able to return competence to all limbs with a significant improvements in QoL over 12 months. However, despite these

optimistic results ASVAL has yet to be formally investigated as a treatment for SVI in a clinical trial.

Endovenous thermal ablation (EVTA)

Endovenous thermal ablative (EVTA) techniques have revolutionised the management of SVI since their inception two decades ago and are now regarded by NICE as the first choice treatment for SVI[152]. EVTA is based on the concept that a large amount of thermal energy will destroy cells within the vein wall, which in turn will result in a durable non-thrombotic occlusion which will ultimately be replaced by scar tissue. The standard endovenous technique is detailed below (page 120) but is broadly as follows. First, an endovenous catheter is placed percutaneously into the incompetent venous axis under ultrasound control. Second, the catheter is carefully advanced to the level of the junction. Thirdly, tumescent anaesthesia (TLA) is infiltrated into the surrounding perivenous space. Finally, the endovenous instrument is inserted via the endovenous catheter and, once safely positioned, is activated and withdrawn slowly down the vein. The precise procedure often varies depending on the device and the manufacturers' guidance. One of the most critical steps in the EVTA technique is the infiltration of TLA, an innovation which EVTA would not be viable without.

Tumescent anaesthesia

Local anaesthesia was first reported in September 1884 by the Viennese Ophthalmologist Carl Koller (1857-1944) as a topical cocaine preparation for corneal surgery[357, 358]. The discovery caused great interest and merely four months later William Halstead (1852-1922) and Richard John Hall (1856-1897) demonstrated that cocaine anaesthesia could be used for intradermal infiltration and

nerve blockade[359]. Local anaesthesia was further advanced when the Chemist Alfred Einhorn (1856-1917) synthesised novocaine[360], a substance pioneered in its use by Heinrich Braun (1862-1934) who often added epinephrine to prolong its action[361]. By the 1920's TLA was a widely accepted technique in surgical textbooks and was usually termed "massive" or "hard infiltration" anaesthesia[362]. Interestingly, the techniques depicted are almost indistinguishable from modern TLA, with pressurised infiltration, anatomical landmarks and special anaesthetic formulations remarkably similar to modern TLA practices, although the technique itself slowly fell out of fashion over the subsequent decades[363, 364]. TLA was brought into vogue in the late 1980's as a promising and safe analgesic method for cosmetic surgery and it was not long until TLA was also adopted into venous surgery[365-367]. Encouraged by its safety and effectiveness, TLA was used in the first clinical EVTA trials and soon proved to be an essential step in the endovenous procedure[368-373]. Early practitioners of TLA technique often performed TLA manually, usually infiltrating only 30 to 60 ml of 0.5% lidocaine, and it was not until the mid-2000's until large pump delivered volumes became commonplace[374, 375].

TLA has several functions during EVTA. As well as an effective method of anaesthesia the tumescent fluid also acts as a heat sink, thereby protecting nearby tissues and skin from thermal damage[375-377]. Hydrodissection of the tissues during TLA also has the dual benefit of compressing the treatment vein and pushing the surrounding tissues away from the EVTA device[378]. Compressing the vein can reduce the volume of intraluminal blood and may decrease postoperative bruising, as well as increasing the amount of thermal damage delivered directly to the vein wall[379]. In expert hands nerves can be identified under ultrasound and can be carefully pushed away and protected using the TLA fluid[375]. Indeed, evidence

suggests that TLA can itself almost halve the incidence of nerve injury from 14.5% to 9.1%[377].

Of the various EVTA products, NICE currently recommends only two modalities[152], endovenous laser ablation (EVLA) and radiofrequency ablation (RFA). Other thermal techniques such as endovenous steam ablation (EVSA) and endovenous microwave ablation (EMA) are relatively new and have yet to be fully appraised for inclusion into the national guidelines.

Endovenous laser ablation (EVLA)

EVLA treatment for SVI was first reported in 1999[372] and two years later the first case series was published[373, 380]. The EVLA technique works by transmitting a laser through an optical fibre into a vein lumen, whereby the energy is absorbed by chromophores which radiate a significant amount of heat. The high temperatures generated result in extensive damage which results in venous ablation. The first laser device was constructed in 1960 by Theodore Maiman (1927 – 2007) and was based on the theoretical works of Arthur Schawlow (1921 – 1999) and Charles Townes (1915 -2015). The word "laser" is derived from the acronym "Light Amplification by the Stimulated Emission of Radiation" (LASER) and is defined as a directed beam of light which is monochromatic (one wavelength), coherent (in phase in both space and time) and collimated (low beam divergence)[381]. Most modern medical laser generators are carefully designed to produce a specific wavelength, which in EVLA often conforms to the absorption spectra of haemoglobin or water[382]. Earlier EVLA designs typically used the shorter wavelengths (810 nm, 940 nm and 980 nm) which target haemoglobin but newer EVLA machines tend to use the longer wavelengths (1319 nm, 1320 nm, 1470 nm and 1500nm) which target water. It is theorised that the longer wavelengths will be able to produce the same amount of

thermos-ablative damage but with a lower power because less energy is lost to the haemoglobin containing erythrocytes in the blood[383, 384]. As the longer wavelengths selectively target the vein wall it is presumed that patient discomfort and morbidity would be reduced[385]. Another technical modification of the EVLA device is the use of a continuous or pulse firing laser. Earlier designs often delivered short one second pulses of laser, but evidence suggests that technical outcomes are superior when the laser fibre is allowed to fire continuously[386]. A recent development in EVLA technology is the modification of the actual laser fibre design. Most manufacturers have now dispensed with the standard bare tipped optical fibre[387] in favour of new tip designs, such as gold-jacket[388], radial firing[389] and tulip centring [390] fibre tips.

The exact mechanism of action behind EVLA is still uncertain. One theory purports that ablation is a direct consequence of laser energy absorption within the vein wall [371, 391] whereas another theory states that ablation is in fact an indirect consequence of thermal damage caused by steam bubbles generated next to the EVLA tip, estimated to be often over 1000 Celsius[392, 393]. The role of the laser fibre itself has also been contested, with some histopathological evidence suggesting that ablation is caused by direct contact of the laser fibre on the wall of the vein [394]. Conversely, mathematical modelling suggests that temperatures generated by the EVLA fibre are so large that the vein wall is obliterated by thermal conduction before contact is made[395]. Ex vivo experiments suggest that extensive carbonation at the tip of the EVLA fibre make the laser beam an unlikely source of thermal damage compared to the high temperatures generated [394, 396]. Despite this ambiguity, clinical studies have shown that fluence (J/Cm^2) is a reliable measure of predicting technical success[397, 398]. In practice, the energy delivered during EVLA is often reported as a Laser

Energy Density (LED) (J/cm), with most practitioners recommending around 80 J/cm to achieve a successful ablation[399].

The EVLA technique is considered to be one of the most effective methods of treating SVI[308, 400-402]. An early meta-analysis of clinical studies using EVLA calculated an initial success rate of 92.9% (95% C.I. 90.2 to 94.8%)[400]. Long term outcomes were also high, with success at one year estimated at 93.3% (95% C.I. 91.1 to 95.0%) and at five years estimated at 95.4% (95% C.I 79.7 to 99.1%). When compared to conventional surgery, EVLA was shown to significantly more effective (OR 1.54 (95% C.I. 1.02 to 2.07)[400]. A recent Cochrane meta-analysis of randomised clinical trials with conventional surgery and EVLA reported that technical failure was much more likely following conventional surgery (OR 0.29, 95% CI 0.14 to 0.60) [308]. Long term outcomes were however similar in both DUS detected recurrence (OR 0.72; 95% CI 0.43 to 1.22) and symptomatic recurrence (OR 0.87, 95% CI 0.47 to 1.62).

Several randomised clinical trials comparing conventional surgery and EVLA have investigated clinical and QoL outcomes[403-408]. Four studies found no difference in VCSS improvement between conventional surgery and EVLA[403, 404, 409, 410]. Of two trials measuring SF-36, neither study detected any difference between conventional surgery and EVLA[409, 410]. EQ5D was measured in two studies. Biemans et al[408] found no difference but Pronk et al[411] reported that there was significant impairment in the EQ5D subgroups of mobility, daily activity and self-care amongst those receiving EVLA. The validity of comparing specific EQ5D subgroups in this manner as opposed an overall computed score is however dubious. Disease specific QoL using the AVVQ was measured in three studies and no significant difference detected between the two treatments[403, 409, 410].

Radiofrequency ablation (RFA)

RFA was first introduced to Europe and the United States in 1998 and aims to generate thermal ablation via an electrical current in an endovenous device[412]. The early RFA systems were typically bipolar designs, with an electric current passing between two electrodes using the vein wall as a conductor. The inherent resistance of the vein wall would produce heat and would hence ablate the vein. The temperatures could be considerable, often in excess of 90 degrees Celsius, but these early devices were unfortunately beset with numerous problems, such as excessive coagulation at the tip of the device impairing its use and necessitating frequent cleaning. RFA soon fell out of favour but the technique was reinvigorated after the introduction of a newer and more popular device, the ClosureFast™ (VNUS Medical Technologies, San Jose, California, USA). Instead of two electrodes, the ClosureFast has a monopolar design with an electrically insulated heater coil at its tip used to generate a temperature around to 120 Celsius, with simultaneous feedback to prevent overheating. Most systems have a 7 cm active element with a treatment cycle recommended at 20 seconds and a withdrawal rate of 6.5 cm per after each treated segment (although variations in size and length have been developed with their own respective manufacturer instructions). The RFA system is popular and now less difficult to use than the previous RFA designs, and several innovations in devices and techniques (e.g. double heat cycling[413]), have increased its attractiveness as a treatment option

As with EVLA, RFA is regarded as a highly successful treatment of SVI[308, 400]. In an early meta-analysis, the initial success rate for RFA was estimated to be 88.8% (95% C.I 83.6 to 92.5%)[400]. Unlike EVLA, the early success of RFA did not appear to be sustained well into the long term, with treatment success one year estimated at

87.7% (95% C.I. 83.1 to 91.2%) and at five years estimated at 79.9% (95% C.I 59.5 to 91.5%). However, when compared to conventional surgery, RFA was still a significantly more effective treatment (OR 0.87 (95% C.I 0.29 to 1.45).

A Cochrane[308] meta-analysis of randomised clinical trials reported that the technical failure rate was similar between conventional surgery and RFA (OR 0.82, 95% CI 0.007 to 10.10). Long term recurrence was also similar in both DUS detected recurrence (OR 0.82, 95% CI 0.49 to 1.39 and symptomatic clinical recurrence (OR 2.00, 95% CI 0.30 to 13.26).

Several studies comparing RFA and conventional surgery have investigated clinical and QoL outcomes[409, 414-416]. Whereas improvement in VCSS was similar in two studies[409, 414], the EVOLVeS Study[307] detected an early benefit among those receiving RFA at one week, although both groups were similar by one month. In the only study measuring SF-36, Rasmussen et al[409] reported that the RFA group saw a significant benefit in the physical domains of Bodily Pain (BP), Physical Functioning (PF) and Role Physical (RP) in those undergoing RFA compared to those receiving conventional surgery. Disease specific QoL using the AVVQ was measured in two studies and both saw similar improvements between both treatment modalities[409, 417].

Endovenous steam ablation (EVSA)

Endovenous steam ablation (EVSA) is a relatively new EVTA technique which uses steam to ablate veins[418]. The EVSA device is designed to deliver a pulse of pressurised steam via an endovenous catheter which is heated to 120 Celsius. Histological studies of veins that have undergone EVSA suggest that it is comparable in both thermal damage and temperature profile to RFA and EVLA[393,

[418, 419]. However, unlike RFA and EVLA, vein wall contact is reduced during EVSA and this may potentially decrease the pain and postoperative ecchymosis[419, 420].

In clinical studies EVSA has been shown to be both safe and effective[421, 422]. Two randomised clinical trials involving EVSA been published, one versus conventional surgery[423] and one versus EVLA[424] and both reported EVSA to be less painful than their comparator arm. However, while clinical outcomes were similar between EVSA and conventional surgery[423], at one year EVSA was reported to be inferior to EVLA[424]. As reported by Van den Bos et al, [424] initial success of EVLA and EVSA was similarly high with an anatomical success rate of 97.1% (95% C.I. 93.8 to 100%) and 93.9% (95% C.I. 89.5 to 98.3%) respectively, but at one year EVLA was superior to EVSA with an anatomical success rate of 96.0% (95% C.I. 92 to 100) compared to 86.9% (95% C.I. 80.5 to 93.3%) respectively.

Both randomised trials saw a similar improvement in objective clinical disease severity measured by the VCSS[423, 424]. While only one study measured QoL, no significant difference was detected between EVSA and EVLA in generic QoL (SF-36, EQ5D) or disease specific QoL (AVVQ) [424].

Endovenous microwave ablation (EMA)

Endovenous microwave ablation is very new treatment for SVI. Early clinical studies were encouraging but marred with high rates of skin burn and nerve injury[425, 426]. Two year technical outcomes appear respectable, with abolition of reflux and complete abolition of flow reported to be 88.5% and 79.8% respectively[427]. In a randomised clinical comparing EMA with conventional surgery, complete occlusion was 95.1% by one month and 97.0% by one year with an overall lower recurrence rate[428]. However, while sensory impairment was still higher among those receiving

conventional surgery, significant skin burns were evident in 10.2% of patients. Despite this both VCSS and AVVQ improved similarly between both treatments[428].

Complications of EVTA

Complications after EVTA are uncommon and a major reason why minimally invasive techniques have now superseded conventional surgery[152, 308, 401]. Procedural pain is significantly less for those undergoing EVLA and RFA compared to conventional surgery[308, 429-431]. In a meta-analysis reported by Siribumrungwong et al[431] the mean difference between EVLA and RFA versus conventional surgery on a visual analogue pain scale was analysed. The first reported pain was significantly lower after EVLA (-0.6 (95% C.I. -1.1 to -0.2) and RFA (-1.6 (95% C.I. -2.1 to -1.1) as was the maximum reported pain after EVLA (-0.6 (95% C.I -1.0 to -0.1) and RFA (-1.6 (95% C.I -2.0 to -1.1). Return to normal activities and work was also significantly slower after conventional surgery, with fewer days taken to recover after EVLA (-3.5 days (95% C.I. -6.0 to 0.6 days) and RFA (-4.9 days (95% C.I. -7.1 to -2.7).

Due to the high temperatures generated a common concern following EVTA is the risk of nerve injury, especially of the saphenous nerve. Unfortunately, terminology and definitions vary significantly between studies making overall comparison difficult[308, 429, 431]. The reported neurological injury rates therefore range between 1% and 36.5% depending on the study definitions[429]. However, when compared to conventional surgery the rate of nerve injuries are similar. A meta-analysis reported by Siribumrungwong et al [431] reported that paraesthesia rates were similar following EVLA (RR 0.8 (95% C.I 0.6 to 1.1) and RFA (RR 1.0 (95% C.I. 0.5 to 1.7) compared to conventional surgery. Saphenous nerve injury also appeared to be similar, with a Cochrane meta-analysis reporting that of RCTs investigating EVLA

and conventional surgery the overall rate of saphenous nerve injury 2.4% for both treatments and of RCTs investigating RFA and conventional surgery the rate of saphenous nerve injury was 11.7% and 12.4% respectively.

The risk of haematoma formation is significantly reduced following EVTA compared to conventional surgery. Overall rates of haematoma formation within RCTs comparing EVLA and conventional surgery are 4.6% and 1.2% respectively, and of RCTs comparing RFA and conventional surgery are 19.3% and 3.6% respectively[308]. The relative risk reduction of haematoma formation has been reported by Siribumrungwong et al [431] to be 50% less for EVLA (RR 0.5 (95% C.I. 0.3 to 0.8) and 60% less for RFA (RR 0.4 (95% C.I. 0.1 to 0.8) compared to conventional surgery. In addition there are significantly fewer wound infections after the EVTA techniques compared to conventional surgery with an estimated 70% relative risk reduction in their incidence (RR 0.3 (95% C.I. 0.1 to 0.7)[431]

Major complications after EVTA are rare. Clinically important DVTs are estimated to be less than 1%[432]. Extension of a thrombus into the junction, termed endovenous heat-induced thrombosis (EHIT), is currently of uncertain clinical significance but has been reported in up to 0.5% of cases[433]. Injury to other important bloods vessels have been reported in isolated cases [429], as have iatrogenic arteriovenous fistulae [434].

Endovenous chemical ablation

Sclerotherapy for varicose veins was first described in 1855 by Édouard Chassaignac (1805 – 1879) but fell out of favour due to the number of side effects and relatively poor long term outcomes[435]. A resurgence in sclerotherapy began in the middle of the 20th century following several innovations to the traditional injection method, such as the “air block” technique which used a volume of air ahead of liquid

sclerosant to reduce the dilution of the active ingredient in the blood[436-438]. Using sclerotherapy to treat varicose veins soon became popular with patients, mainly because of its relatively low impact and avoidance of risks associated with conventional surgery[439, 440]. However, whilst the short term outcomes were encouraging, the long term results of sclerotherapy were disappointing when compared to conventional surgery[435, 441]. The introduction of ultrasound foam sclerotherapy (UGFS) reinvigorated the practice of sclerotherapy and several studies suggested that UGFS was superior to liquid sclerotherapy in both technical success and recurrence reduction[442-444]. It is understood that the bolus of foam during UGFS effectively pushes away intraluminal blood, reducing dilution and increasing surface contact with the vein wall and sclerosant, therefore improving reliability and effectiveness[445]. There are three classes of sclerosant; osmotic sclerosant (e.g. hypertonic sodium chloride), chemical irritants (e.g. chromated glycerine) and detergent sclerosants (e.g. polidocanol or sodium tetradecyl sulphate)[445-447]. In UGFS the most widely used class are the detergent sclerosants, which cause cell death by a mechanism called "protein theft denaturation", whereby the detergent molecules form an aggregated micelle sheet which disrupts the cell surface membrane and causes irreversible denaturation of essential cell proteins[448]. Unlike other sclerosants, detergent sclerosants do not cause haemolysis nor provoke direct intraluminal coagulation.

Ultrasound guided foam sclerotherapy (UGFS)

Using ultrasound to control foam sclerotherapy revolutionised the technique of sclerotherapy and changed it from a peripheral treatment to one which could treat axial and complex disease. While sclerotherapy has a long history it is the development of the Tessari technique[442], in combination with ultrasound, which is

often cited as the point in which interest in sclerotherapy became revitalised. In short, the Tessari technique describes how a small volume of sclerotherapy liquid passed rapidly between two syringes can be agitated enough to produce a stable foam. A smooth homogeneous foam with an even consistency can then be injected into the vein with the ultrasound control ensuring that the foam is limited to the area of treatment, not extending into the deep venous system. While a simple technique it has been proposed that preparing the foam in a certain way, such as in an atmosphere of physiological gas[449] or carbon dioxide[450], may improve outcomes. Encouraging results have also been reported using a catheter to direct the foam within the GSV[451].

In expert hands, UGFS is reportedly a highly successful treatment with success rates above 80% to five years[452-454]. In an early meta-analysis the initial success rate for UGFS was estimated at 82.1% (95% C.I 72.5 to 88.9%), but at one year was estimated at 80.9% (95% C.I. 71.8 to 87.6%) and at five years estimated at 73.5% (95% C.I 62.8 to 82.1%)[400]. The effectiveness of UGFS was determined to be no different than conventional surgery (OR 0.15 (95% C.I -0.49 to 0.80) [400].

A Cochrane[308] meta-analysis of randomised clinical trials reported that the technical failure rates were similar between conventional surgery and UGFS (OR 0.44, 95% CI 0.12 to 1.57). Long term recurrence was also similar between the two treatments in both DUS detected recurrence (OR 1.74, 95% CI 0.97 to 3.12) and symptomatic clinical recurrence (OR 1.28, 95% CI 0.66 to 2.49).

Mechanochemical ablation (MOCA)

Mechanochemical ablation (MOCA) is a new concept in endovenous treatment of SVI and aims to dispense with the need for the uncomfortable injection of TLA[455, 456]. Essentially, by not using thermal ablation it is hoped that painful and time

consuming TLA administration might be avoided. The first MOCA device to be developed, Clarivein® (Vascular Insights, Madison, CT, USA), uses a rotating wire to abrade the vein wall whilst injecting liquid sclerosant at its tip. Histological evidence suggests that this combination of physical and chemical trauma is highly effective at irreparably damaging vein intima and causing venous ablation[457 458]. Early clinical trials report a technical a success rate greater than 95% [459-461] and a pain profile which is significantly less than EVLA and RFA[462]. Because there is no risk of thermal damage the MOCA device has also been used in ways which is not possible with EVTA, such as antegrade ablation and even ablation under an ulcer bed[463, 464]. A randomised clinical trial of MOCA and RFA found that both treatments were 92% effective at one month, with MOCA significantly less painful overall[465]. The MOCA method is a rapidly developing field and much research is being undertaken in refining the technique and in determining its long term outcomes[466]

Complications

It is common for patients to report minor complications such as pigmentation or matting following sclerotherapy. A systematic review estimated that the median incidence rate was 31.6% amongst RCTs with a reported range between 7.8 to 55.1% [467]. Thrombophlebitis is also common, estimated to have a median incidence rate of 4.7% following treatment[467]. While peripheral neurological complications (i.e. saphenous nerve injury) are rare[308], unusual central neurological symptoms have been reported. It is estimated that 1.4 and 4.2% of patients may report visual disturbance during their UGFS treatment[467, 468]. Some serious neurological complications have also been reported. In a large review of 10,819 patients, the rate of CVA and TIA was reported to be 0.1% respectively[469]. Of the 21 patients suffering a CVA, 11 were subsequently found to have a right to left shunt, an

unusual abnormality which appears to have an association with SVI [470]. Rates of DVT following UGFS are low and can be reduced by careful selection of treatment veins, restricted volumes of foam and adjusted sclerotherapy formulations[308, 467, 471].

1.7 Long term SVI studies

The majority of studies which have investigated varicose vein treatments have tended to only follow up patients for one year or less, although most recent high quality randomised clinical trials are usually designed with longer follow up periods in mind [409, 472]. Long term follow up does not have to take place within the confines of a clinical trial, however. For example, patient registries, such as the Vascular Quality Initiative®[473] and the VQI® Varicose Vein Registry™ [474, 475], have recently been implemented in the United States as a method to follow up large numbers of patients, allowing measurement and comparison of outcomes nationally. Local registries may also exist in certain treatment units, with the added advantage that trends over time can be more closely observed [476]. In the UK the largest registry is the Hospital Episode Statistics (HES)[477], which aims to collect the outcomes of every patient undergoing an elective varicose vein treatment in England. While the advantage of these huge datasets are that lots of information can be gathered, the disadvantages are that they very much depend on the quality of the information being collected, they are by their nature large and difficult to modify (significant changes may even invalidate or make previous data incompatible), might be unclear in their objective and can be very difficult to manage over a substantial time frame[478]. Nevertheless, large sums of research funding are currently being dedicated to such efforts, with improvements in genetic analysis and technology purported as potential avenues for revolutionary discoveries, although some critics are wary of such claims[479]. The fact remains however, that currently the best way to answer a

specific medical hypothesis is a well-designed randomised clinical trial with sufficient numbers and a diligent follow up.

Fortunately, several randomised clinical studies have had their follow up periods extended with long term data published. In the most recent analysis of varicose vein treatments by the Cochrane systematic review group[480], only one long term randomised clinical trial was available to be evaluated[481]. Since the Cochrane review was completed four long term clinical studies with five year data have been published[482-485]. It is important to note that the included studies are for interventions performed in their standard approach only. For example, two randomised clinical trials did have five year data reported but their treatments (cryo-stripping during conventional surgery[486] and ligation of the GSV during EVLA[487]) have not been widely adopted are therefore have limited relevance.

One of the earliest randomised clinical trials to investigate EVLA and report data at five years was published by Rasmussen et al[481]. In the study, 121 patients (137 legs) were randomly allocated to either EVLA using a 980 nm laser with concomitant phlebectomy or conventional surgery. The primary outcome measure was technical success, defined as a closed GSV in the laser group and absent GSV in the surgery group, with technical failure defined as a reopened segment >5cm. At 12 weeks, technical success was reported in 66 of 68 limbs after conventional surgery and in all 67 limbs after EVLA. After 6 months, technical success was reported in 49 of 50 limbs after conventional surgery and 51 of 54 limbs after EVLA[406]. At five years, while a technical success rate was not explicitly reported, technical failure was reported in 2 out of 68 and 3 out of 69 limbs after conventional surgery and EVLA respectively. However, almost half of the study group reported clinical recurrence, with 24 out of 68 limbs after surgery and 25 of 69 limbs after EVLA reporting some

evidence of reflux. Unfortunately, losses to follow up were significant, with only 19 patients in the conventional surgery group and 21 patients in the EVLA group attending their clinical assessment at 5 years. This was significantly below the initial study power calculation of 60 limbs per group and, as noted by the authors, meaningful interpretation of the study is therefore limited, especially due to the risk of a type 2 error (i.e. a study population too small to detect a true statistical difference).

Van der Velden et al[482] reported a larger study of 240 patients equally randomised to one of three treatments; conventional surgery, EVLA and UGFS. The EVLA was performed using a 940nm laser with concomitant phlebectomy, and the UGFS was performed using the Tessari technique with GSV axial treatment initially with subsequent tributary treatment at a later date if required. The primary outcome measure was abolition or absence of the treated part of the GSV 5 years after treatment. The DUS findings were divided into 4 groups, group 1 were completely open with reflux, group 2 were partially open or segmentally obliterated with reflux, group 3 were partially open or segmentally obliterated with antegrade flow and group 4 were totally obliterated with absent flow. Technical success was limited to group 4 only. The study was powered to detect a 10% difference in occlusion proportion between EVLA and UGFS and a 20% difference between EVLA and conventional surgery, resulting in 80 legs required per treatment arm. One year technical success was reported to be 88.2% after conventional surgery and 88.5% after EVLA, with UGFS significantly lower at 72.7%[408]. Five year technical success was 85% (95% C.I. 75-92%) after conventional surgery, 77% (95% C.I. 66-86%) after EVLA and 23% (95% C.I. 14-33%) after UGFS. In addition, above knee reflux was more likely to be abolished after conventional surgery and EVLA compared to

UGFS (ELVA vs UGFS OR 0.7 (95% C.I. 0.6-0.8); Conventional surgery vs UGFS OR 0.7 (95% C.I. 0.6-0.8). While EQ5D scores improved globally among all three groups, disease specific QoL improvement was similar between EVLA and conventional surgery group but significantly worse among the UGFS group compared to the EVLA group. Intervention rates were also much higher among the UGFS group with 32% of limbs requiring one or more interventions compared to only 10% of limbs after conventional surgery or EVLA. The five year follow up rate was respectable, with 193 (86.2%) legs attending for review, nearly meeting the 80 limb study power calculation minimum.

A study published by Flessenkamper et al[483] investigated conventional surgery and two approaches of EVLA using a 980 nm laser; EVLA as performed in the standard approach and EVLA in combination with high ligation of the of the GSV and its tributaries under general anaesthesia. The study was randomised using a lottery system to determine each patient's treatment, with 500 tickets allocated on a 1:1:1 ratio. Of 449 patients, 159 underwent conventional surgery, 142 underwent standard EVLA and 148 underwent EVLA with high ligation. The primary measure was defined as the rate of clinical inguinal reflux, with reflux itself was defined as any reflux from the saphenofemoral junction into the GSV lasting more than 0.5 seconds, as measured on DUS. Using this measure, by two months clinical inguinal reflux was documented in 10 (6.7%) patients after EVLA with high ligation, 38 (26.7%) patients after standard EVLA and was not detected in any patient after conventional surgery[404]. Follow up to 72 months was completed by 43 patients after conventional surgery, 38 after standard EVLA and 58 patients after EVLA with high ligation. While the exact figures are not stated in the paper, the rough probability that patients will be free from clinical recurrence is around 30% after standard EVLA, 40% after

conventional surgery and 50% after EVLA with high ligation, although no statistical difference was detected between the groups. Unfortunately, the Flessenkamper et al[483] paper was also limited in its small follow up rate and omission of any health related QoL data.

One of the largest studies yet conducted, the RELACS study[488], randomised 400 patients to receive conventional surgery or 810 nm laser EVLA and concomitant phlebectomy. The primary outcome measure was a recurrence free rate as defined as the presence of any new or palpable varicosities on the study leg as per the classification of recurrent varices after surgery (REVAS)[489]. The study was powered to detect an 11% difference in REVAS between the two groups, requiring 200 patients per group, allowing for a 10% drop out rate. Early axial occlusion was reported in 183 (98.9%) of 185 patients after EVLA and all 161 patients after conventional surgery[407]. The two year recurrence rates were similar between both treatments, with 83.8% of the EVLA and 76.9% of the conventional surgery groups reporting recurrence. Five year follow up was completed by 82% of the study population, with 152 EVLA and 129 conventional surgery patients attending an appointment. At five years the clinical recurrence rate was 45% following EVLA and 54% following conventional surgery and was statistically similar between both groups. The majority of recurrence following EVLA (50%) was related to the same site of treatment, whereas recurrence following conventional surgery (31%) was more related to clinical disease progression at a different site. In addition, disease specific QoL showed a sustained improvement over the study period in both groups. While the study did not meet its minimum study population at the outset, the high quality nature of its follow up and large size mean that it is one of the most important long term studies of varicose vein outcomes after treatment.

A study by Gauw et al[485] compared conventional surgery and EVLA with a 980 nm laser. The study power calculation assumed a 10% difference in recurrent varicose veins on DUS imaging which required a minimum of 137 patients per group[411]. Although 332 patients were assessed for eligibility, 130 patients were subsequently randomised between the two groups, with 68 allocated to conventional surgery and 62 to EVLA. The primary outcome measure was detection of recurrent varicose veins over a study period of 10 years, with recurrence itself defined as visible or palpable varicosities in the area of the treated GSV, classified as CEAP ≥ C2. Specifically, a recurrent vein after conventional surgery was defined as a tortuous vein in the GSV area with a diameter ≥ 3 mm, originating in the groin and connected with the femoral vein, and showing reflux > 0.5 seconds, and after EVLA was defined as the ability to compress the GSV, or as reflux > 0.5 s in a vein originating in the groin and connected with the femoral vein. A new refluxing vein < 3 mm and clinically visible was also considered as a recurrence. After one year there was no statistical difference in the recurrence varicose vein rate between conventional surgery and EVLA, with 5 (9%) of 56 conventional surgery patients and 5 (10%) of 49 EVLA patients recording recurrence, of which 3 patients in each group had a visible varicosity[405]. At five years, 10 conventional surgery and 25 EVLA patients had evidence of recurrence. Freedom from recurrence rate was therefore statistically worse after EVLA, with 17% of conventional surgery and 33% of EVLA patients showing clinical recurrence at the groin. DUS recurrence was also statistically higher after EVLA, with 49% after EVLA and 23% after conventional surgery estimated to have groin recurrence on a life time survival curve. Despite this dissimilarity, both groups improved in venous symptoms and the EQ5D QoL remained stable in both groups. The rate of secondary procedures was also similar between the groups, with

80% of conventional surgery and 70% of EVLA patients avoiding further intervention over five years[485].

Chapter 2 – Aims and Objectives

Prior to the commencement of this study, little was known about the short or long term outcomes of endovenous laser ablation treatment for patients with symptomatic SVI. Indeed, much of the evidence was limited to either a few, small clinical trials or cohort studies, with no trial sufficiently powered to properly explore the intricacies of QoL over a substantial time frame. The preliminary results of the HELP-1 randomised clinical trial[490, 491] helped develop a quality evidence base for EVLA. In February 2010 the National Institute for Health and Clinical Excellence (NICE) was tasked by the Department of Health to produce clinical guidance on the management of varicose veins[492]. After a review of the available evidence, NICE published its recommendations in July 2013 and advised that minimally invasive treatments be offered above conventional open surgery in patients with symptomatic SVI [152]. But NICE also noted that there were gaps in the literature which limited its recommendations. A significant challenge was that, whilst there was overwhelming evidence of the short term benefits of minimally invasive endovenous treatments, little was known about the long term outcomes, including its effects on patients QoL beyond one year. Questions also remained about the optimum treatment of varicose tributaries and very few trials had investigated the efficacy of treatment options at various stages of disease severity.

Keeping in mind these issues highlighted by NICE, the ultimate aim of this study was to investigate the long term outcomes of endovenous laser ablation for symptomatic SVI and to explore how EVLA treatments can be optimised. Four broad areas are to be covered and these are as follows:

1. The long term outcomes of endovenous laser ablation versus conventional open surgery
2. The long term outcomes of concomitant phlebectomy versus sequential phlebectomy
3. The long term outcomes of treating those with the complications of SVI versus those without the complications of SVI.
4. The long term outcomes of different endovenous laser devices and techniques in treating superficial venous insufficiency with EVLA.

Across these four objectives, seven studies were undertaken as follows:

2.1 Study 1 – Long term clinical and technical outcomes of EVLA versus open surgery for SVI

The HELP-1 trial remains one of the largest randomised studies in varicose vein research and one of the few studies to investigate QoL with sufficient power at one year post treatment. In brief, the HELP-1 study equally randomised patients suffering symptomatic SVI to conventional open surgery (the control group) or endovenous laser ablation (the experimental group). The initial results of the HELP-1 trial reported that EVLA has several advantages over conventional surgery and therefore supported the NICE guidelines in preferring its use in preference to conventional open surgery in treating patients with SVI. However, the HELP-1 study only reported patient outcomes to one year and it was uncertain if these advantages could be maintained into the long term. The aim of this study was to extend the HELP-1 trial follow to five years and to document the long term clinical and technical outcomes. The main outcome measure was patient QoL, as measured using the generic QoL SF-36. The long time period of this follow up also allows for

clinical recurrence, an uncommon and often elusive occurrence in most venous studies, to be accurately recorded and documented. The impact of recurrence on QoL and any further treatments also adds a further dimension to the study trial follow up.

2.2 Study 2 – A cost comparison of EVLA versus open surgery for SVI

While the clinical benefits of EVLA versus conventional surgery were demonstrated in the early results of the HELP-1 study, the relative costs of both treatments have yet to be established. This is important because, as recommended in the new NICE guidance, endovenous treatments such as EVLA should be performed ahead of conventional surgery and if the costs of EVLA treatment are significantly different this could influence the eventual provision of SVI treatment across the country after implementation of the new guidelines[493]. To date, economic analyses of minimally invasive treatments have been either direct cost comparisons within short term clinical trials[156, 157] or advanced mathematical modelling which uses extrapolated assumed costs of treatments to calculate a range of cost probabilities across a number of hypothetical scenarios[472, 494-496]. However these studies are limited in that, firstly, costs calculated from short term trials may not fully appreciate any long term costs (especially if further treatments or care is required), and secondly, that mathematical models have few high quality long term studies with which to accurately base their simulations beyond the short term. It is therefore essential that an economic analysis of the HELP-1 trial is undertaken to provide both short and long term costs over five years.

2.3 Study 3 – Long term clinical and technical outcomes comparing concomitant versus sequential phlebectomy with EVLA for SVI

Prior to the commencement of the HELP-1 study there was disagreement within the venous community about how best to manage the superficial varicose tributaries which frequently arise with SVI. Whilst it is common practice in conventional surgery to use special hooks or clips to remove the varicose tributaries during surgery, it has been suggested that EVLA of the axis may be sufficient enough to allow natural regression of most superficial tributaries without the need for further intervention[497, 498]. Any remaining residual symptomatic veins could then be treated on an ad hoc basis, thereby reducing the overall requirement for phlebectomy and limiting the impact of treatment on QoL and hospital resources.

The EVLTAP trial, the first randomised clinical trial of concomitant or sequential phlebectomy, found this not to be the case. Patients receiving concomitant phlebectomy at the same time as their index EVLA procedure were in the short term significantly better off in disease specific quality of life (AVVQ), disease severity (VCSS) and avoided more additional procedures over the following year. For the HELP-1 trial it was determined that to achieve a fair comparison of conventional surgery and EVLA, it was necessary for EVLA patients to undergo phlebectomy as they would have had if they were randomised to conventional surgery. But the long term consequences of a policy of concomitant or sequential phlebectomy during EVLA are unknown. The main outcome of this study was to therefore follow up and record the AVVQ outcomes of the EVLTAP trial at five years.

2.4 Study 4 – A cost comparison of concomitant or sequential phlebectomy with EVLA for SVI

As mentioned previously, the aim behind a policy of sequential phlebectomy is to reduce the overall requirement for phlebectomy among patients undergoing EVLA. The rationale being that if fewer patients require phlebectomy after an interim period, as opposed to all patients during their index procedure, this could potentially offset significant costs and result in considerable resource savings. The aim of this study was to therefore compare the direct treatment costs for the EVLTAP trial over five years. In addition, a specialised mathematical model was developed to simulate different amounts of sequential intervention. Some clinicians may have a different thresholds for offering sequential phlebectomy. A high threshold to perform sequential phlebectomy would be cheaper than a low threshold, but overall could still be more expensive than concomitant phlebectomy. This model would be able to calculate at what threshold a policy sequential phlebectomy would be cost neutral, and at what point sequential or concomitant treatment would be more cost effective.

2.5 Study 5 – Long term clinical and technical outcomes of treating those with and without complications of SVI

The degree of venous disease can vary widely in patients with SVI, starting from a spectrum of simple varicose veins all the way to significant tissue damage and venous ulceration. While most patients will present with the milder forms of venous disease, some patients, if left untreated, may progress to the more severe forms of

venous disease. A question raised by NICE was that it is difficult to determine if disease severity can influence eventual outcomes. Often, studies exclude any patients with a CEAP severity of C3 and above, whereas some studies may include all grades of CEAP but report outcomes together as a whole, rather than by disease stage. The main aim of this study was to compare the long term QoL outcomes using the SF-36 between those with uncomplicated C2 venous disease and those with complicated C3 to C4 disease.

2.6 Study 6 – A cost comparison of treating those with and without the complications of SVI

In addition to the long term clinical and technical outcomes reported above, it is also important to establish what the economic consequences are of a policy which treats SVI early compared to a policy which only treats patients once complications have arisen. A particular concern are that financial constraints may force some healthcare providers to begin limiting the accessibility of SVI treatments, potentially leading to a situation where only patients who meet the requirement of complications of SVI (C3 and greater) are offered treatment, whereas those with relatively uncomplicated venous disease are forced to wait until complications arise. The aim of this study was to compare the costs of treating those with uncomplicated C2 disease and those with complicated C3 to C4, and to establish the cost effectiveness of such a policy.

2.7 Study 7 – Comparison of endovenous laser design, technique and clinical outcomes in the treatment of superficial venous insufficiency.

The EVLA technique has undergone several modification since its inception. Some of more significant changes between the older and newer EVLA models are in the design of the EVLA generator device, specifically, in the laser power (wattage) and laser frequency (continuous or pulse) generated to the EVLA fibre. As EVLA technology has matured several manufacturers have modified their products on recommendations put forward by clinicians and laboratory based bench-testing. While several studies have investigated short term outcomes, few have been able to establish the long term outcomes of such modifications. It is the aim of this study to compare the outcomes of various EVLA devices and techniques. Using the EVLA arm of the HELP-1 trial, the results of the EVLTAP trial and a randomised clinical trial performed at this unit which compared a 12 watt intermittent pulse EVLA versus 14 watt continuous EVLA laser, the outcomes of various EVLA modifications can be explored

Chapter 3 – Methods

3.1 Study 1 – Long term clinical and technical outcomes of EVLA versus conventional open surgery for SVI

Study design

The HELP-1 randomised clinical trial (ClinicalTrials.gov NCT00759434) was undertaken in a dedicated vascular unit within a large tertiary hospital in the UK. This thesis is an extension of the previous study performed at one year, with work from this thesis specifically done at the five year time point. The HELP-1 trial methodology has been reported previously[490, 491]. In brief, all patients consecutively referred to a single vascular surgeon were evaluated for eligibility for trial inclusion. Patients underwent outpatient clinical assessment consisting of history, examination and documentation of baseline clinical disease status (CEAP and VCSS). Patients then underwent a venous DUS assessment, as per international protocol[158]. Patients deemed eligible if they met the following inclusion and exclusion criteria:

Inclusion criteria

Clinical criteria

- Primary symptomatic superficial venous insufficiency of a lower limb which is classified between C2 to C6, as per the CEAP classification
- Willingness to undergo endovenous laser ablation (EVLA) with ambulatory phlebectomy under local anaesthetic

- Willingness to undergo conventional open surgery with ambulatory phlebectomy under general anaesthesia

Duplex ultrasound criteria

- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-Formal junction into the great saphenous vein
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the great saphenous vein at least the level of the knee.

Administrative criteria

- Willing to participate in a randomised clinical trial
- Willing to complete additional clinical and duplex assessments and completion of research questionnaires with analysis and publication of the results

Exclusion criteria

Clinical criteria

- Age less than 18 years old
- Any previous venous intervention
- Presence of lower limb venous disease which is classified at and less than C1, as per the CEAP classification
- Pregnancy
- Symptoms or clinical evidence of arterial insufficiency (including ankle brachial pressure ratio less than 0.8)
- Known thrombophilia state or disease
- Any malignancy

- Any allergy to any local anaesthetic medication used in the procedure

Duplex ultrasound criteria

- Presence of any deep venous axis incompetence
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-popliteal junction into the great saphenous vein or short saphenous vein
- Presence of any incompetent superficial venous axis, aside from the GSV, which in the opinion of the operating surgeon would be optimally treated with endovenous ablation or conventional surgery with vein stripping rather than ambulatory phlebectomy
- Anterior to posterior GSV diameter less than four millimetres as measured by DUS at the proposed cannulation point.

Administrative criteria

- Inability or unwillingness to participate in a randomised clinical trial
- Inability or unwillingness to give informed consent for trial participation

Randomisation

Following completion of the consent documentation, enrolled patients were then randomised equally into one of two parallel treatment arms using opaque sealed envelopes. The control group was to receive conventional open surgery with ambulatory phlebectomy under general anaesthesia whereas the experimental group was to receive EVLA with ambulatory phlebectomy under local anaesthesia. Both groups were also offered sequential phlebectomy of any symptomatic residual venous tributaries after six weeks. Treatment for symptomatic recurrence was

offered on an individualised basis depending the specific patient requirements and needs.

Sample size calculation

The primary outcome of the HELP-1 randomised trial was to detect if there was a 5-10 point difference in the SF-36 physical domains between the two groups. Using a power calculation with an alpha of 0.05 and a beta of 0.20 (i.e. 80% power), each treatment arm would require 120 patients. An overall a target recruitment of 140 patients per arm was set to accommodate any loss to follow-up.

Treatment methods

Both groups underwent their allocated treatment at a specialised regional vascular unit, with conventional open surgery and EVLA performed in a dedicated vascular theatre and outpatient procedure room respectively. The treatment techniques for the two procedures are outlined below.

Preoperative procedure

Both groups had their treatment limb marked preoperatively with indelible ink prior to intervention. Using ultrasound guidance with a portable MicroMaxx® ultrasound machine (Sonosite Ltd, Hichin, UK) the location of the Sapheno-Femoral junction was identified with the patient standing and any incompetent perforators and symptomatic varicose tributaries duly marked. Patients then underwent their index procedures as follows:

Conventional Surgery

Following induction of general anaesthetic, patients were given a dose of antibiotics in accordance with departmental guidelines[304]. Once placed in the Trendelenburg

position, the skin was prepared with 10% povidone-iodine in water (Betadine®, Purdue Pharma L.P, Connecticut, USA) or, if contraindicated due to allergy, 2% chlorhexidine gluconate in 70% isopropyl alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK). The leg was then draped with sterile sheets. After an oblique incision over the anatomical location of the SFJ, the tissues were then dissected down to the level of the saphenous facia. Beneath the facia the SFJ was identified and any additional tributaries were ligated. A flush ligation of the SFJ was performed and the stripper device inserted into the opened GSV and secured with a tight suture. The GSV was then stripped by the inversion technique and removed around the level of the knee. Deep wounds were then closed with a 2-0 uncoated polyglactin 910 (Vicryl® Ethicon, Cincinnati USA) and the skin closed using a subcuticular 3-0 poliglecaprone 25 (Monocryl® Ethicon, Cincinnati OH, USA). Incompetent perforators and varicose tributaries were then treated as required as detailed below (see page 121).

Endovenous laser ablation (EVLA)

In the reverse Trendelenburg position the limb was prepared with 10% povidone-iodine in water or 2% chlorhexidine gluconate in 70% isopropyl alcohol if contraindicated due to allergy. After draping with sterile sheets, the location of GSV was identified using a portable ultrasound machine and a 5 French catheter percutaneously inserted into the distal GSV using the Seldinger technique. The location of the cannulation point adjusted over the course of the trial, with perigenicular cannulation soon being replaced with cannulation the lowest point of reflux, usually just above the medial malleolus. With the tip of the catheter confirmed at the level of SFJ, the patient was levelled and the limb prepared for infiltration of TLA, a solution of 2% lidocaine with 1:200,000 adrenaline in 0.9%

normal saline. Under ultrasound guidance the tumescent solution was infiltrated into the fascial compartment of the GSV at an approximate volume of 10 mls per 1 cm of GSV. A 600 μm bare-tipped laser fibre (AngioDynamics, Cambridge, UK) was then inserted and locked into the sheath. The laser generator unit was then activated and set to a wavelength of 810 nm, power of 14 watts and a setting of continuous laser energy delivery. With the laser activated, controlled withdrawal of the fibre and sheath was then initiated with the ultimate aim of providing a LEED of at least 60-80 J/cm^{-1} along the vein. Additional tumescent solution was also infiltrated into the tissues surrounding the marked venous tributaries with treatment as detailed below.

Concomitant phlebectomy

Perforators were divided and ligated via a small incision and varicose tributaries avulsed using a Kocherised mosquito clip or Oesch vein hook. All wounds were then infiltrated with local anaesthetic (0.5% Levobupivacaine) and dressed as appropriate.

Post treatment

After the completion of treatment the limb was then circumferentially bound with an elastic adhesive bandage, Panelast® (Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, DE), which was to remain for one week. Patients were also provided with a thigh length T.E.D™ anti-embolism stocking (Tyco Healthcare, Gosport, UK), which was then to be worn for a further five weeks after removal of the compression bandages. All patients were discharged with Diclofenac 50 mg to be taken regularly three times a day for 1 week and Paracetamol 1 g for breakthrough pain (maximum four times a day).

Follow-up appointments

After treatment patients were invited to attend several follow up appointments over the following five years. The prescribed schedule was at 1 week, 6 weeks, 12 weeks, 1 year, 2 years and 5 years, with the option of early review if any problems arose. All appointments were conducted at a dedicated vascular research unit and performed by a medically trained research investigator with ultrasound accreditation. The appointment consisted of a Qol questionnaire, clinical review and a DUS examination of the limb.

QoL Questionnaires

A paper booklet containing the QoL questionnaires was completed in private by the patient prior to the clinical and duplex assessments. The booklet consisted of three QoL questionnaires, two generic QoL measurements (SF-36 and EQ-5D), and a disease specific QoL measurement (AAVQ). All three were identical to the preoperative questionnaires.

Clinical review

Following a focussed history and clinical examination, the VCSS and CEAP scores were evaluated and documented. Special attention was made for any evidence of clinical recurrence, defined as new symptomatic varicose vein greater than 3 cm which had arisen 12 weeks after treatment. Patients were also asked to mark on a 10 cm VAS scale their cosmetic opinion of their treatment limb and overall satisfaction.

Venous duplex ultrasound protocol

All ultrasound examinations were undertaken using the same research Toshiba Aplio MX (Toshiba Medical Systems Ltd, Crawley, UK) machine with a 6-12 MHz linear transducer array. Using default venous duplex settings, the ultrasound examination

was undertaken in accordance with international guidelines[158]. Settings such as harmonic imaging and compounding were used as standard to enhance image accuracy and the Doppler detection sensitivity was lowered to venous flow levels of between 5-10cms^{-1}. At all stages of the examination the image settings were dynamically optimised to the specific area of interest, with depth, focus, gain control (GC) and time gain control (TCG) all being optimised to improve visualisation of the underlying anatomy. Colour boxes and gain were used to filter Doppler images and help reduce image artefacts. Incompetence was defined as retrograde flow greater than or equal to 1 second for the deep vein and greater or equal to 0.5 second for the superficial vein on spectral Doppler. Assessment for incompetence was then performed using manual flow augmentation at a site greater than 10 cm distal to the region of insonation or, when interrogating the distal calf, the foot. Any required anterio-posterior measurements were made using the electronic callipers positioned at the most anterior echo of the anterior wall and the most posterior echo of the posterior wall of the vein and were measured to the nearest 0.1 mm.

In a warm and dimly lit ultrasound room, the patient was positioned while standing towards the examiner with their treatment leg externally rotated and slightly flexed at the knee. The ultrasound examination first starts at the level of the SFJ and inspects the groin for any evidence of reflux or neovascularisation from the SFJ, abdominal/ pelvic veins, aberrant groin tributaries and deep perforators. The GSV is then followed inferiorly to the ankle and any evidence of reflux, recurrent tributaries or perforators recorded and mapped. Other incompetent venous axes from the groin, thigh or calf are then investigated as above.

Once the superficial system has been examined the investigator then proceeds to examine the deep venous system. Any evidence of obstruction, thrombosis, or

incompetence involving the common femoral vein were used as indications to extend the examination to iliac veins and inferior vena cava. If there was any concern further imaging, such as venography, may be then considered with appropriate referral.

For assessment of the Sapheno-popliteal system and the deep veins of the calf, the patient was turned around with their back towards the examiner and their hip returned back to the anatomical position. First, the SSV was identified at the level of the ankle and then traced up to the SPJ. The level of the junction was noted and the examination then proceeds to assess the distal tributaries, including the Giacomini vein if present. Presence of incompetent perforators were also noted, and finally, the popliteal and crural veins were then assessed for patency and reflux.

Outcome measurements

The primary outcome measure was Quality of Life, as measured by the SF-36. Several secondary outcomes were also recorded and grouped into the following three broad categories; QoL, clinical and DUS outcomes

Quality of Life outcomes

- Generic QoL – Short Form 36 (Primary outcome measurement)
- Utility Index QoL – EuroQol 5 Dimension
- Disease Specific QoL – Aberdeen Varicose Vein Questionnaire
- Utility Index QoL – SF6D

Clinical outcomes

- Objective clinical assessment of venous disease – VCSS
- Cosmetic satisfaction

- Overall satisfaction
- Clinical recurrence – defined as development of new segments of incompetence (or recurrence of preoperative reflux) within superficial veins and perforators.
- Requirement for further procedures

Duplex ultrasound outcomes

- Long term technical success
    - After EVLA - treated section of GSV remains occluded and non-compressible
    - After conventional surgery – sustained disconnection of all groin tributaries from the SFJ with flush ligation of the GSV and absent the GSV in the thigh.
- Recurrence of reflux and patterns of venous incompetence as follows;
    - Recurrence at the groin – any observed disease progression in the groin and proximal limb
    - Neovascularisation - defined as serpentine vessels emanating from the SFJ that were not present on duplex imaging at 1 or 6 weeks.
    - SFJ Incompetence
    - Recannalisation – any flow detected through a previously treated and occluded segment of vein
    - AASV and Superficial proximal thigh veins
    - Perforator incompetence – development of incompetent perforators which were not present during treatment
    - SPJ incompetence
    - SSV incompetence

- Recurrence of varicose tributaries – the development of any new varicose tributaries which are >3mm post treatment (excluding residual veins)
- Recurrence of incompetent tributaries – the development of incompetence within recurrent varicose tributaries

3.2 Study 2 – A cost comparison of EVLA versus conventional open surgery for SVI

A health-economic analysis was performed based on the HELP-1 study with the intention of establishing the cost effectiveness of both treatments over the long term. The economic methodology is outlined below

Clinical background

As detailed in the HELP-1 study methodology above, patients were followed up for five years and any patients developing symptomatic clinical recurrence during this time were offered the options of conservative management (with or without compression) or an interventional treatment. Interventional treatments were offered on an individualised basis by an experienced surgeon with a special interest in the management of venous disease. Potential treatment options could include one or more combinations of phlebectomy, ultrasound guided perforator ligation, perforator ablation, UGFS, EVLA and open surgery. All treatments were performed under local anaesthesia with no sedation or regional anaesthesia, except for open surgery which was performed under GA. The economic analysis methodology is as follows

Health Utility Calculation

Generic index QoL was self-recorded by study participants at baseline and weeks 1, 6, 12, 52, 104 and 260 using the Time Trade Off (TTO) of EQ5D[499] as per NICE recommendations[500]. From this Quality Adjusted Life Years (QALYs) were estimated for each patient using the area under the curve (AUC). Discounting was applied at a rate of 3.5% per annum. A sensitivity analysis if missing data was also undertaken, with missing results determined using interpolation, last value carried forward or group mean. Sensitivity analysis of the discount rate was also performed, with a rate of 0% and 5% also used.

Costs Calculation

The metrics of resource expenditure were collected prospectively in the trial and costs per patient were estimated from the perspective of a third party payer, in this case the National Health Service (NHS). These costs are detailed in Table 7. The Primary and secondary healthcare staffing costs were taken from the "Unit Costs of Health & Social Care (2014)"[501], which calculates the unit cost per hour of health professionals working within the NHS. This calculation also includes factors such as staffing overheads, training, estate costs and resource utilisation. The cost of venous duplex scans and outpatient appointments were taken from the NHS Reference Cost of Service Tariffs 2013-2014[502]. Operative costs were calculated per minute based on the recorded time between the patient entering and leaving the procedure room. Staff members present during phlebectomy and endovenous interventions under local anaesthesia were as follows; a Vascular Surgeon and two assistant nurses. The same team were used for conventional surgery with the addition of a consultant Anaesthetist. Single use disposable equipment was counted as a cost per unit and the specific capital

costs of essential equipment annuitized. It was assumed that the laser generator would be loaned free of charge to the NHS, with the EVLA laser fibre and guide wire bought for each patient separately. These consumable, annuitized costs and additional theatre overheads were taken from the multicentre UK based RCT[472, 503]. The costs of follow up and additional treatments were also calculated in the same manner. In order to allow for the time preference of expenditure, discounting was applied at a standard rate of 3.5% per annum.

Management Stage		Cost (£)	Source
Referral and diagnosis	GP appointment	45	PSSRU 2014
	Vascular Outpatient clinic (1st visit)	169	DOH 2013-14
	Diagnostic Ultrasound (>20 minutes)	62	DOH 2013-14
Staff Costs	Consultant Surgeon*	142	PSSRU 2014
	Consultant Anaesthetist*	140	PSSRU 2014
	Scrub Nurse*	58	PSSRU 2014
	Operating Department Practitioner*	49	PSSRU 2014
	Circulating Nurse*	41	PSSRU 2014
	Theatre assistant*	21	PSSRU 2014
Procedure Costs	Preparation cost of clinic/theatre	24.86	UK Multicentre
	Laser kit	256.00	UK multicentre
	Laser Consumables	65.06	UK multicentre

	Surgery Consumables	159.56	UK multicentre
	ECG, Pulse oximetry, blood pressure monitor	4.15	UK multicentre
	Foam Sclerotherapy	5.52	UK multicentre
	UGFS Consumables	50.20	UK multicentre
	Phlebectomy Consumables	26.23	UK multicentre
	Ultrasound machine	8.78	UK multicentre
	Theatre overheads*	218	UK multicentre
Post treatment costs	Per day stay cost	217	DOH 2013-14
	Rehabilitation	461	DOH 2013-14
	Follow up venous ultrasound (<20 minutes)	52	DOH 2013-14
	Vascular Outpatient appointment (follow up)	142	DOH 2013-14

Table 7. Unit Costs of Health & Social Care (2014) * costs per hour

Parameter uncertainty

Figure 2 represents the presumed clinical patient pathway for the purposes of cost calculation in this analysis. Treatment of the GSV, SSV or perforator was assumed to require a single outpatient and duplex ultrasound assessment. Treatment of just varicose tributaries by phlebectomy or UGFS was assumed to require a face-to-face appointment only. Patients with no residual symptomatic disease after one year were assumed to be discharged and any further recurrence would require re-referral from a GP and re-assessment in the outpatient clinic.

As the costs and benefits may be incurred at different times for each group, this raises the possibility that the level of discounting may affect the results. It was therefore decided that uncertainty in the discounting level should be explored using a sensitivity analysis with variation of the rate from 0% to 5% per annum.

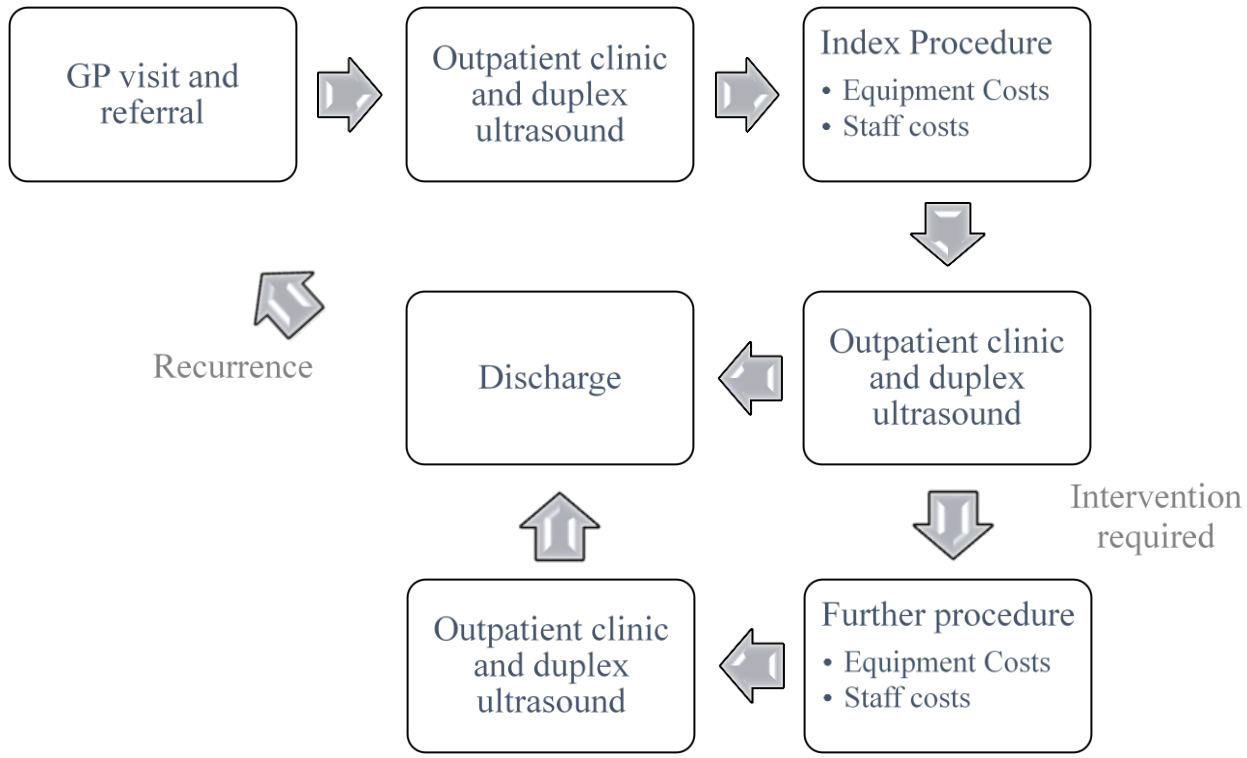


Figure 2. HELP-1 Patient pathway. Follow up duplex was only performed following treatment to an axis

Cost Effectiveness

For this economic analysis to be useful it needs to take into account both the clinical efficacy and costs of both interventions. Essentially, if one treatment is simultaneously more clinically effective and less expensive this option would be said to "dominate" and would therefore be encouraged. However, sometimes a treatment is more clinically effective but more costly. The first step in a cost effective analysis

is a Cost Benefit Analysis (CBA), which is defined by Michael Drummond[504] as a technique in which all costs and benefits are measured in terms of money. In truth, money is an arbitrary choice of common unit, although in practice it is a natural and intuitive unit which best fits the values in modern society. The CBA can then determine which option has a greater net benefit i.e. difference between the cost and the benefit (it is important to note that this figure can even be negative). A Cost Effectiveness Analysis (CEA) will then go on to determine which treatment will have the greater benefit at the same or lower cost. If there are limited resources in a healthcare system the treatment with the greatest net gain would usually expected to be recommended over the alternative. However situations may arise when one treatment provides some gain but at a smaller cost. A Cost Effective Analysis (CEA) can establish a Cost Effectiveness Ratio (CER) which calculates the cost divided by the benefit, or more commonly (and as recommended by NICE[505]) an Incremental Cost Effectiveness Ratio (ICER) which is the costs and benefits of each treatment compared with their next best alternative, rather than a common alternative. The ICER is an important tool because it states the cost of money needed to obtain an extra unit of heath gain compared to an alternative option. While the CBA can be used to determine if the treatment is an efficient use of healthcare resources, the ICER can determine which treatment is the most efficient use of resources overall. The ICER is calculated by first establishing the "value for money" of both treatments by determining the cost (£) per QALY gained. The ICER can then be calculated as the difference in mean cost divided by the difference in mean QALY between one alternative compared with another. NICE generally considers the ceiling of cost effectiveness to be £20,000-£30,000 ICER[506]. An intervention above this would not be considered a cost effective treatment alternative.

Beyond the ICER a Cost Utility Analysis (CUA) can be undertaken which focuses on QALYs rather than costs. Essentially, the CUA appreciates efficiency gains in the value of heath rather than that of just health care expense. The advantage of the CUA are that net benefits can be derived in terms of money or QALYs. Using the CUA approach also allows for net benefits to be calculated, bearing in mind the ceiling ratio of cost effectiveness which is usually around £20,000. Essentially, if the incremental costs are £30,000 and the incremental gains are 2 QALYs, the ceiling ratio of the QALY gain should be £40,000 (i.e. 2 x £20,000). The net benefit of this treatment is therefore £10,000 (i.e. £40,000-£30,000) with a net cost equivalent of 1.5 QALYS (i.e. £30,000 / £20,000) and net health benefit of 0.5 QALYs (i.e. 2 – 1.5 QALYs). As these are positive the trajectory of the net benefit is also positive and therefore deemed cost effective. Afterwards, a statistical sensitivity analysis using a Cost Effectiveness Acceptability Curve (CEAC) is a helpful adjunct and can remove the need for a confidence intervals to describe uncertainty. ICER values are simulated and compared to the ceiling ratio, with the proportion of simulated values acceptable to the ratio recorded. The ceiling ratio can then be altered, with the proportion acceptable to the new ceiling ratio captured and a probability curve that the intervention is cost effective illustrated across a range of scenarios.

3.3 Study 3 – Long term clinical and technical outcomes comparing concomitant versus sequential phlebectomy with EVLA for SVI

Study design

The EVLTAP randomised clinical trial (ClinicalTrials.gov NCT02017106) was performed at the same unit as the HELP-1 study and its methods have been reported

previously[507]. As with the HELP-1 study, all patients consecutively referred to a single vascular surgeon were evaluated for trial inclusion eligibility. Patients first underwent outpatient clinical assessment and venous duplex ultrasonography and were deemed eligible if they met the following inclusion and exclusion criteria:

Inclusion criteria

Clinical criteria

- Primary symptomatic superficial venous insufficiency of a lower limb which is classified between C2 to C5, as per the CEAP classification
- Willingness to undergo endovenous laser ablation without ambulatory phlebectomy under local anaesthetic
- Willingness to undergo endovenous laser ablation with ambulatory phlebectomy under local anaesthetic

Duplex ultrasound criteria

- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-Formal junction into the great saphenous vein
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the great saphenous vein at least the level of the knee.

Administrative criteria

- Willing to participate in a randomised clinical trial
- Willing to complete additional clinical and duplex assessments and completion of research questionnaires with analysis and publication of the results

Exclusion criteria

Clinical criteria

- Age less than 18 years old
- Any previous venous intervention
- Presence of lower limb venous disease which is classified at and less than C1, as per the CEAP classification
- Pregnancy
- Symptoms or clinical evidence of arterial insufficiency (including ankle brachial pressure ratio less than 0.8)
- Known thrombophilia state or disease
- Any malignancy
- Any allergy to any local anaesthetic medication used in the procedure

Duplex ultrasound criteria

- Presence of any deep venous axis incompetence
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-popliteal junction into the great saphenous vein or short saphenous vein
- Presence of any incompetent superficial venous axis, aside from the GSV, which in the opinion of the operating surgeon would be optimally treated with endovenous ablation or conventional surgery with vein stripping rather than ambulatory phlebectomy
- Anterior to posterior GSV diameter less than 4 millimetres as measured by DUS at the proposed cannulation point.

Administrative criteria

- Inability or unwilling to participate in a randomised clinical trial
- Inability or unwilling to give informed consent for trial participation

Randomisation

Following completion of the consent documentation, enrolled patients were then randomised equally into one of two parallel treatment arms using opaque sealed envelopes. The control group were to receive EVLA alone without concomitant phlebectomy under local anaesthesia and the experimental group were to receive EVLA with ambulatory phlebectomy under local anaesthesia. Both groups were offered sequential phlebectomy of any symptomatic residual venous tributaries present after six weeks. Treatment for symptomatic recurrence was offered on an individualised basis depending the specific patient requirements and needs.

Sample size calculation

The primary outcome of the EVLTAP randomised trial was to detect if there was a significant difference in AVVQ between the two treatment groups. A sample size calculation was based the assumption that the average AVVQ following EVLA alone was 3.94[508] compared to an average of 0.60 following EVLA and concomitant phlebectomy[509]. Using a power calculation with an alpha of 0.05 and a beta of 0.20 (i.e. 80% power), and assuming a loss to follow up of 10%, each treatment arm required 25 patients.

Treatment methods

Both groups underwent their allocated treatment in a dedicated outpatient procedure room without sedation. The treatment techniques for the procedures are outlined below.

Preoperative procedure

Both groups had their treatment limb marked preoperatively with indelible ink prior to intervention. Using ultrasound guidance with a portable MicroMaxx® ultrasound machine with the patient standing, the location of the SFJ was first identified and the course of the GSV mapped. If the patient was to receive concomitant phlebectomy any symptomatic varicose tributaries were identified by the patient and marked for removal. Patients then underwent the procedures as follows:

Endovenous laser ablation (EVLA)

Once in the reverse Trendelenburg position the limb was prepared with 10% povidone-iodine in water or, if contraindicated due to allergy, 2% chlorhexidine gluconate in 70% isopropyl alcohol. After draping with sterile sheets the location of GSV was identified using the portable ultrasound machine and a 5 French catheter percutaneously inserted into the vein at the level of the knee using the Seldinger technique. With the tip of the catheter confirmed at the level of SFJ, the patient was levelled out and the limb prepared for infiltration of tumescent local anaesthesia, a solution of 2% lidocaine with 1:200,000 adrenaline in 0.9% normal saline. Under ultrasound guidance the tumescent solution was infiltrated into the fascial compartment of the GSV with an approximate volume of 10 mls per 1 cm of GSV. Once anesthetised, a 600 μm bare-tipped laser fibre was inserted and then locked into the sheath. The laser generator unit was then activated and set to a wavelength

of 810 nm, power of 14 watts and a setting of continuous laser energy delivery. With the laser switched on, controlled withdrawal of the laser fibre and sheath was then commenced with the aim of providing a LEED of at least 60-80 J/cm^{-1} along the vein length. Once completed the puncture point was dressed and the leg either prepared for bandaging or concomitant phlebectomy, as detailed below.

Concomitant phlebectomy

Additional tumescent solution was infiltrated into the tissues surrounding the marked venous tributaries and incompetent perforators, with treatment undertaken as required. Perforators were divided and ligated via a small incision. Varicose tributaries were avulsed using a Kocherised mosquito clip or an Oesch vein hook. All wounds were then infiltrated with local anaesthetic (0.5% Levobupivacaine) and dressed as appropriate.

Post treatment

After the completion of treatment the limb was then circumferentially bound with an elastic adhesive bandage, Panelast®, which was to remain for one week. Patients were also provided with a thigh length T.E.D™ anti-embolism stocking, which was then to be worn for a further five weeks after removal of the compression bandages. All patients were discharged with Diclofenac 50 mg to be taken regularly three times a day for 1 week and Paracetamol 1 g for breakthrough pain (maximum four times a day).

Follow-up appointments

Following their randomised procedure patients were then invited to attend several follow up appointments over the following five years. The prescribed schedule was at 1 week, 6 weeks, 12 weeks, 1 year, 2 years and 5 years, with the option of early

review if any problems arose. All appointments were conducted at a dedicated vascular research unit and performed by a medically trained research investigator with ultrasound accreditation. The follow up appointment consisted of Qol questionnaires, clinical review and a DUS examination of the treatment limb.

QoL Questionnaires

A paper booklet containing the QoL questionnaires was completed in private by the patient prior to the clinical and duplex assessments. The booklet consisted of three QoL questionnaires, two generic QoL measurements (SF-36 and EQ-5D), and a disease specific QoL measurement (AAVQ). All three were identical to the preoperative questionnaires.

Clinical review

Following a focussed history and clinical examination, the VCSS and CEAP scores were assessed and documented. Special attention was made for any evidence of clinical recurrence, defined as new symptomatic varicose vein greater than 3 cm which have arisen 12 weeks after their initial treatment. Patients were also asked to mark on a 10 cm VAS scale their opinion of the cosmetic appearance of their treatment limb and overall satisfaction with treatment.

Venous duplex ultrasound protocol

All ultrasound examinations were undertaken using the same research Toshiba Aplio MX machine with a 6-12 MHz linear transducer array. Using default venous duplex settings the ultrasound examination was undertaken in accordance with international guidelines[158], and are outlined above on page 122.

Outcome measurements

The primary outcome measure was Quality of Life measured by the AVVQ. Several secondary outcome measurements were recorded and are grouped into the following three categories; QoL, clinical and DUS outcomes.

Quality of Life outcomes

- Disease Specific QoL – Aberdeen Varicose Vein Questionnaire (primary outcome measurement)
- Generic QoL – Short Form 36
- Utility Index QoL – EuroQol 5 Dimension
- Utility Index QoL – SF6D

Clinical outcomes

- Objective clinical assessment of venous disease – VCSS
- Recurrence of symptomatic and asymptomatic varicosities
- Cosmetic satisfaction
- Overall satisfaction
- Requirement for further procedures

Duplex ultrasound outcomes

- Long term technical success
- Recurrence of reflux and patterns of venous incompetence
- Presence of new axial vein incompetence

3.4 Study 4 – Cost comparison of concomitant or sequential phlebectomy with EVLA for SVI

Clinical background

As with the EVLTAP study methodology outlined above, patients were followed up for five years. Any patients developing symptomatic clinical recurrence were offered conservative management (with or without compression) or an interventional treatment. Interventional treatments were offered on an individualised basis by an experienced surgeon with a special interest in the management of venous disease. Potential treatment options could include one or more combinations of phlebectomy, ultrasound guided perforator ligation, perforator ablation, UGFS, EVLA and open surgery. All but open surgery were routinely performed under local anaesthesia. The economic analysis methodology is as follows

Health Utility Calculation

Generic index quality of life was self-recorded by study participants at baseline and weeks 1, 6, 12, 52, 104 and 260 using the TTO of EQ5D[499] as per NICE recommended methodology[142]. From this Quality Adjusted Life Years (QALYs) were estimated for each patient using the area under the curve (AUC). A sensitivity analysis of missing data was also calculated, with missing results determined using interpolation, last value carried forward or group mean. Sensitivity analysis of the discount rate was also performed, with a rate of 0% and 5% used.

Costs Calculation

As with the economic analysis of the HELP-1, study the metrics of resource expenditure in the EVLTAP study were collected prospectively and estimated from

the perspective the NHS. Primary and secondary healthcare staffing costs were determined from "Unit costs of health & social care 2013"[143]. Cost of venous duplex scans, outpatient and research appointments and were determined against the NHS reference cost of service tariff 2013-2014[502]. Operative costs were calculated per minute based on the recorded time between the patient entering and leaving the room procedure room. Single use disposable equipment was counted as a cost per unit and the specific capital costs for EVLA, such as the laser generator and access to portable duplex ultrasound, were annuitized. Consumable annuitized costs and theatre overheads were taken from a large multicentre UK based RCT[510]. The costs of follow up and secondary treatments were similarly calculated. In order to allow for the time preference of expenditure, discounting was applied at a rate of 3.5% per annum.

Parameter uncertainty

Figure 3 represents the presumed clinical patient pathway for the purposes of cost calculation in this sensitivity analysis. Treatment of an axis, such as the GSV or a perforator, was assumed to be followed up with a single outpatient and DUS assessment, whereas treatment of only varicose tributaries, such as phlebectomy or foam sclerotherapy, was followed by an outpatient appointment only. Patients with no residual symptomatic disease were assumed to be discharged and further recurrence required re-referral and re-assessment.

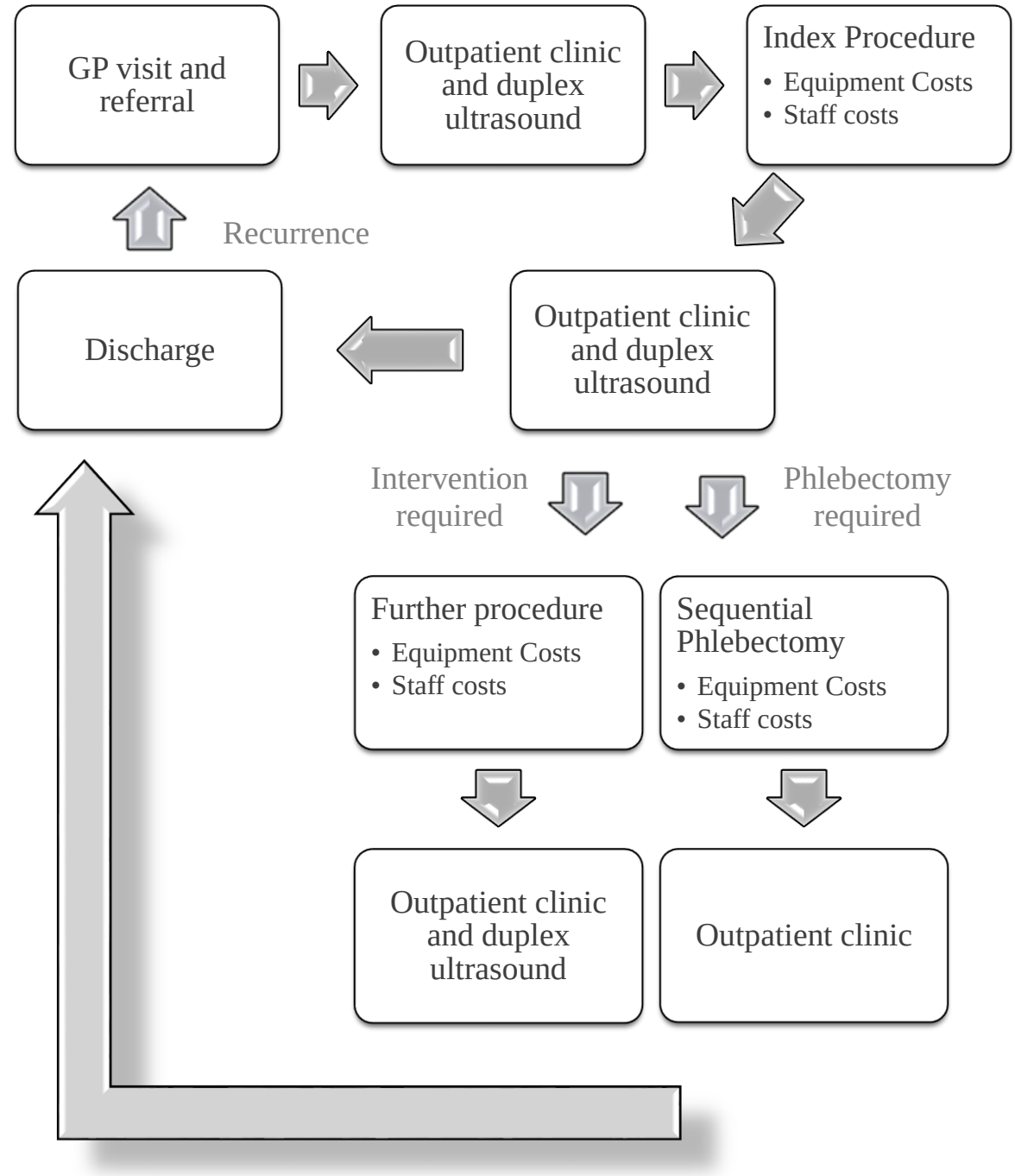


Figure 3. EVLTAP patient pathway

Monte Carlo Analysis

Proponents of sequential treatment have argued that they have a higher threshold for secondary treatment of residual tributaries than was reported in the EVLTAP trial and therefore this is also an important parameter to explore. The impact of differing thresholds for re-intervention poses a more complex problem and was therefore explored using a Monte Carlo simulation. A computer generated population of 10,000 patients were simulated to receive each treatment allocation. The costs of the initial procedure were randomly drawn from the observed natural distribution of costs. The threshold for re-intervention was then proportionally varied simultaneously for both groups. The groups were then randomly allocated to receive a secondary procedure according the threshold level for re-intervention and for those undergoing further treatment. The cost was again drawn from the observed distribution in the trial. Finally the total costs of the two groups were compared at each threshold level to calculate the probability of one treatment being more cost effective, in this case EVLA alone being more cost-effective than EVLAP. However, a key assumption of this model is that varying the threshold of re-intervention has no effect upon the overall effectiveness of treatment and QoL improvement between the two groups.

3.5 Study 5 – Long term clinical and technical outcomes of treating those with and without complications of SVI

Study Design

Using data collected from the HELP-1 trial, a subgroup analysis of different levels of venous disease was undertaken. Using the CEAP classification, whereby C0

represents no venous disease and C6 represents active venous ulceration, special focus was made on the longer term differences between uncomplicated (C2) and complicated (C3-4) SVI. The aim of this study was to compare the long term outcomes of those with and without the complications of SVI.

Study Groups

Groups were divided according to their recorded baseline CEAP severity. Group 1 consisted of patients with documented baseline C2 disease whereas group 2 consisted of patients with documented baseline C3 and C4. Patients with C0, C1, C5 and C6 disease were not included in this analysis.

Outcomes

The primary aim of this regression was to estimate the average change in SF-36 QoL per group. Several secondary outcome measurements were as follows

- Long term success
- Requirement for secondary procedures
- Clinical recurrence

3.6 Study 6 – Cost comparison of treating those with and without the complications of SVI

Clinical background

Using the clinical and economic data from the HELP-1 trial, an economic subgroup analysis was performed comparing the costs of treating those with and those without the complications of venous disease. Again, over the follow up period any additional costs of further treatments were counted and included into the final analysis.

Health Utility Calculation

Generic index quality of life was self-recorded by study participants at baseline and weeks 1, 6, 12, 52, 104 and 260 using the TTO of EQ5D[499] as per NICE recommended methodology[511]. QALYs were estimated to provide an AUC. Discounting was applied at a rate of 3.5% per annum. Missing data was imputed using interpolation between time points (on an intention to treat basis) unless missing data was due to mortality, in which case data was input as the last result carried forward.

Costs Calculation

Costs were taken from the economic analysis of the HELP-1 study which were collected prospectively and estimated from the perspective the NHS. Again, primary and secondary healthcare staffing costs were determined from "Unit costs of health & social care 2013"[512]. Cost of venous duplex scans, outpatient and research appointments and were determined against the NHS reference cost of service tariff[502]. Operative costs were calculated per minute based on the recorded time between the patient entering and leaving the room procedure room. Single use disposable equipment counted as a cost per unit and the specific capital costs for EVLA, such as the laser generator and access to portable duplex ultrasound were annuitized. These consumable and annuitized costs were taken from the multicentre estimates of a large UK based RCT[513]. The costs of follow up and secondary treatments were also similarly calculated. In order to allow for the time preference of expenditure, discounting was applied at a rate of 3.5% per annum.

Parameter uncertainty

As with the HELP-1 economic analysis a sensitivity analysis was conducted with variation of the discounting rate from 0% to 5% per annum.

3.7 Study 7 – Comparison of endovenous laser design, technique and clinical outcomes in the treatment of superficial venous insufficiency.

Study design

This subgroup analysis is based on the results of three randomised clinical trials; the HELP-1 study[152, 153] and EVLTAP study[507] and a third study which preceded both, a randomised clinical trial comparing the 12 Watt and 14 Watt endovenous laser fibre design[386]. All three studies were undertaken within the same dedicated vascular unit in a large tertiary hospital in the UK[490, 491]. Patients underwent outpatient clinical assessments consisting of history, examination and measurement of baseline clinical disease status (CEAP and VCSS) followed by DUS assessment using an international protocol[158]. Patients were then deemed eligible if they met the following inclusion and exclusion criteria:

Inclusion criteria

Clinical criteria

- Primary symptomatic superficial venous insufficiency of a lower limb which is classified between C2 to C4, as per the CEAP classification

(HELP-1 clinical criteria)

- Willingness to undergo endovenous laser ablation with ambulatory phlebectomy under local anaesthetic
- Willingness to undergo conventional open surgery with ambulatory phlebectomy under general anaesthesia

(EVLTAP clinical criteria)

- Willingness to undergo endovenous laser ablation without ambulatory phlebectomy under local anaesthetic
- Willingness to undergo endovenous laser ablation with ambulatory phlebectomy under local anaesthetic

(12 Watt vs 14 Watt laser fibre clinical criteria)

- Willingness to undergo endovenous laser ablation with ambulatory phlebectomy under local anaesthetic

Duplex ultrasound criteria

- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-Formal junction into the great saphenous vein
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the great saphenous vein at least the level of the knee.

Administrative criteria

- Willing to participate in a randomised clinical trial
- Willing to complete additional clinical and duplex assessments and completion of research questionnaires with analysis and publication of the results

Exclusion criteria

Clinical criteria

- Age less than 18 years old
- Any previous venous intervention
- Presence of lower limb venous disease which is classified at and less than C1, as per the CEAP classification
- Pregnancy
- Symptoms or clinical evidence of arterial insufficiency (including ankle brachial pressure ratio less than 0.8)
- Known thrombophilia state or disease
- Any malignancy
- Any allergy to any local anaesthetic medication used in the procedure

Duplex ultrasound criteria

- Presence of any deep venous axis incompetence
- Presence of one or more seconds (≥1 sec) of retrograde venous flow in the Sapheno-popliteal junction into the great saphenous vein or short saphenous vein
- Presence of any incompetent superficial venous axis, aside from the GSV, which in the opinion of the operating surgeon would be optimally treated with endovenous ablation or conventional surgery with vein stripping rather than ambulatory phlebectomy
- Anterior to posterior GSV diameter less than 4 millimetres as measured by DUS at the proposed cannulation point.

Administrative criteria

- Inability or unwilling to participate in a randomised clinical trial
- Inability or unwilling to give informed consent for trial participation

Study groups

- Group 1 – 12 Watt EVLA with Ambulatory Phlebectomy
- Group 2 – 14 Watt EVLA with Ambulatory Phlebectomy
- Group 3 – 14 Watt EVLA alone without Ambulatory Phlebectomy

Treatment methods

All three groups underwent their endovenous treatments as described above within the HELP-1 and EVLTAP trials respectively. In the EVLA fibre study, both groups underwent the same endovenous technique as described in the HELP-1 trial, with the only differences being applied to the settings of the EVLA laser generator. In brief, after insertion of the EVLA catheter and perivenous TLA, both laser fibres were set to an 810 nm wavelength with the Watts and energy delivery setting depending on the group randomisation. For the 12 Watt group, a setting of 12 Watts and pulse energy delivery was selected whereas the 14 Watt group a setting of 14 Watts and continuous energy delivery was selected. Pulse energy delivery was set to one second on one second off with a 2 mm/s withdrawal of the laser fibre during intervals. Continuous energy delivery had laser energy continuously with 2 mm/s withdrawal of the laser fibre throughout.

Follow-up appointments

Following their procedure all patients were invited to attend several follow up appointments over five years, with appointments set at 1 week, 6 weeks, 12 weeks, 1

year, 2 years and 5 years, with the option of early review if any problems arose. All appointments were conducted at the same dedicated vascular research unit and performed by a medically trained research investigator with ultrasound accreditation. The follow up appointment consisted of Qol questionnaires, clinical review and a DUS examination of the treatment limb,

Outcome measurements

The primary outcome was change in QoL, as measured by the SF-36. Secondary outcome measurements were as follows

Quality of Life outcomes

- Generic QoL – Short Form 36 (Primary outcome measurement)
- Utility Index QoL – EuroQol 5 Dimension
- Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

Clinical outcomes

- Objective clinical assessment of venous disease – VCSS
- Requirement for further procedures

Duplex ultrasound outcomes

- Long term technical success
- Recurrence

Chapter 4 – Results

4.1 Study 1 - Long term clinical and technical outcomes of EVLA versus open surgery for SVI

As shown in the HELP-1 CONSORT diagram (Figure 4), of the initial 280 patients randomised 218 (79%) attended for their appointment at five years.

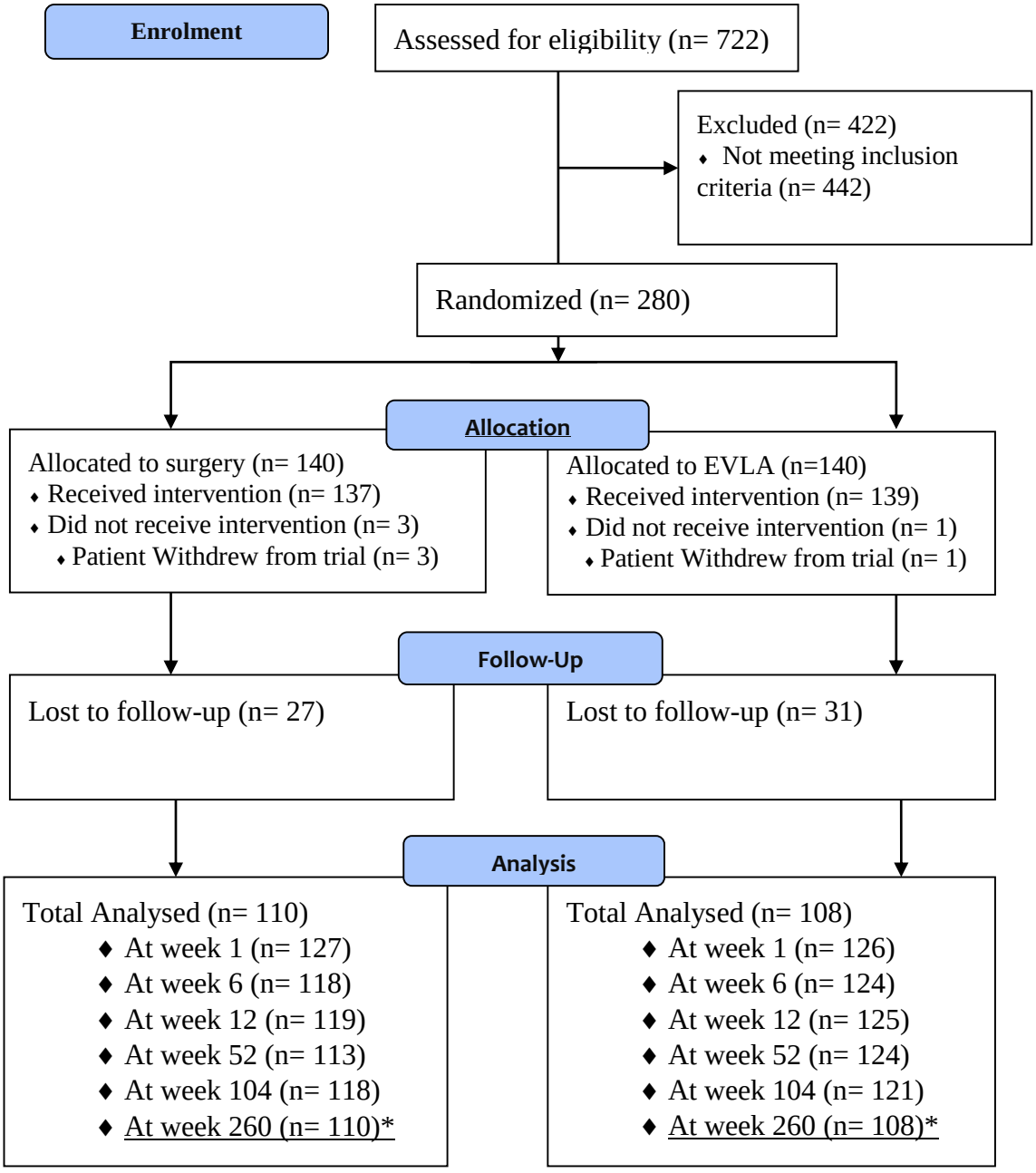


Figure 4. HELP-1 CONSORT flow chart (Study 1) *Time period of this study

Of these followed up to five years, 110 (80.3%) had undergone surgery and 108 (77.7%) had undergone EVLA. There was a similar proportion of patients lost to follow up between the two groups (27 vs 31 P=0.658 χ^2). Five year mortality was also similar between the groups with three Surgery and seven EVLA patients passing away over the course of the trial (P=0.377 χ^2). However, of these, seven managed to attend an appointment at two years.

Generic Quality of Life - Short Form - 36

The SF-36 scores over five years are detailed in Table 8 and shown in Figure 5 to Figure 20. Both groups were broadly similar in their baseline SF-36 measurements, aside from the Mental Health domain which was marginally lower in the conventional surgery group. Whilst statistically significant this initial difference was minor and of doubtful clinical importance[198, 207, 514]. Over the study period statistical and clinically significant early differences were noted in the domains of Physical Function, Role-Physical, Bodily Pain, Vitality, Social Function and Role-Emotional whereas a late difference was only seen in Social Function. These results are described below.

Conventional surgery

At one week, following conventional surgery a significant early impairment was noted in five of the eight SF-36 domains (Physical function P<0.001, Role physical P<0.001, Bodily pain P<0.001, Social function P=0.001 and Role emotional P=0.029: WSR). By six weeks, all of these domains had recovered and two physical domains had even improved significantly beyond their baseline scores (Physical function P=0.001), Body pain P<0.001 WSR). Of the remaining domains, although not impacted at one week, these were also noted to be significantly better than their

baseline scores by six weeks (General health P<0.001, Vitality P=0.001 and Mental health P<0.001 WSR). Between 12 weeks and two years, the SF-36 domains of Physical function, Body pain, Vitality and Mental health were sustained above their early improvement. Temporary early improvement was also observed in three domains (General health P=0.001 Social Function P=0.008 and Role emotional P=0.046 WSR), although this receded back to baseline levels by one year. Aside from the early impairment at one week, no SF-36 domain fell significantly below their baseline level over two years.

At five years, six of the eight domains, including Physical function and Body pain, had returned to pre-intervention baseline levels. As shown in Figure 20, above baseline improvement was still sustained in the Mental health domain. However, the Social function domain was significantly worse than its baseline level at five years and this was likely a clinically noticeable outcome (Figure 16).

EVLA

Following EVLA a significant early impairment was noted in two of the eight SF-36 domains by one week (Physical Function P=0.018 and Role Physical P<0.001 WSR). However, at six weeks both of these physical domains had recovered and, of these, the Physical function domain had even improved beyond its initial baseline level (Figure 6, (P=0.004) WSR). It was also revealed that four of the other six domains had shown above baseline improvement by six weeks (Body pain P=0.001 General Health P=0.036 Vitality P<0.001 and Mental health P=0.027 WSR). Aside from week one, no SF-36 domain deteriorated over six weeks.

Between 12 weeks and two years, the SF-36 domains of Physical function and Body Pain showed sustained above baseline improvement. Temporary benefit was also

seen in the domains of Role Physical, General Health and Vitality at one year but, by two years, this had dissipated. Again, no domain showed any deterioration.

At five years, seven of the eight SF-36 domains had returned to pre-intervention levels, with one domain, Social Function, showing significant deterioration (Figure 16).

Intergroup comparison

Both statistical and clinically important differences were detected between EVLA and conventional surgery over the study period. As demonstrated in Table 8 and Figure 5 to Figure 19, early impairment of the SF-36 was much more pronounced following conventional surgery when compared to those receiving EVLA, with six of eight SF-36 domains demonstrating significantly worse scores following conventional surgery (Physical Function P=0.012, Role-Physical P=0.005, Bodily Pain P=0.031, Vitality P=0.049, Social Function P=0.004 and Role-Emotional P=0.027 MWU). Between six weeks and two years, both treatments were broadly similar across all eight SF-36 domain. At five years seven of the eight SF-36 domains had broadly comparable scores. However in the domain of Social Function, while both groups saw a deterioration below pre-intervention levels at five years (Figure 16), the fall was much steeper in those who had received conventional surgery (P=0.003 MWU).

Early deterioration after treatment was much more pronounced after Conventional surgery compared to EVLA in the domains of Physical Function, Role Physical and Role Emotional. As shown in Figure 6 and Figure 8, those undergoing Conventional surgery were impaired by more than double of the mean (and therefore highly likely to be clinically significant) of those receiving EVLA in Physical Function (mean

(s.d.) improvement Conventional surgery -11 (22) vs EVLA -5 (19) P=0.010) and Role Physical (mean (s.d.) improvement Conventional surgery -32 (44) vs EVLA -14 (38) P=0.001). In Role Emotional, while those receiving Conventional surgery experienced a drop in QoL, those reviving EVLA saw a marginal increase (mean (s.d.) improvement Conventional Surgery -7 (35) vs EVLA 1 (32) P=0.041). As shown in Figure 20, Mental health improvement was consistently greater among those receiving Conventional surgery until five years, although this also had the overall effect of bringing Conventional surgery into parity with those who had undergone EVLA, negating the overall preoperative difference and is of doubtful clinical significance.

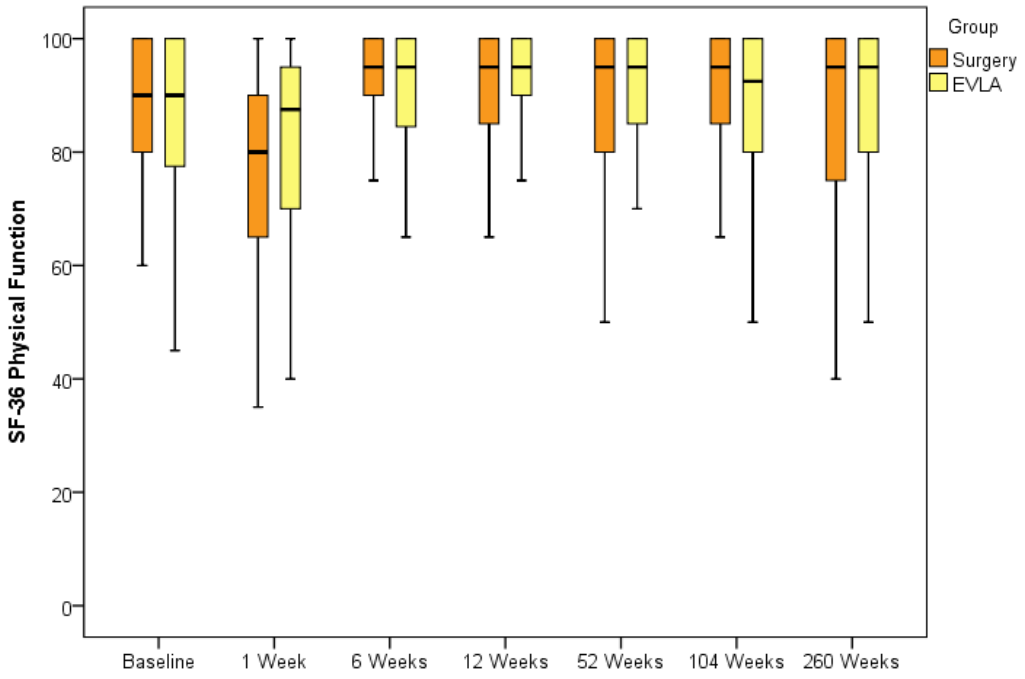


Figure 5 SF-36 Physical function scores over five years (Study 1)

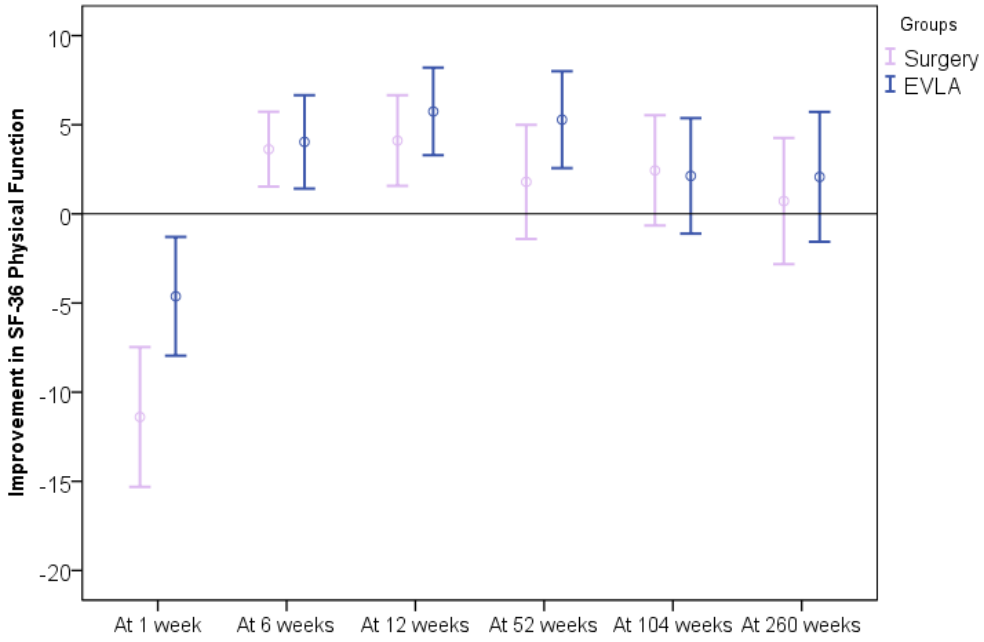


Figure 6 Improvement in SF-36 Physical function over five years (Study 1)

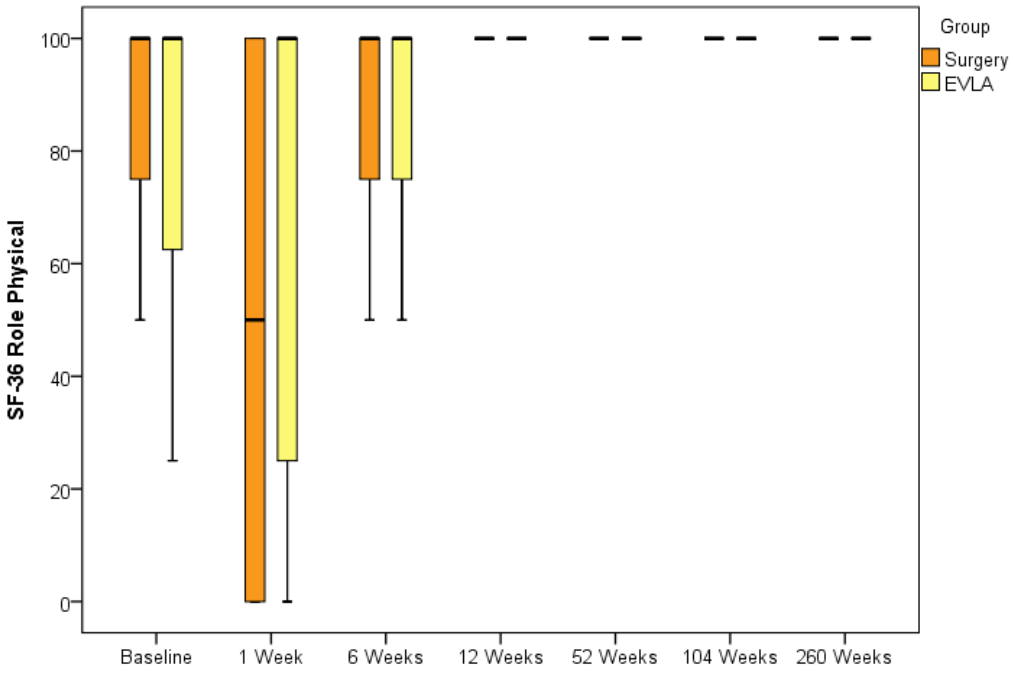


Figure 7 SF-36 Role physical scores over five years (Study 1)

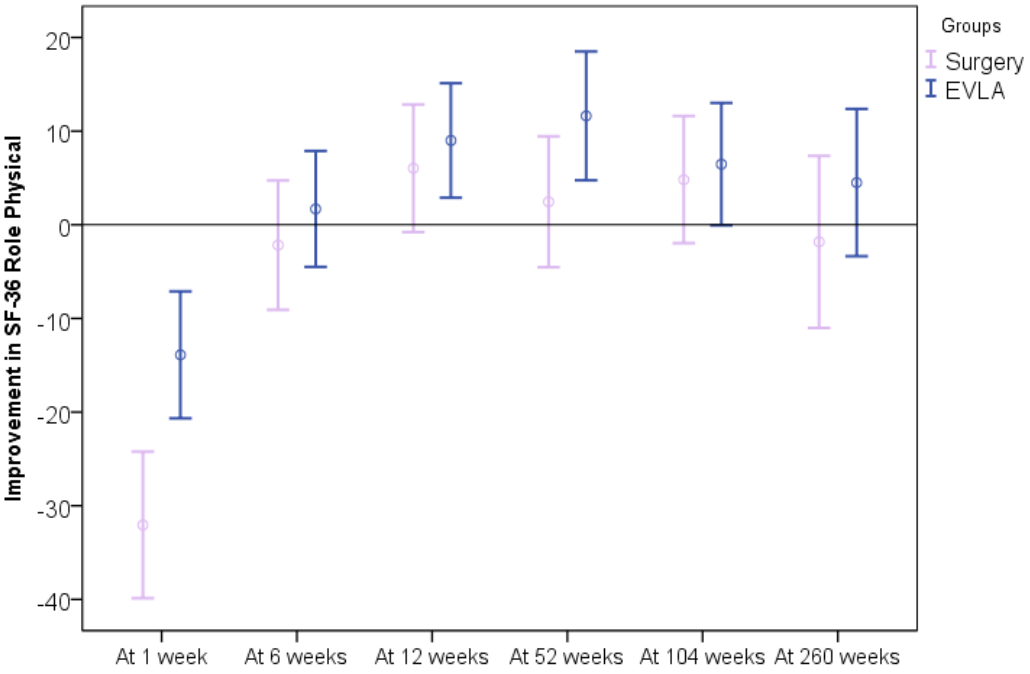


Figure 8 Improvement in SF-36 Role Physical over five years (Study 1)

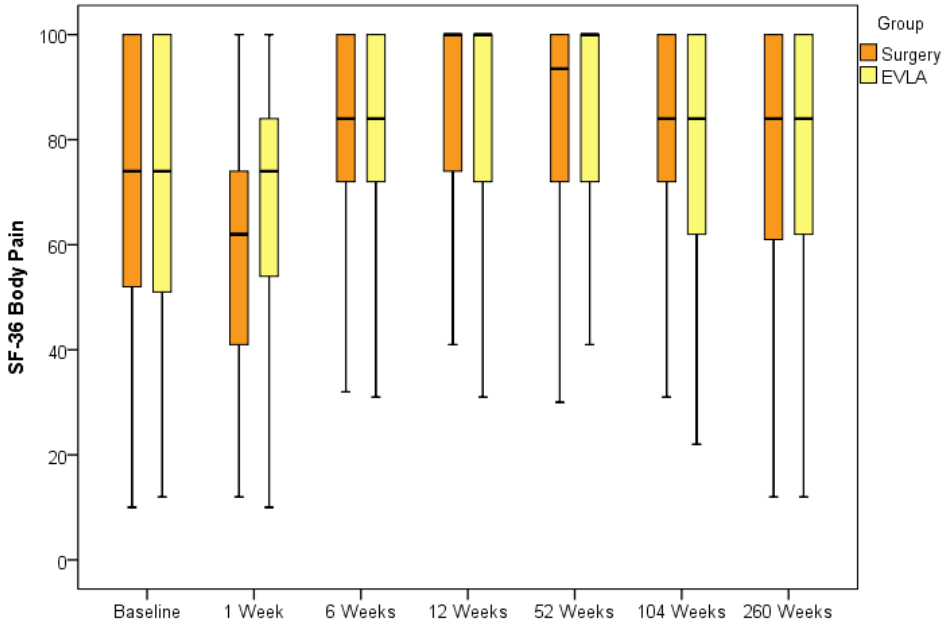


Figure 9 SF-36 Body pain scores over five years (Study 1)

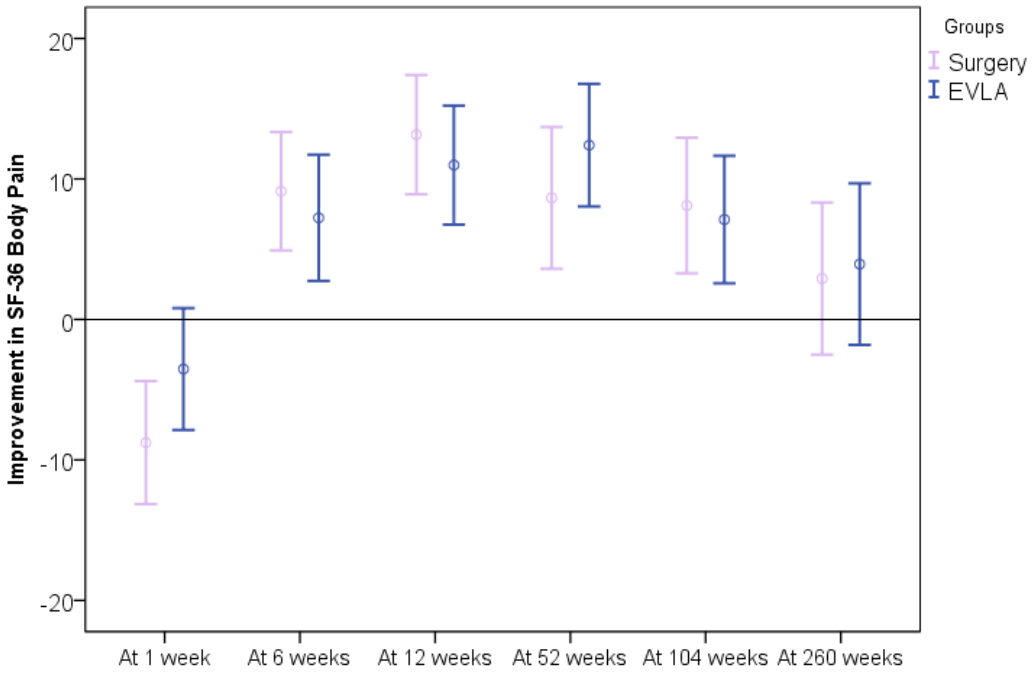


Figure 10 Improvement in SF-36 Body Pain over five years (Study 1)

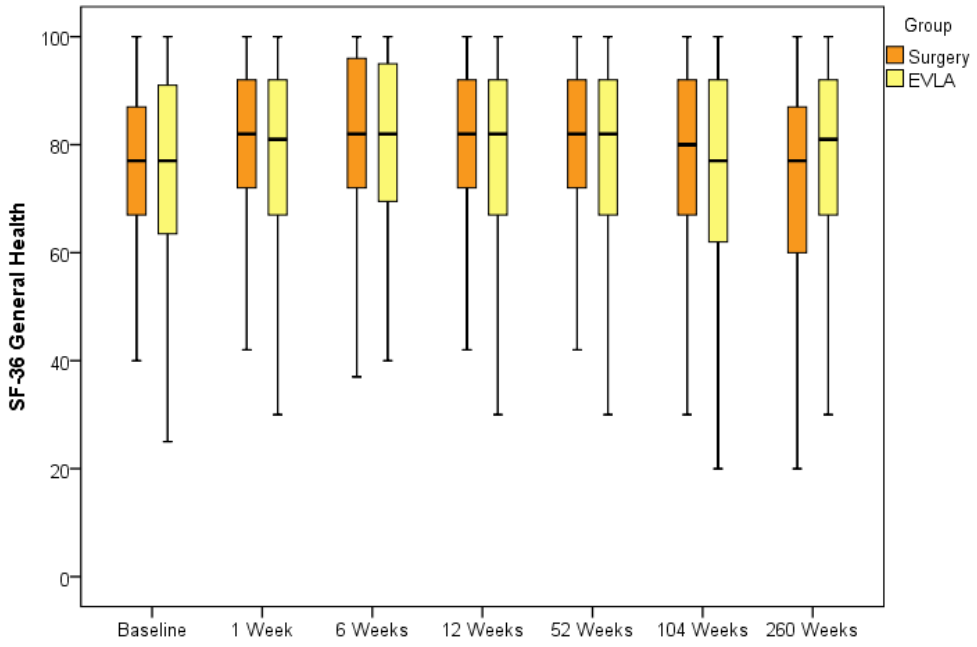


Figure 11 SF-36 General health scores over five years (Study 1)

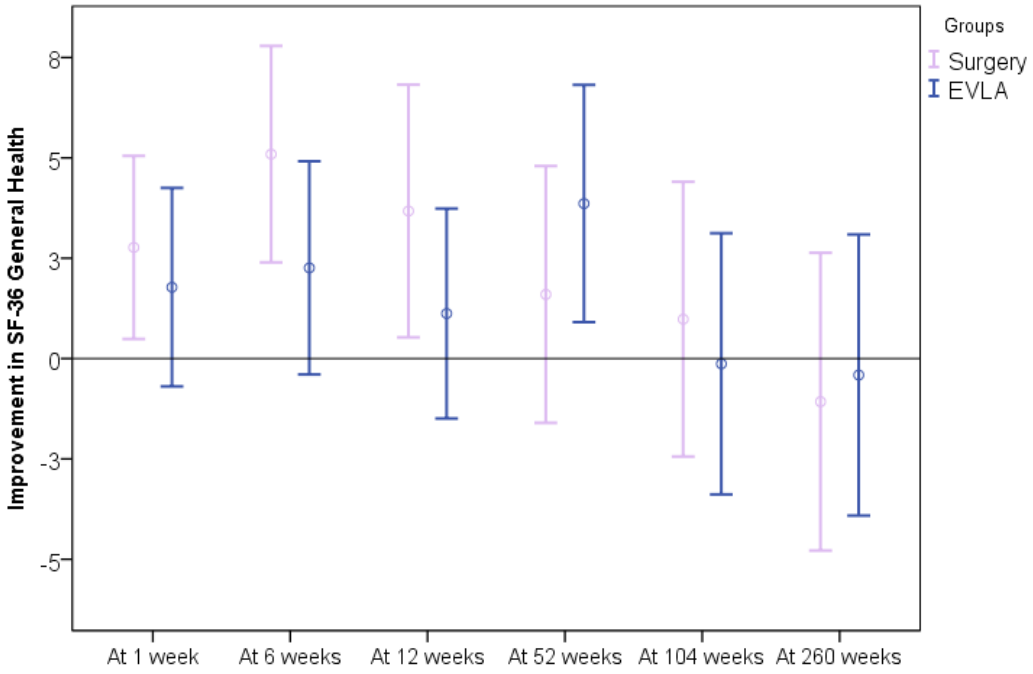


Figure 12 Improvement in SF-36 General Health over five years (Study 1)

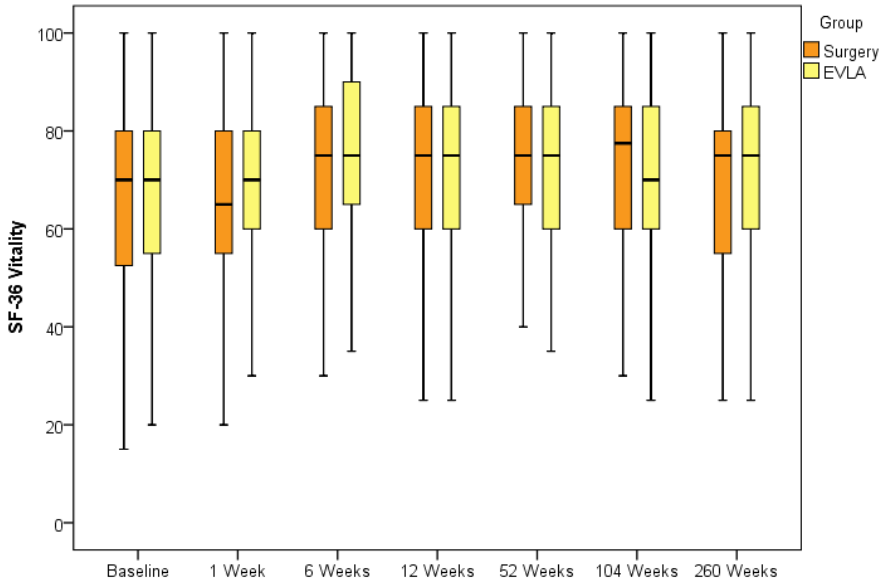


Figure 13 SF-36 Vitality scores over five years (Study 1)

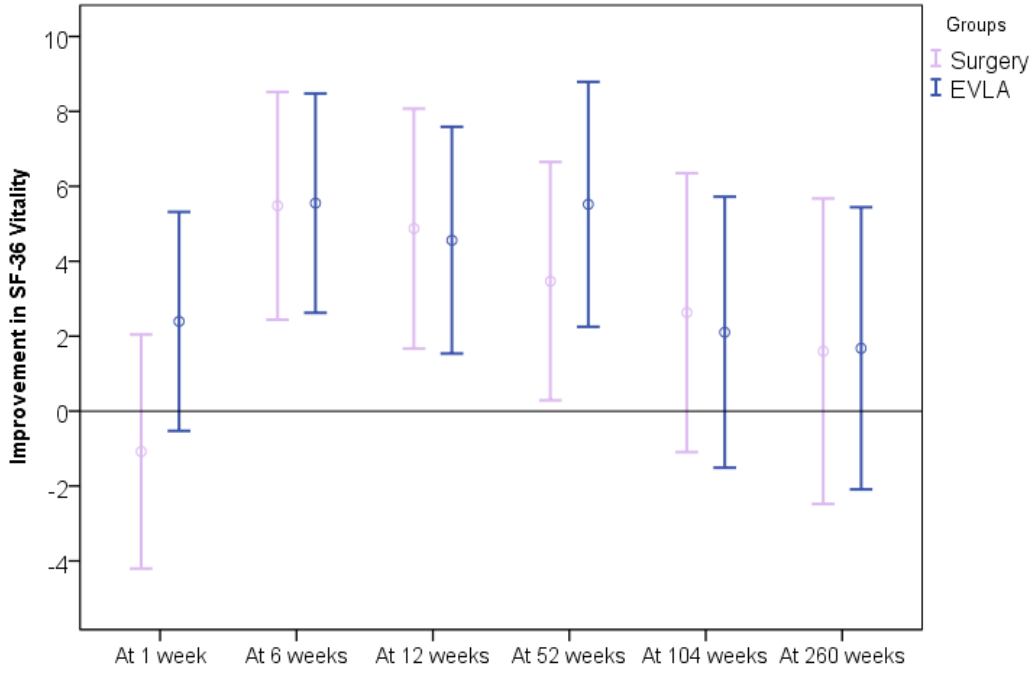


Figure 14 Improvement in SF-36 Vitality over five years (Study 1)

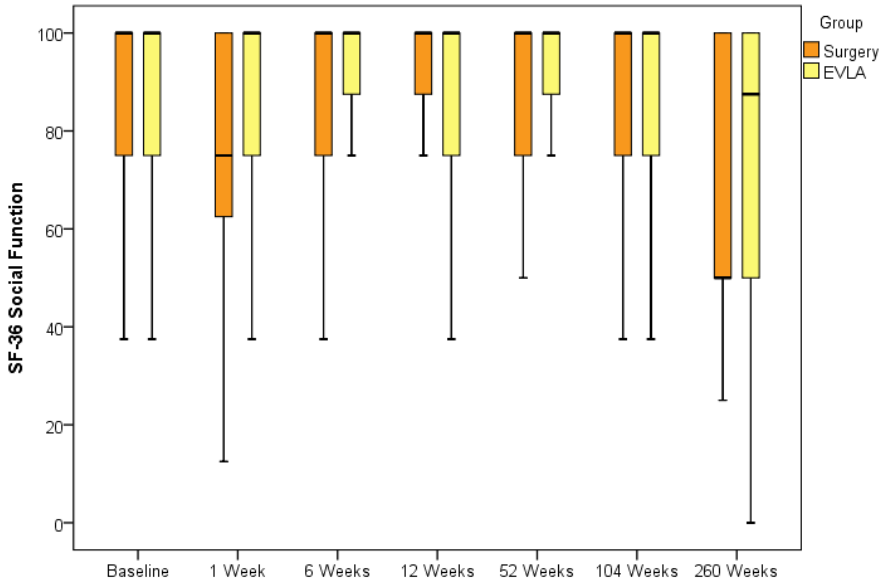


Figure 15 SF-36 Social function scores over five years (Study 1)

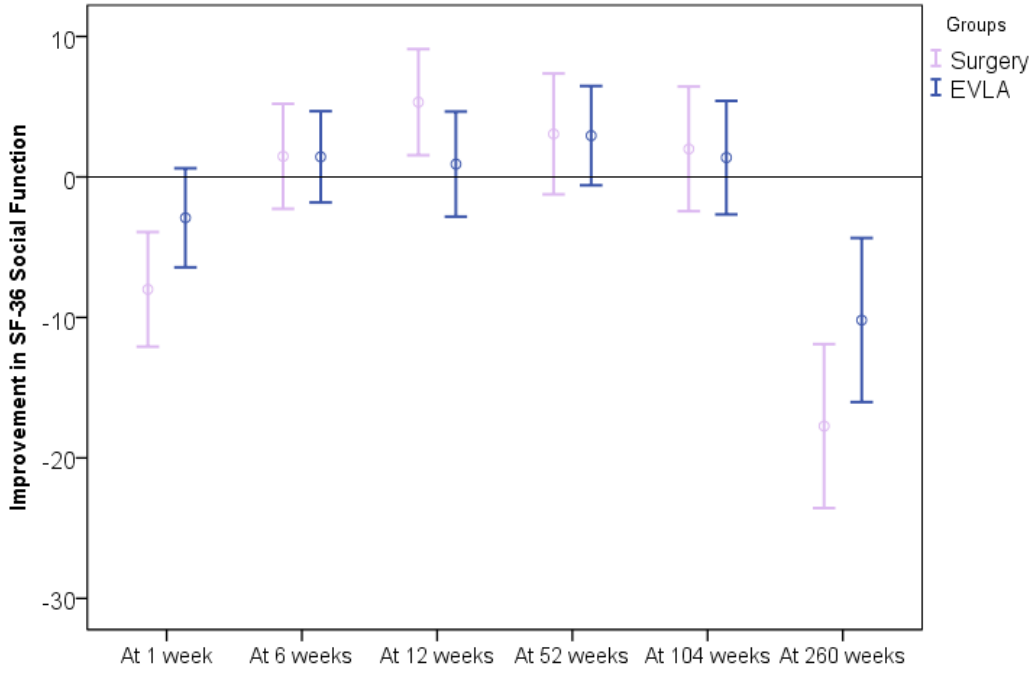


Figure 16 Improvement in SF-36 Social Function over five years (Study 1)

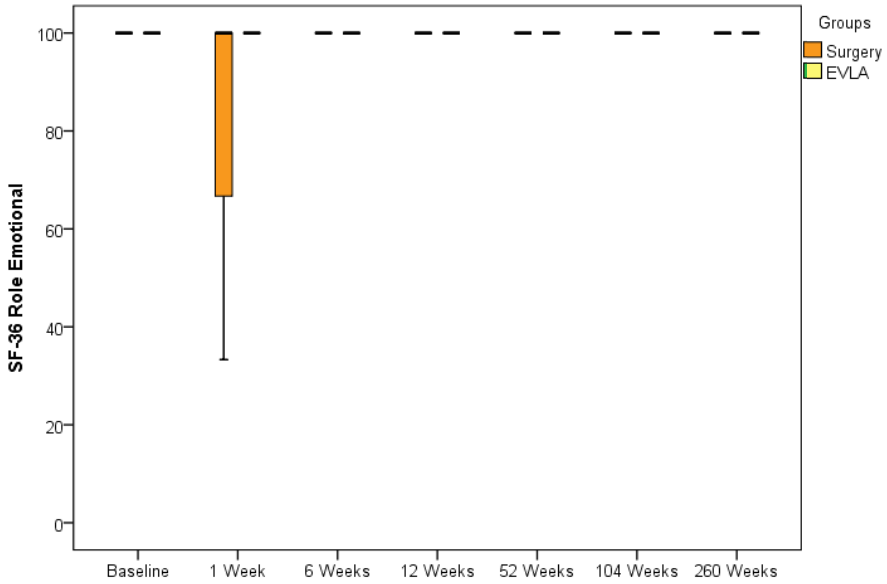


Figure 17 SF-36 Role emotional scores over five years (Study 1)

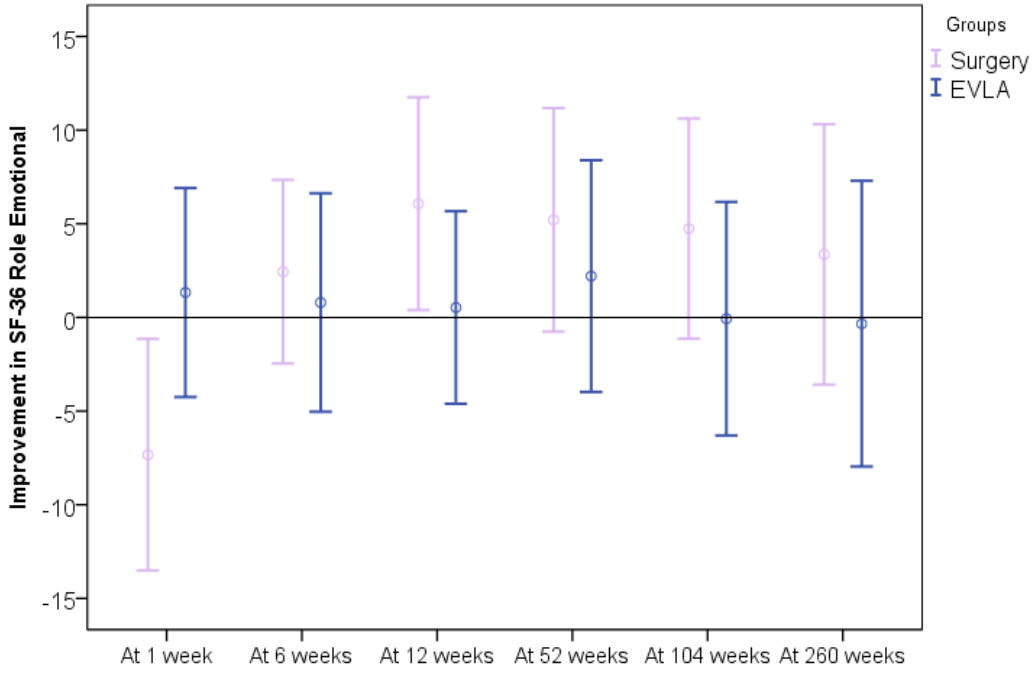


Figure 18 Improvement in SF-36 Role Emotional over five years (Study 1)

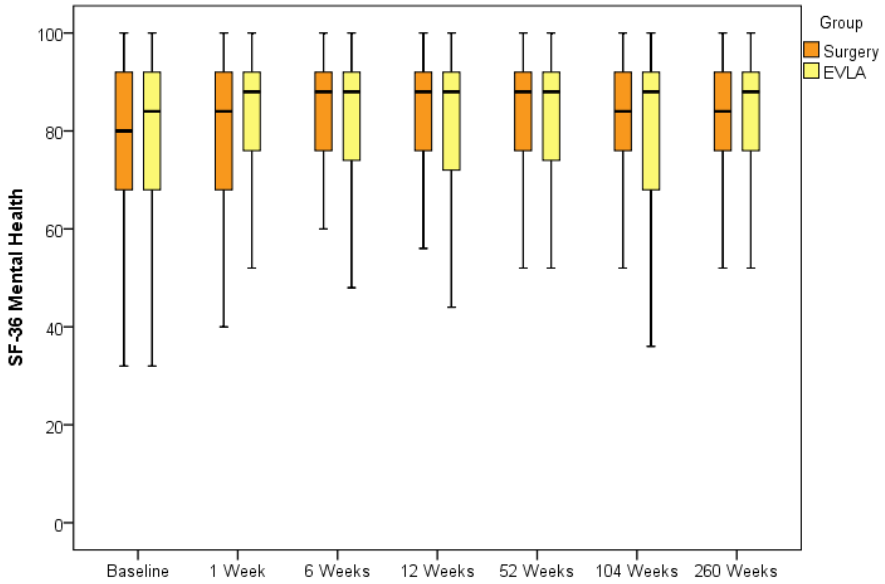


Figure 19 SF-36 Mental Health scores over five years (Study 1)

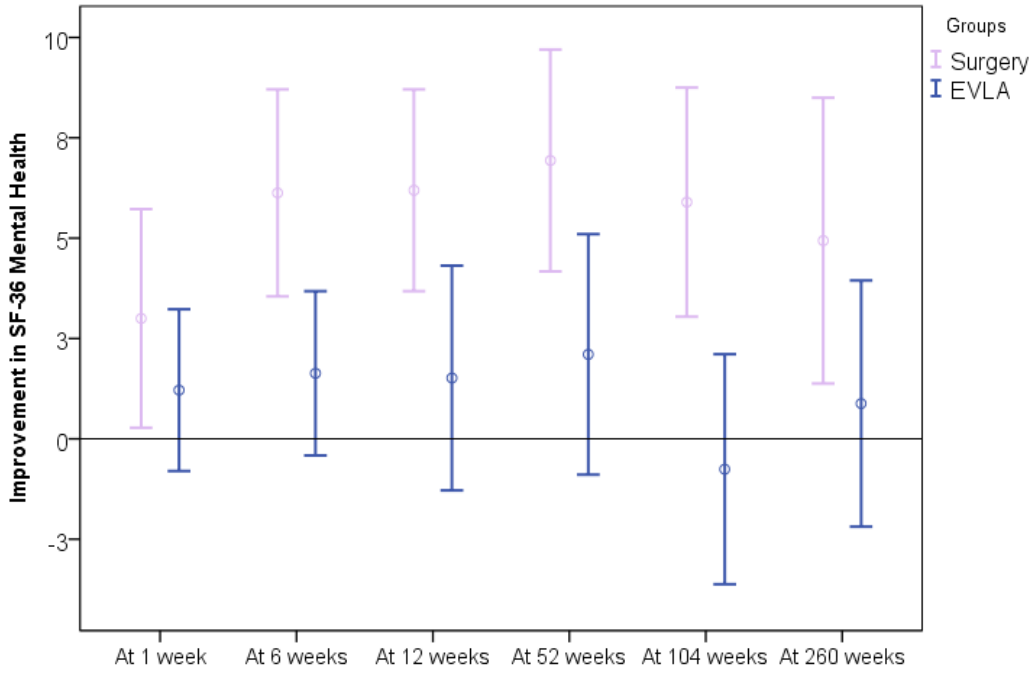


Figure 20 Improvement in SF-36 Mental Health over five years (Study 1)

SF-36 Domain	Weeks	Surgery	EVLA	P
Physical Function	0	90 (80-100)	90 (75-100)	0.644
	1	80 (65-90)	88 (70-95)	0.012
	6	95 (90-100)	95 (84-100)	0.809
	12	95 (85-100)	95 (88-100)	0.598
	52	95 (80-100)	95 (85-100)	0.771
	104	95 (85-100)	93 (80-100)	0.190
	260	95 (75-100)	95 (80-100)	0.687
Role Physical	0	100 (75-100)	100 (50-100)	0.152
	1	50 (0-100)	100 (25-100)	0.005
	6	100 (75-100)	100 (75-100)	0.738
	12	100 (100)	100 (100)	0.992
	52	100 (100)	100 (100)	0.393
	104	100 (100)	100 (100)	0.613
	260	100 (94-100)	100 (100)	0.780
Body Pain	0	74 (52-100)	74 (51-100)	0.650
	1	62 (41-74)	74 (54-84)	0.031
	6	84 (70-100)	84 (72-100)	0.750
	12	100 (74-100)	100 (72-100)	0.798
	52	93.5 (72-100)	100 (72-100)	0.503
	104	84 (70-100)	84 (62-100)	0.737
	260	84 (59-100)	84 (62-100)	0.420
General Health	0	77 (67-87)	77 (62-92)	0.411
	1	82 (72-92)	81 (67-92)	0.928

	6	82 (72-97)	82 (67-95)	0.798
	12	82 (72-92)	82 (67-92)	0.478
	52	82 (72-92)	82 (67-92)	0.669
	104	80 (67-92)	77 (62-92)	0.426
	260	77 (59-89)	82 (67-92)	0.705
Vitality	0	70 (50-80)	70 (55-80)	0.640
	1	65 (55-80)	70 (60-80)	0.049
	6	75 (60-85)	75 (65-90)	0.375
	12	75 (60-85)	75 (60-85)	0.507
	52	75 (65-85)	75 (60-85)	0.904
	104	77.5 (60-85)	70 (60-85)	0.460
	260	75 (55-80)	75 (60-85)	0.609
Social Function	0	100 (75-100)	100 (75-100)	0.267
	1	75 (63-100)	100 (75-100)	0.004
	6	100 (75-100)	100 (88-100)	0.388
	12	100 (81-100)	100 (75-100)	0.359
	52	100 (75-100)	100 (88-100)	0.754
	104	100 (75-100)	100 (75-100)	0.380
	260	50 (50-100)	88 (50-100)	0.003
Role emotional	0	100 (100)	100 (100)	0.553
	1	100 (0-100)	100 (100)	0.027
	6	100 (100)	100 (100)	0.578
	12	100 (100)	100 (100)	0.578
	52	100 (100)	100 (100)	0.926

	104	100 (100)	100 (100)	0.775
	260	100 (100)	100 (100)	0.990
Mental Health	0	80 (68-90)	84 (68-92)	0.027
	1	84 (68-92)	88 (75-92)	0.081
	6	88 (76-92)	88 (72-92)	0.855
	12	88 (76-92)	88 (72-92)	0.738
	52	88 (76-92)	88 (73-92)	0.915
	104	84 (76-92)	88 (68-92)	0.880
	260	84 (76-92)	88 (76-92)	0.478

Table 8. EVLA and conventional surgery SF-36 measurements over five years (Study 1)

Utility Index QoL - EuroQol 5 Dimension

As detailed in Table 9, Figure 21 and Figure 22, a significant fall in EQ5D QoL was noted at one week following both treatments (conventional surgery P=0.003 and EVLA P=0.024 WSR). At six weeks this deficit had recovered and both treatment groups reported a higher EQ5D than their original baseline. This improvement was sustained to five years with no return to pre-baseline levels.

EQ5D index score	Week	Surgery	EVLA	P
	Baseline	0.841 (0.796-1.000)	0.848 (0.796-1.000)	0.954
	1	0.801 (0.691-0.895)	0.796 (0.760-1.000)	0.301
	6	1.000 (0.841-1.000)	1.000 (0.796-1.000)	0.811
	12	1.000 (0.877-1.000)	1.000 (0.877-1.000)	0.479
	52	1.000 (0.841-1.000)	1.000 (0.877-1.000)	0.248
	104	1.000 (0.848-1.000)	1.000 (0.816-1.000)	0.130
	260	1.000 (0.796-1.000)	1.000 (0.799-1.000)	0.179

Table 9 EVLA and conventional surgery EQ5D scores over five years (Study 1)

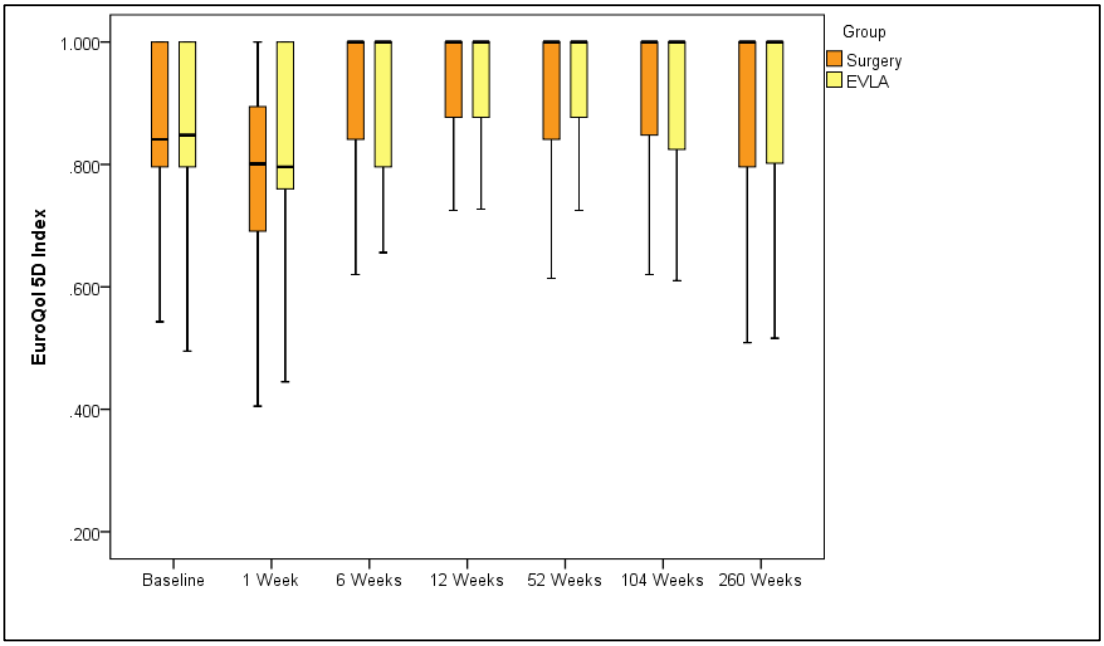


Figure 21 EQ5D scores over five years (Study 1)

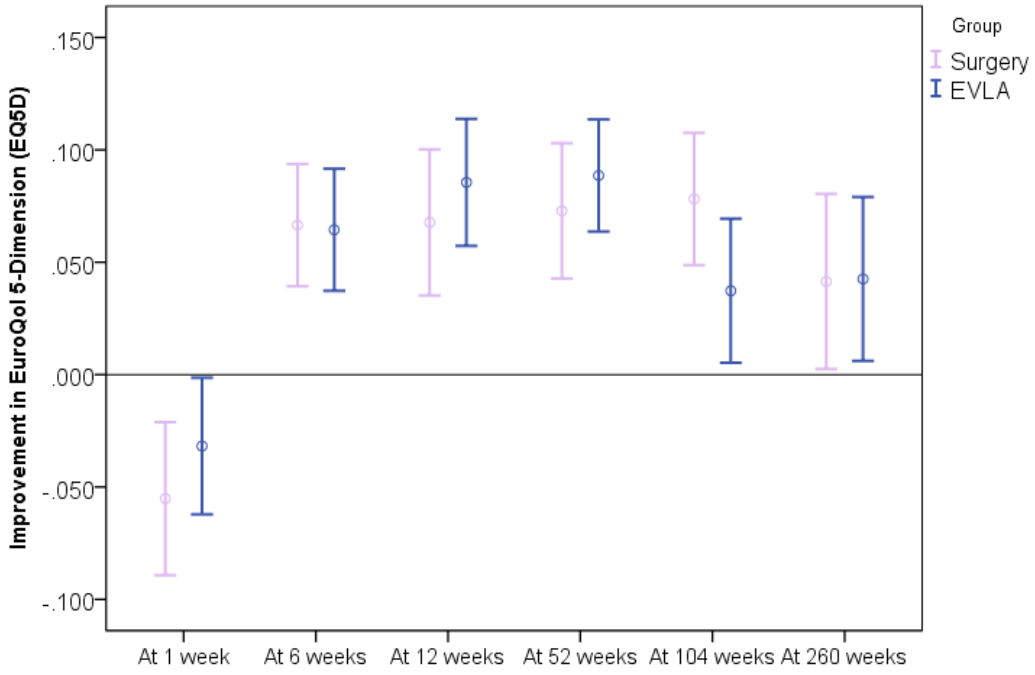


Figure 22 Improvement in EQ5D over five years (Study 1)

Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

As shown in in Table 10, Figure 23 and Figure 24, both treatment groups reported an initial increase (worsening) in their AVVQ score at one week (Conventional surgery P<0.001, ELVA P<0.001 WSR). After six weeks this deficit had recovered and was significantly lower (better) than baseline and this clinical benefit was sustained to five years.

AVVQ	Week	Surgery	EVLA	P
	Baseline	13.7 (9.9-18.2)	12.6 (9.5-17.3)	0.177
	1	16.5 (12.2-22.7)	16.6 (12.4-21.1)	0.573
	6	6.9 (5.5-11.3)	8.7 (5.5-13.4)	0.329
	12	2.5 (0.0-5.3)	2.0 (0.0-6.7)	0.567
	52	2.0 (0.0-5.3)	2.0 (0.0-5.3)	0.551
	104	2.3 (0.0-6.4)	2.0 (0.0-6.2)	0.479
	260	4.6 (1.6-10.3)	3.4 (0.2-7.1)	0.057

Table 10 EVLA and conventional surgery AVVQ scores over five years (Study 1)

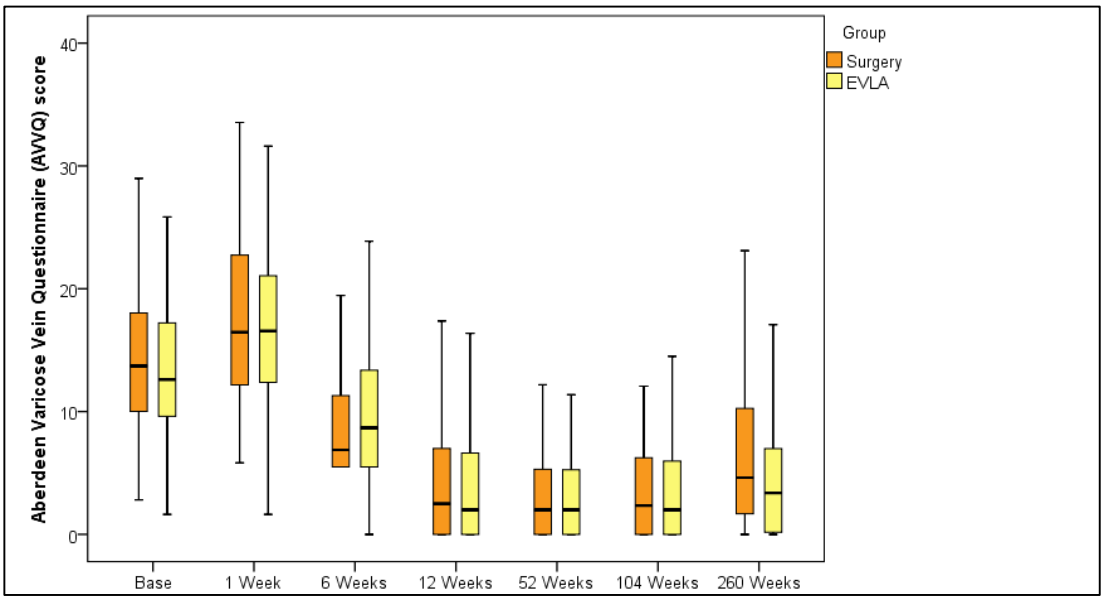


Figure 23 Aberdeen Varicose Vein Questionnaire (AVVQ) scores over five years (Study 1)

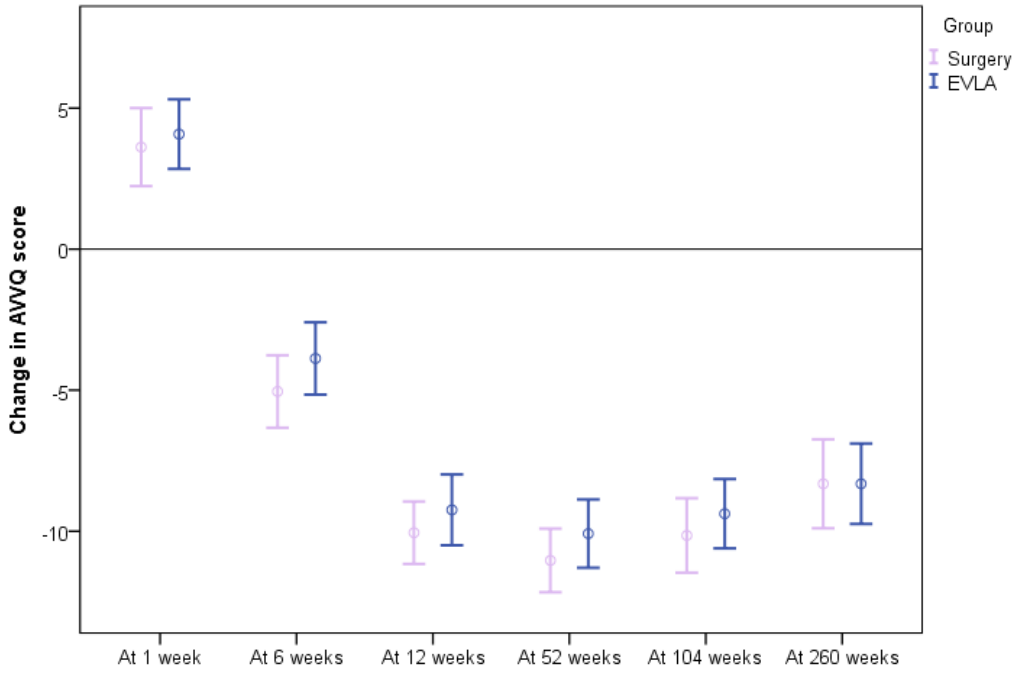


Figure 24 Improvement in AVVQ score over five years (Study 1)

Utility Index QoL - SF6D

As detailed in Table 11 and Figure 25, after one week a significant deficit in SF6D was detected following conventional surgery whereas pre-intervention SF6D levels were maintained after EVLA (Conventional surgery P<0.001, EVLA P=0.141) WSR). At six weeks both groups reported that SF6D levels had significantly improved beyond their baseline and this was sustained to two years. However, at five years both groups had returned to pre-intervention SF6D levels (Conventional surgery P=0.631, EVLA P=0.655) WSR.). As shown in Figure 26, deterioration was greater following Conventional surgery compared to EVLA (Conventional surgery – 0.035 (0.081) vs EVLA -0.011 (0.072) P=0.012) and this would have likely reflected a clinically noticeable difference.

SF6D index	Week	Surgery	EVLA	P
	Baseline	0.795 (0.717-0.847)	0.804 (0.744-0.856)	0.172
	1	0.759 (0.672-0.830	0.796 (0.735-0.838)	0.003
	6	0.833 (0.768-0.867)	0.836 (0.783-0.867)	0.682
	12	0.852 (0.785-0.877)	0.848 (0.783-0.883)	0.648
	52	0.835 (0.777-0.878	0.843 (0.773-0.876)	0.527
	104	0.834 (0.770-0.872)	0.834 (0.756-0.877)	0.902
	260	0.794 (0.745-0.837)	0.815 (0.760-0.857)	0.087

Table 11 EVLA and conventional surgery SF6D scores over five years (Study 1)

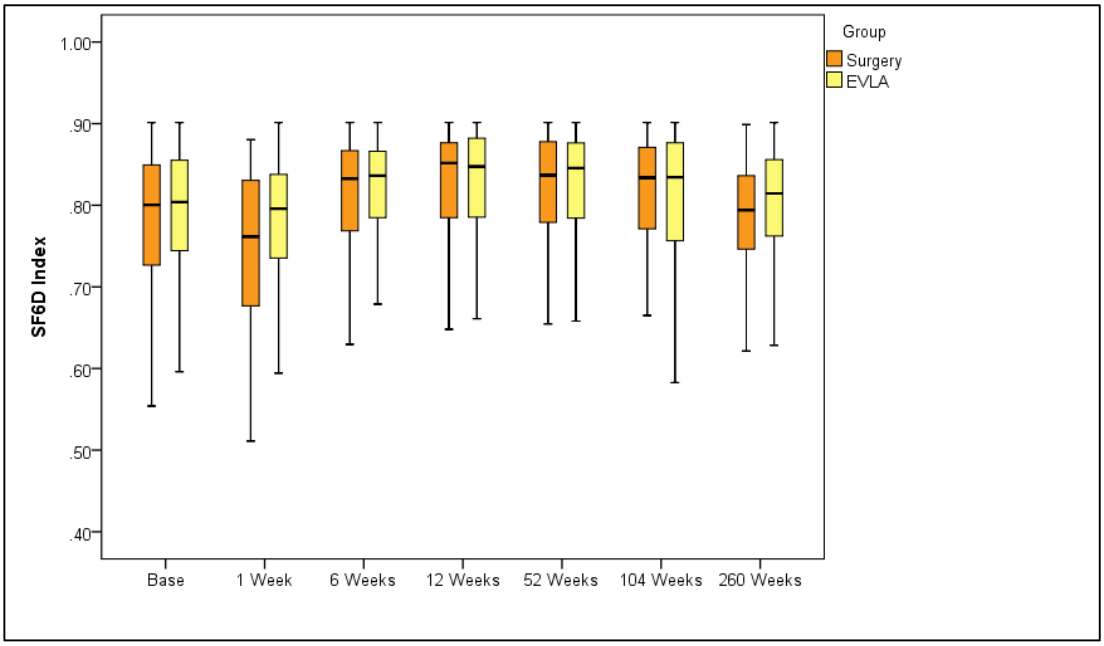


Figure 25 SF6D scores following treatment (Study 1)

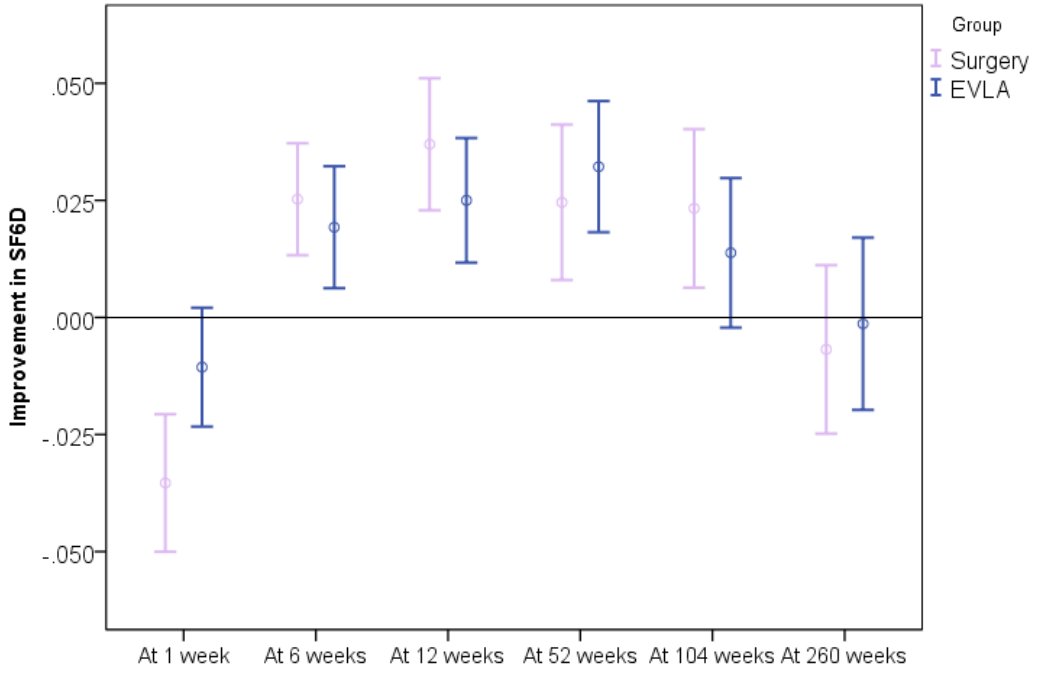


Figure 26 Improvement in SF6D Scores over five years (Study 1)

Objective clinical assessment – VCSS

As detailed in Table 12 and Figure 27, both treatments saw a significant improvement in VCSS scores at one week (Conventional surgery P<0.001, EVLA P<0.001 WSR.) and this improvement was maintained to five years. A statistical difference was detected at five years with the conventional surgery group reported slightly worse VCSS scores compared to the EVLA groups. By its very nature this would reflect a slight, but clinically noticeable significant difference.

VCSS	Week	Surgery	EVLA	P
	0	4 (3-5)	4 (3-5)	0.919
	12	0 (0-1)	0 (0-1)	0.764
	52	0 (0-1)	0 (0-1)	0.123
	104	0 (0-1)	0 (0-1)	0.286
	260	1 (0-2)	0 (0-1)	0.031

Table 12 EVLA and conventional surgery VCSS scores over five years (Study 1)

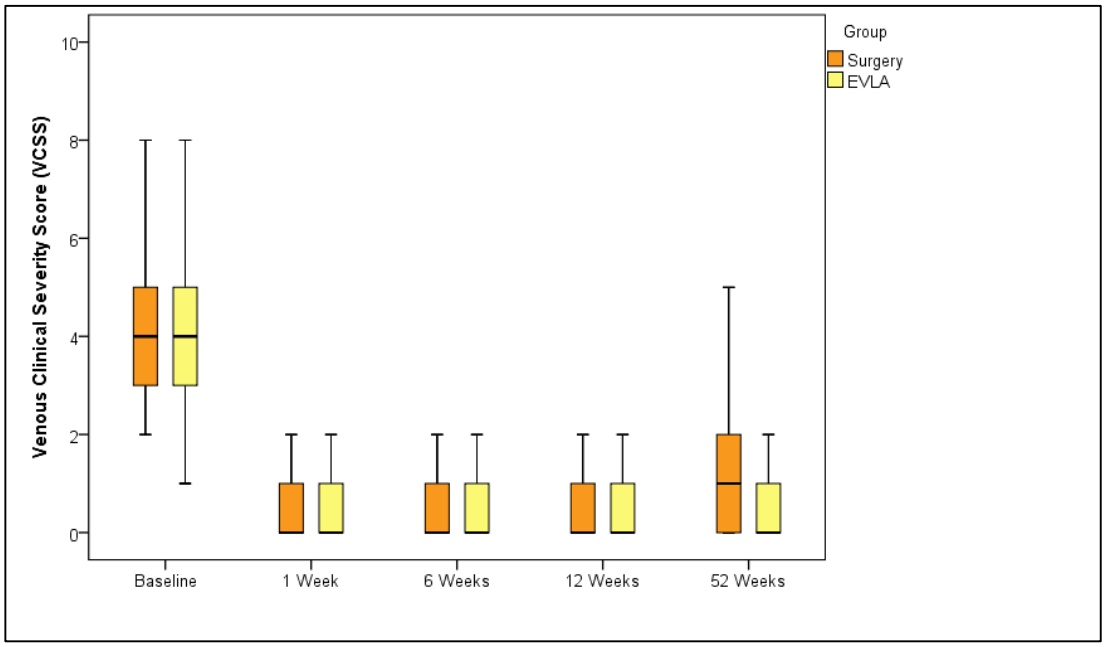


Figure 27 VCSS scores over five years (Study 1)

Cosmetic satisfaction

As shown in Table 13 and Figure 28 cosmetic satisfaction was high following both treatments with a slight enhancement in those who had undergone EVLA at one year (P=0.034). At five years cosmetic satisfaction remained high.

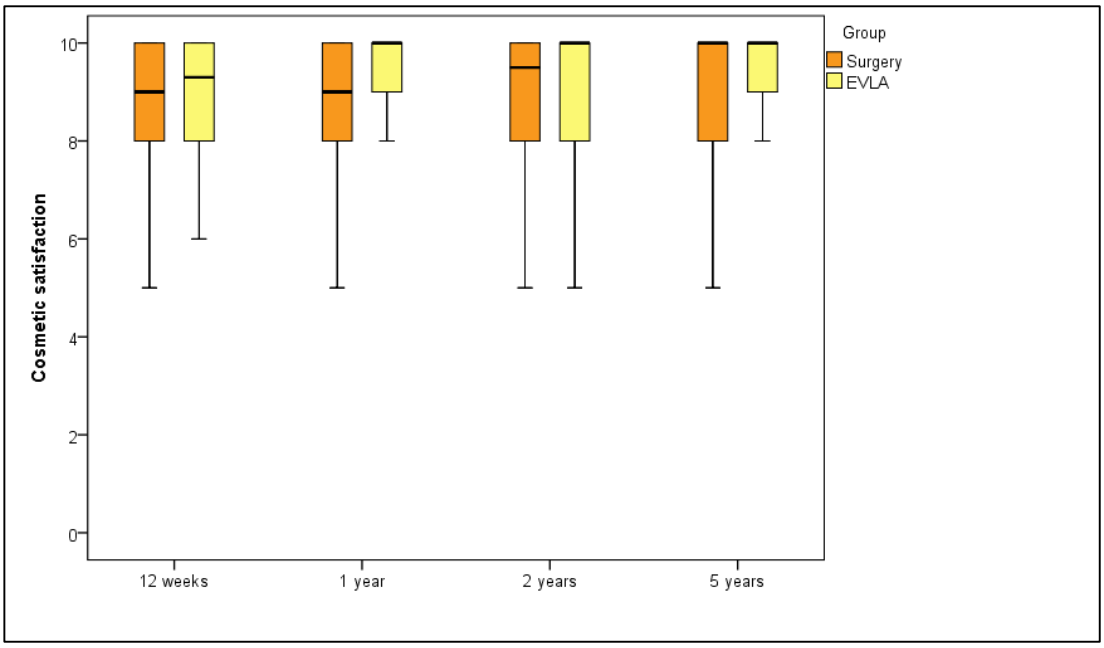


Figure 28 Cosmetic satisfaction over five years (Study 1)

Cosmetic satisfaction	Week	Surgery	EVLA	P
	12	9 (8-10)	9 (8-10)	0.540
	52	9 (8-10)	10 (9-10)	0.034
	104	9.5 (8-10)	10 (8-10)	0.870
	260	10 (8-10)	10 (9-10)	0.111

Table 13 EVLA and conventional surgery cosmetic satisfaction scores over five years (Study 1)

Overall satisfaction

As shown in Table 14 and Figure 29, overall satisfaction was high following both conventional surgery and EVLA and remained so for five years.

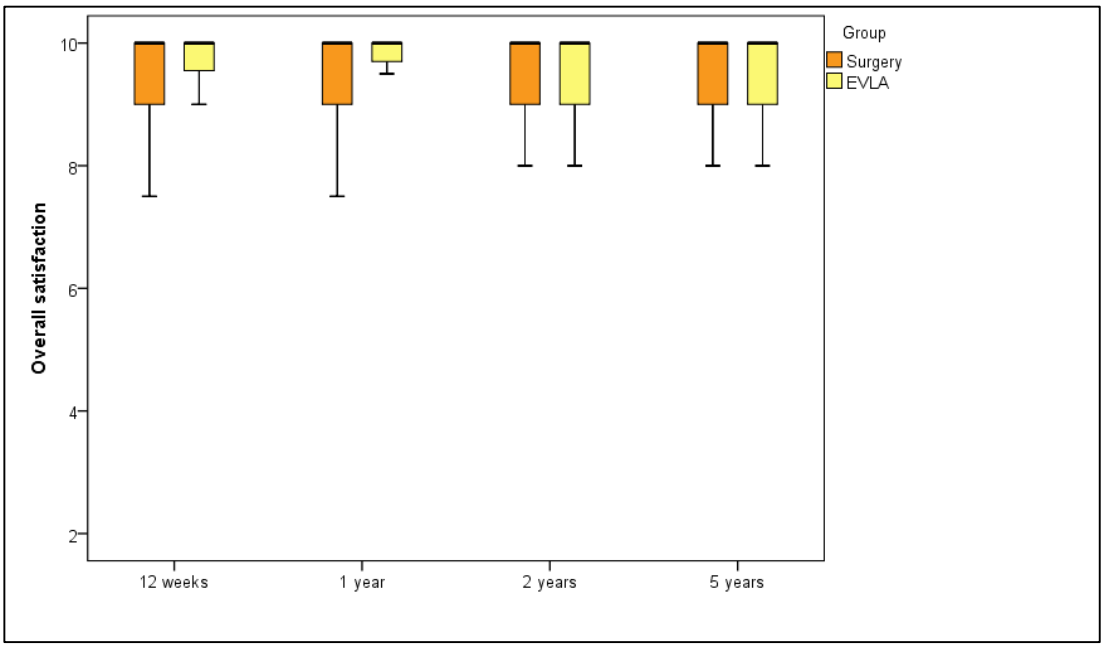


Figure 29 Overall satisfaction over five years (Study 1)

Overall satisfaction	Week	Surgery	EVLA	P
	12	10 (9-10)	10 (9.5-10)	0.058
	52	10 (9-10)	10 (9.7-10)	0.257
	104	10 (9-10)	10 (9-10)	0.225
	260	10 (9-10)	10 (8.75-10)	0.181

Table 14 EVLA and conventional surgery satisfaction scores over five years (Study 1)

Clinical recurrence

Of those patients reviewed at five years, about half experienced some form of clinical recurrence (Conventional surgery 62/110 (56.4%) vs EVLA 48/108 (44.4%) P=0.078). A further five patients (Conventional surgery n=2, EVLA n=3) had a documented clinical recurrence but did not attend their scheduled five year appointment. However, these five had all attended their appointment at two years and one of each treatment group had also undergone an additional procedure for symptoms after to this two year appointment. At five years, one EVLA patient was contacted by telephone but had moved out of the area, three patients remained uncontactable and one conventional surgery patient had passed away. The contacted patient, whilst initially satisfied with conservative treatment for a symptomatic recurrence (which had arisen after their one year review) was now intending to pursue referral for treatment locally. At their last appointment, the remaining EVLA patient with clinical recurrence was asymptomatic, as was the conventional surgery patient who subsequently passed away.

As shown in Figure 30 and Table 15, the survival distribution of clinical recurrence was lower among those who received surgery compared to those who received EVLA over five years (P=0.031 LR). The estimated average time to develop a recurrence after surgery was 213 weeks (95% CI 197-229 weeks) whereas after EVLA it was 240 weeks (95% CI 229-252 weeks).

A general pattern which arises in the Kaplan Meier graph (and which is repeated in later graphs) are notable drops around 52, 104 and 260 weeks. The majority of the falls are likely related to scheduled follow up visits, although some drops are seen when patients attend between these appointments for an expedited clinical review.

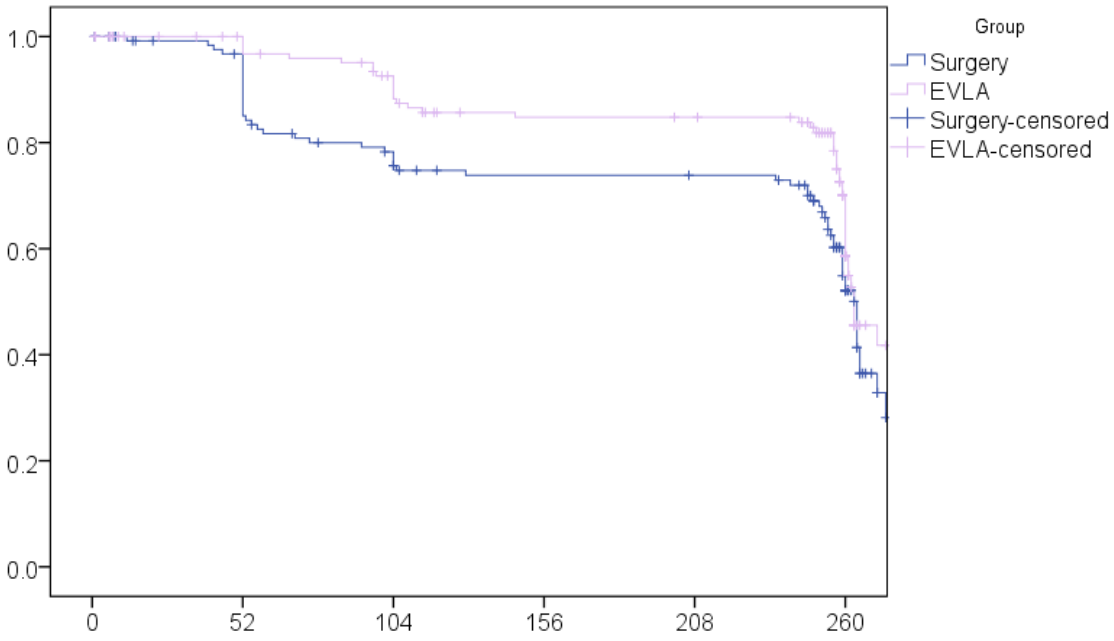


Figure 30. Kaplan-Meier Survival plot showing the proportion of patients free from recurrence over five years (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	102	85	80	79	30
EVLA	139	118	103	93	92	32

Table 15 Patient numbers at risk at each time point for clinical recurrence (Study 1)

Clinical recurrence sensitivity analysis

As detailed in Table 16, a sensitivity analysis of the possible clinical status of those lost to follow up was undertaken. Overall, most assumptions did not differ significantly from the trial outcome. The only assumption which was significantly different assumed that all lost conventional surgery and no EVLA patients developed recurrence (P<0.001). In this case the number needed to treat with EVLA to avoid a clinical recurrence that would have occurred after conventional surgery was around 3

patients. Otherwise both treatments were similar in outcomes and an NNT was therefore incalculable for most other assumptions[515].

Assumption	Surgery	EVLA	P	Relative Risk	Absolute Risk Reduction
Trial data	62/110 (56.4%)	48/108 (44.4%)	0.104	0.79 (0.60-1.03)	0.12 (-0.01-0.25)
1. No lost patients have recurred				0.79 (0.60-1.03)	0.11 (-0.01- 0.22)
2. All lost patients have recurred				0.88 (0.72-1.06)	0.08 (-0.03-0.20)
3. All EVLA lost have recurred but no Surgery lost recurred				1.26 (0.99-1.59)	-0.12 (-0.23-0.00)
4. All Surgery lost have recurred but no EVLA lost recurred				0.53 (0.41-0.69)	0.30 (0.19-0.42)

Table 16 Sensitivity analysis of recurrence rates (Study 1)

Symptomatic recurrence

In total, 18 conventional surgery patients and 19 EVLA patients developed a symptomatic recurrence over the five years (P=0.862 χ^2-test). Prior to one year, four conventional surgery and two EVLA patients developed a symptomatic recurrence. After one year, symptomatic recurrence occurred in a further 14 conventional surgery and 17 EVLA patients (P=0.704 χ^2-test). Treatment for symptomatic recurrence was common. Only four patients opted for conservative treatment, with 15 Conventional surgery and 18 EVLA patients undergoing an additional treatment for their symptomatic recurrence.

As shown in Figure 31 and Table 17, the survival distribution for symptomatic recurrence was similar between both treatment groups over five years (P=0.893 LR).

The estimated average time to develop a recurrence after surgery was 268 weeks (95% CI 254-281 weeks) whereas after EVLA it was 276 weeks (95% CI 265-288 weeks).

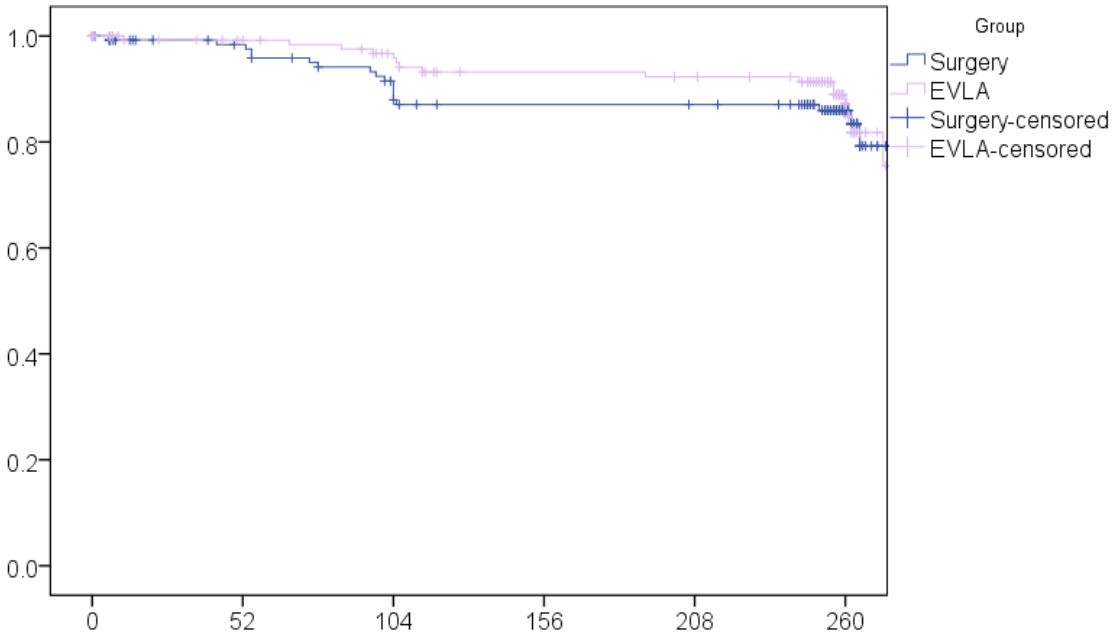


Figure 31 Kaplan-Meier Survival plot showing the proportion of patients free from symptomatic recurrence over five years (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	115	99	96	94	36
EVLA	139	120	108	98	97	37

Table 17 Sensitivity analysis of symptomatic recurrence rates (Study 1)

Conventional Surgery

As shown in Table 18, the most common recurrence pattern leading to symptoms was the development of groin neovascularisation leading to axial reflux in the AASV and proximal superficial thigh veins. This recurrence often traversed the length of

the thigh and would occasionally reconnect directly into the residual GSV remnant (the distal portion which was not stripped) or distal axes, causing below knee incompetence with recurrence of superficial varicose tributaries. Other forms of symptomatic recurrence were less common but often arose at the peri-genicular or calf area with junctional incompetence or incompetent perforators often associated. Of the 10 patients with a technical failure of their original surgery, six subsequently developed a symptomatic recurrence and of these, five underwent an additional intervention by five years. One technical failure also developed recannalisation after groin neovascularisation reconnected with the proximal thigh GSV remnant. This portion of GSV had remained after it "snapped" during stripping in the original operation, and while it was initially free of duplex detected blood flow, this failed after neovascular blood flow eventually returned patency to the axis.

EVLA

The most common pattern of symptomatic recurrence following EVLA was SFJ incompetence with consequential junctional reflux into the axial AASV and proximal superficial thigh veins. As with the conventional surgery group above, this recurrence frequently progressed down the thigh and would often result in incompetence into the distal GSV and development of superficial varicose tributaries. Overall, recannalisation of the GSV was detected in eight EVLA patients and of these, three were symptomatic and subsequently also required additional intervention by five years. The only patient with a technical failure of EVLA treatment remained asymptomatic at five years despite developing new incompetence in the AASV and proximal superficial thigh veins.

Treatment	DUS reflux pattern	Proportion of symptomatic recurrence
Conventional surgery (n=18)	Neovascularisation	10 (56%)
	AASV	4 (22%)
	Below knee GSV incompetence	11 (61%)
	Perforator incompetence	6 (33%)
	GSV recannalisation	1 (6%)
	SPJ	3 (17%)
	SSV	3 (17%)
	Superficial tributaries	12 (67%)
EVLA (n=19)	Sapheno-Femoral Junction incompetence	9 (47%)
	AASV	7 (37%)
	Below knee GSV incompetence	10 (53%)
	Perforator incompetence	5 (26%)
	GSV recannalisation	3 (16%)
	SPJ	3 (16%)
	SSV	1 (5%)
	Superficial tributaries	11 (58%)

Table 18 DUS patterns of symptomatic recurrence (Study 1)

Symptomatic recurrence sensitivity analysis

As shown in Table 19, a sensitivity analysis regarding possible symptomatic clinical recurrences of those lost to follow up was performed. Overall, most assumptions were not dissimilar from the original trial. The only sensitivity analysis which was significant assumed that all conventional surgery patients and no EVLA patients lost

developed symptomatic recurrence (P<0.001). In this case the number needed to treat with EVLA to avoid a symptomatic recurrence that would have occurred after conventional surgery was around 5 patients. Otherwise both treatments were similar in sensitivity analysis.

Assumption	Surgery	EVLA	P	Relative Risk	ARR
Trial data	18/110	19/108	0.951	1.08 (0.60-1.93)	-0.01 (-0.11-0.09)
1. No lost patients have recurred				1.04 (0.57-1.90)	-0.01 (-0.09-0.08)
2. All lost patients have recurred				1.10 (0.79-1.52)	-0.03 (-0.14-0.08)
3. All EVLA lost have recurred but no Surgery lost recurred				2.74 (1.70-4.44)	-0.23 (-0.32-0.13)
4. All Surgery lost have recurred but no EVLA lost recurred				0.42 (0.26-0.67)	0.19 (0.09-0.29)

Table 19 Sensitivity of symptomatic recurrence rates (ARR = Absolute Risk Reduction) (Study 1)

Patterns of clinical recurrence

Recurrence at the groin

As shown in Figure 32, recurrence at the groin detected by DUS was relatively common with evidence of proximal disease recurrence observed in 34 surgery and 23 EVLA patients over the course of the trial. Over five years the survival distribution of groin recurrence was lower after Conventional surgery, with an

estimated 70.8% of surgery and 83.1% of EVLA patients estimated to be free of groin recurrence by five years (P=0.063 LR).

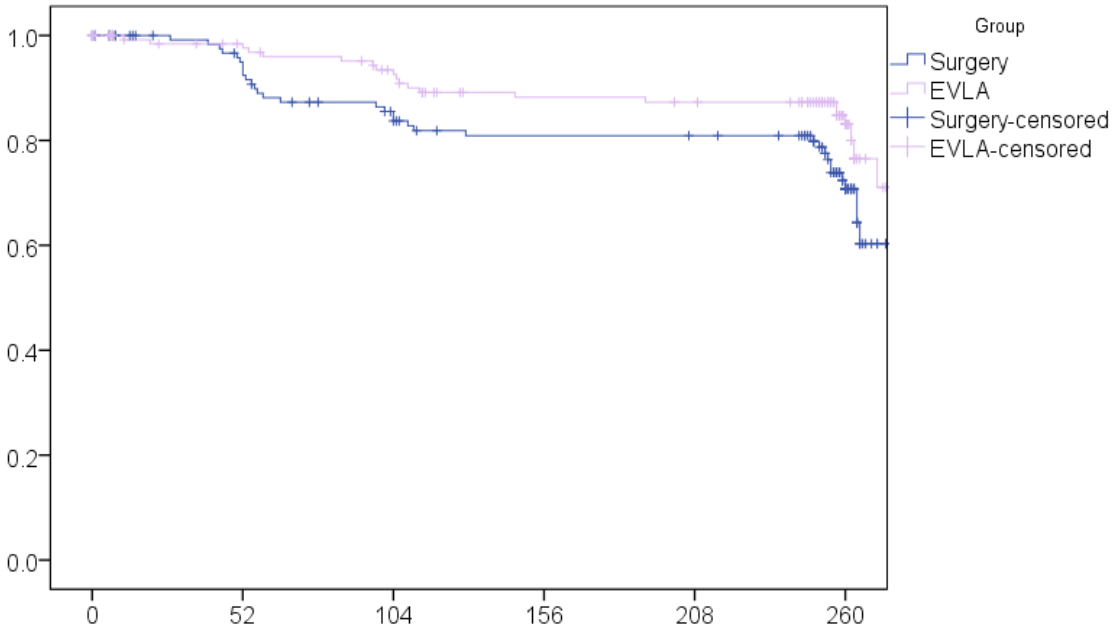


Figure 32 Kaplan-Meier Survival plot showing the proportion of patients free from recurrence at the groin (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	108	91	84	83	32
EVLA	139	119	108	95	93	34

Table 20 Patient numbers at risk at each time point for groin recurrence (Study 1)

Neovascularisation

As shown by Figure 33, neovascularisation was much more common after Conventional surgery (P<0.001 LR). Whereas 39 Conventional surgery patients developed groin neovascularisation, only one EVLA patient did over five years. In this patient neovascularisation was detected around the SFJ but did not involve any part of the treated GSV axis. Instead the neovascularisation fed an incompetent

AASV which travelled down the thigh and connected to the untreated portion of GSV (the length distal to the cannulation point), resulting in below knee GSV incompetence. It was estimated that after five years, 64.7% of Conventional surgery and 95.7% of EVLA patients would be free from neovascularisation respectively.

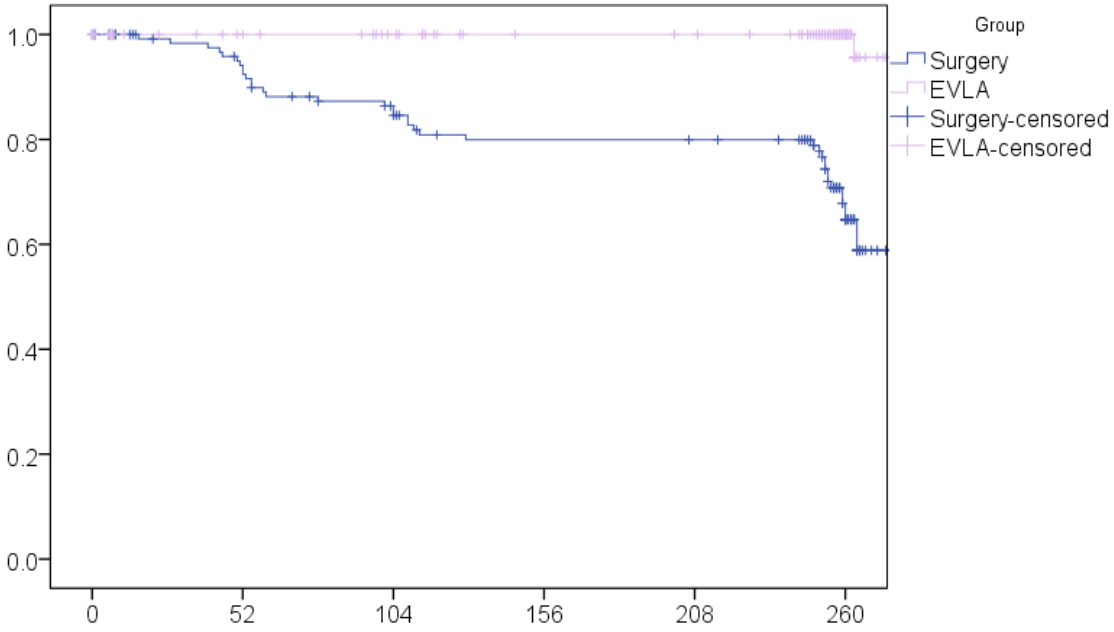


Figure 33 Kaplan-Meier Survival plot showing the proportion of patients free from neovascularisation (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	108	92	83	82	32
EVLA	139	121	115	105	104	3

Table 21 Patient numbers at risk at each time point for neovascularisation (Study 1)

SFJ Incompetence

As shown in Figure 34, SFJ incompetence was much more common after EVLA than Conventional surgery (P<0.001). This was observed in 18 EVLA and one Conventional surgery patient. In this conventional patient, the SFJ remained

incompetent as it could not be located at the time of original surgery. The estimated proportion of those free of SFJ incompetence at five years was 99.2% and 86.0% for Conventional surgery and EVLA respectively.

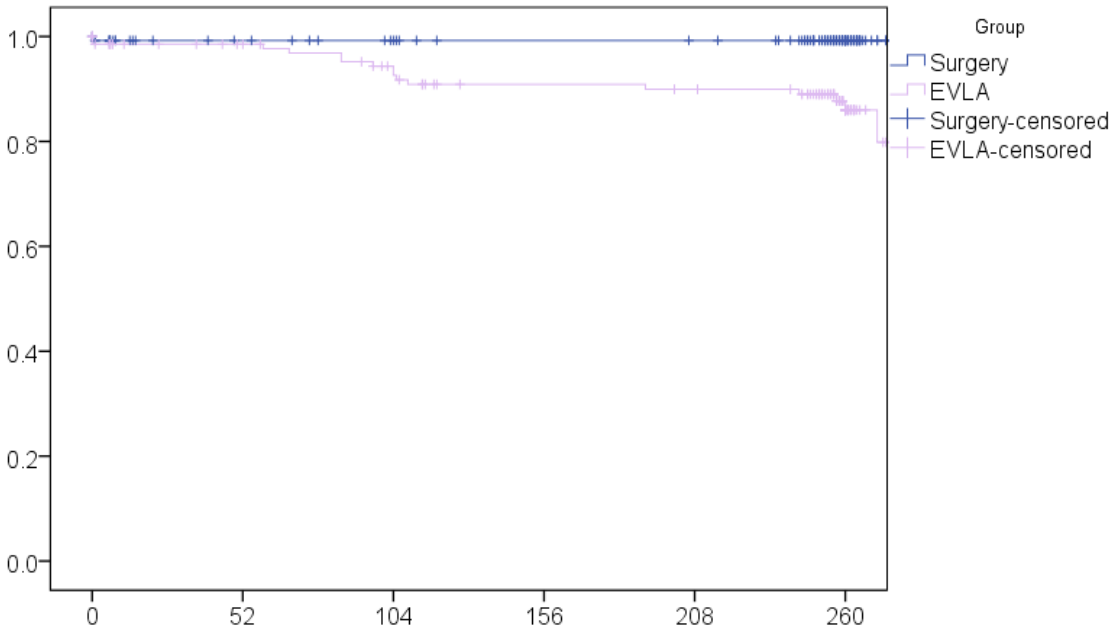


Figure 34 Kaplan-Meier Survival plot showing the proportion of patients free from recurrent SFJ incompetence (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	115	108	104	103	42
EVLA	139	119	107	98	96	35

Table 22 Patient numbers at risk at each time point for SFJ incompetence (Study 1)

Recannalisation

As shown in Figure 35, the occurrence of recannalisation was broadly similar in both treatment groups (P=0.248 LR). Evidence of recannalisation was observed in twelve patients, eight following EVLA and four following Conventional surgery. Of those recannalising after EVLA, five were associated with SFJ incompetence, two with an

incompetent perforator, and two with just a segment of axial incompetence, of which one was associated with an incompetent below knee GSV. Recannalisation did not appear to be related to the energy density deployed during EVLA nor the vein diameter treated. The energy density of those recannalising was on average 92 (15) J/cm^{-1} compared to an energy density of 95 (15) J/cm^{-1} in those who did not recannalise (P=0.560). Size of the pre-treatment vein diameter at the groin (recannalisation 8.7mm (7.3-12.1) vs no recannalisation 8.3mm (6.9-10.0mm) P=0.445) or the knee (recannalisation 7.2mm (5.9-8.0mm) vs 6.2mm (5.4-7.6mm) P=0.250) were also not significantly dissimilar.

In those four who developed recannalisation following Conventional surgery, this arose in the portion of GSV which remained in the limb after stripping and which became absent of flow following vein disconnection. In three patients groin neovascularisation reconnected with this GSV remnant, and in two patients an incompetent perforator led to recurrence of flow within a previously silent GSV remnant.

It was estimated that 97.2% of Conventional surgery and 91.0% of EVLA patients would be free from recannalisation by five years.

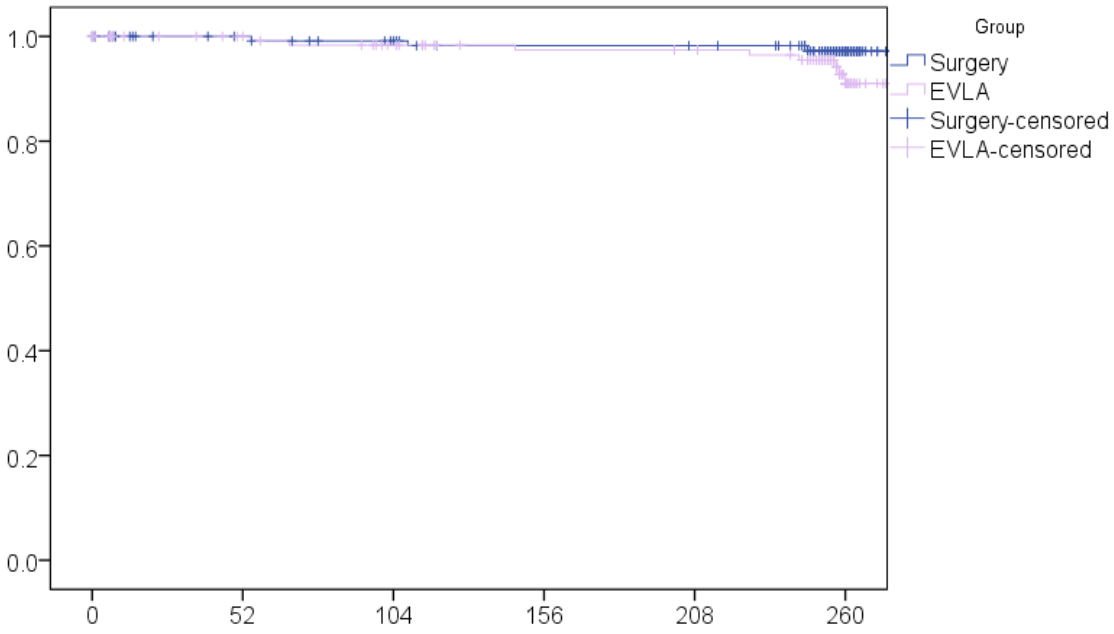


Figure 35. Kaplan-Meier Survival plot showing the proportion of patients free from recannalisation (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	117	109	104	103	43
EVLA	139	121	113	104	103	35

Table 23 Patient numbers at risk at each time point for recannalisation (Study 1)

AASV and superficial proximal thigh veins

As shown in Figure 36, the survival distribution of the development of axial incompetence in the AASV or proximal superficial thigh veins was similar between the two treatment groups (P=0.113 LR). This was observed after 11 Conventional surgery and 19 EVLA patients. It was estimated that 90.6% of Conventional surgery and 86.3% of EVLA patients would be free from developing such a recurrence over five years.

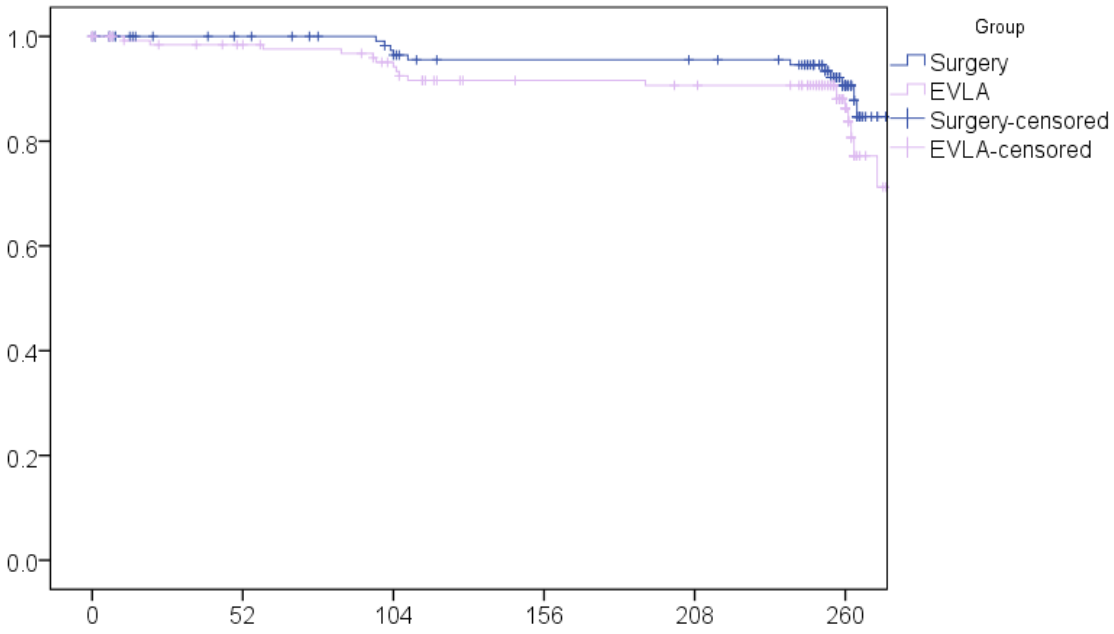


Figure 36 Kaplan-Meier Survival plot showing the proportion of patients free from AASV or superficial proximal thigh varicosities (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	116	106	101	100	40
EVLA	139	119	109	97	95	34

Table 24 Patient numbers at risk at each time point for AASV and superficial thigh recurrence (Study 1)

Perforator Incompetence

As shown in Figure 37, survival distribution of incompetent perforator development was similar between the two treatment groups (P=0.218 LR). An incompetent perforator arose after Conventional surgery in 26 patients and after EVLA in 17 patients. It was estimated that 80.4% of Conventional surgery and 86.2% of EVLA patients would be free from developing an incompetent perforator over five years.

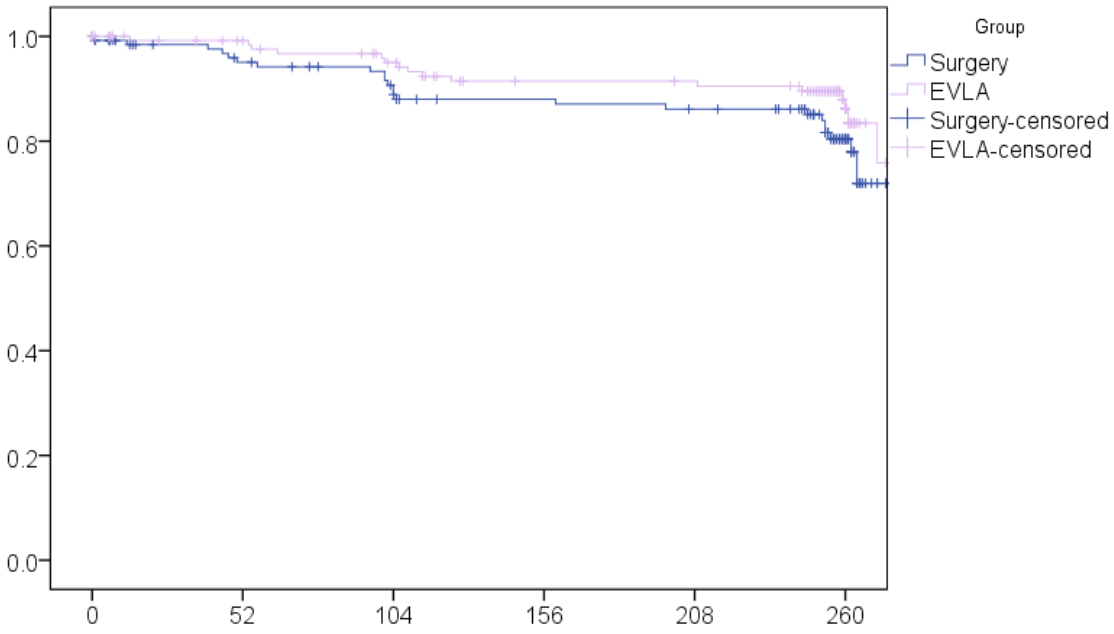


Figure 37 Kaplan-Meier Survival plot showing the proportion of patients free from incompetent perforators (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	112	99	94	91	37
EVLA	139	120	110	97	96	31

Table 25 Patient numbers at risk at each time point for perforator incompetence (Study 1)

SPJ incompetence

As shown in Figure 38, survival distribution of the development of SPJ incompetence was similar between the two treatment groups (P=0.501 LR). This was detected in six Conventional surgery and four EVLA patients. It was estimated that 94.8% of Conventional surgery and 96.3% of EVLA patients would be free from developing SPJ incompetence over five years.

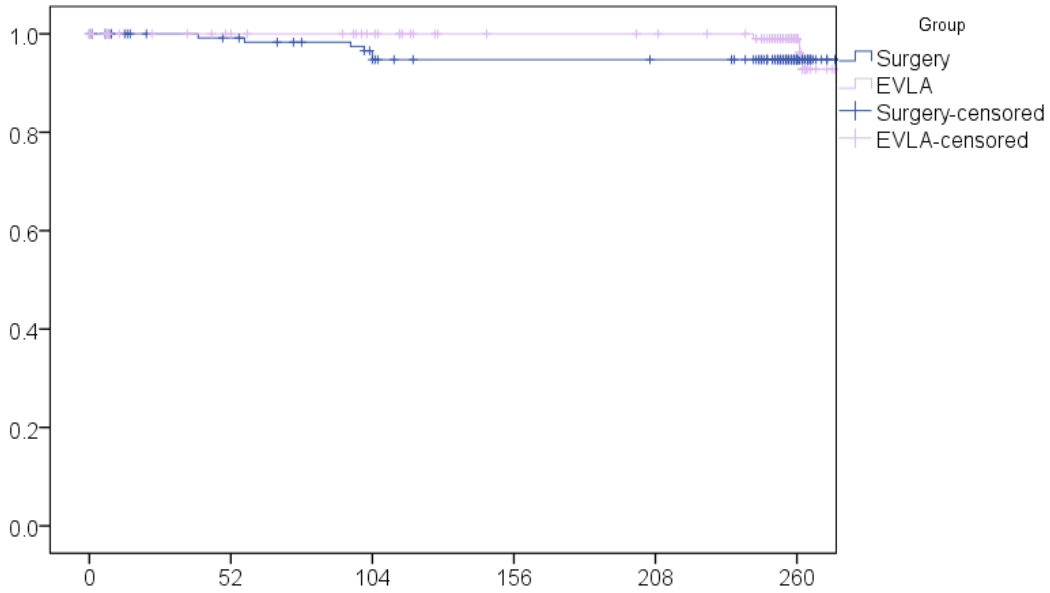


Figure 38 Kaplan-Meier Survival plot showing the proportion of patients free from SPJ incompetence (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	116	104	100	99	38
EVLA	139	121	115	105	104	36

Table 26 Patient numbers at risk at each time point for SPJ incompetence (Study 1)

SSV incompetence

As shown in Figure 39, development of incompetence in the SSV was slightly more prevalent following Conventional surgery compared to EVLA (P=0.047). Following Conventional surgery, eight patients developed incompetence within the SSV and of these, five were directly related to an SPJ incompetence. In one patient development groin neovascularisation led to incompetence within the SSV, but in two others no central or junctional source of SSV incompetence was identified aside from incompetent superficial varicose tributaries. One further SPJ incompetence did not

lead to SSV recurrence but the junction itself had become incompetent from the involvement of groin neovascularisation and AASV incompetence down the limb.

Following EVLA, two patients developed incompetence within the SSV, both due to SPJ incompetence. The two further patients with SPJ incompetence did not progress to SSV incompetence but instead the junction had become incompetent following recurrence of SFJ incompetence and proximal disease progression. It was estimated that 94.7% of Conventional surgery and 96.2% of EVLA patients would be free from developing SSV incompetence over five years.

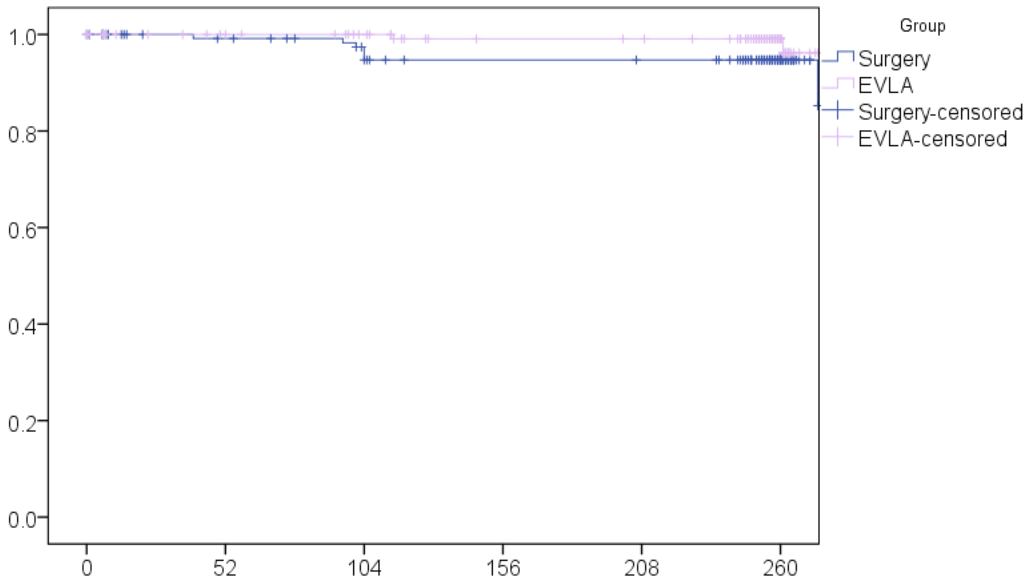


Figure 39 Kaplan-Meier Survival plot showing the proportion of patients free from SSV incompetence (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	116	104	100	99	39
EVLA	139	121	115	104	103	34

Table 27 Patient numbers at risk at each time point for SSV incompetence (Study 1)

Recurrence of varicose tributaries

As shown in Figure 40, the survival distribution of recurrence of varicose tributaries (superficial veins greater than 3 mm in diameter) was similar between the two treatment groups (P=0.410 LR). This was observed after Conventional surgery in 30 patients and after EVLA in 26 patients. It was estimated that 76.6% of Conventional surgery and 80.2% of EVLA patients would be free from developing such a recurrent tributaries over five years.

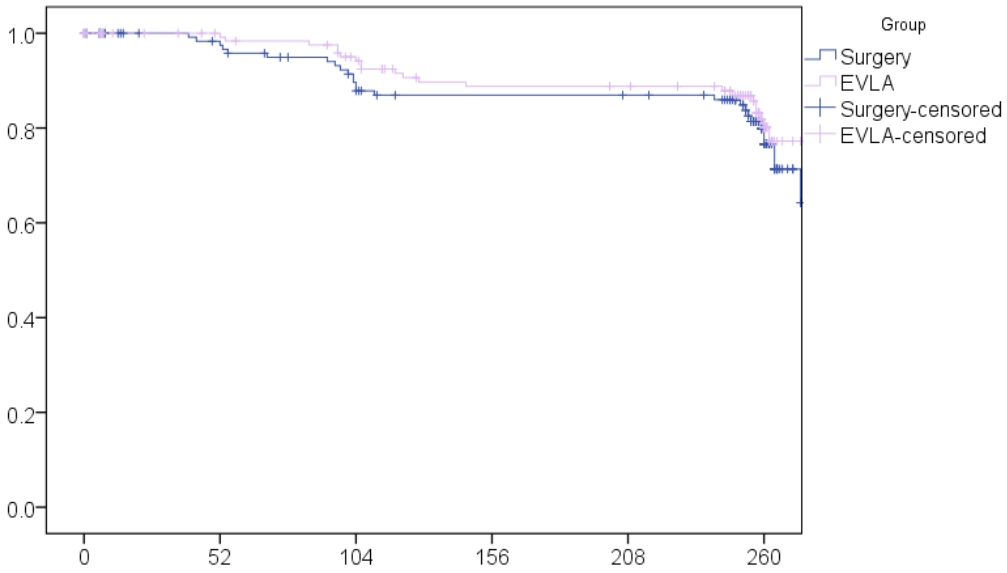


Figure 40 Kaplan-Meier Survival plot showing the proportion of patients free from recurrence of tributaries (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	114	97	92	91	37
EVLA	139	121	110	97	96	34

Table 28 Patient numbers at risk at each time point for recurrence of varicose tributaries (Study 1)

Recurrence of incompetent tributaries

As shown in Figure 41, development of recurrent varicose tributaries which are also incompetent was similar between the two treatment groups (P=0.061 LR). This was observed after Conventional surgery in 14 patients and after EVLA in 6 patients. It was estimated that 86.8% of Conventional surgery and 93.7% of EVLA patients would be free from developing such a recurrence over five years.

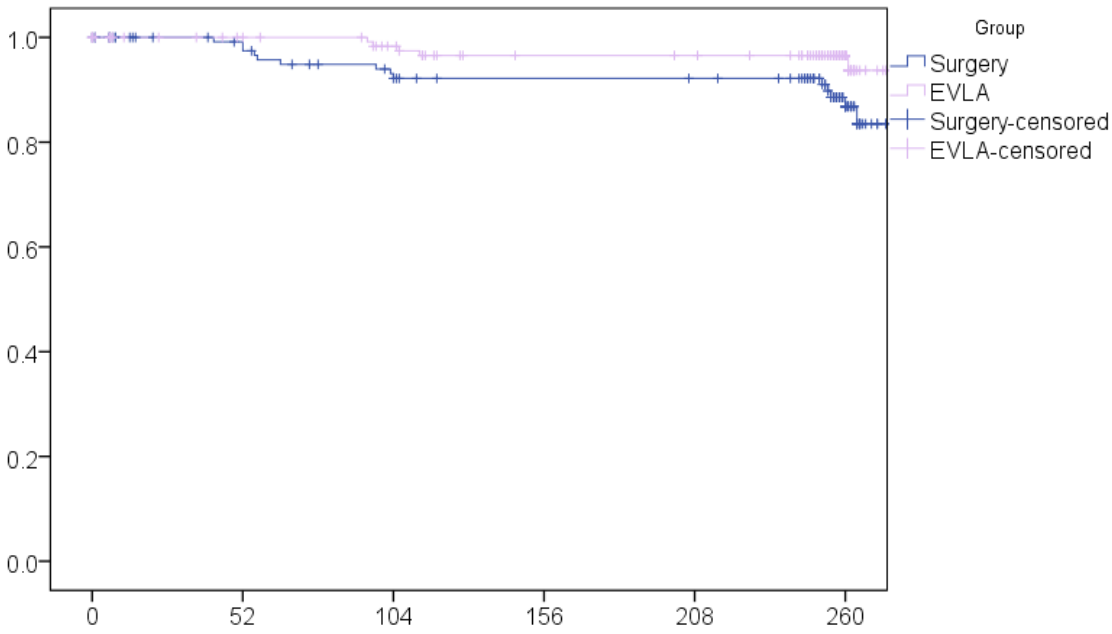


Figure 41 Kaplan-Meier Survival plot showing the proportion of patients free from incompetent varicose tributaries (Study 1)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
Surgery	137	113	101	97	96	37
EVLA	139	121	113	101	100	34

Table 29 Patient numbers at risk at each time point for incompetence varicose tributaries (Study 1)

Long term technical success

Compared to those undergoing EVLA, Conventional surgery patients were more likely to develop a technical failure by five years (Conventional surgery 28.5% (39/137) vs EVLA 12.9% (18/137) P=0.002).

Requirement for additional procedures

As detailed in Table 30, a total of 53 additional procedures were required by 45 patients over five years. Both the total number of additional procedures (Conventional surgery n=26; EVLA n=27; P=0.461) and the proportion of patients requiring additional procedures (Conventional surgery n=22 (16%) vs EVLA n=23 (17%) P=1.000) were similar between the two groups. Five Surgery and seven EVLA patients required treatment for residual disease or technical failure in the absence of recurrence with the remainder treated for symptomatic recurrence and persistent disease.

Conventional surgery

Of the patients undergoing conventional surgery, 19 patients underwent one additional procedure, two underwent two additional procedures and one patient underwent three additional procedures. At one year, nine patients had undergone ambulatory phlebectomy with or without perforator ligation, one patient required EVLA to the GSV and AASV owing to a technical failure of surgery (extensive groin scarring preventing safe exposure of the SFJ) and one patient developed new axial SPJ incompetence into the SSV and distal GSV which required EVLA treatment with concomitant phlebectomy.

At two years eight patients underwent an additional treatment, two of which had already received an intervention at one year. Endovenous treatment for axial incompetence was required in three patients, of which one received a combined procedure consisting of UGFS treatment of groin neovascularisation, EVLA treatment of GSV axial incompetence and concomitant phlebectomy of an incompetent AASV and recurrent tributaries. At their own request, one patient with an active venous ulcer (C6) at the time of their index treatment underwent an elective below knee amputation due to recurrent ulceration with significant impairment of quality of life. Of those receiving a second additional procedure, one patient had previously undergone ambulatory phlebectomy with perforator ligation but subsequently developed neovascularisation at the level of the SPJ. This led to symptomatic SSV incompetence with tributary recurrence and required a combination of UGFS to the neovascularisation, EVLA to the incompetent axes and phlebectomy to the symptomatic venous tributaries. The other patient had already received EVLA treatment to the GSV and SSV by one year, but proximal thigh neovascularisation led to proximal tributaries which required an additional treatment of EVLA and concomitant phlebectomy.

At five years six patients underwent an additional procedure, one of which required two interventions. Three patients required a combination procedure of UGFS and EVLA to neovascularisation and axial vein incompetence. One patient, who had already received UGFS treatment for SSV incompetence at two years, required EVLA treatment of a still patent and incompetent SSV axis. Unfortunately this was itself insufficient and the patient required and third and final treatment of UGFS and EVLA, which was finally successful.

EVLA

Of the patients undergoing EVLA, 20 patients underwent one additional procedure, two patients underwent two additional procedures and one patient underwent three additional procedures. At one year, seven patients received ambulatory phlebectomy with or without perforator ligation.

At two years, nine additional procedures were performed, one of which was in addition to a previous phlebectomy. Two patients underwent open surgery for recurrent SFJ incompetence, both of which were technically successful at 12 weeks but had begun to show DUS evidence of recurrent SFJ incompetence by one year. Three patients required additional axial endovenous treatments, two of which were due to SPJ incompetence. One patient, who had already received an additional ambulatory phlebectomy at one year, required a further treatment of UGFS to an incompetent GSV and AASV at two years. While detected on DUS at one year, recurrence at the SFJ was initially asymptomatic and minor but progressed significantly over the following year.

At five years, 11 patients underwent additional procedures, two of which had already received an additional intervention. Of these, three patients underwent surgery, one of which had previously undergone ambulatory phlebectomy at two years. Again, despite an initially successful EVLA procedure, in all three patients a recurrence of SFJ incompetence was detected by DUS one year after primary treatment. Five patients required an additional endovenous treatment, two of which were due to late recurrence of SFJ incompetence, one due to a new incompetence in the remnant distal GSV, one due to a thigh perforator causing recannalisation of the GSV and one due to AASV incompetence. Despite already having axial treatment at two years,

one patient required additional phlebectomy of a tortuous and symptomatic AASV recurrence at five years.

Treatment Group	Time point	Additional Procedures required after index treatment
Surgery	1 year	n = 6 Ambulatory phlebectomy n = 2 Ambulatory phlebectomy with perforator ligation n = 1 Ambulatory phlebectomy and micro-sclerotherapy n = 1 EVLA of GSV & AASV n = 1 EVLA of GSV & SSV with perforator ligation and phlebectomy
	2 years	n = 2 Ambulatory phlebectomy n = 1 EVLA & UGFS of GSV with phlebectomy n = 1 EVLA of GSV n = 1 UGFS of SSV with phlebectomy n = 1 Below knee amputation n = 1 EVLA of GSV & SSV of UGFS with phlebectomy (redo) n = 1 EVLA of GSV & AASV with phlebectomy (redo)
	5 years	n = 2 EVLA & UGFS to GSV & AASV with phlebectomy n = 1 EVLA & UGFS to GSV n = 2 phlebectomy n = 1 EVLA to SSV with phlebectomy (redo) n = 1 EVLA & UGFS to SSV (redo)
EVLA	1 year	n = 5 Ambulatory phlebectomy

		n = 2 Ambulatory phlebectomy with perforator ligation
	2 years	n = 2 Open surgery with phlebectomy n = 2 ambulatory phlebectomy n = 1 ambulatory phlebectomy with perforator ligation n = 1 EVLA to GSV & SSV with phlebectomy n = 1 EVLA to GSV with phlebectomy n = 1 EVLA to SSV with phlebectomy n = 1 UGFS to GSV & AASV (redo)
	5 years	n = 2 Open surgery with phlebectomy n = 1 Ambulatory phlebectomy n = 1 Ambulatory phlebectomy with perforator ligation n = 2 EVLA & UGFS to GSV & AASV with phlebectomy n = 1 EVLA to GSV & SSV with phlebectomy n = 1 UGFS to AASV n = 1 UGFS to GSV n = 1 Open surgery (redo) n = 1 Ambulatory phlebectomy (redo)

Table 30 Additional procedures undertaken after index treatment (Study 1)

Burden of clinical recurrence

Clinical recurrence was associated with a significant impairment in both clinical and Quality of life measurements. These are detailed below.

Objective clinical assessment of venous disease – VCSS

As shown in Figure 42, VCSS was significantly worse in those with recurrence compared to those without a recurrence. However, those developing recurrence were also slightly worse at baseline, with a median VCSS of 3 (3-5) when compared to a median VCSS of 4 (3-5) (P=0.016) among those developing recurrence.

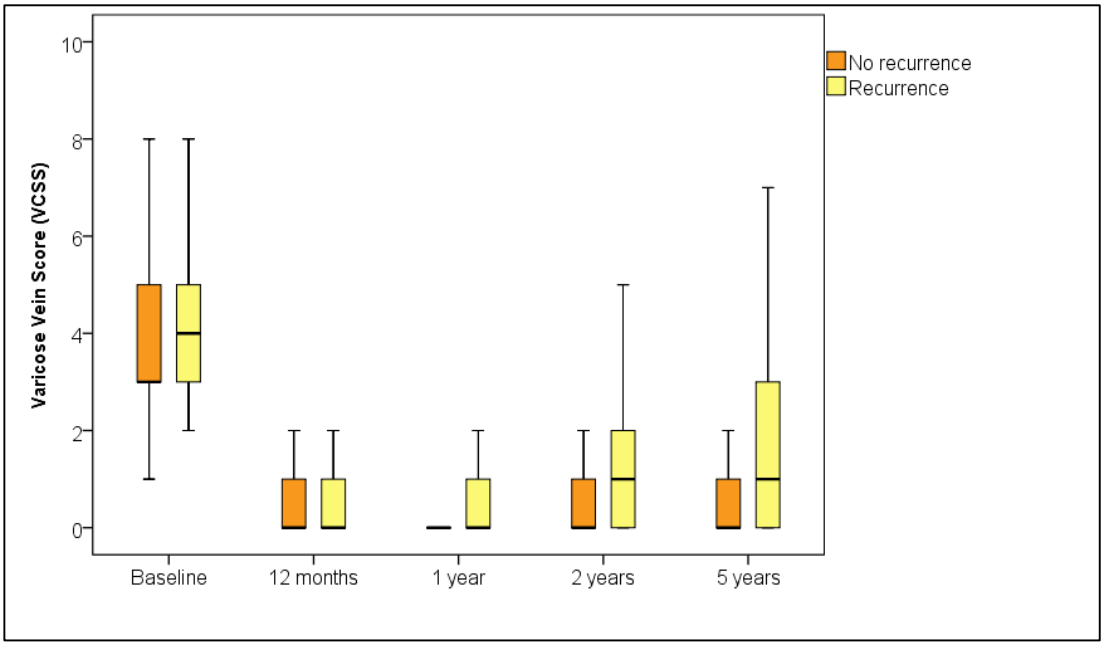


Figure 42 Comparison of Varicose Vein Severity Scores (VCSS) among those with and without clinical recurrence (Study 1)

Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

As shown in Figure 43, AVVQ was significantly worse amongst those who developed clinical recurrence. However, unlike the VCSS, there was no difference in baseline AVVQ between the two groups (No recurrence 12.76 (9.62-17.30), Recurrence 13.90 (9.85-18.23) P=0.274). As shown in Figure 44, within those

developing clinical recurrence only, symptoms were associated with an additional impairment of AVVQ.

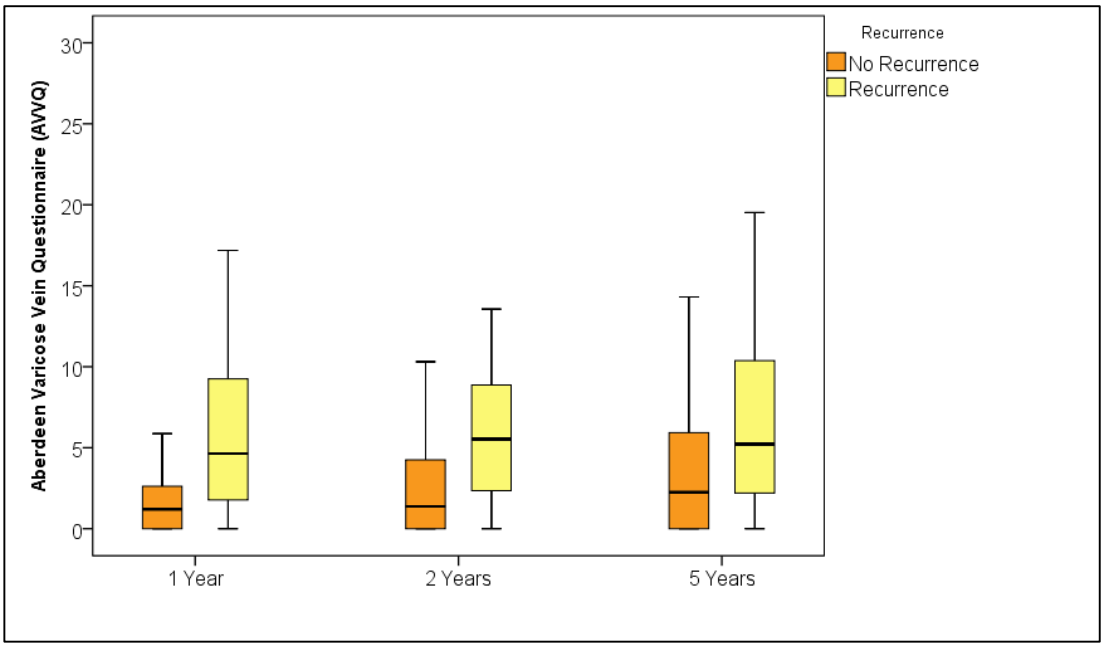


Figure 43 Comparison of Aberdeen Varicose Vein Questionnaire (AVVQ) score among those with and without clinical recurrence (Study 1)

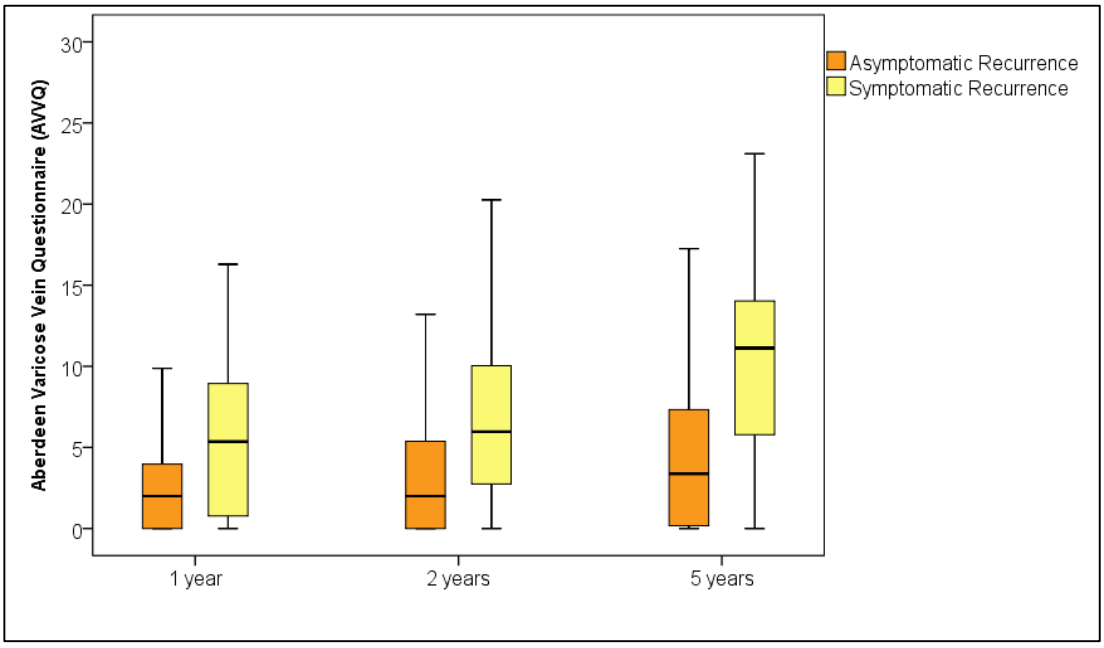


Figure 44 Comparison of Aberdeen Varicose Vein Questionnaire (AVVQ) score among those with and without symptomatic clinical recurrence (Study 1)

Cosmesis and overall satisfaction

As shown in Figure 45and Figure 46, clinical recurrence significantly impaired patient's opinion of cosmetic result and overall satisfaction with treatment.

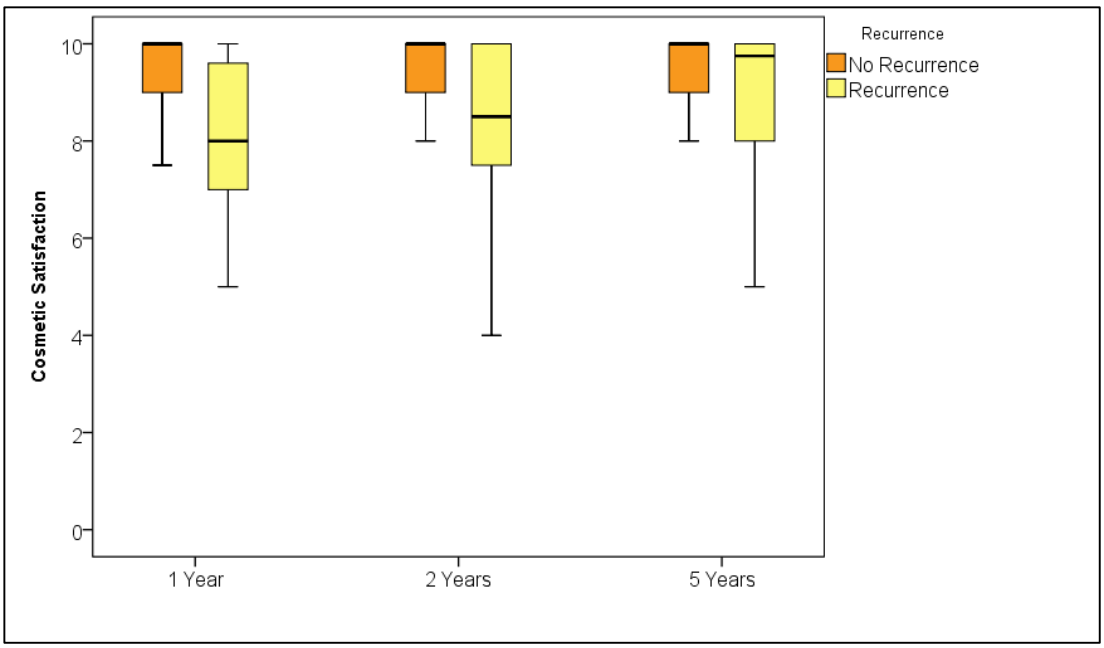


Figure 45 Clinical recurrence and cosmetic satisfaction (Study 1)

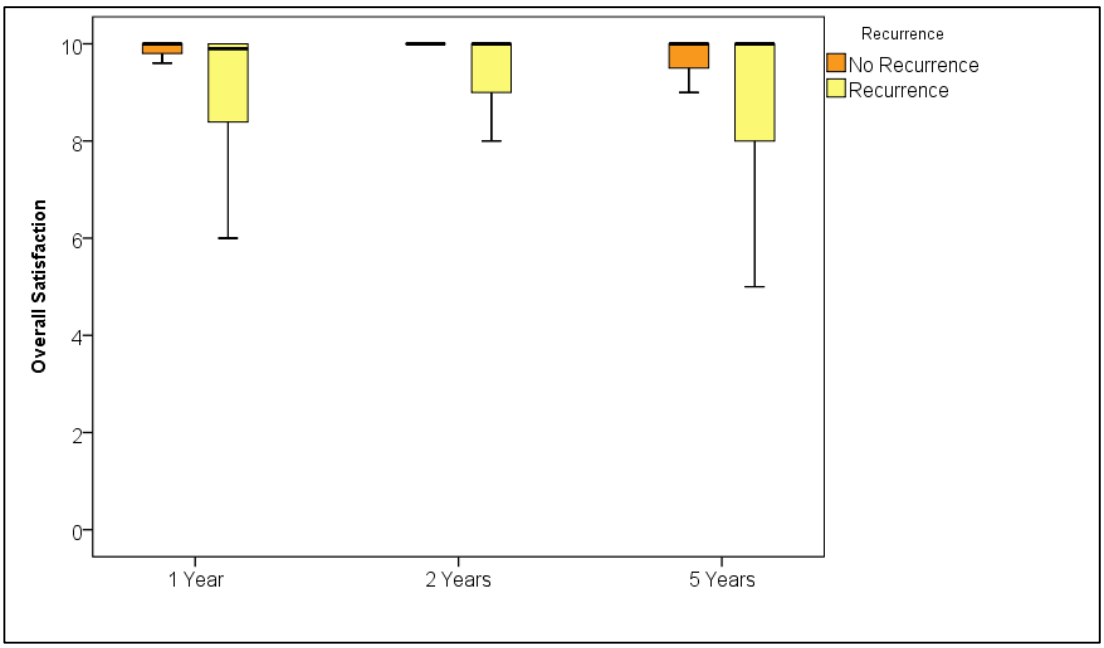


Figure 46 Clinical recurrence and overall satisfaction (Study 1)

4.2 Study 2 - A cost comparison of EVLA versus Conventional surgery for SVI

As detailed above in HELP-1 (page 151), of 280 equally randomised patients, 137 underwent Conventional surgery and 139 underwent EVLA for SVI .The economic analysis of the randomised trial is detailed below.

Primary treatment costs

The costs of primary treatment are detailed in Table 31. Mean procedure time was significantly quicker for those undergoing Conventional surgery compared to those undergoing EVLA (mean (s.d.) 61 (15) vs 67 (16) min P=0.001). However, additional staffing and procedure costs related to Conventional surgery were greater compared to those associated with EVLA. The primary treatment cost of Conventional surgery was therefore significantly more expensive than EVLA (P<0.001)

Procedure Stage	Cost item	Conventional surgery	EVLA
Referral and diagnosis	GP clinic	45	45
	Outpatient visit	169	169
	Diagnostic Venous Duplex	62	62
Intervention	Operation Time (mins)	61 (15)	67 (16)
	Medical personnel	288 (69)	160 (37)
	Nursing personnel	101 (24)	111 (26)
	Procedure costs	411 (53)	355

After care	Follow up Venous Duplex	52	52
	Routine follow up Outpatient Department	142	142
Total cost		1227 (137)	1049 (53)

Table 31. EVLA and conventional surgery primary treatment costs. Values are mean (S.D.) (Study 2)

Additional procedures

As detailed above on page 194, an additional 53 procedures were required over five years. A breakdown of the additional mean costs accrued per treatment group at various intervals is detailed in Table 32. Overall, there was no significant difference in the cost of an additional treatment at one year (P=0.228), two years (P=0.965) nor five years (P=0.810).

	Procedure time stage	**Conventional surgery**	**EVLA**
1 year	DUS	62	-
	Procedure time	44 (13) min	40 (6) min
	Personnel costs	178 (51)	161 (26)
	Procedure costs	107 (124)	51
	Aftercare	151 (21)	142
	Total	**448 (195)**	**354 (26)**
2 year	Referral & diagnosis	226 (32)	228 (31)
	Procedure time	63 (37) min	71 (26) min

	Personnel costs	280 (199)	317 (110)
	Procedure costs	247 (186)	213 (170)
	Aftercare	175 (27)	177 (26)
	Total	**928 (366)**	**935 (280)**
5 year	Referral & diagnosis	231 (30)	238 (25)
	Procedure time	48 (22) min	79 (36) min
	Personnel costs	191 (89)	366 (166)
	Procedure costs	250 (162)	256 (178)
	Aftercare	179 (25)	185 (21)
	Total	**992 (559)**	**1008 (327)**

Table 32. EVLA and conventional surgery additional costs accrued per additional treatment episode. Values are mean (S.D.) (Study 2)

Overall treatment costs

As shown in Figure 47, Conventional surgery was overall more expensive when compared to EVLA, being on average £156 more costly than EVLA over five years (P=0.002). As detailed in Table 33, the overall costs of Conventional surgery were consistently greater than EVLA at one, two and five years. The additional expense of Conventional surgery was upheld in sensitivity analysis, with an annual discount rate of 0% giving a mean difference of £154 (95% CI; £52 - £257) P=0.003 t-test) and an annual discount rate of 5% giving a mean difference of £157 (95% CI; £58 - £255) P=0.002) between the two groups.

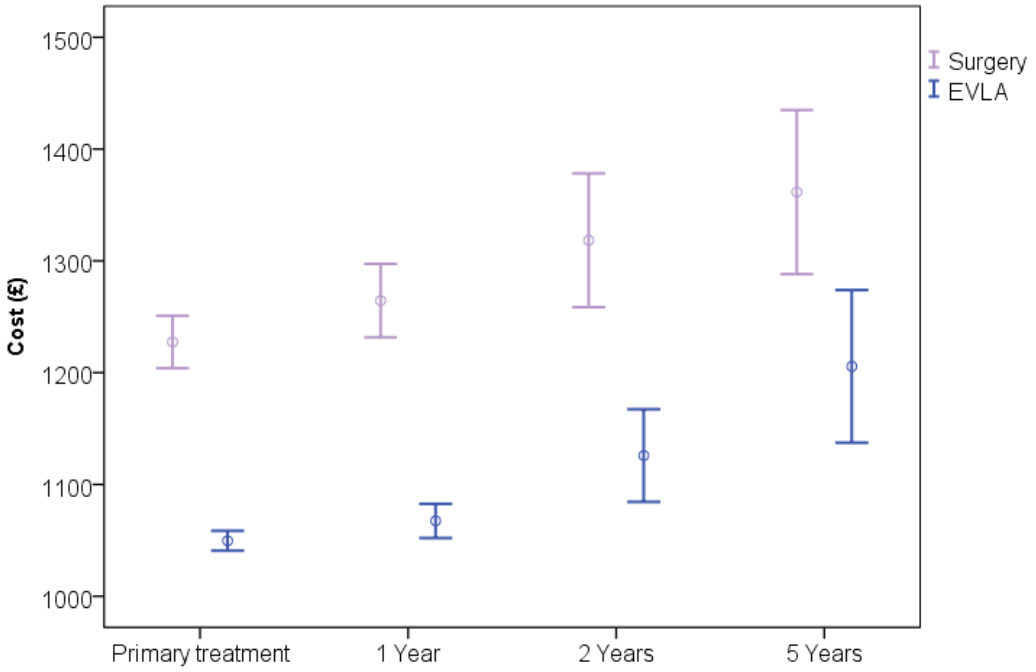


Figure 47 EVLA and conventional surgery mean cost of treatment over five years with 3.5% discounting of costs per annum. Bars represent 95% Confidence intervals (Study 2)

Time point	Conventional surgery	EVLA	Mean difference	95% CI lower	95% CI higher
Primary treatment	£1227 (137)	£1050 (53)	£178	£153	£202
1 year	£1265 (192)	£1067 (91)	£197	£162	£233
2 year	£1318 (349)	£1126 (247)	£193	£121	£264
5 year	£1362 (428)	£1206 (407)	£156	£56	£256

Table 33 Cumulative treatment costs of Conventional surgery and EVLA over five years. 3.5% discounting per annum (Study 2)

Health outcomes – EuroQol 5 Dimension

As detailed in Table 34, both groups improved over the study period with a slight benefit in EQ5D after Conventional surgery noted at two years. However, both groups were similar in overall QALY AUC over five years. As detailed in Table 35, this similarity was maintained in a sensitivity analysis.

Time point	Conventional surgery	EVLA	Mean difference	95% CI
EQ5D Score				
Baseline	0.840 (0.167)	0.842 (0.177)	-0.002	-0.043 to 0.039
1 week	0.789 (0.183)	0.814 (0.171)	-0.025	-0.069 to 0.190
6 weeks	0.909 (0.146)	0.909 (0.151)	0.001	-0.037 to 0.039
12 weeks	0.911 (0.165)	0.928 (0.137)	-0.017	-0.055 to 0.022
1 year	0.911 (0.142)	0.925 (0.157)	-0.013	-0.052 to 0.025
2 years†	0.924 (0.136)	0.875 (0.210)	0.049	0.002 to 0.095
5 years	0.886 (0.168)	0.895 (0.203)	-0.009	-0.061 to 0.043
AUC				
0 to 1 year	0.907 (0.131)	0.922 (0.129)	-0.015	-0.051 to 0.022
1 to 2 year	0.889 (0.114)	0.879 (0.194)	0.009	-0.033 to 0.052
2 to 5 year	2.245 (0.326)	2.427 (0.578)	0.017	-0.118 to 0.153
Total AUC				
0 to 5 years	4.289 (0.495)	4.224 (0.668)	0.065	-0.118 to 0.247

Table 34. EVLA and conventional surgery EQ5D scores over five years. Values in mean (S.D.) with 3.5% discounting per annum †Significant difference in means at the 5% level (Study 2)

Missing Value replacement	Discount rate	Conventional surgery	EVLA	Mean difference	95% CI
Nil	0%	4.602 (0.534)	4.529 (0.723)	0.072	-0.125 to 0.269
	3.5%	4.289 (0.494)	4.225 (0.668)	0.065	-0.118 to 0.247
	5%	3.891 (0.445)	3.836 (0.598)	0.055	-0.108 to 0.219
Interpolation	0%	4.508 (0.677)	4.473 (0.931)	0.034	-0.179 to 0.248
	3.5%	4.202 (0.629)	4.172 (0.860)	0.030	-0.167 to 0.227
	5%	3.813 (0.567)	3.788 (0.769)	0.025	-0.152 to 0.201
Last result carried forward	0%	4.474 (0.789)	4.491 (0.888)	-0.017	-0.218 to 0.183
	3.5%	4.170 (0.734)	4.189 (0.820)	-0.018	-0.204 to 0.168
	5%	3.783 (0.662)	3.802 (0.733)	-0.019	-0.186 to 0.148
Group mean	0%	3.600 (1.647)	3.686 (1.632)	-0.086	-0.475 to 0.304
	3.5%	3.984 (0.761)	3.945 (0.978)	0.040	-0.189 to 0.268
	5%	3.622 (0.678)	3.588 (0.869)	0.034	-0.169 to 0.238

Table 35 Sensitivity analysis of different discounting rates and missing value imputations for the five year EQ5D QALY AUC. (Study 2)

Health outcomes – SF6D

As detailed in Table 36, both groups improved over the study period with a slight improvement in SF6D after EVLA noted at one week. However, both groups were similar in overall QALY AUC over five years. As detailed in Table 37, this similarity was maintained in a sensitivity analysis of both discounting rate variations and different missing value imputations.

Time point	Conventional surgery	EVLA	Mean difference	95% CI
SF6D Score				
Baseline	0.779 (0.092)	0.784 (0.095)	-0.005	-0.028 to 0.017
1 week†	0.746 (0.095)	0.778 (0.088)	-0.033	-0.056 to 0.010
6 weeks	0.809 (0.079)	0.808 (0.091)	0.001	-0.022 to 0.023
12 weeks	0.817 (0.081)	0.814 (0.094)	0.003	-0.020 to 0.026
1 year	0.811 (0.087)	0.815 (0.086)	-0.005	-0.028 to 0.018
2 years	0.808 (0.088)	0.799 (0.102)	0.009	-0.016 to 0.035
5 years	0.776 (0.087)	0.787 (0.103)	-0.011	-0.038 to 0.016
AUC				
0 to 1 year	0.815 (0.074)	0.817 (0.079)	-0.002	-0.025 to 0.020
1 to 2 year	0.781 (0.077)	0.779 (0.084)	0.002	-0.020 to 0.024
2 to 5 year	2.143 (0.206)	2.144 (0.242)	-0.001	-0.066 to 0.065
Total AUC				
0 to 5 years	3.769 (0.303)	3.758 (0.373)	0.011	-0.101 to 0.123

Table 36 EVLA and conventional surgery SF6D scores over five years. Values in mean (S.D.) with 3.5% discounting per annum †Significant difference in means at the 5% level (Study 2)

Missing Value replacement	Discount rate	Conventional surgery	EVLA	Mean difference	95% CI
Nil	0%	4.041 (0.325)	4.031 (0.400)	0.010	-0.110 to 0.130
	3.5%	3.769 (0.303)	3.758 (0.373)	0.011	-0.101 to 0.123
	5%	3.658 (0.293)	3.647 (0.361)	0.011	-0.098 to 0.119
Interpolation	0%	3.981 (0.381)	4.002 (0.423)	-0.021	-0.129 to 0.087
	3.5%	3.720 (0.354)	3.731 (0.393)	-0.015	-0.115 to 0.086
	5%	3.607 (0.343)	3.621 (0.381)	-0.014	-0.111 to 0.083
Last result carried forward	0%	3.978 (0.402)	4.000 (0.446)	-0.022	-0.124 to 0.081
	3.5%	3.709 (0.374)	3.728 (0.415)	-0.019	-0.114 to 0.076
	5%	3.599 (0.362)	3.618 (0.402)	0.018	-0.110 to 0.074
Group mean	0%	3.513 (0.851)	3.580 (0.807)	-0.066	-0.262 to 0.131
	3.5%	3.280 (0.791)	3.338 (0.748)	-0.059	-0.241 to 0.124
	5%	3.184 (0.766)	3.242 (0.724)	-0.057	-0.235 to 0.120

Table 37 Sensitivity analysis of different discounting rates and missing value imputations for five year the SF6D QALY AUC. (Study 2)

Cost effective analysis – EuroQol 5 Dimension

A summary of the statistics used in the EQ5D cost effective analysis are detailed in Table 38. Over five years EVLA was associated with significantly lower cost compared to Conventional surgery but with a similar amount of QALYs gained. The subsequent mean ICER was therefore calculated as positive at £2,942 per QALY gained.

		Conventional surgery	EVLA	Difference
Effect (QALY)	Mean	4.289	4.225	-0.065
	Variance of mean	0.00306	0.00538	0.00844
Cost (£)	Mean	£1,368	£1,178	£-191
	Variance of mean	£2,191	£1,588	£3,778
Cost and Effect	Covariance	-64.795	-40.052	-1.239
	Correlation	-0.313	-0.147	-0.219
Incremental Cost Effectiveness Ratio (£/QALY)				£2,942

Table 38. Summary of the Cost effective analysis statistics using the EQ5D (Study 2)

Incremental Net Benefit (INB)

The Incremental Net Benefit (INB) of EVLA compared to Conventional surgery was calculated. As detailed in Table 39 and shown in Figure 48 the INB appears to decrease as the cost effective threshold increases, suggesting that the estimated INB reduces slightly as more value is placed on each QALY gained. However, at the typical NICE threshold value of £20,000 - £30,000, there is significant uncertainty in the overall model and the value of the estimated INB is uncertain.

Cost Effective Threshold (£/QALY)	Incremental net benefit	Variance	95% CI lower	95% CI higher
£0	£191	£3,778	£70	£311
£5000	-£133	148,721	-£1,068	£801
£10,000	-£448	£872,510	-£2,289	£1,373
£15,000	-£782	£1,939,845	-£3,512	£1,948
£20,000	-£1,106	£3,429,161	-£4,736	£2,523
£25,000	-£1,430	£5,340,456	-£5,960	£3,099
£30,000	-£1,755	£7,673,731	-£7,184	£3,675
£35,000	-£2,079	£10,428,987	-£8,409	£4,251

Table 39 Incremental net benefit of intervention (EVLA) vs Control (Conventional Surgery) (Study 2)

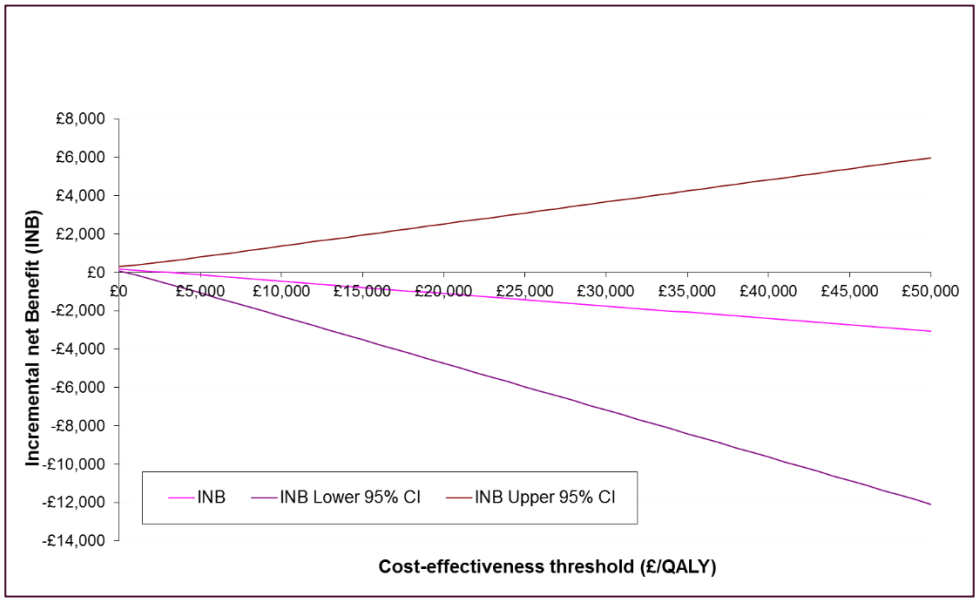


Figure 48 Incremental Net Benefit (IBM) of EVLA vs Conventional surgery using the EQ5D (Study 2)

Cost-effectiveness acceptability curve (CEAC)

As shown in Figure 49, a CEAC curve was generated to assess if EVLA is cost effective compared to conventional surgery. At the typical WTP threshold of £20,000, the probability that EVLA would be more cost effective than conventional surgery was estimated at less than 30%.

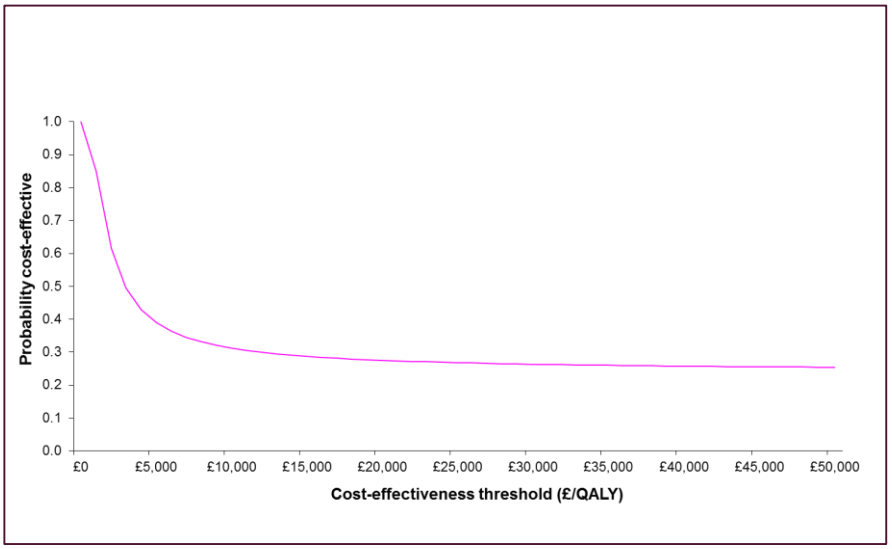


Figure 49 CEAC curve of EVLA vs Conventional surgery using the EQ5D (Study 2)

Confidence ellipses

As shown in Figure 50, uncertainty around the estimated mean difference in costs and effects were explored using a cost effectiveness plane. A point estimate placed in the south-east or north-west quadrants of the plane would suggest that an "experimental" group is likely to be "dominant" over or "dominated" by the control group (i.e. less costly with more benefit or more costly with less benefit). In this study the point estimate of EVLA is located in the south-west quadrant with confidence intervals crossing the y axis. This suggests that there is a strong probability that if this study was expanded that EVLA will likely to be shown to be

less expensive than Conventional surgery, with a small chance of EVLA being more effective.

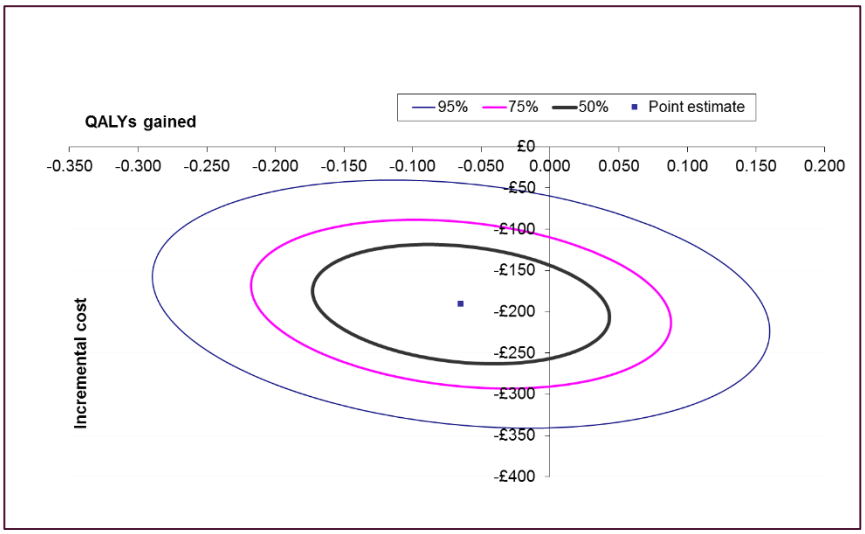


Figure 50 ICER estimates of EVLA vs Conventional surgery using the EQ5D (Study 2)

Cost effective analysis – SF6D

A summary of the statistics used in the SF6D cost effective analysis are detailed in Table 40. Over five years EVLA was associated with significantly lower cost compared to Conventional surgery but with a similar amount of QALYs gained. The subsequent mean ICER was therefore calculated as positive at £18,355 per QALY gained.

		Conventional surgery	EVLA	Difference
Effect (QALY)	Mean	3.769	3.758	-0.011

	Variance of mean	0.00133	0.00183	0.000316
Cost (£)	Mean	£1,375	£1,162	-£213
	Variance of mean	£2,647	£1,412	£4,059
Cost and Effect	Covariance	-25.469	-9.355	-0.492
	Correlation	-0.197	-0.077	-0.138
Incremental Cost Effectiveness Ratio (£/QALY)				£19,070

Table 40 Summary of the Cost effective analysis statistics using the SF6D (Study 2)

Incremental Net Benefit (INB)

The Incremental Net Benefit (INB) of EVLA compared to Conventional surgery was calculated. As detailed in Table 41 and shown in Figure 51 the INB appears to decrease as the cost effective threshold increases. However, at the typical NICE threshold value of £20,000 - £30,000, the INB is slightly negative, although again there is significant uncertainty in the overall model.

Cost Effective Threshold (£/QALY)	Incremental net benefit	Variance	95% CI lower	95% CI higher
£0	£213	£4,059	£89	£338
£5000	£157	£87,894	-£424	£739
£10,000	£102	£329,7554	-£1,024	£1,227
£15,000	£46	£729,040	-£1,628	£1,719
£20,000	-£10	£1,286,353	-£2,233	£2,213
£25,000	-£66	£2,001,489	-£2,839	£2,707

£30,000	-£122	£2,874,451	-£3,445	£3,201
£35,000	-£178	£3,905,239	-£4,052	£3,695

Table 41 Incremental net benefit of intervention (EVLA) vs Control (Conventional Surgery) (Study 2)

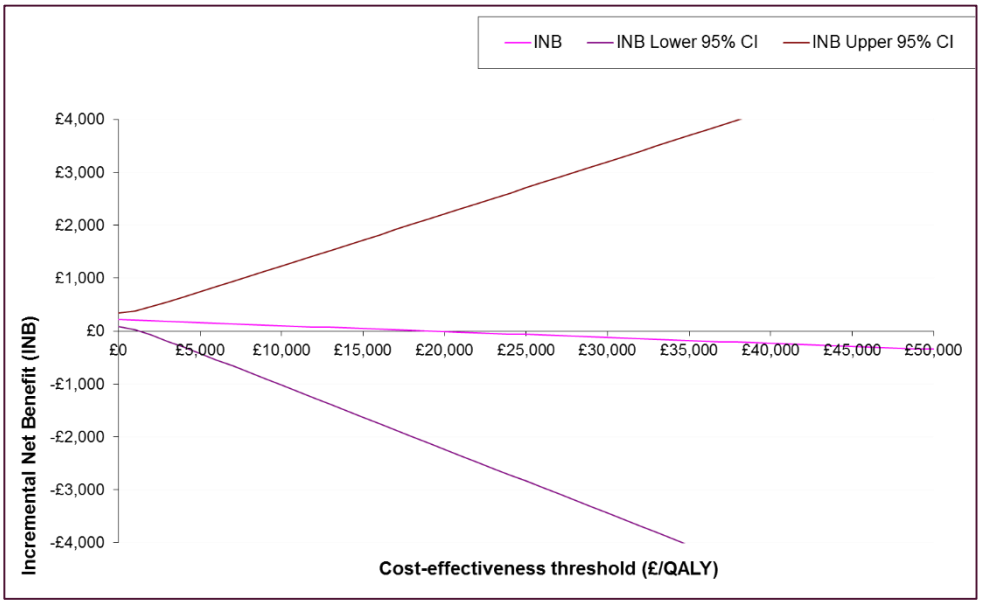


Figure 51 Incremental Net Benefit (IBM) of EVLA vs Conventional surgery using the EQ5D (Study 2)

Cost-effectiveness acceptability curve (CEAC)

As shown in Figure 52, a CEAC curve was generated to assess if EVLA is cost effective compared to Conventional surgery. At the typical WTP threshold of £20,000, the probability that EVLA would be more cost effective than Conventional surgery was estimated at around 50%.

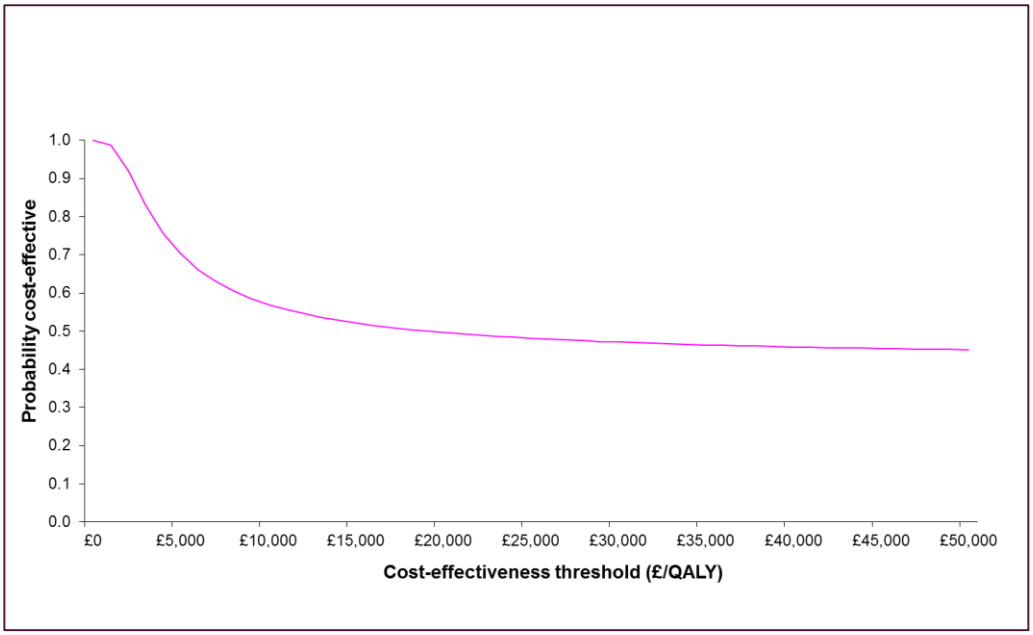


Figure 52 CEAC curve of EVLA vs Conventional surgery using the SF6D (Study 2)

Confidence ellipses

As shown in Figure 53, the point estimate was placed in the south-west quadrant. Although the majority of repeated observations are likely to recur in the south-west quadrant, a proportion may arise in the "dominant" south-east quadrant.

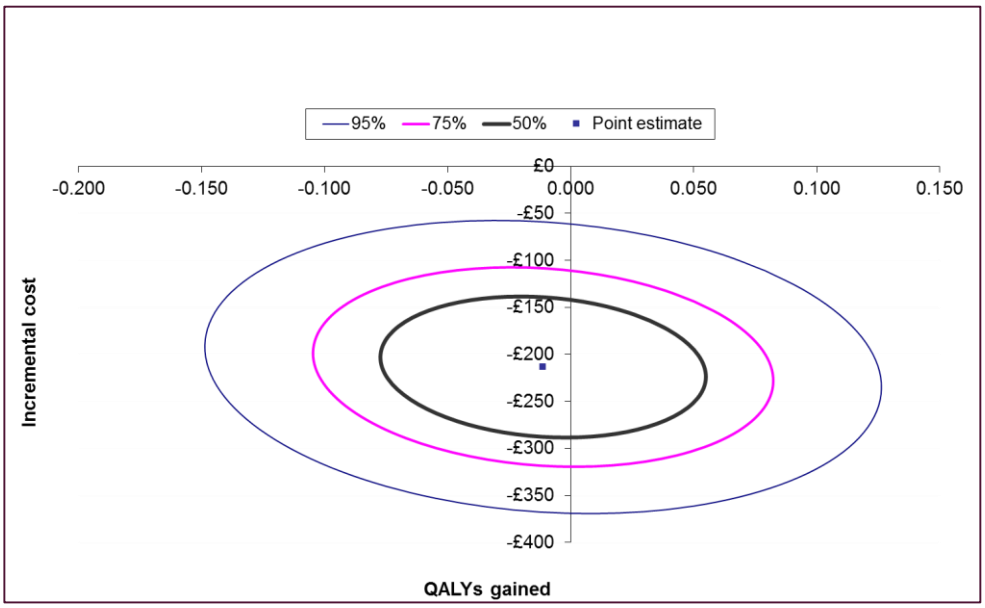


Figure 53 ICER estimates of EVLA vs Conventional surgery using the SF6D (Study 2)

4.3 Study 3 - Long term clinical and technical outcomes comparing concomitant versus sequential phlebectomy with EVLA for SVI

As shown in the EVLTAP CONSORT diagram (Figure 54), of the initial 50 patients randomised 39 (78%) attended for their appointment at five years.

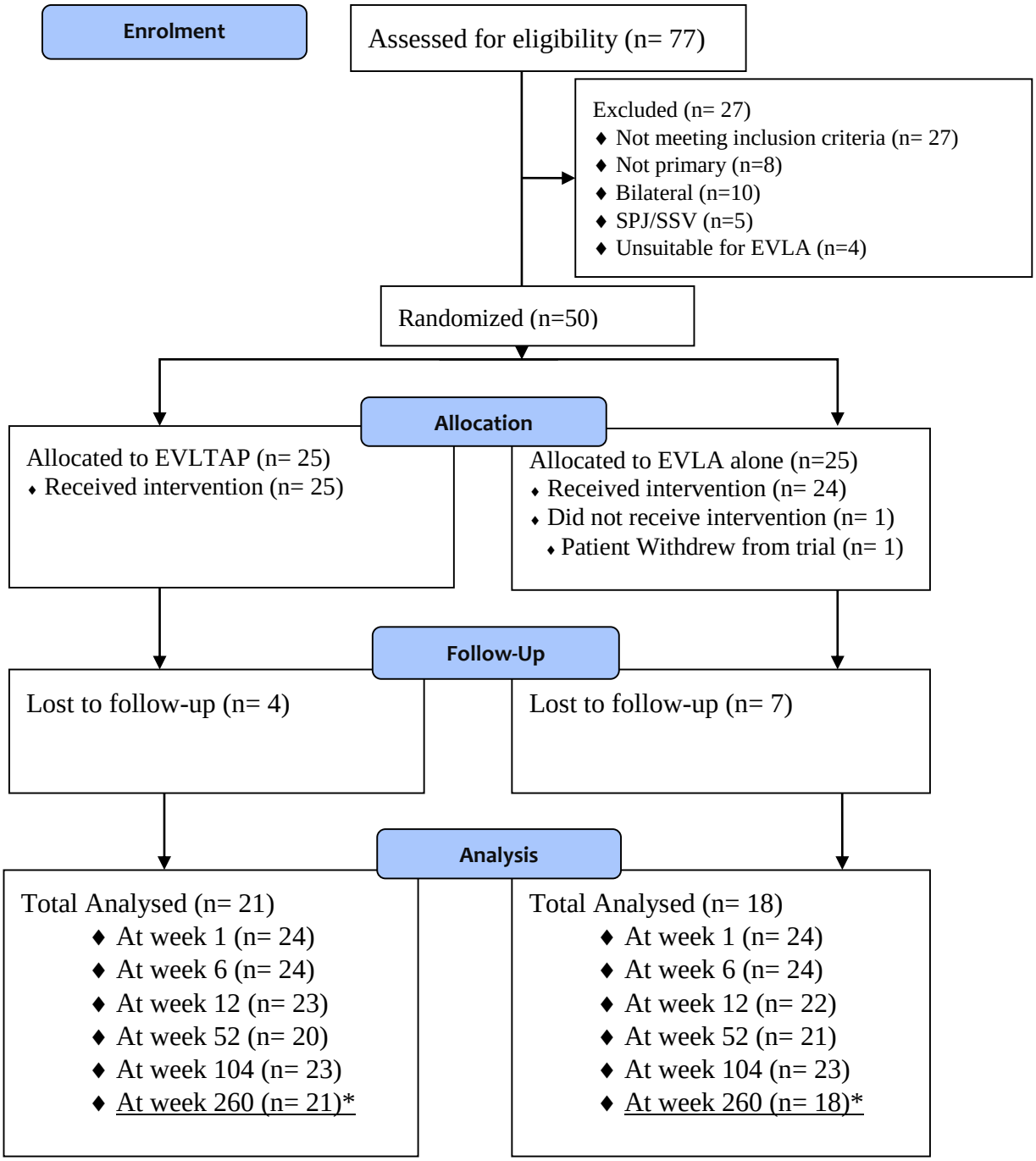


Figure 54. EVLTAP CONSORT flow chart (Study 3) *Time period of this study

Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

As shown in Figure 55, both treatment groups reported a significant reduction in AAVQ scores following treatment and this was maintained for five years (EVLA alone P<0.001, EVLTAP P<0.001, FT). Whereas the EVLTAP group reported a significant decrease in AVVQ scores by six weeks (P=0.008 WSR), the EVLA alone group did not experience any improvement (P=1.000 WSR) but instead showed only a modest change by 12 weeks (P=0.018 WSR), leading to comparatively worse scores at six (P<0.001 MWU) and 12 weeks (P=0.015 MWU) compared to those undergoing concomitant phlebectomy, this would have also resulted in a significant clinical difference. By one year, scores in both groups had become similar (P=0.841 MWU) and this was sustained to five years (P=0.835 MWU) with no sign of deterioration.

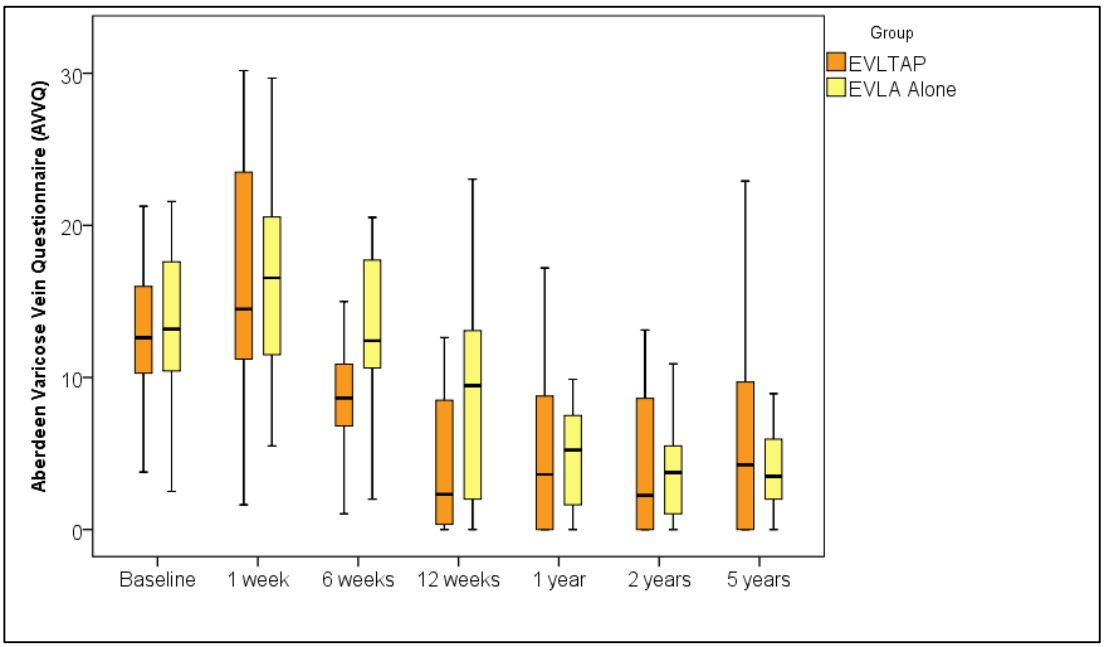


Figure 55. Aberdeen Varicose Vein Questionnaire (AVVQ) scores over five years (Study 3)

Generic Quality of Life - Short Form – 36

As shown in Figure 56 to Figure 63, both groups showed an improvement in the SF-36 Role-Physical domain (EVLA Alone P=0.005, EVLTAP P=0.024 FT), but only the EVLTAP group had a significant improvement in the SF-36 Physical Function (P=0.043 FT) and Body-Pain (P=0.027 FT) domains. No statistically significant difference between the groups in any SF-36 domains were observed at any other time point.

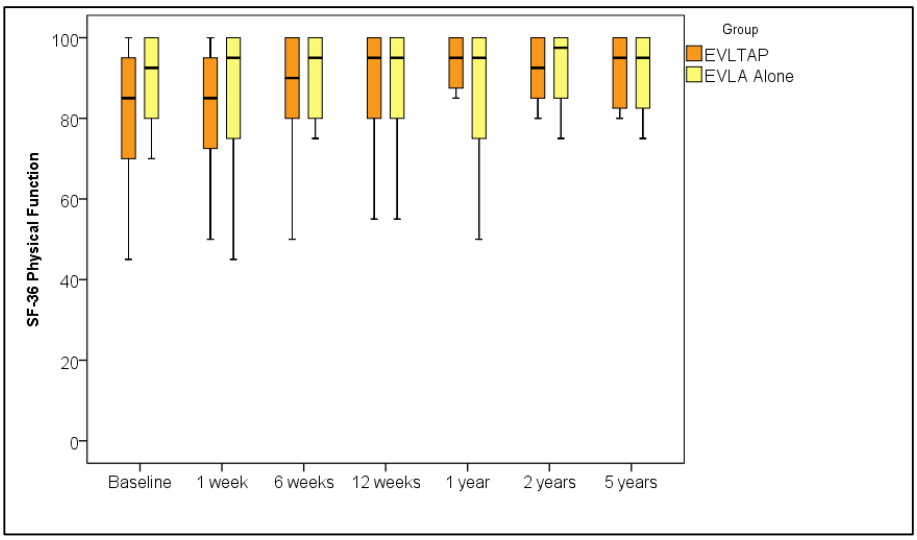


Figure 56 SF-36 Physical function scores over five years (Study 3)

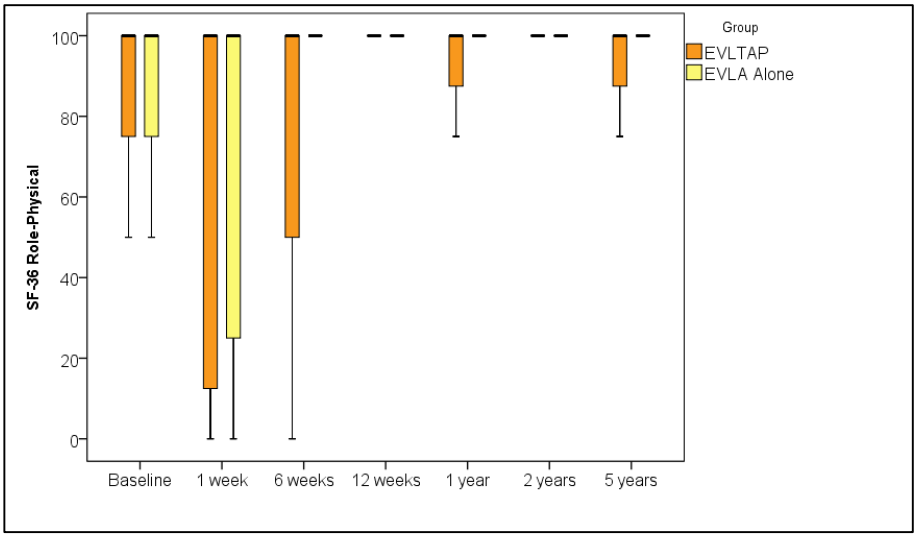


Figure 57 SF-36 Role-Physical function scores over five years (Study 3)

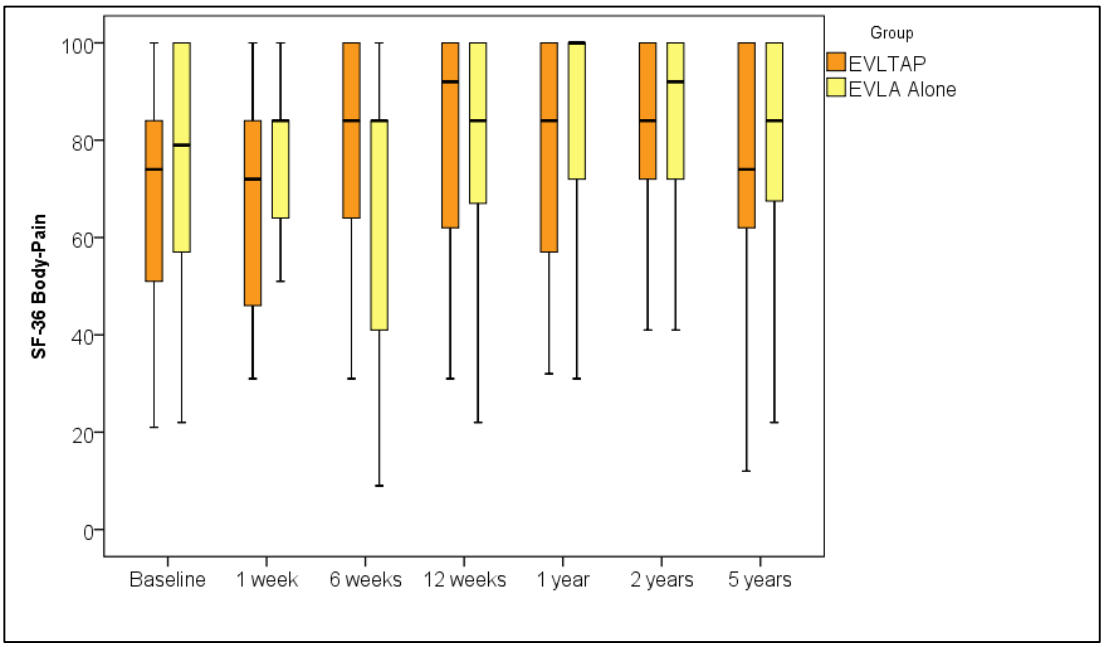


Figure 58 SF-36 Body Pain scores over five years (Study 3)

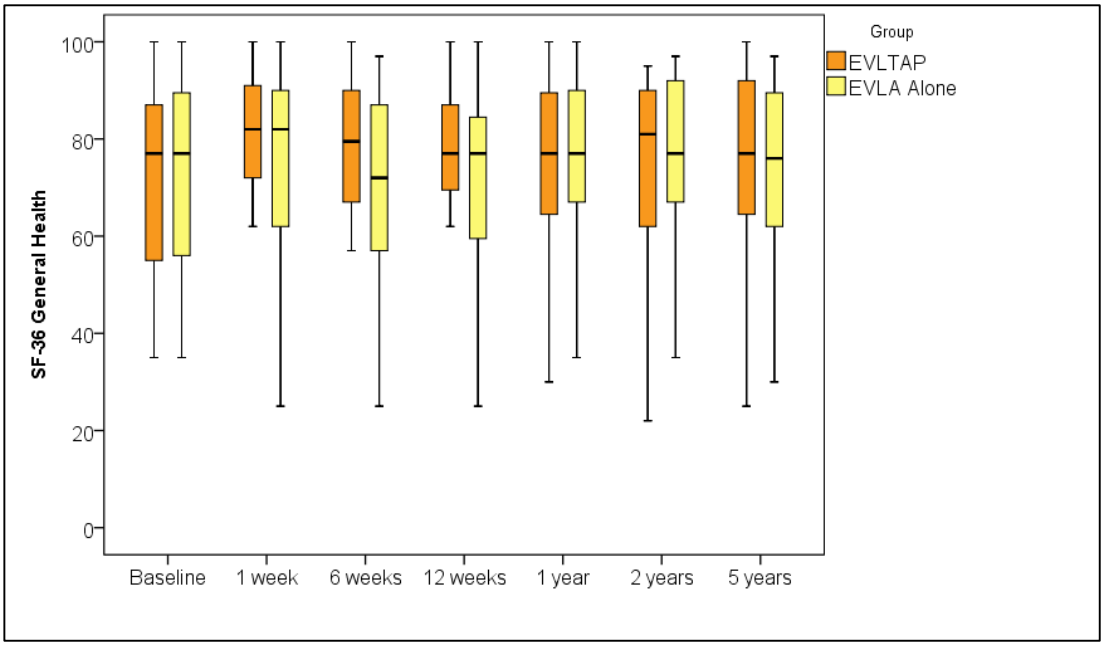


Figure 59 SF-36 General Health scores over five years (Study 3)

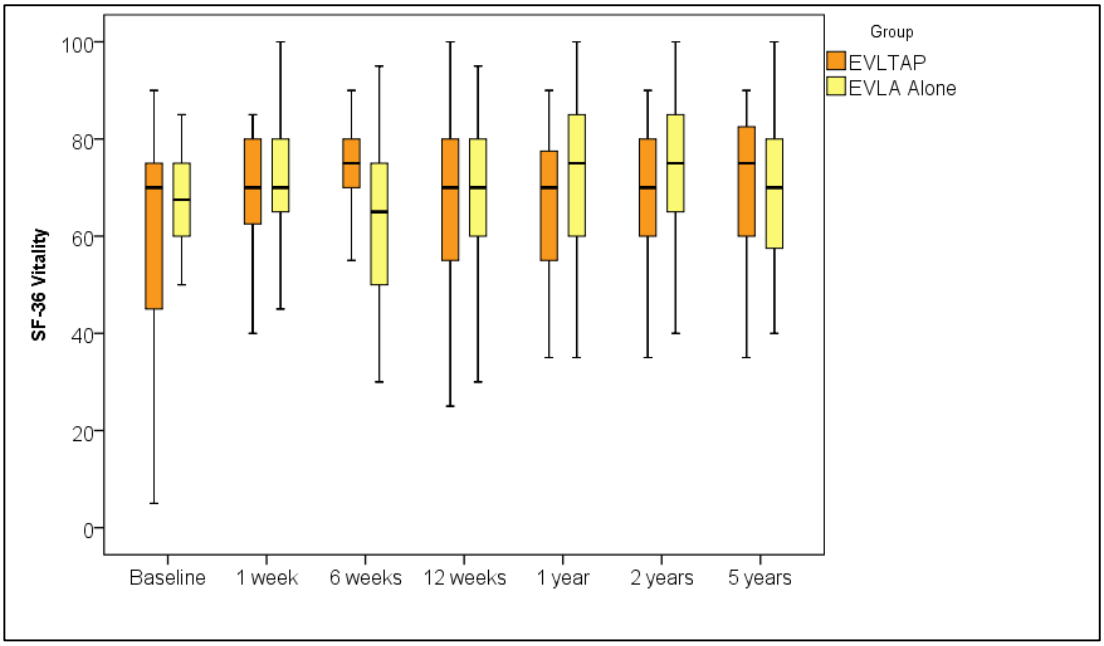


Figure 60 SF-36 Vitality scores over five years (Study 3)

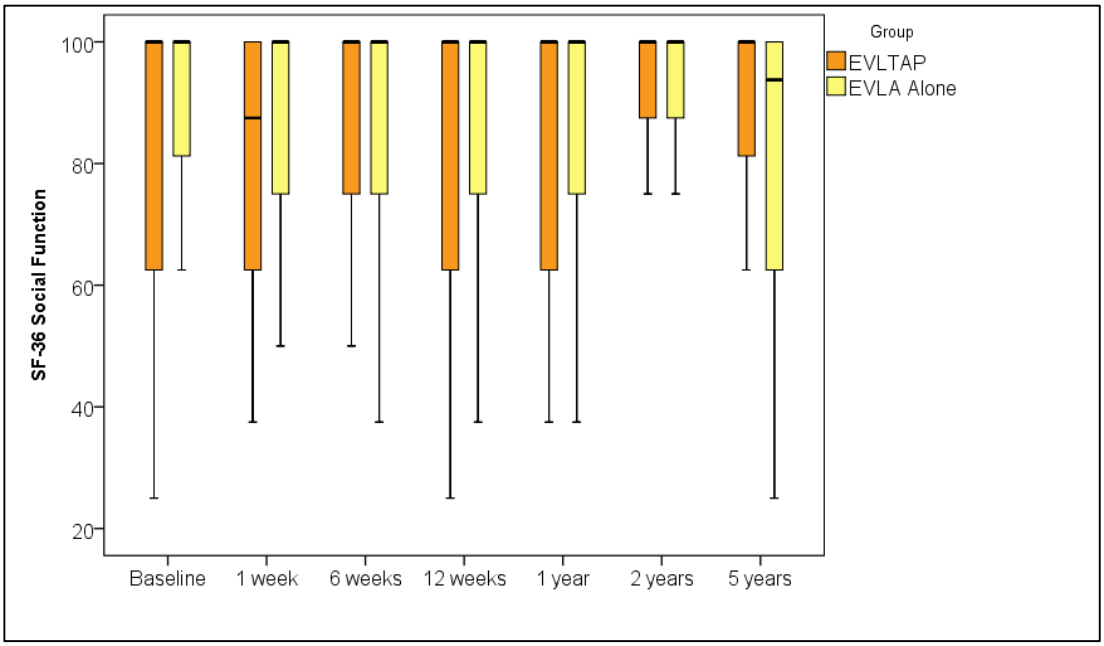


Figure 61 SF-36 Social Function scores over five years (Study 3)

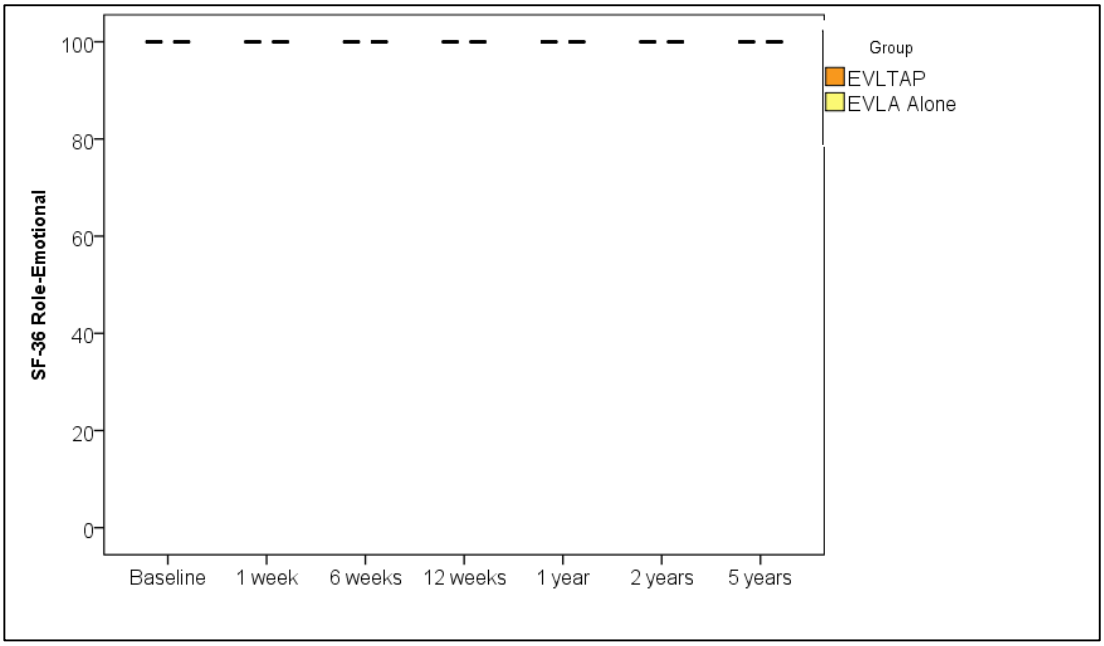


Figure 62 SF-36 Role-Emotional scores over five years (Study 3)

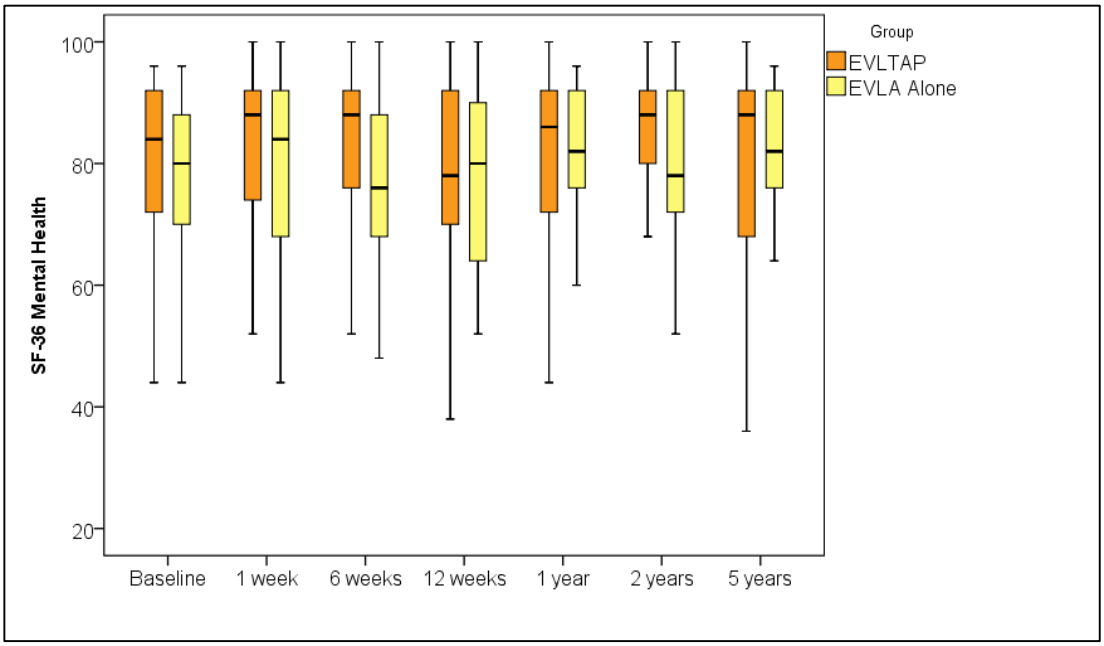


Figure 63 SF-36 Mental Health scores over five years (Study 3)

Utility Index QoL - EuroQol 5 Dimension

As shown in Figure 64, both groups improved in EQ5D score over the five years (EVLA alone P=0.007, EVLTAP P<0.001 FT). Whereas improvement in EQ5D was noted as early as six weeks after EVLTAP (P=0.002 WSR), significant improvement was not seen in the EVLA alone group until one year post treatment (P=0.007 WSR). At two years both groups were significantly improved from their baseline (EVLA alone P=0.006, EVLTAP P<0.001 WSR.) and this was sustained to five years (EVLA alone P=0.046, EVLTAP P=0.43 WSR.). No significant difference in EQ5D was noted between the groups at any time point over five years.

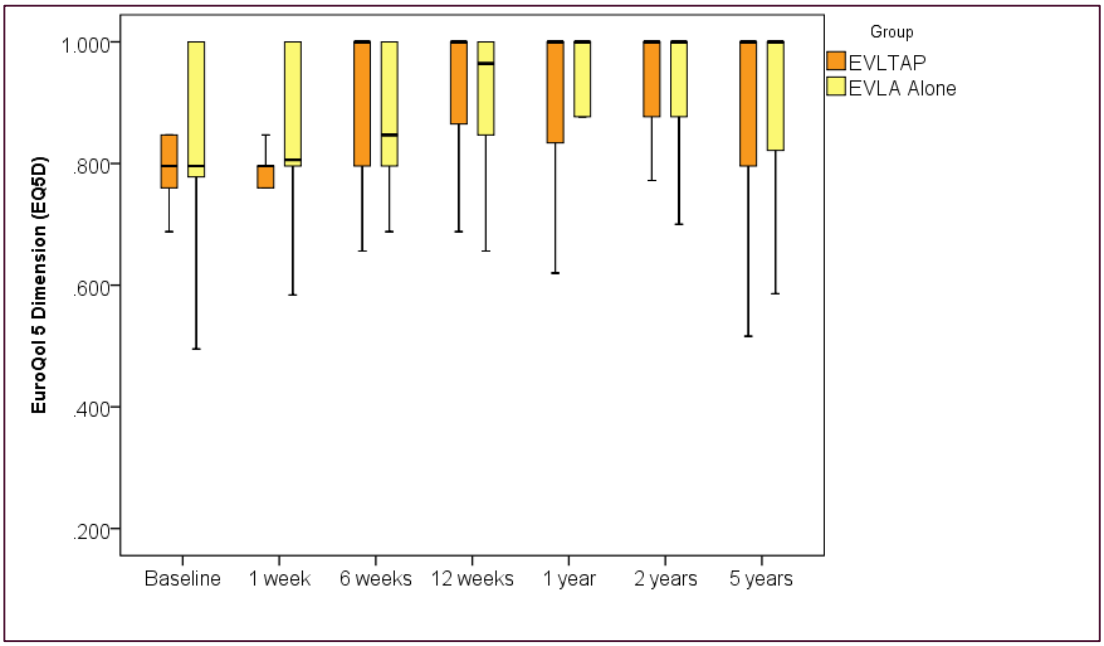


Figure 64 EQ5D scores over five years (Study 3)

Utility Index QoL - SF6D

As shown in Figure 65, neither group experienced a significant improvement in SF6D over the five year time period (EVLA alone P=0.568, EVLTAP P=0.374 FT). No significant difference in SF6D was noted between the groups at any time point.

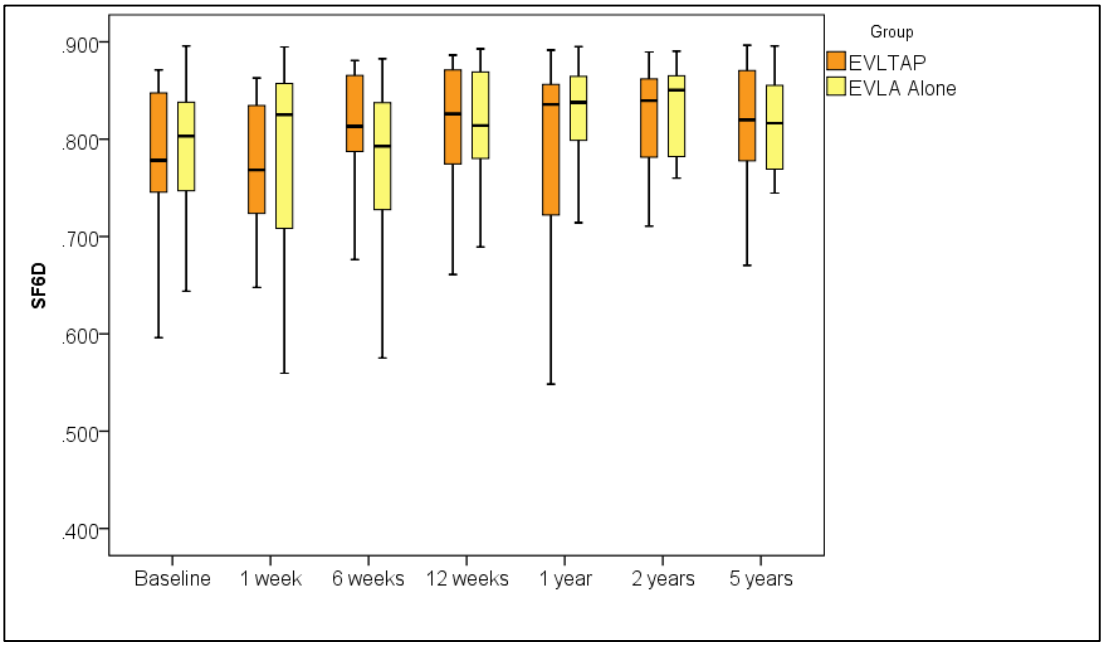


Figure 65 SF6D scores following treatment (Study 3)

Objective clinical assessment of venous disease – VCSS

As shown in Figure 66, both treatments saw a significant improvement in VCSS scores following treatment that was maintained to five years (P<0.001 FT.). The EVLTAP group demonstrated significantly better VCSS scores at 12 weeks (EVLA alone 2 (0-2) vs EVLTAP 0 (0-1) P<0.001 MWU), but there was no difference at one, two or five years.

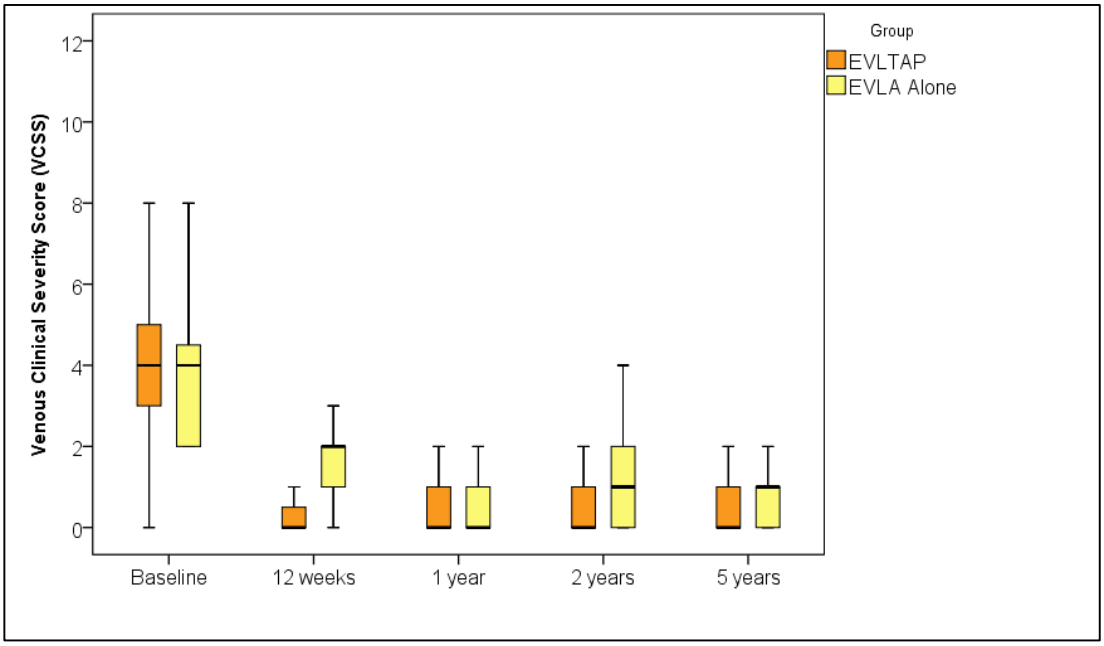


Figure 66 VCSS scores over five years (Study 3)

Cosmetic satisfaction

Opinion of cosmesis after treatment was high in both groups at two years (EVLA alone 9.75 (8-10) vs EVLTAP 9.5 96.75-10) P=0.307 MWU) and at five years (EVLA alone 10 (9-10) vs EVLTAP 10 (8-10) P=0.309 MWU)

Overall satisfaction

Both treatment groups were similarly satisfied with treatment at two (EVLA alone 10 (10) vs EVLTAP 10 (9-10) P=0.066 MWU) and five years (EVLA alone 10 (10) VS EVLTAP 10 (8.25-10) P=0.165 MWU)

At 2 years, 21 of 23 patients in the EVLTAP group and 21 of 23 in the EVLA group stated that they would have EVLA again if necessary or recommend it to a friend (P=1·000). At 5 years, all patients in both groups stated they would have EVLA again or recommend it to a friend (P =1·000).

Clinical recurrence

After 6 weeks, residual varicosities as defined above were present in five of 25 patients after EVLTAP and in 19 of 24 after EVLA (P <0·001). Clinical recurrence, as defined at 5 years, was seen in four patients after EVLTAP and in five after EVLA (P =0·725). The most common pattern associated with clinical recurrence following EVLA was the development of new reflux into tributaries including the anterior accessory saphenous vein (EVLTAP n=4; EVLA alone n=3). Other sources of recurrence were new reflux in a Giacomini vein (EVLA alone n=1) and non-axial tributaries (EVLA n=1).

	Source of recurrence on duplex ultrasonography	Proportion of recurrences
EVLA-AP	Groin Neovascularisation Sapheno-femoral junction	3 of 4 1 of 4
EVLA alone	Groin Neovascularisation Giacomini Sapheno-femoral junction Non Axial tributaries	2 of 5 1 of 5 1 of 5 1 of 5

Table 42 Association of patterns of reflux on duplex ultrasonography with clinical recurrence. (Study 3)

Requirement for additional procedures

As detailed in Table 43, in the first year secondary intervention was required by only one of the 25 patients in the EVLTAP group, whereas 16 of 24 patients had a secondary procedure following EVLA (P <0·001). After 1 year, the rate of secondary procedures was equivalent between the groups: four patients after EVLTAP and three after EVLA alone (P =1·000). In total after 5 years, seven secondary procedures were undertaken in five patients in the EVLTAP group, and 23 in 19 patients in the EVLA group (P <0·001).

EVLA alone	< 1 year	N=13 Ambulatory phlebectomy N=3 Ambulatory phlebectomy with perforator ligation
	1 – 2 years	N=1 EVLA N=1 Open surgery
	2 – 5 years	N=1 Ambulatory phlebectomy

	Repeat Secondary Procedure	N=4 Ambulatory phlebectomy
EVLTAP	< 1 year	n=1 Ambulatory phlebectomy with perforator ligation
	1 – 2 years	n=1 Foam sclerotherapy n=2 Open surgery
	2 – 5 years	N=1 Ambulatory phlebectomy
	Repeat Secondary Procedure	N=1 Open surgery N=1 Ultrasound guided foam sclerotherapy

Table 43 Secondary procedures required over five years (Study 3)

4.4 Study 4 – A cost comparison of concomitant or sequential phlebectomy with EVLA for SVI

As detailed above in EVLTAP (page 217), of 50 equally randomised patients, 24 underwent EVLA alone and 25 underwent EVLA with concomitant phlebectomy (EVLTAP). The economic analysis of the randomised trial is detailed below.

Primary treatment costs

The costs of primary treatment are detailed in Table 31. The mean operative time was quicker among the EVLA alone group compared to the EVLAP group and consequently the costs were smaller for those not undergoing phlebectomy during their primary procedure (P=0.022).

	Cost item	EVLA alone	EVLTAP
Referral and diagnosis	GP clinic	£45	£45
	Outpatient visit	£169	£169
	Diagnostic Venous Duplex	£62	£62
Intervention	Operation Time (mins)	50 (17)	61 (17)
	Medical personnel	£118 (40)	£145 (40)
	Nursing personnel	£83 (28)	£101 (28)
	Procedure costs	£354	£354
After care	Follow up DUS	£52	£52
	Outpatient Department	£142	£142
Total cost		**£1071 (67)**	**£1026 (68)**

Table 44 Primary treatment costs. Values are mean (S.D.) (Study 4)

Secondary treatment

The costs of performing secondary procedures per patient in the first year are outlined in Table 45. Secondary procedures were required in 16 of 24 patients in the EVLA group for symptomatic residual tributaries, compared to only 1 of 25 in the EVLAP group. These secondary procedures considerably inflated the mean cost of treatment in the EVLA group making it considerably more expensive up to the end of the first year (£1277 (197) vs £1085 (70) P<0.001)

	Procedure time stage	EVLA alone	EVLTAP
Secondary treatment costs	Procedure time	46 (20) mins	35 min
	Personnel costs	£185 (80)	£141

	Procedure costs	£51	£51
	Aftercare	£142	£142
	Total	**£378 (80)**	**£334**

Table 45 Costs of secondary treatment (Study 4)

Costs after one year

After 1 year, there was no difference in those requiring further additional procedures in either group, as shown in Table 43. Breakdown of the actual costs of these treatments are detailed in Table 46.

	Procedure time stage	EVLA alone	EVLTAP
2 - 5 years	Referral & diagnosis	£276	£276
	Procedure time	45 (45 -58) mins	77 (29-132) mins
	Personnel costs	£181 (181-233)	£437 (115-838)
	Procedure costs	£51 (51-355)	£334 (76-668)
	Aftercare	£194	£194
	Total	**£711 (675-979)**	**£1197 (641-1949)**

Table 46. Mean (s.d.) additional costs accrued per additional treatment episode. (Study 4)

Overall treatment costs

As shown in Figure 67 and Table 47, while EVLA alone was initially less expensive compared to EVLTAP , at five years EVLA alone was overall more expensive when compared to EVLA,(£1399 (£1289-1848) vs £1105 (£1066-1186) P=0.003). This

difference was maintained in a sensitivity analysis of discounting with both 0% (P=0.004) and 5 % (P=0.003).

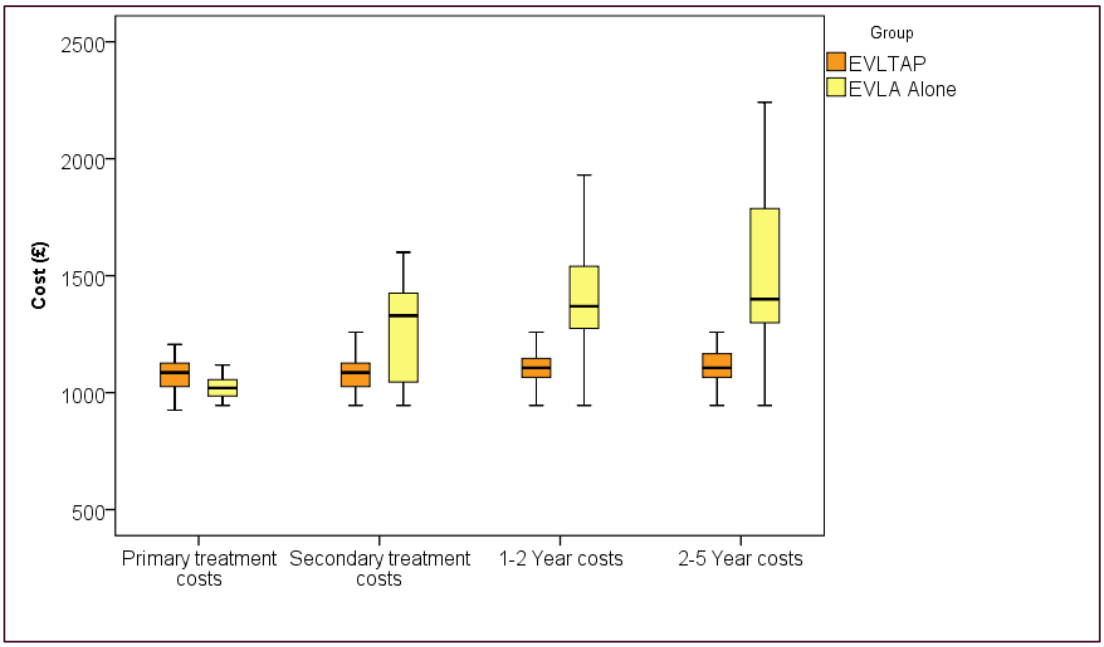


Figure 67 Cost of treatment over five years with 3.5% discounting of costs per annum. (Study 4)

Time point	EVLA alone	EVLTAP	P
Primary treatment	£1026 (68)	£1071 (67)	0.022*
Secondary treatment	£1277 (197)	£1085 (70)	<0.001*
1- 2 year	£1369 (1273-1570)	£1106 (1056-1156)	0.005
2 - 5 year	£1399 (1289-1848)	£1106 (1066-1186)	0.003

Table 47 Median (IQR) Treatment costs of EVLA alone and EVLTAP (Study 4)

*mean (s.d.) t-test

Monte Carlo Simulation

Figure 68 demonstrates the results of the Monte Carlo simulation. This shows that at the threshold of re-intervention observed in the clinical trial (i.e. 16 of 24 patients or 66.7%, the probability of EVLA being more cost-effective than EVLAP was only

0.12. Even a threshold allowing a 5% intervention rate would be unlikely to be more cost effective, with a probability estimated at 0.29%. This is drastically less the re-intervention rate which was observed in the trial.

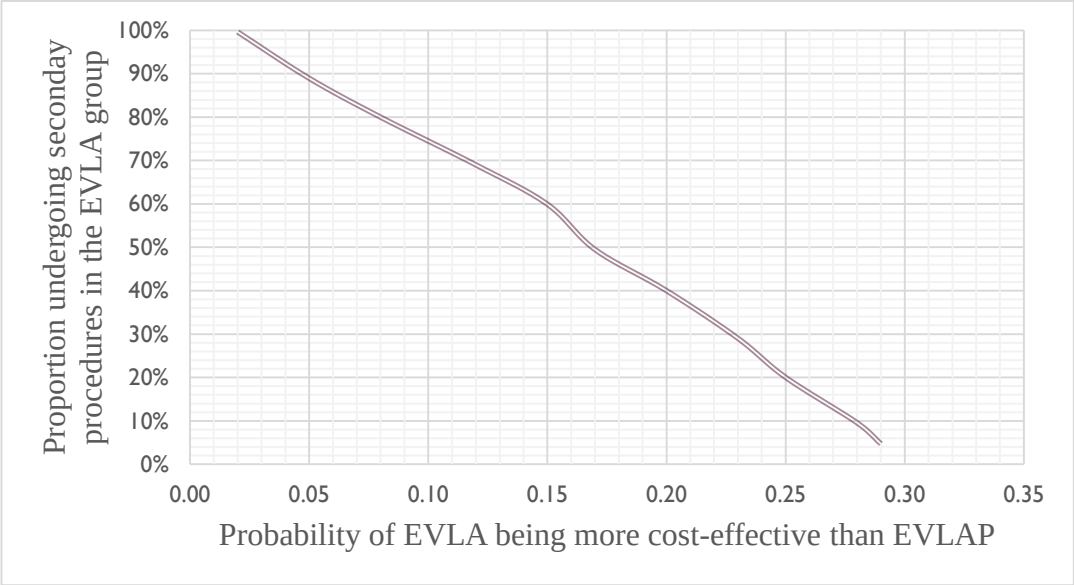


Figure 68 Monte-Carlo simulation of 10,000 patients undergoing EVLTAP or EVLA alone and thresholds for sequential intervention (Study 4)

4.5 Study 5 - Long term clinical and technical outcomes of treating those with and without complications of SVI

The HELP-1 Study is detailed on page 151. Of the 280 equally randomised patients, 191 patients were preoperatively identified as clinical grade C2 and 76 patients were identified as clinical grade C3-C4. The proportion of those undergoing treatment was similar between the groups. Of those in the group C2, 96 (50%) underwent conventional surgery and 95 (50%) underwent EVLA and of those in the group C3-C4, 36 (47%) underwent conventional surgery and 40 (53%) underwent EVLA. The proportion was similar in both groups (P=0.670 χ^2-test).

Both groups were similar in age, height, and treatment limb side. In comparison however, the C2-C3 group were older (mean age C2, 47 (13) years vs C3-C4 53 (13), P=0.001 *t*-test), more likely to be male (Female C2, 136 (71.2%); C3-C4, 32 (42%) P<0.001 χ^2-test) and of a much greater BMI (mean BMI C2 25.2 (3.8) vs C3-C4 29.0 (5.1) P<0.001 *t*-test). It was also noted that those with C3-C4 disease were much more likely to smoke or have smoked in the past (Smoking history C2, 47 (47%); C3-C4, 45 (63%), P=0.045 χ^2-test). The preoperative axial vein diameter was larger in the C3-C4 group at the level of the groin (mean diameter C2, 7.9mm (2.4); C3-C4 9.9mm (3.1), P<0.001 *t*-test) and at the level of the knee (mean diameter C2 6.3mm, (1.8); C3-C4, 7.5mm (1.6), P<0.001 *t*-test).

After one year, 168 (88%) C2 and 71 (93%) C3-C4 had attended review, at two years 165 (86%) C2 and 66 (87%) C3-C4 patients had attended review and at five years 154 (81%) C2 and 59 (78%) C3-C4 patients had attended review. Follow up losses were similar at one year (P=0.189 χ^2-test), two years (P=0.582 χ^2-test) and five years (P=0.922 χ^2-test).

Generic Quality of Life - Short Form - 36

As detailed in Table 48, and shown in Figure 69 to Figure 84, both groups were similar in their baseline SF-36 measurements, except Physical Function which was significantly lower (worse) at baseline among those with C3-C4 disease compared to those with C2 disease. Over the period of the study significant statistical and clinically relevant differences were noted in the early post treatment period, favouring those with C2 disease in Physical Function, Role Physical, Body Pain and General Health. However, in the long term while some significant statistical benefit

remained in the C2 group (Physical Function and General Health) the difference in the scores, and therefore clinical relevance, became less marked at five years.

C2 group

An early impairment was detected in six of the eight SF-36 domains at one week. (Physical Function P<0.001, Role Physical P<0.001, Body Pain P=0.009, General Health P=0.004, Social Function P=0.009, Mental Health P=0.005; WSR). By six weeks all six domains had recovered, of which three had improved above their baseline (Physical function P=0.001, Body pain P<0.001, Mental health P<0.001; WSR.). While not impacted at one week, the SF-36 Vitality domain was also significantly improved at six weeks (P<0.001 WSR).

Between 12 weeks and two years, the SF-36 domains of Physical Function, Role Physical, Body Pain, General Health, Vitality, Mental Health had sustained their improvement. Social function also improved above baseline during this period, and Role Emotional showed some temporary improvement at one year.

At five years, the domains of Physical function, Body Pain and Mental Health continued to show substantial improvement whereas the domains of Role Physical, General Health, Vitality and Role Emotional had returned to pre-intervention baseline levels. At five years the domain of Social function was substantially worse compared to pre-treatment baseline levels.

C3-C4 group

Due to already low SF-36 domains at baseline, only three domains were noted to be significantly impaired after treatment (Role Physical P<0.001, Body pain P=0.004 and Social function P=0.002 WSR). At six weeks, all three had recovered with one domain, Body Pain, also showing a substantial above baseline improvement

(P=0.016 WSR). Of the remaining five domains only two showed improvement at six weeks (Physical Function P=0.001, Vitality P=0.005 WSR)

After 12 weeks the improvement seen in Physical Function and Body Pain and Vitality had subsided by two years. Of the remaining five domains, only Mental Health showed some temporary improvement at one year, with the remaining domains largely unchanged.

At five years no domain was significantly improved compared to pre-treatment baseline levels. Only one domain, Social Function, showed any significant difference and this was much lower compared to baseline

Intergroup comparison

Patients with a clinical grade of C2 reported a much higher (better) score in the domain of Physical Function compared to those with C3-C4 disease. One week after treatment, Physical Function was significantly impaired among those in the C2 group but remained stable among those in the C3-C4 group. This had the overall effect that both groups became similarly impaired in Physical Function scores. After one week both groups improved substantially, but scores were consistently much higher among those with C2 disease. By two years the improvement in Physical Function had begun to wane amongst those with C3-C4 disease, but continued to be high in those with C2 disease.

At 12 weeks, the two domains of Role Physical and Body Pain were significantly better among those with C2 disease compared to those with C3-C4 disease. While only momentary in the domain of Role Physical, this benefit was sustained for two years in the Body Pain domain. The General Health domain was also noted diverge at two years, with much better scores among the C2 group at two and five years

(Figure 76) . This was due to maintained benefit amongst those with C2 disease whereas those with C3-C4 disease reported that their General Health domains scores had returned to baseline levels.

Early improvements in SF-36 scores were largely similar between the two treatment groups aside from Body Pain (Figure 74) which had improved significantly more among those with C2 disease at 12 weeks (mean improvement C2 +15 (21) vs C3-C4 +6 (25) P=0.007 *t*-test), at one year (mean improvement C2 +15 (25) vs C3-C4 +6 (25) P=0.011 *t*-test) and at two years (mean improvement C2 +11 (25) vs C3-C4 +2 (20) P=0.021 *t*-test). This difference was likely both statistically and clinically significant. However at five years, despite a slight deterioration among those with C3-C4 disease, both groups had become similar in change from baseline scores (mean improvement C2 +6 (28) vs C3-C4 -0.2 (27) P=0.166 *t*-test). It was also noted that General Health had begun to deteriorate among those with C3-C4 disease by two years (mean improvement C2 +3 (15) vs C3-C4 -3 (21) P=0.018 *t*-test) and this continued to five years (mean improvement C2 +1 (17) vs C3-C4 -5 (18) P=0.035 t-test) (Figure 76). There was no significant difference in improvement of the remaining SF-36 domains

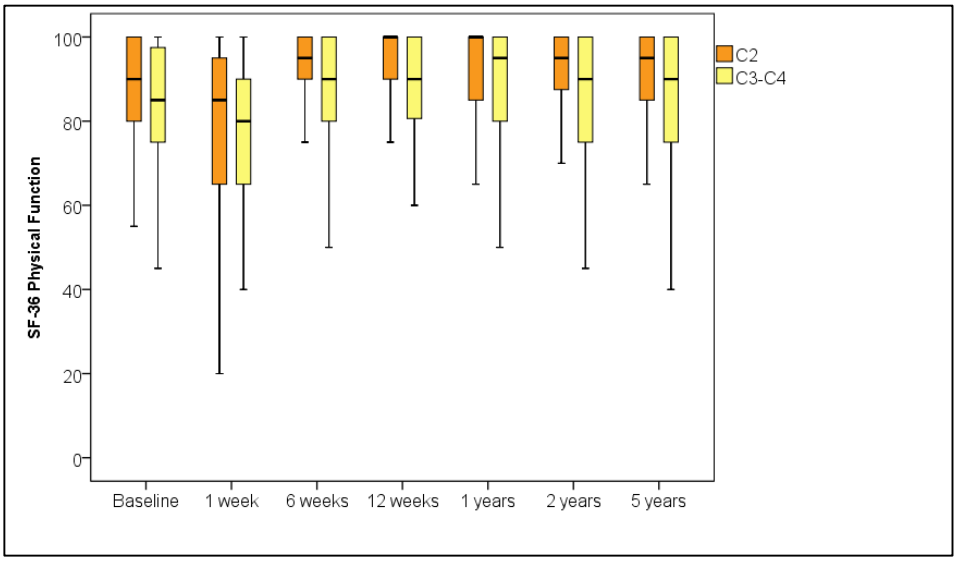


Figure 69 SF-36 Physical Function scores over five years (Study 5)

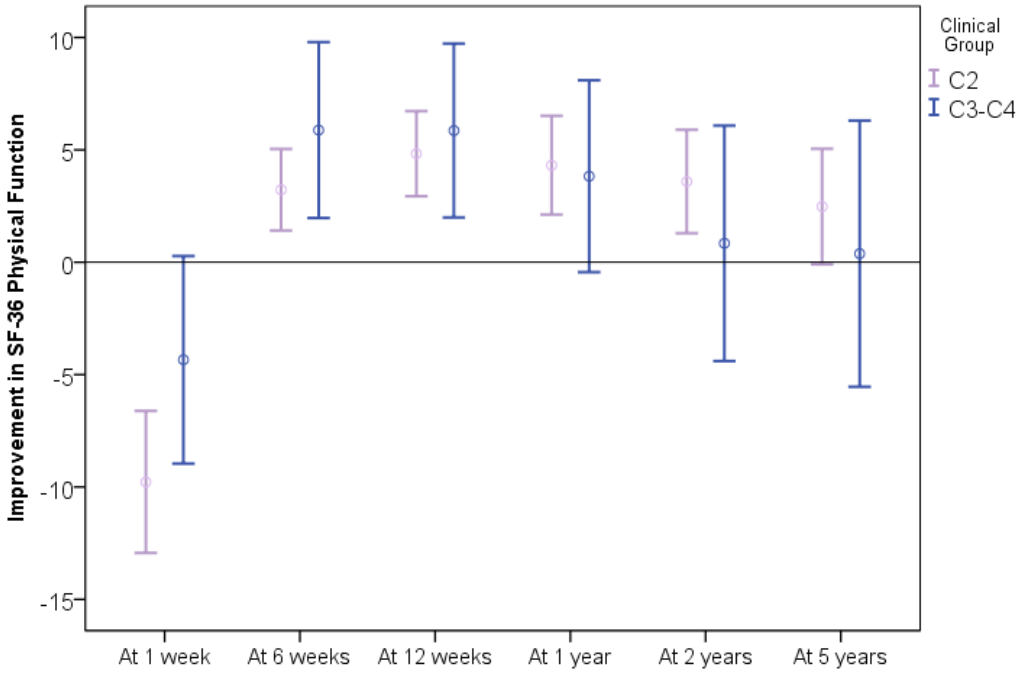


Figure 70 Improvement in SF-36 Physical Function scores over five years (Study 5)

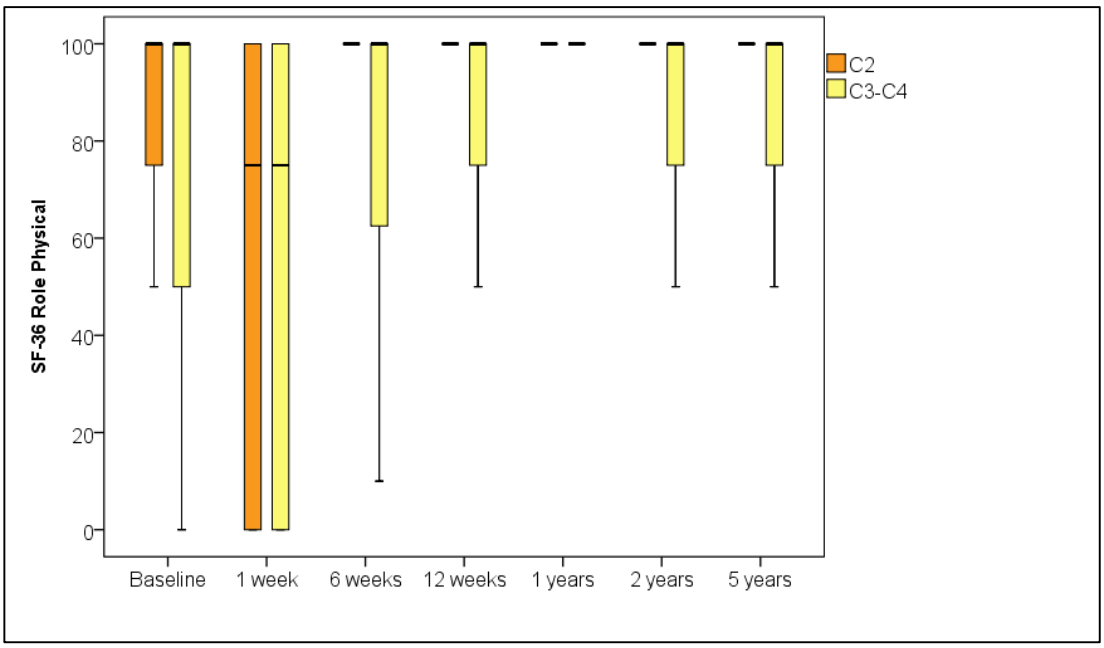


Figure 71 SF-36 Role physical scores over five years (Study 5)

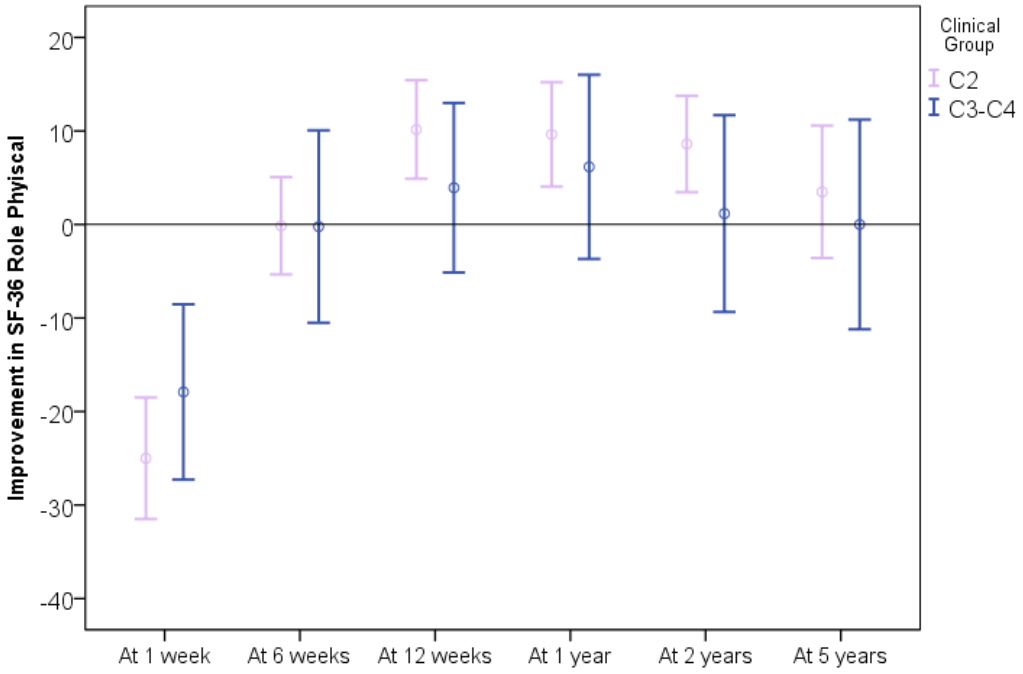


Figure 72 Improvement in SF-36 Role Physical scores over five years (Study 5)

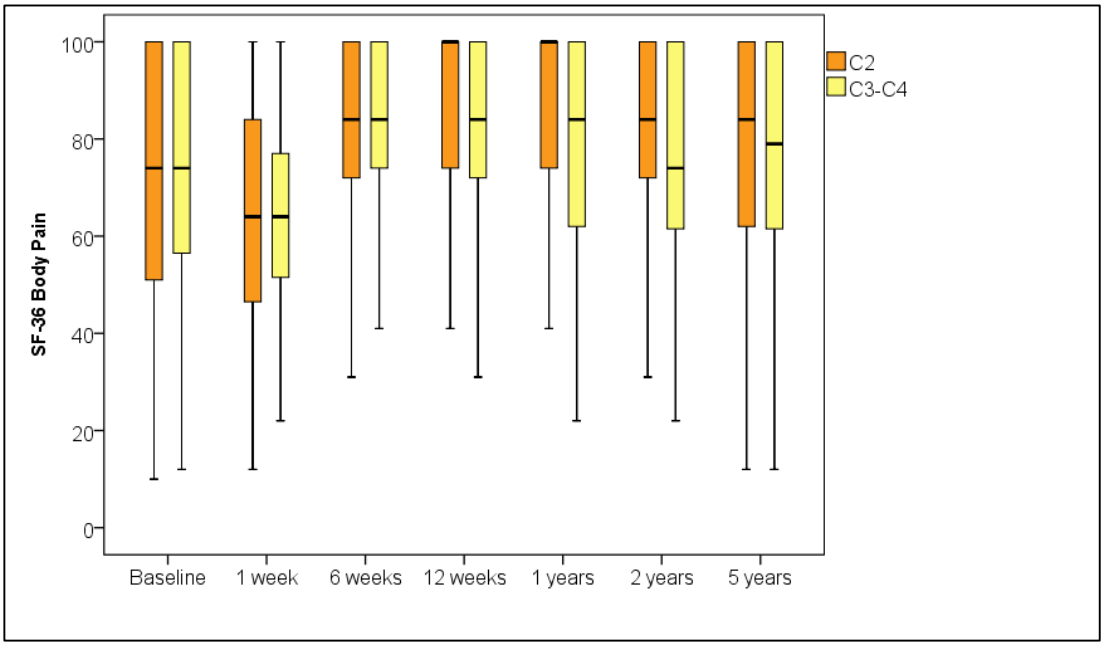


Figure 73 SF-36 Body Pain scores over five years (Study 5)

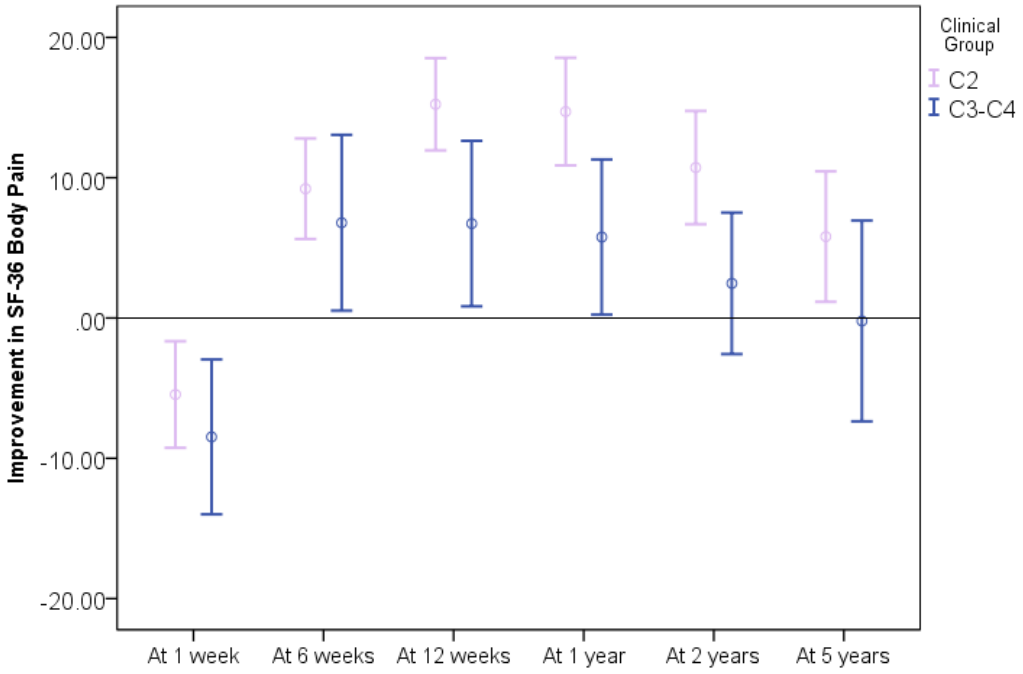


Figure 74 Improvement in SF-36 Body pain scores over five years (Study 5)

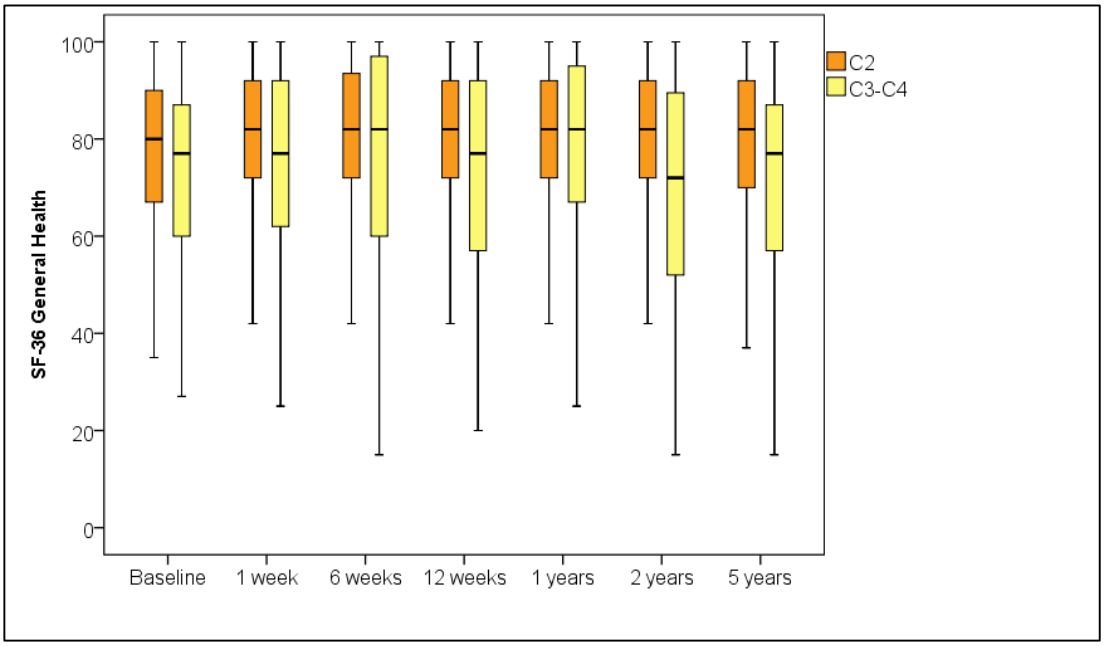


Figure 75 SF-36 General health scores over five years (Study 5)

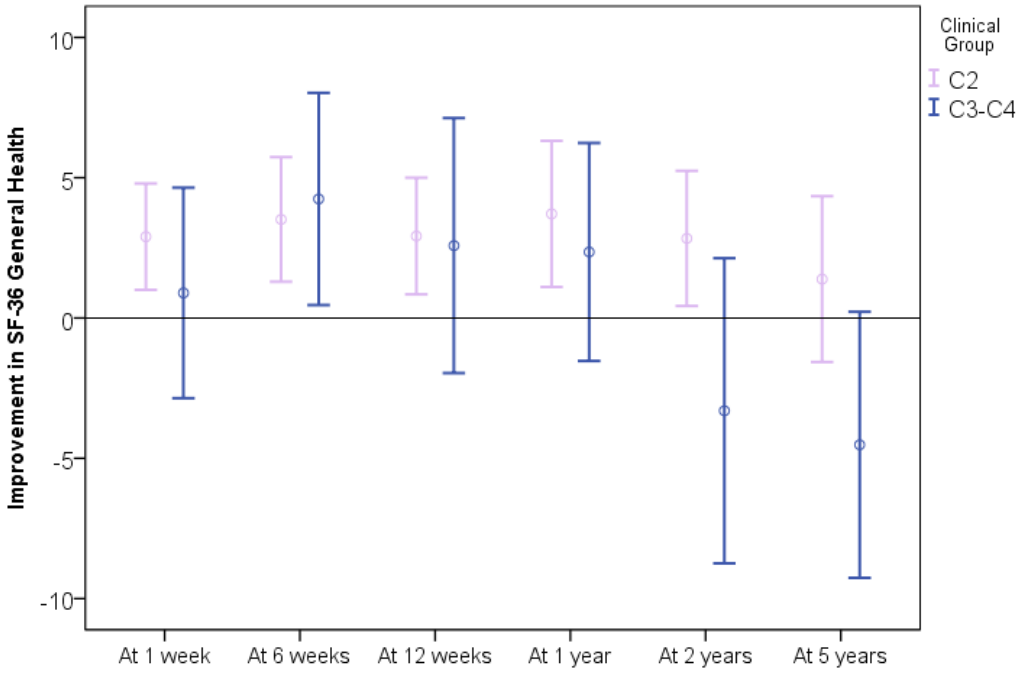


Figure 76 Improvement in SF-36 General health scores over five years (Study 5)

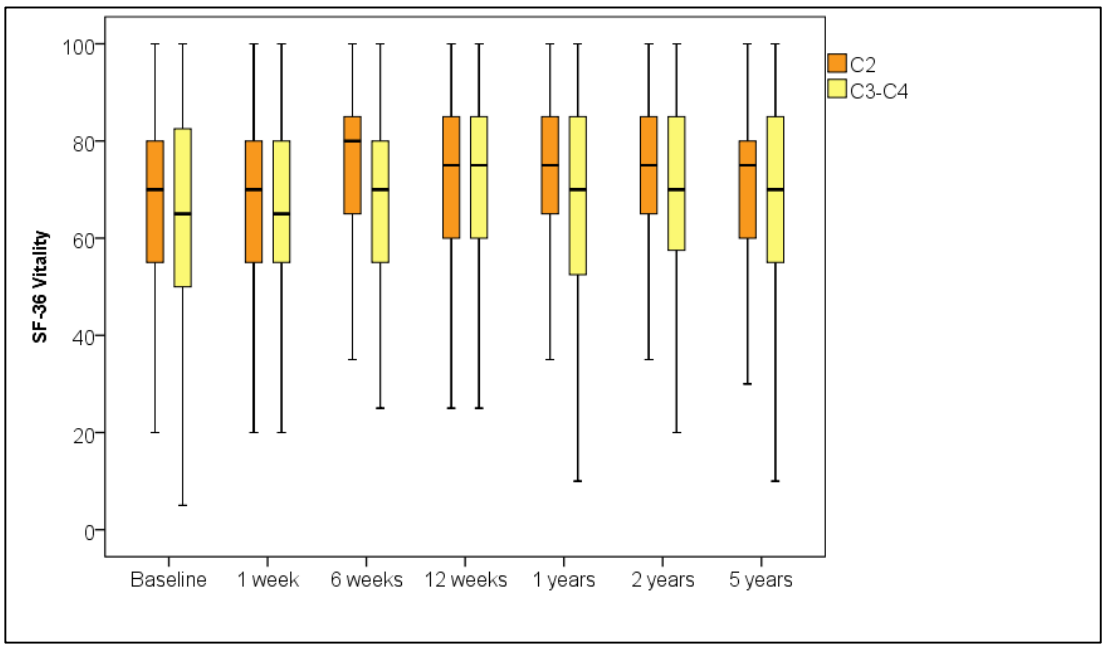


Figure 77 SF-36 Vitality scores over five years (Study 5)

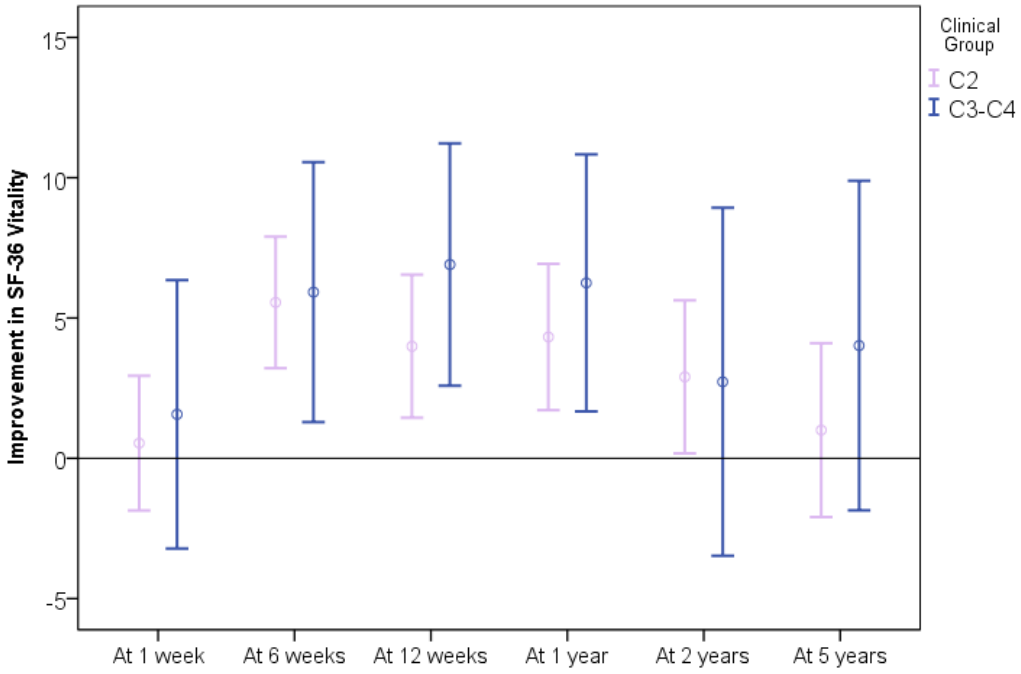


Figure 78 Improvement in SF-36 Vitality scores over five years (Study 5)

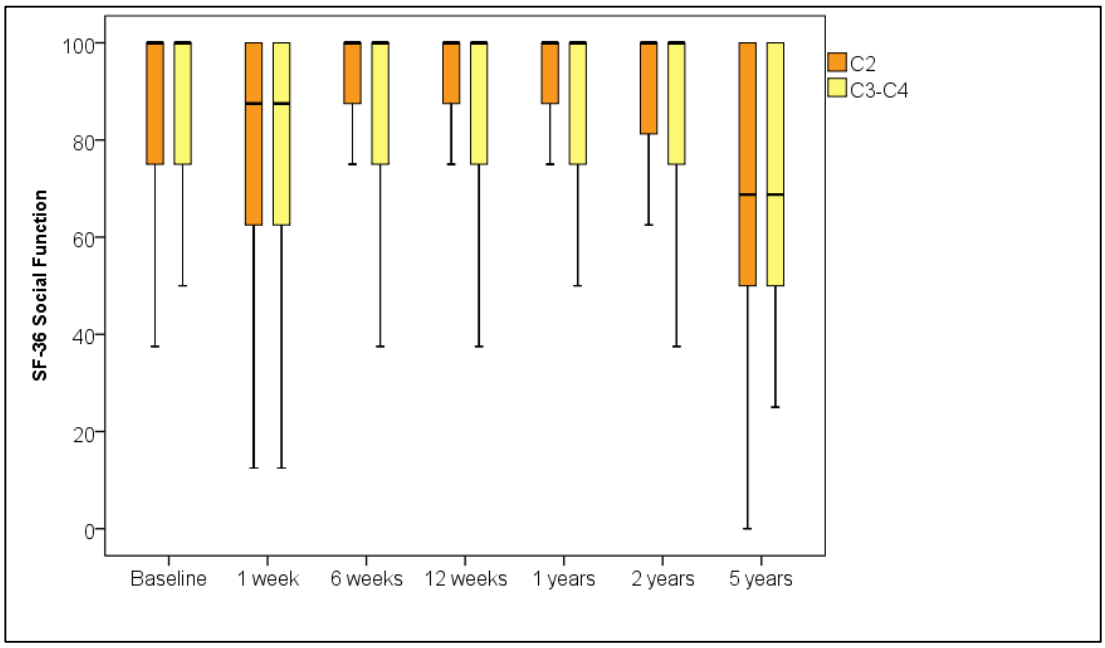


Figure 79 SF-36 Social Function scores over five years (Study 5)

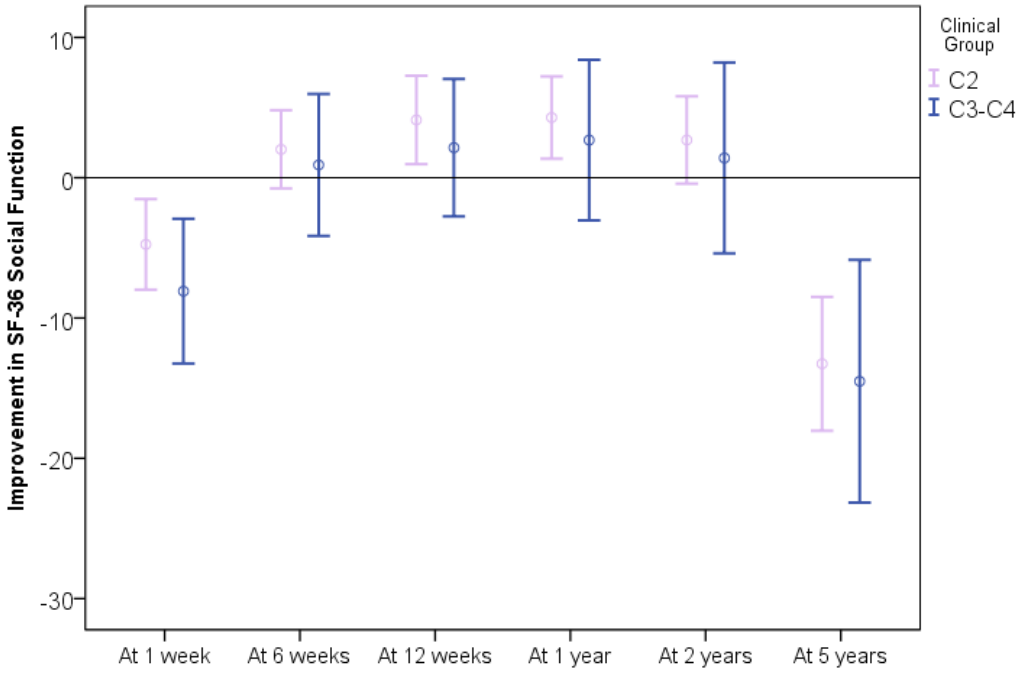


Figure 80 Improvement in SF-36 Social Function scores over five years (Study 5)

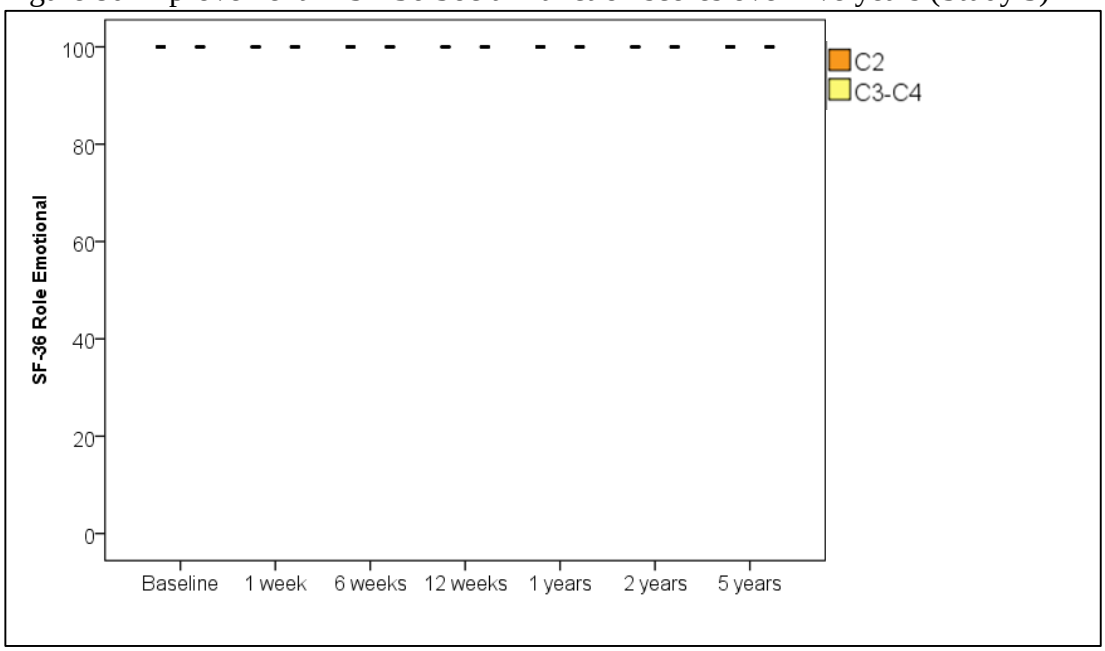


Figure 81 SF-36 Role Emotional scores over five years (Study 5)

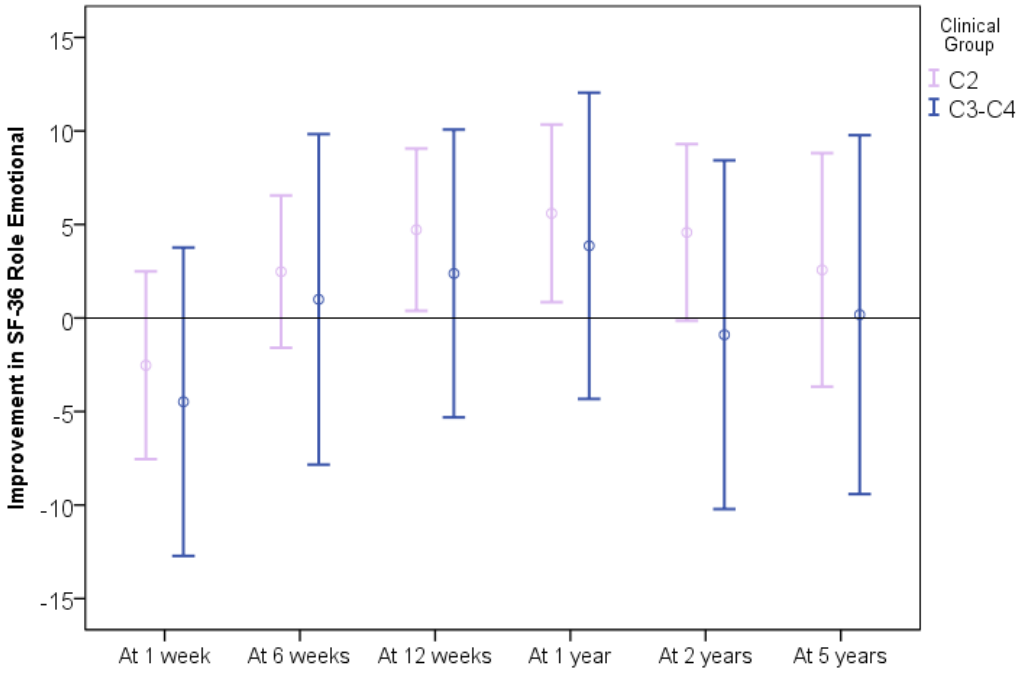


Figure 82 Improvement in SF-36 Role emotional scores over five years (Study 5)

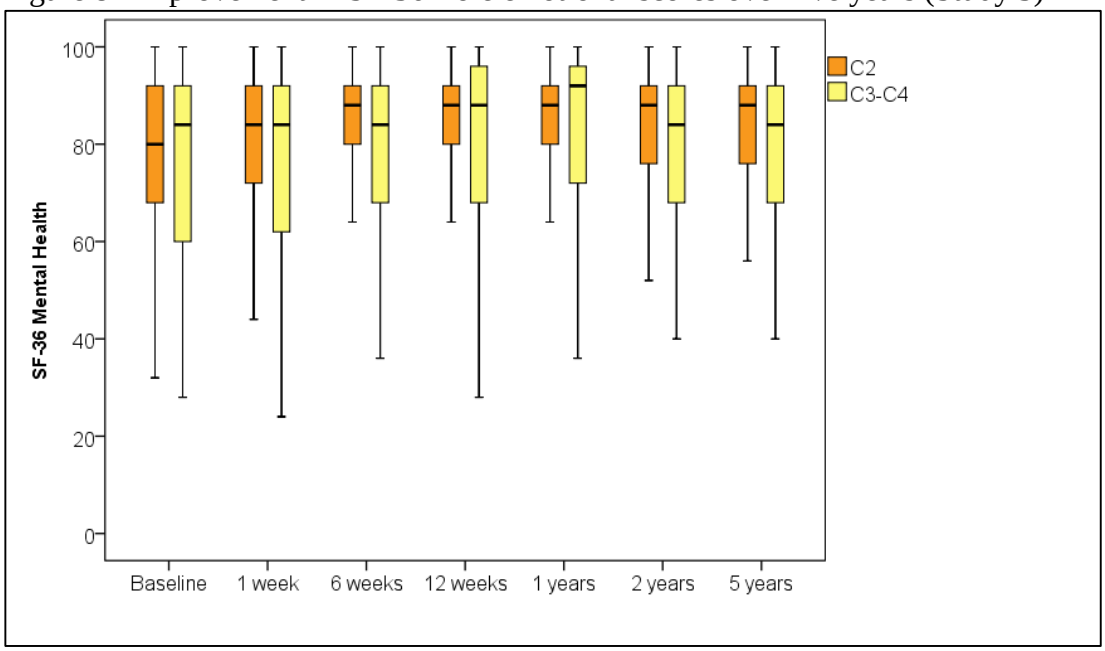


Figure 83 SF-36 Mental Health scores over five years (Study 5)

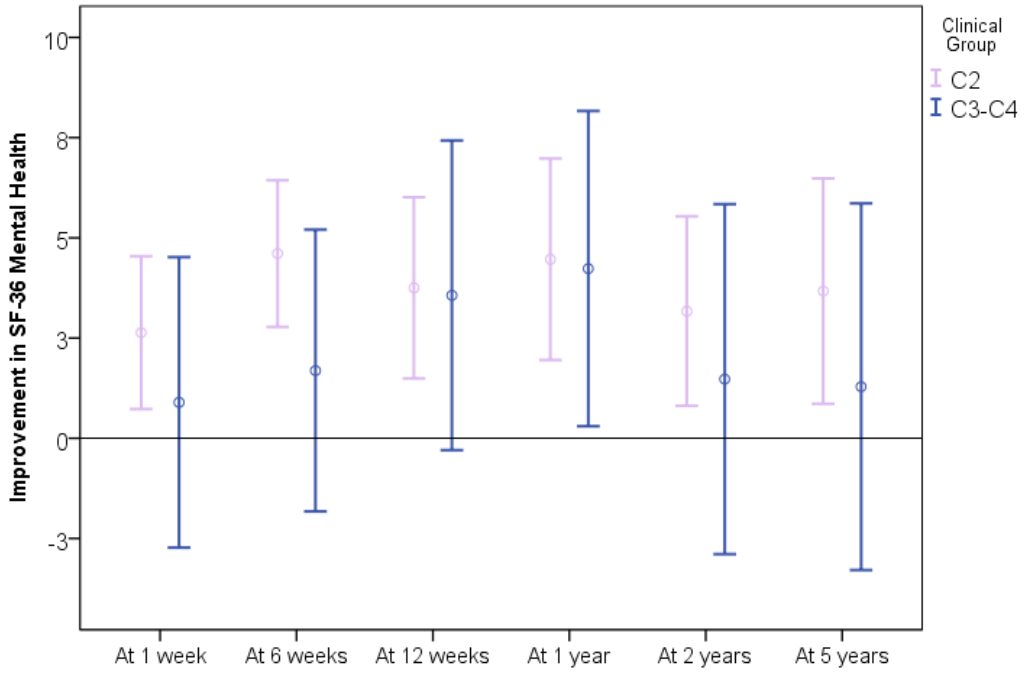


Figure 84 Improvement in SF-36 Mental Health scores over five years (Study 5)

SF-36 Domain	Weeks	C2	C3-C4	P
Physical Function	0	90 (80-100)	85 (75-99)	0.020
	1	85 (65-95)	80 (65-90)	0.471
	6	95 (90-100)	90 (80-100)	0.033
	12	100 (90-100)	90 (80-100)	0.016
	52	100 (85-100)	95 (80-100)	0.082
	104	95 (85-100)	90 (75-100)	0.001
	260	95 (85-100)	90 (75-100)	0.010
Role Physical	0	100 (75-100)	100 (50-100)	0.541
	1	75 (0-100)	75 (0-100)	0.683

	6	100 (100)	100 (56-100)	0.164
	12	100 (100)	100 (75-100)	0.008
	52	100 (100)	100 (100)	0.190
	104	100 (100)	100 (75-100)	0.050
	260	100 (100)	100 (75-100)	0.339
Body Pain	0	74 (51-100)	74 (52-100)	0.574
	1	64 (44-84)	64 (51-80)	0.741
	6	84 (68-100)	84 (74-100)	0.890
	12	100 (74-100)	84 (72-100)	0.052
	52	100 (74-100)	84 (62-100)	0.036
	104	84 (72-100)	74 (61-100)	0.025
	260	84 (62-100)	79 (61-100)	0.430
General Health	0	80 (67-90)	77 (60-88)	0.352
	1	82 (72-92)	77 (62-92)	0.083
	6	82 (72-95)	82 (59-97)	0.723
	12	82 (70-94)	77 (57-92)	0.401
	52	82 (72-92)	82 (65-96)	0.529
	104	82 (72-93)	72 (52-92)	0.025
	260	82 (69-92)	77 (57-87)	0.039
Vitality	0	70 (55-80)	65 (50-85)	0.368
	1	70 (55-80)	65 (55-80)	0.230
	6	80 (65-85)	70 (55-82)	0.149
	12	75 (60-85)	75 (59-85)	0.763
	52	75 (65-85)	70 (51-85)	0.626

	104	75 (65-85)	70 (55-85)	0.140
	260	75 (60-80)	70 (55-85)	0.655
Social Function	0	100 (75-100)	100 (75-100)	0.721
	1	88 (63-100)	88 (63-100)	0.305
	6	100 (84-100)	100 (75-100)	0.388
	12	100 (88-100)	100 (75-100)	0.262
	52	100 (88-100)	100 (75-100)	0.694
	104	100 (75-100)	100 (75-100)	0.779
	260	69 (50-100)	69 (50-100)	0.773
Role emotional	0	100 (100)	100 (100)	0.939
	1	100 (100)	100 (100)	0.844
	6	100 (100)	100 (100)	0.412
	12	100 (100)	100 (100)	0.425
	52	100 (100)	100 (100)	0.996
	104	100 (100)	100 (100)	0.263
	260	100 (100)	100 (100)	0.359
Mental Health	0	80 (68-92)	84 (60-92)	0.932
	1	84 (72-92)	84 (60-92)	0.235
	6	88 (80-92)	84 (68-92)	0.087
	12	88 (79-92)	88 (68-96)	0.825
	52	88 (79-92)	92 (72-96)	0.725
	104	88 (76-92)	84 (68-92)	0.550
	260	88 (76-92)	84 (68-92)	0.110

Table 48 Group C2 and Group C3-4 SF36 scores over five years (Study 5)

Utility Index QoL - EuroQol 5 Dimension

As shown in Figure 85, after an early deterioration at one week after treatment both clinical groups reported significantly higher (better) EQ5D scores at six weeks. This improvement continued to two years. At five years, the C3-C4 group had returned to pre-treatment EQ5D levels whereas those in the C2 group continued to be significantly better than baseline (C2, P<0.001; C3-C4, P=0.110; WSR). As shown in Figure 86, change in EQ5D was similar between the groups. Between the two groups, a slight benefit was also noted among the C2 group between 12 weeks and two years, although at five years both groups had become similar.

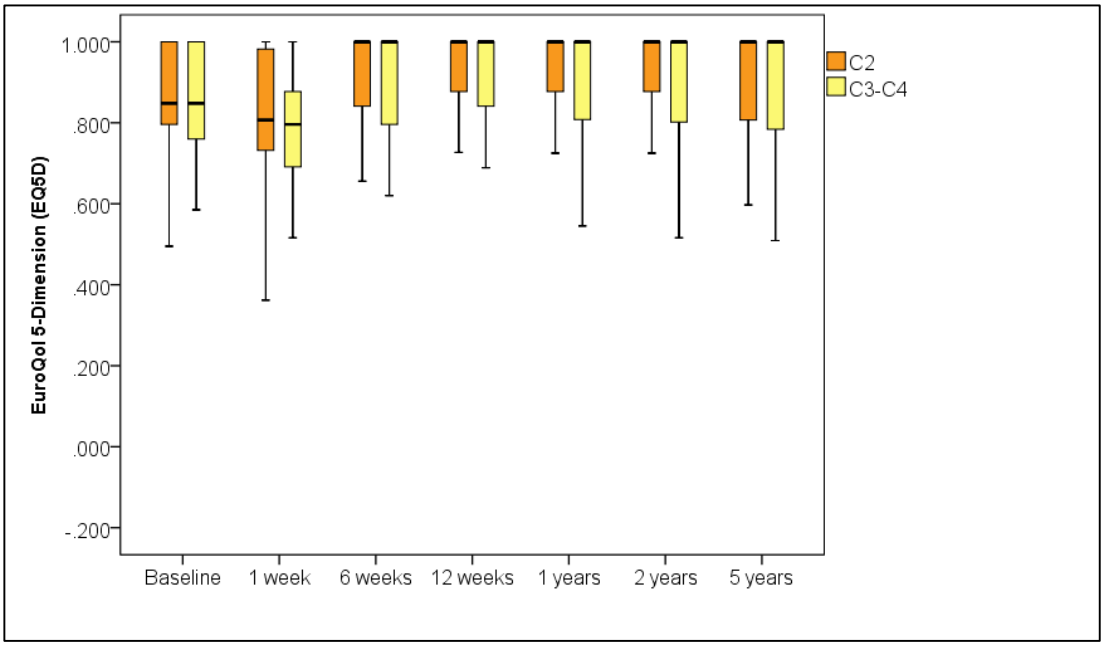


Figure 85 EQ5D scores over five years (Study 5)

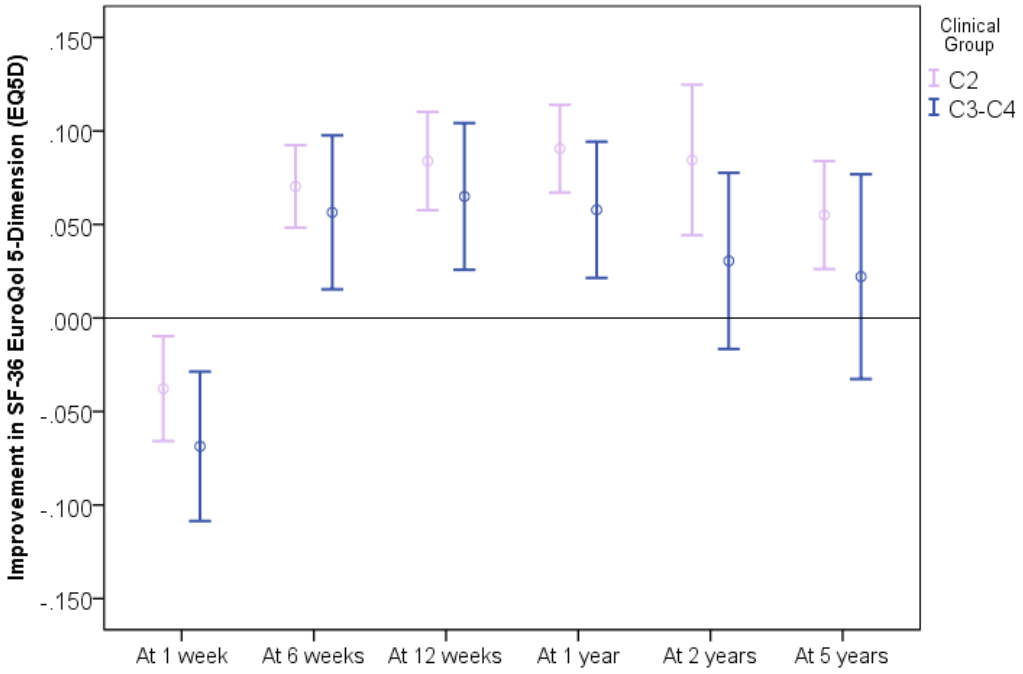


Figure 86 Improvement in EQ5D scores over five years (Study 5)

EQ5D index score	Week	C2	C3-C4	P
	Baseline	0.848 (0.796-1.000)	0.848 (0.796-1.000)	0.359
	1	0.807 (0.730-0.991)	0.796 (0.691-0.877)	0.072
	6	1.000 (0.833-1.000)	1.000 (0.796-1.000)	0.198
	12	1.000 (0.877-1.000)	1.000 (0.841-1.000)	0.047
	52	1.000 (0.877-1.000)	1.000 (0.808-1.000)	0.037
	104	1.000 (0.877-1.000)	1.000 (0.799-1.000)	0.056
	260	1.000 (0.806-1.000)	1.000 (0.778-1.000)	0.361

Table 49 Group C2 and group C3-4 EQ5D scores over five years (Study 5)

Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

As shown in Figure 87 and Figure 88, both clinical groups deteriorated at one week (C2 P<0.001, C3-C4 P=0.001 WSR). At six weeks both groups had significantly improved and this was sustained to five years. As detailed Table 50, while there was no difference in the size of the improvement between the two groups, those clinically graded at C2 reported lower (better) scores at 12 weeks, one year and two years. However at five years both groups had become similar. As shown in Figure 88, size of improvement was largely similar between both groups

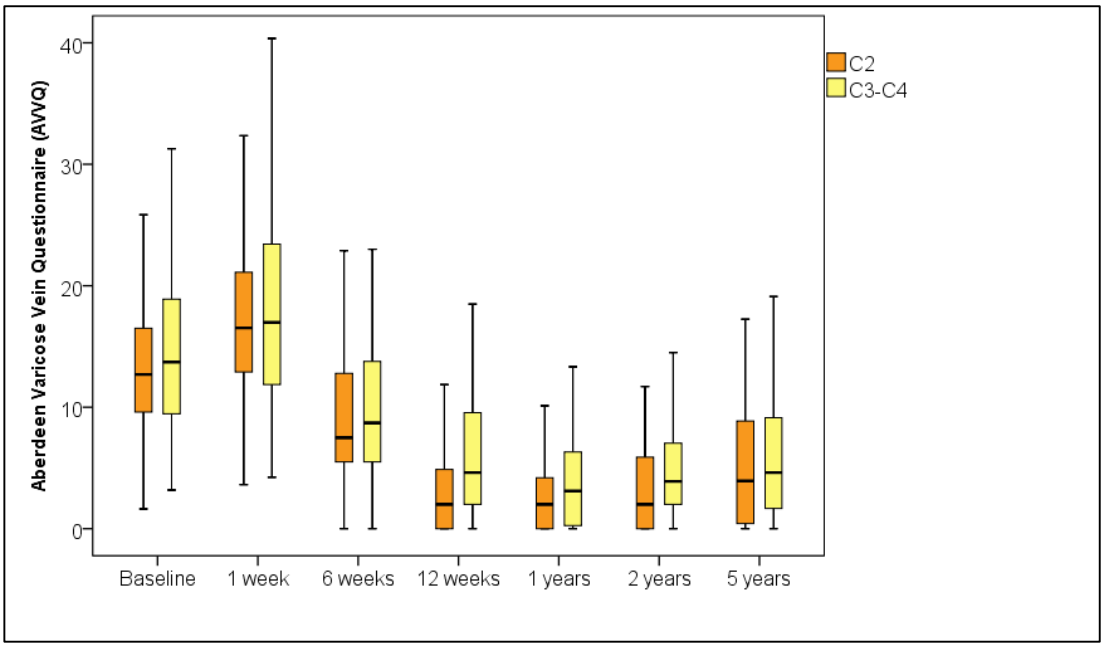


Figure 87 AVVQ scores over five years (Study 5)

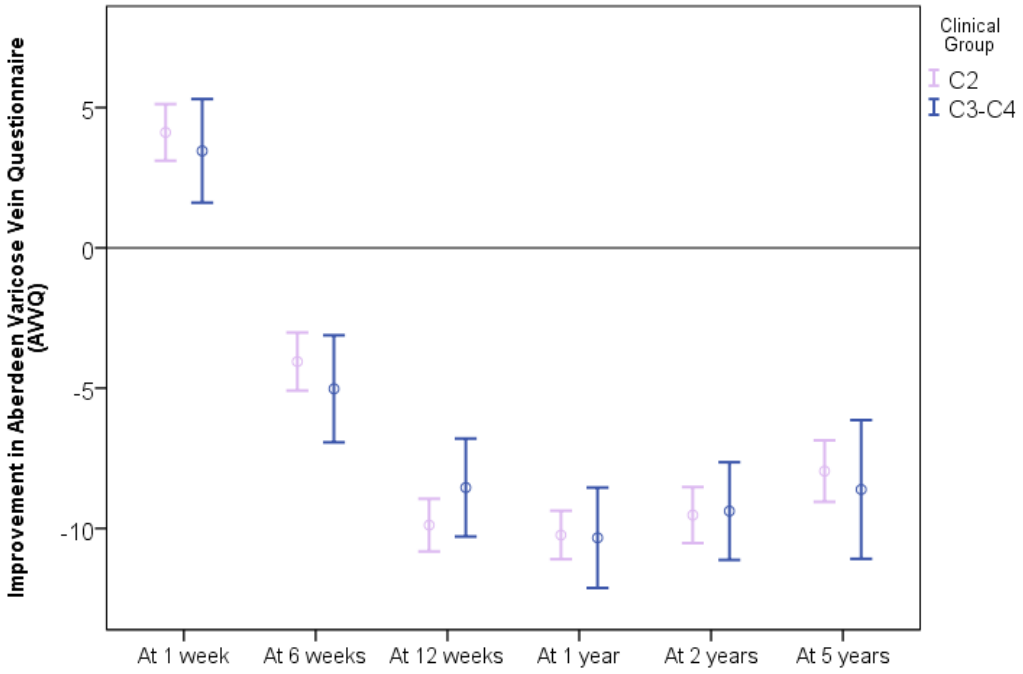


Figure 88 Improvement in AVVQ score over five years (Study 5)

AVVQ	Week	C2	C3-C4	P
	Baseline	12.7 (9.5-16.5)	13.7 (9.4-19.0)	0.131
	1	16.5 (12.8-21.2)	17.0 (11.8-23.5)	0.529
	6	7.5 (5.5-12.8)	8.7 (5.5-13.9)	0.473
	12	2.0 (0.0-5.1)	4.6 (2.0-9.6)	<0.001
	52	2.0 (0.0-4.3)	3.1 (0.2-6.5)	0.004
	104	2.0 (0.0-5.9)	3.9 (1.6-7.2)	0.008
	260	3.9 (0.3-8.9)	4.6 (1.6-9.6)	0.402

Table 50 Group C2 and group C3-4 AVVQ scores over five years (Study 5)

Utility Index QoL - SF6D

As detailed in Table 51, and shown in Figure 89 and Figure 90, both clinical groups saw an initial fall one week after treatment (C2 P<0.001, C3-C4 P=0.017). At six weeks this deficit had reversed and become positive, which was sustained to one year. At two years the C3-C4 group was no longer significantly better than baseline (C2; P<0.001, C3-C4 P=0.158 WSR). At five years both groups had lost their significant gain over their baseline levels (C2 P=0.424; C3-C4 P=0.552 WSR)

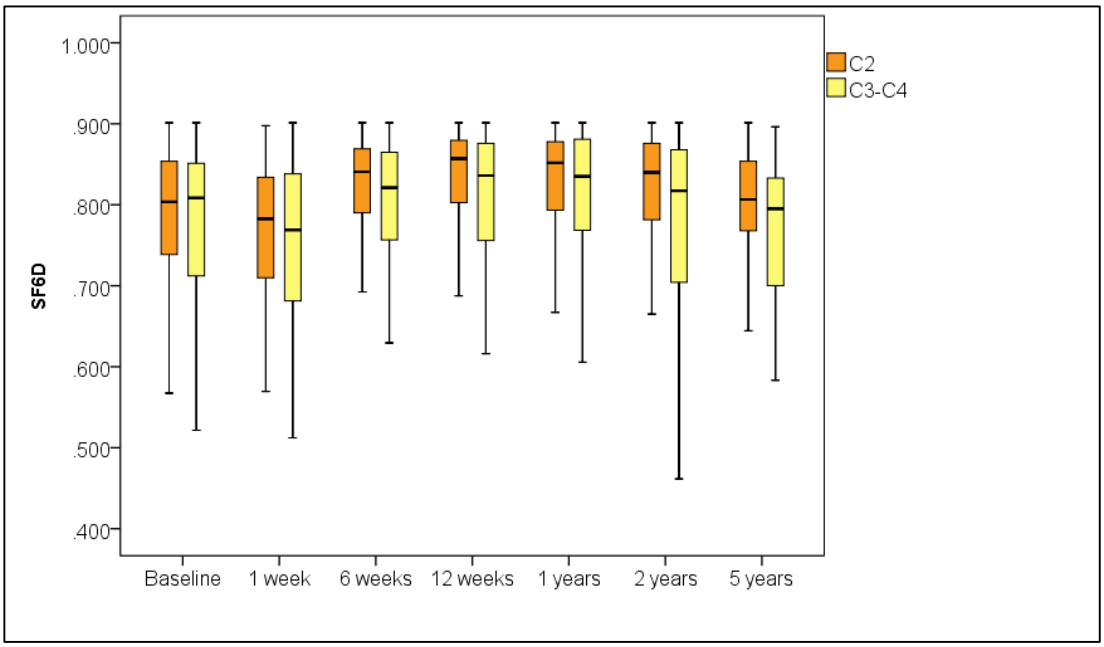


Figure 89 SF6D scores over five years (Study 5)

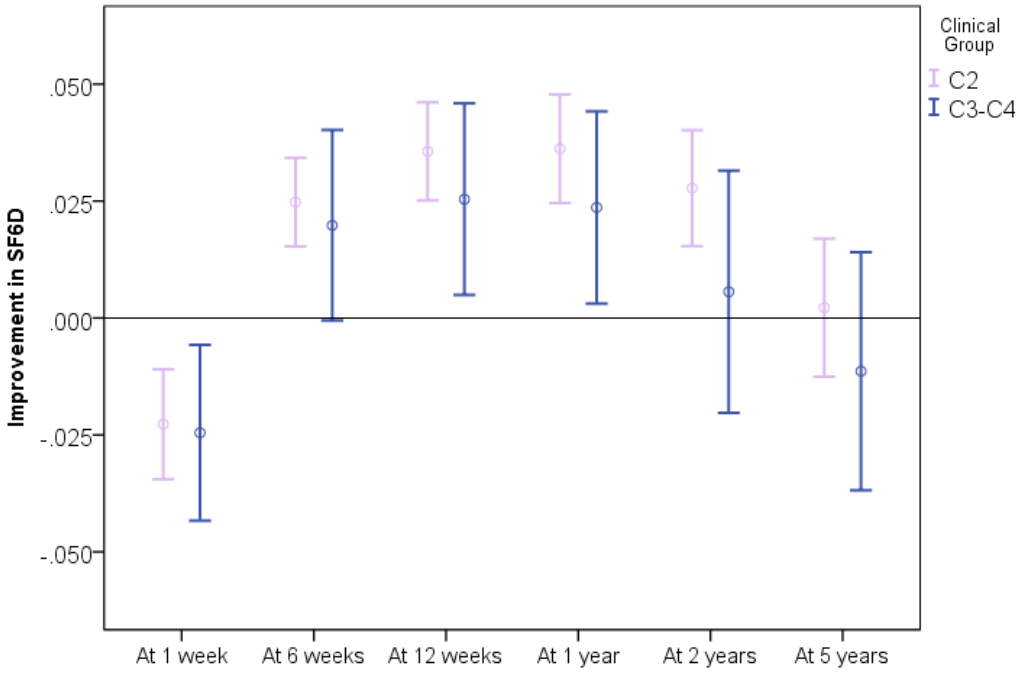


Figure 90 Improvement in SF6D score over five years (Study 5)

SF6D index	Week	C2	C3-C4	P
	Baseline	0.804 (0.737-0.854)	0.809 (0.712-0.852)	0.705
	1	0.783 (0.710-0.834)	0.769 (0.680-0.838)	0.287
	6	0.841 (0.790-0.869)	0.821 (0.754-0.865)	0.156
	12	0.857 (0.802-0.880)	0.836 (0.756-0.876)	0.113
	52	0.852 (0.793-0.878)	0.835 (0.766-0.881)	0.283
	104	0.840 (0.781-0.876)	0.817 (0.703-0.868)	0.055
	260	0.807 (0.767-0.855)	0.795 (0.700-0.833)	0.140

Table 51 Group C2 and group C3-4 SF6D scores over five years (Study 5)

Objective clinical assessment of venous disease – VCSS

As detailed in Table 52 and shown in Figure 91, VCSS was worse at baseline among the C3-C4 group compared to the C2 group. Both groups improved by 12 weeks and this was sustained to five years. VCSS was consistently lower among the C2 group compared to the C3-C4 group.

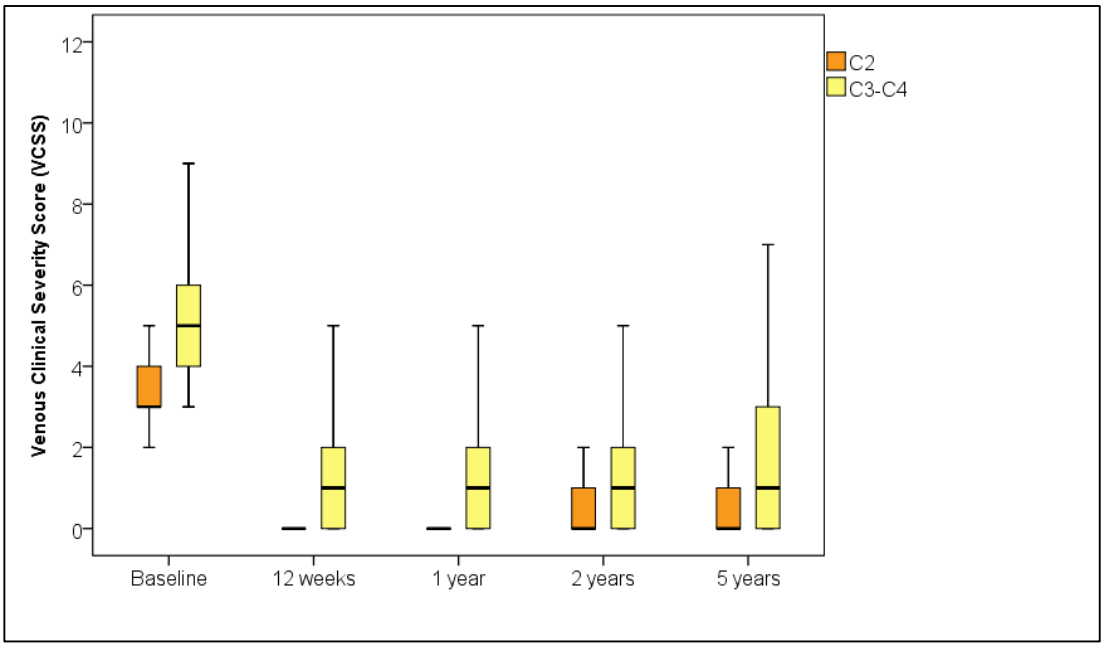


Figure 91 VCSS scores over five years (Study 5)

VCSS	Week	C2	C3-C4	P
	0	3 (3-4)	5 (4-6)	<0.001
	12	0 (0)	1 (0-2)	<0.001
	52	0 (0)	1 (0-2)	<0.001
	104	0 (0-1)	1 (0-2)	<0.001
	260	0 (0-1.5)	1 (0-3)	0.005

Table 52 Group C2 and group C3-4 VCSS scores over five years (Study 5)

Cosmetic satisfaction

As detailed in Table 53, cosmetic satisfaction was high in both clinical groups over five years.

Cosmetic satisfaction	Week	C2	C3-C4	P
	12	9 (8-10)	9 (8-10)	0.657
	52	9.5 (8-10)	9.5 (8-10)	0.972
	104	10 (8-10)	9 (7-10)	0.078
	260	10 (8-10)	9 (7-10)	0.083

Table 53 Group C2 and C3-4 cosmetic satisfaction scores over five years (Study 5)

Overall satisfaction

As detailed in Table 54, both treatment groups were similarly satisfied over five years.

Overall satisfaction	Week	C2	C3-C4	P
	12	10 (9-10)	10 (9-10)	0.455
	52	10 (9.5-10)	10 (9-10)	0.936
	104	10 (9-10)	10 (9-10)	0.389
	260	10 (9-10)	10 (9-10)	0.178

Table 54 Group C2 and C3-4 overall satisfaction scores over five years (Study 5)

Clinical recurrence

At five years, the proportion of patients experiencing a clinical recurrence was much greater amongst those clinically graded with C3-C4 disease compared to those with C2 disease (C2; 66 (43%) vs C3-C4; 41 (70%); P=0.001 χ^2-test). Of those lost to follow up, five had a known recurrence and have been discussed previously (page 176). Of these, only one patient was of C2 disease and had undergone EVLA, with the remaining four patients all being graded C3-C4 and equally randomised between treatments.

Of those reviewed at five years, the proportion of those developing clinical recurrence was much greater among those clinically graded at C3-C4 (C2; 67 (36%) vs C3-C4; 45 (65%); P<0.001 χ^2-test). This was also apparent between the two treatment groups, with those in the C3-C4 group more likely to develop clinical recurrence after Conventional surgery (C2; 40 (43%) vs C3-C4 22 (63%); P=0.040 χ^2-test) and after EVLA (C2; 27 (29%) vs C3-C4; 23 (58%); P=0.002 χ^2-test)

As shown in Figure 92, the survival distribution of clinical recurrence was significantly lower among those clinically graded C3-C4 (P<0.001 LR). Those with C3-C4 disease were estimated to develop recurrence on average at 212 weeks (95% CI 184-239 weeks) after treatment, compared to 276 weeks (95% CI 241-311 weeks) among those with C2 disease. As shown in Figure 93 and Figure 94, earlier recurrence among those in the C3-C4 group was observed following both Conventional surgery (P=0.008 LR) and EVLA (P=0.003 LR).

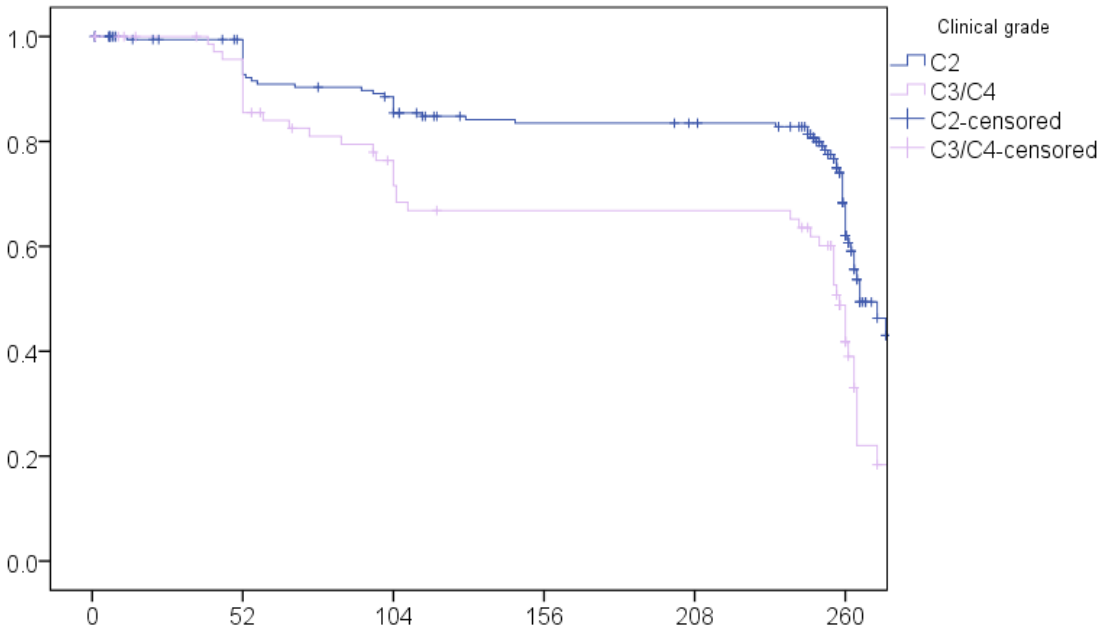


Figure 92 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from clinical recurrence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	153	138	127	125	46
C3/C4	76	59	45	41	41	15

Table 55 Patient numbers at risk at each time point for clinical recurrence (Study 5)

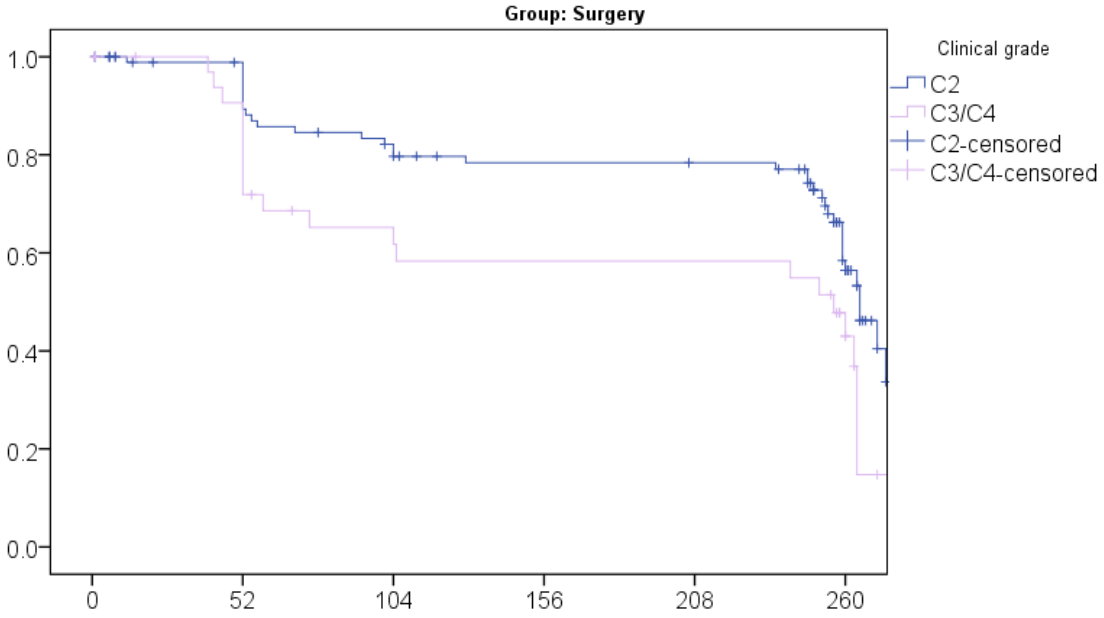


Figure 93 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from clinical recurrence after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	75	64	60	59	22
C3/C4	36	23	18	17	17	7

Table 56 Patient numbers at risk at each time point for clinical recurrence after Conventional surgery (Study 5)

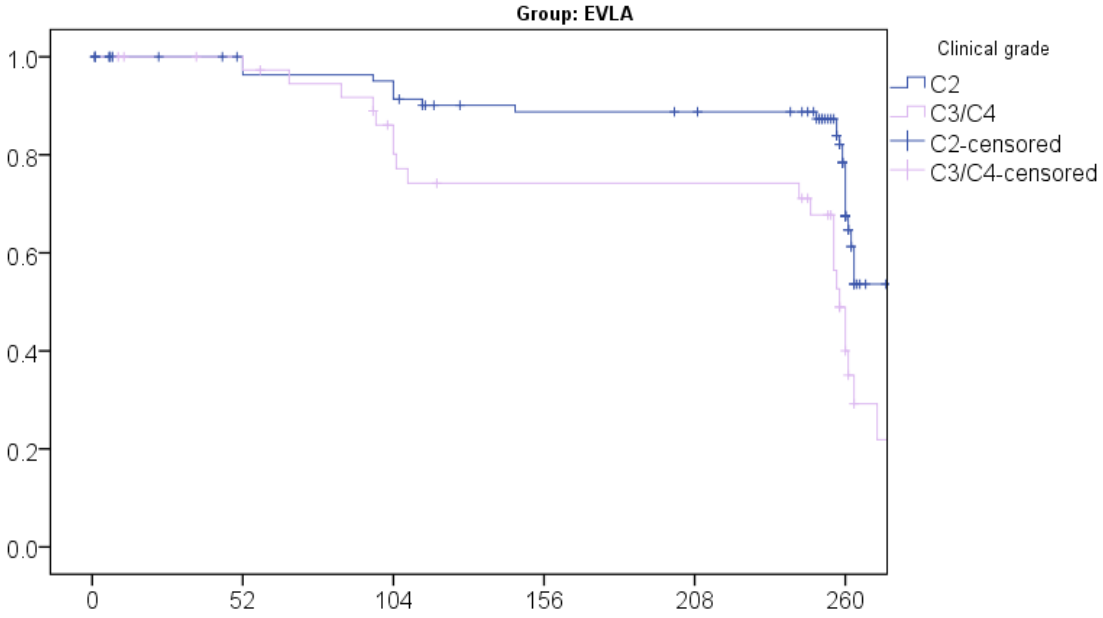


Figure 94 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from clinical recurrence after EVLA. (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	78	74	67	66	24
C3/C4	40	36	27	24	24	8

Table 57 Patient numbers at risk at each time point for clinical recurrence after EVLA (Study 5)

Clinical recurrence sensitivity analysis

A sensitivity analysis was conducted exploring possible outcomes for those lost to follow up. As detailed in Table 58, clinical recurrence was more common among the

C3-C4 group compared to the C2 group. The NNT of those with C2 disease to avoid one clinical recurrence among those C3-C4 was four (95% CI 3-9)

Assumption	C2	C3c4	P	Relative Risk	ARR
Trial data	66/154 (43%)	41/59 (70%)	<0.001	0.62 (0.48-0.79)	0.27 (0.12-0.390
1. No lost patients have recurred				0.64 (0.48-0.85)	0.19 (0.06-0.32)
2. All lost patients have recurred				0.71 (0.59-0.85)	0.22 (0.10-0.33)
3. All those C2 lost have recurred but no C3-C4 lost recurred				1.00 (0.78-1.28)	0.0002 (-0.13 -0.13)
4. All those C3-C4 lost have recurred but no C2 lost recurred				0.45 (0.36-0.57)	0.42 (0.29-0.52)

Table 58 Sensitivity analysis of clinical recurrence (ARR = Absolute Risk Reduction) (Study 5)

Symptomatic recurrence

The proportion of patients developing a symptomatic recurrence was much higher in the C3-C4 group compared to the C2 group (C2, 19/154 (12.3%); C3-C4 16/59 (27.1%); P=0.017 χ^2). As shown in Figure 95, the survival distribution of those in the C3-C4 group was much lower compared to those in the C2 group (P=0.003 LR). This was also observed following Conventional surgery (Figure 96; P=0.038) and EVLA (Figure 97; P=0.003)

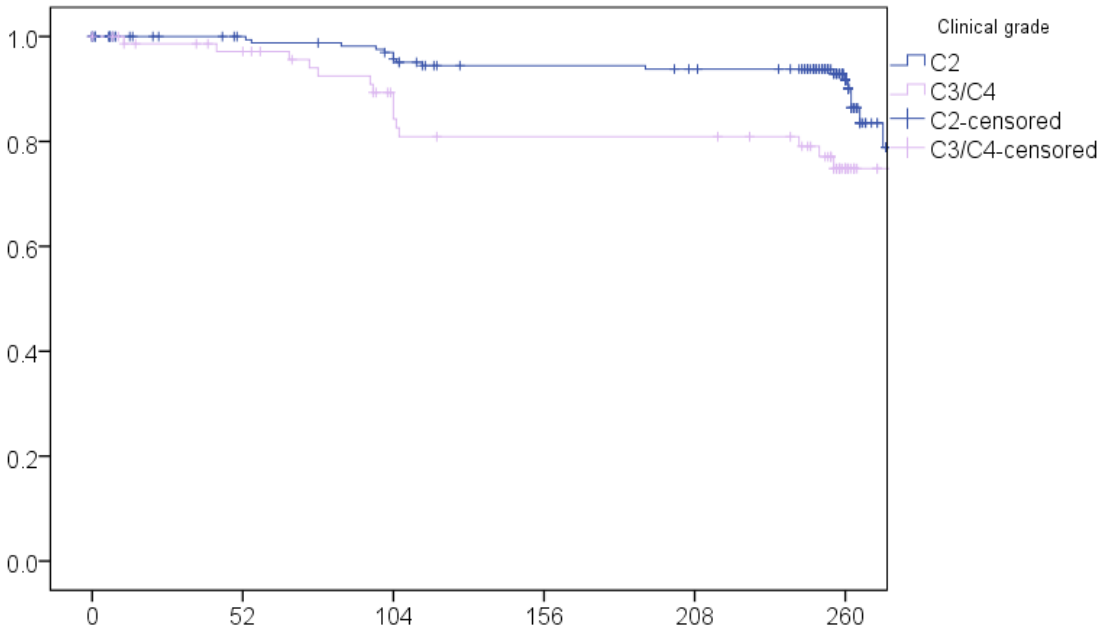


Figure 95 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from symptomatic recurrence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	164	154	144	141	57
C3-C4	76	65	50	47	47	15

Table 59 Patient numbers at risk at each time point for symptomatic recurrence (Study 5)

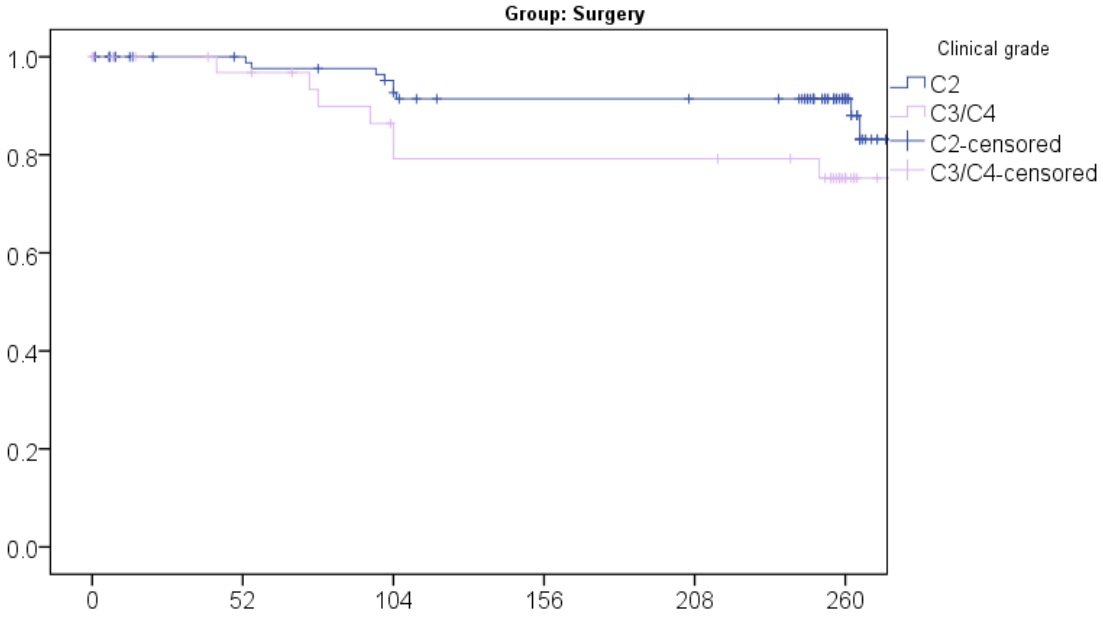


Figure 96 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from symptomatic recurrence after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	83	74	70	69	30
C3-C4	36	30	22	22	22	6

Table 60 Patient numbers at risk at each time point for symptomatic recurrence after Conventional surgery (Study 5)

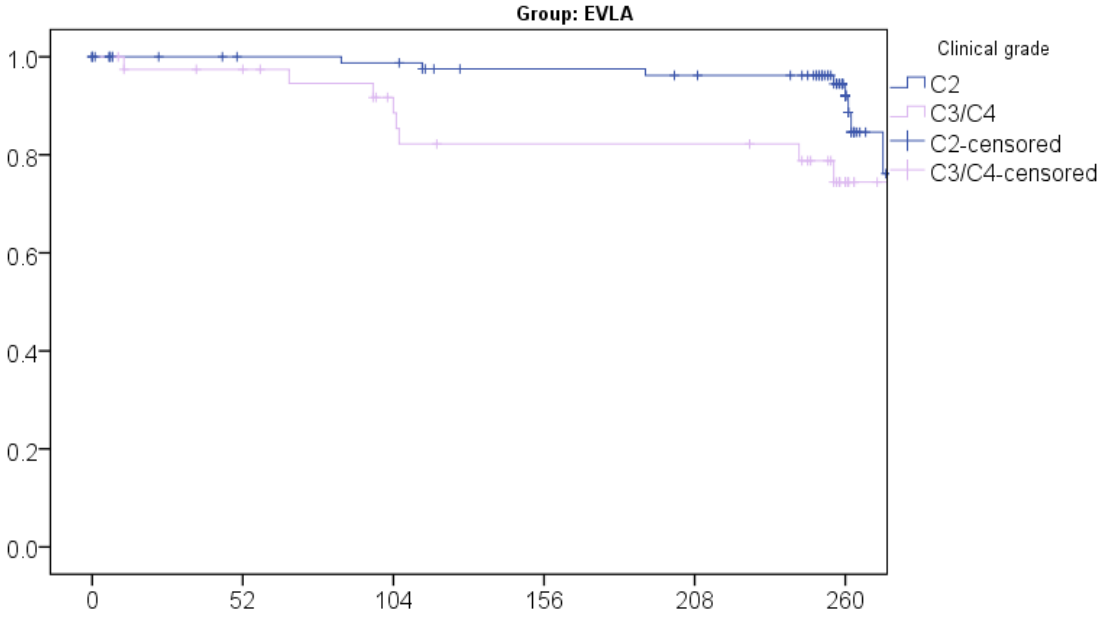


Figure 97 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from symptomatic recurrence after EVLA (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	81	80	74	72	27
C3-C4	40	35	28	25	25	9

Table 61 Patient numbers at risk at each time point for symptomatic recurrence after EVLA (Study 5)

Symptomatic recurrence sensitivity analysis

A sensitivity analysis of symptomatic recurrences is detailed in Table 62. The NNT of those with C2 disease to avoid one symptomatic recurrence with C3-C4 was 7 (95% CI 4-30)

Assumption	C2	C3-C4	P	Relative Risk	Absolute Risk Reduction
Trial data	19/154 (12.3%)	16/59 (27.1%)	0.017	0.46 (0.25-0.82)	0.15 (0.03-0.28)
1. No lost patients have recurred				0.47 (0.26-0.87)	0.11 (0.2-0.22)
2. All lost patients have recurred				0.68 (0.48-0.95)	0.14 (0.02-0.27)
3. All C3-C4 lost have recurred but no C2 lost recurred				0.23 (0.14-0.38)	0.33 (-0.22-0.45)
4. All C2 lost have recurred but no C3-C4 lost recurred				1.39 (0.86-2.27)	-0.08 (-0.19-0.04)

Table 62 Sensitivity of symptomatic recurrence (Study 5)

Patterns of clinical recurrence

Recurrence at the groin

As shown in Figure 98, those with C3-C4 disease were more likely to experience groin recurrence (P<0.001 LR) and, while the survival distribution was significantly different following EVLA (Figure 99, P<0.001 LR), after Conventional surgery both disease groups appeared similar (Figure 100, P=0.065 LR).

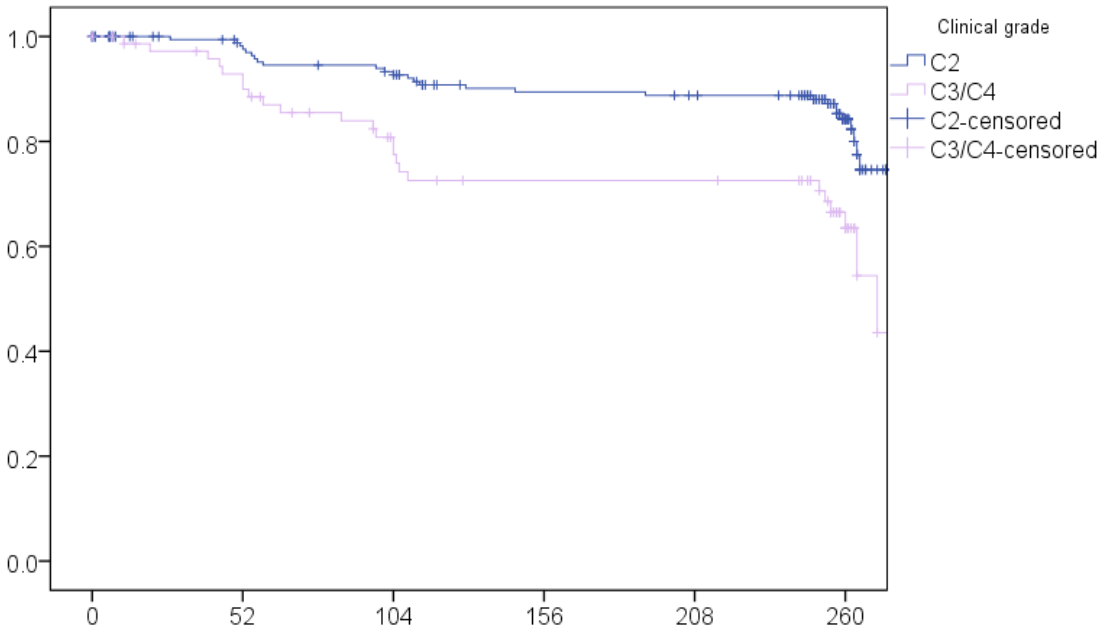


Figure 98 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recurrence at the groin (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	160	149	134	131	51
C3-C4	76	62	47	42	42	15

Table 63 Patient numbers at risk at each time point for groin recurrence (Study 5)

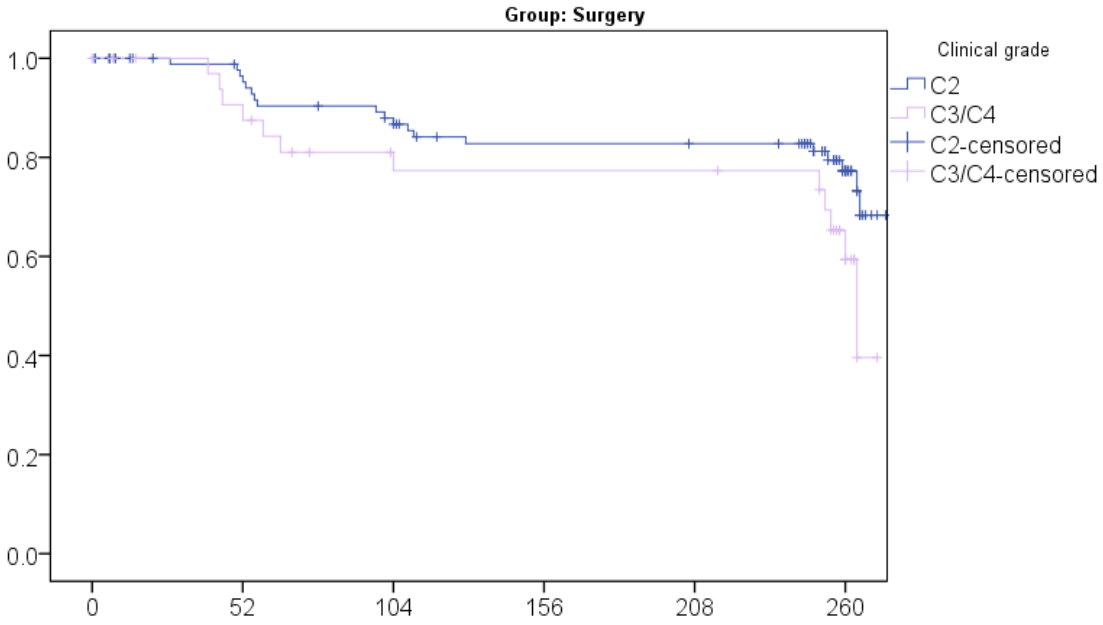


Figure 99 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recurrence at the groin following Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	79	69	62	61	25
C3-C4	36	28	21	21	21	7

Table 64 Patient numbers at risk at each time point for groin recurrence following Conventional surgery (Study 5)

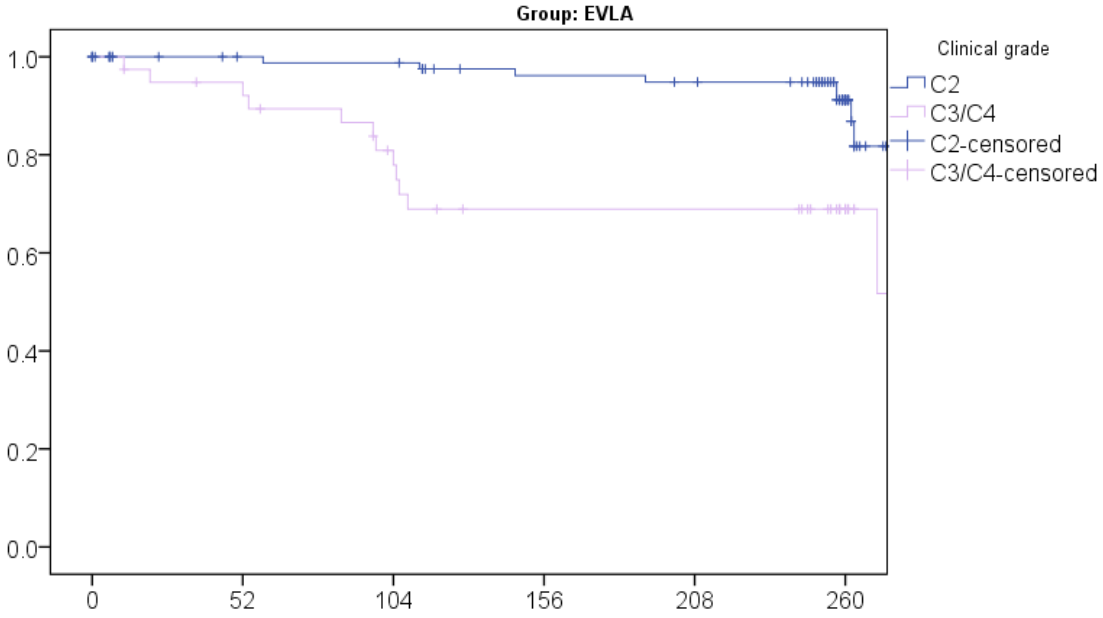


Figure 100 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from Kaplan groin recurrence following EVLA. (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	81	80	72	70	26
C3-C4	40	34	26	21	21	8

Table 65 Patient numbers at risk at each time point for groin recurrence after EVLA (Study 5)

Neovascularisation

As shown in Figure 101, neovascularisation was similar between both disease groups overall (P=0.706 LR) and also similar following Convention surgery (Figure 102 P=0.487 LR)

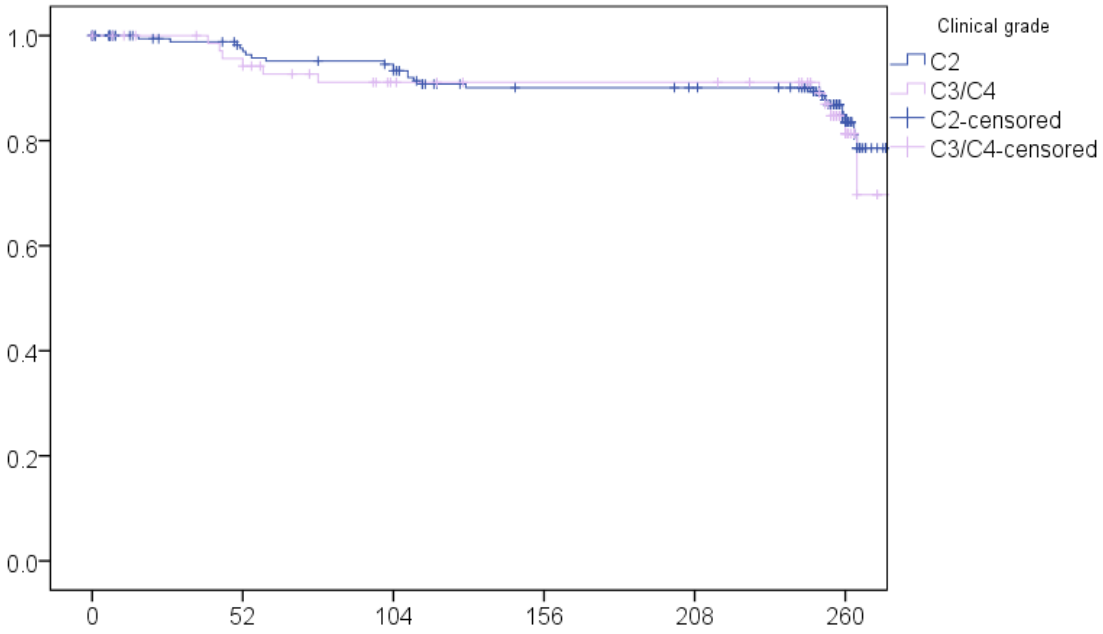


Figure 101 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from neovascularisation (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	159	150	134	132	51
C3-C4	76	64	54	51	51	16

Table 66 Patient numbers at risk at each time point for neovascularisation (Study 5)

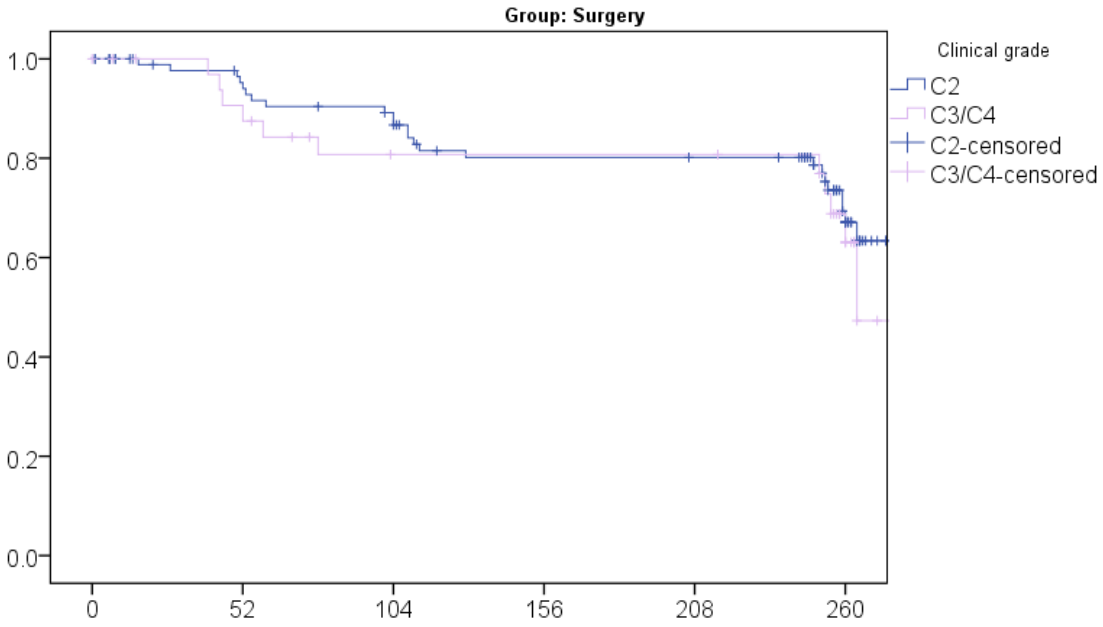


Figure 102 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from neovascularisation after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	78	69	60	59	24
C3-C4	36	28	22	22	22	8

Table 67 Patient numbers at risk at each time point for neovascularisation after Conventional surgery (Study 5)

SFJ Incompetence

As shown Figure 103, those with C3-C4 disease experienced more SFJ incompetence after treatment (P=0.001 LR) and after EVLA (Figure 104; P=0.002 LR)

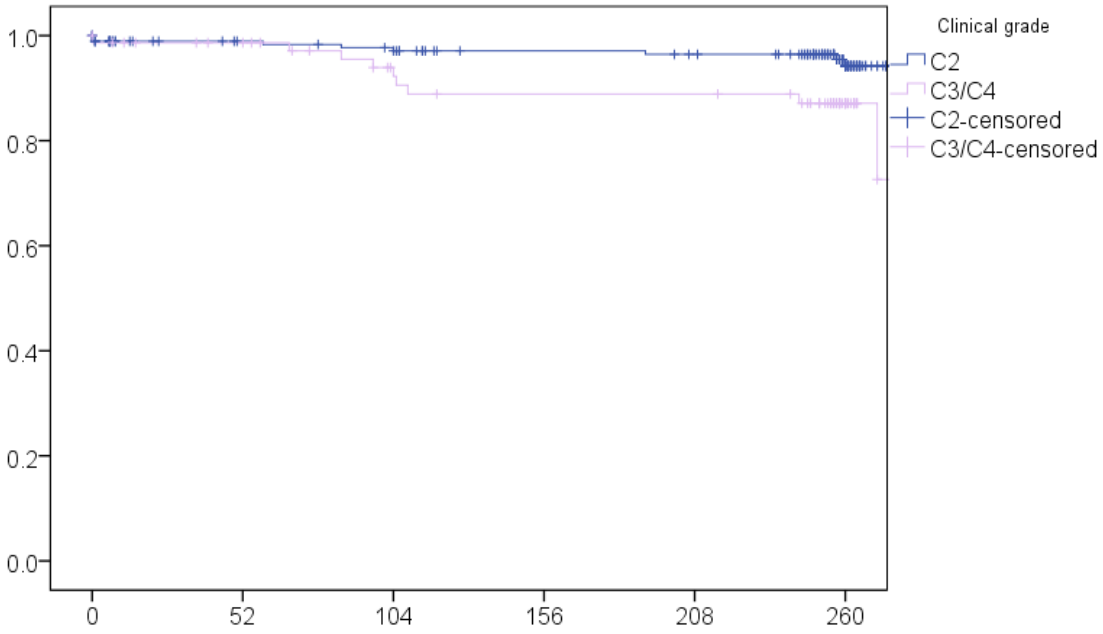


Figure 103 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from SFJ incompetence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	162	156	146	143	59
C3-C4	76	66	55	52	52	18

Table 68 Patient numbers at risk at each time point for SFJ incompetence (Study 5)

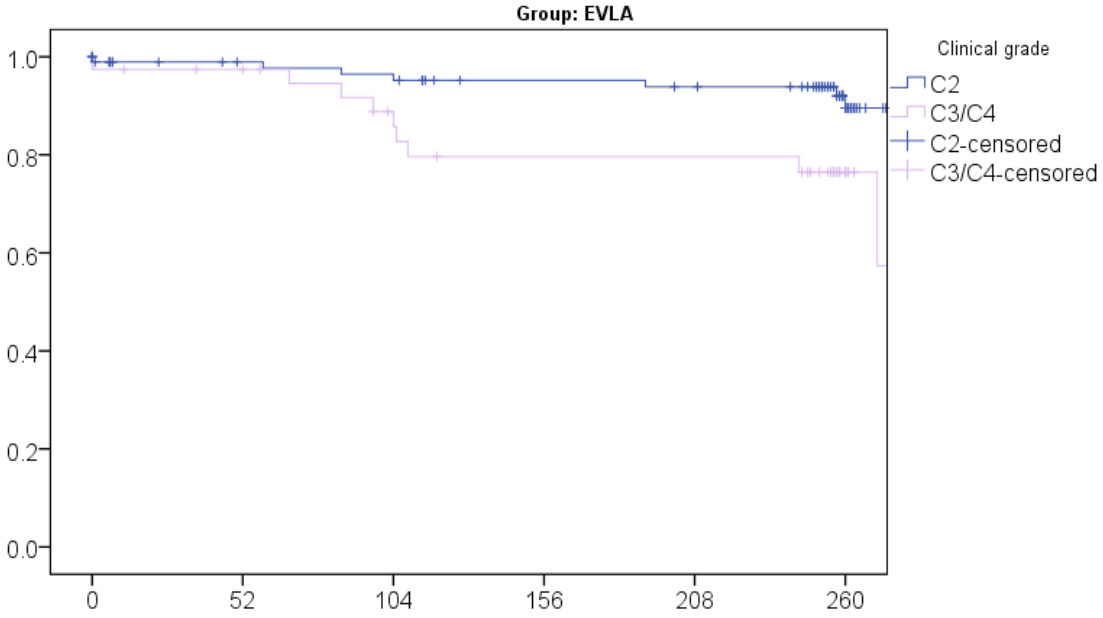


Figure 104 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from SFJ incompetence after EVLA (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	80	77	71	69	27
C3-C4	40	35	28	25	25	8

Table 69 Patient numbers at risk at each time point for SFJ incompetence after EVLA (Study 5)

Recannalisation

As shown in Figure 105, recannalisation was broadly similar between the groups (P=0.194 LR)

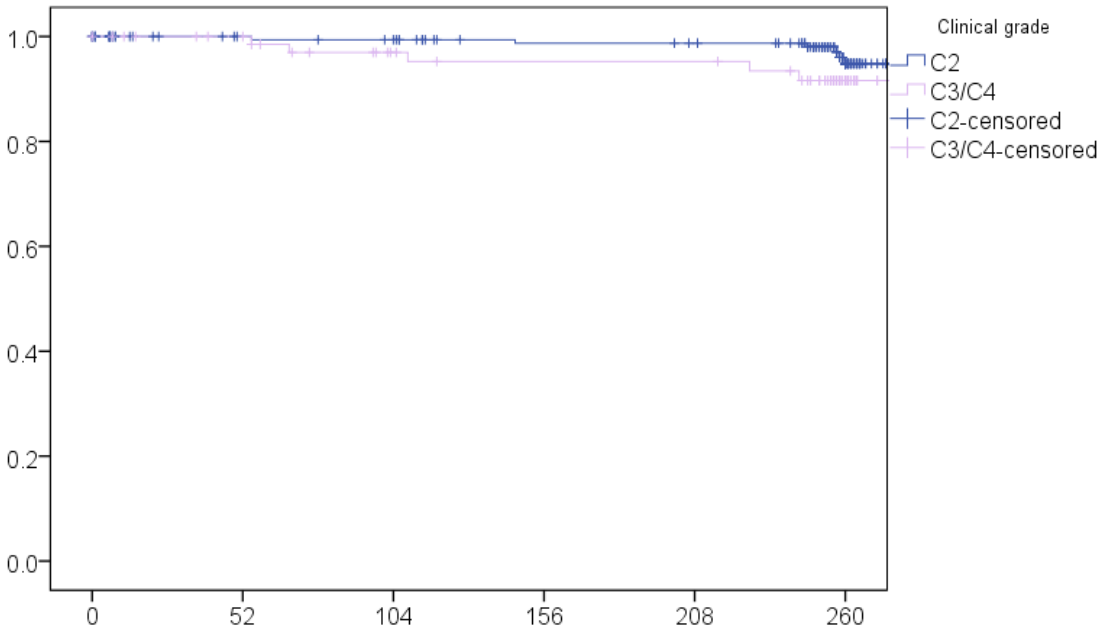


Figure 105 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recannalisation (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	164	160	149	147	59
C3-C4	76	67	57	54	54	18

Table 70 Patient numbers at risk at each time point for recannalisation (Study 5)

AASV and superficial proximal thigh veins

As shown in Figure 106, those with C3-C4 disease were much more likely to develop incompetence in the AASV and superficial proximal thigh veins (P<0.001 LR). As shown Figure 107 and Figure 108, this was also the case for those receiving Conventional surgery (P=0.004 LR) and EVLA (P=0.001 LR)

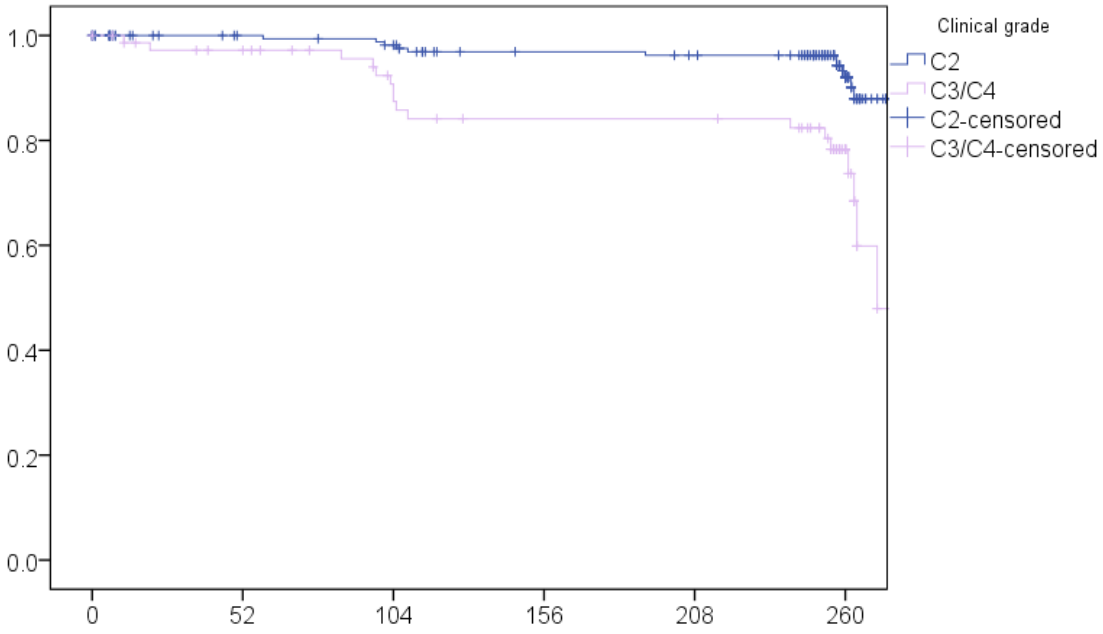


Figure 106 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from AASV and superficial proximal thigh veins (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	164	158	145	142	57
C3-C4	76	65	53	49	49	17

Table 71 Patient numbers at risk at each time point for AASV and superficial proximal thigh veins (Study 5)

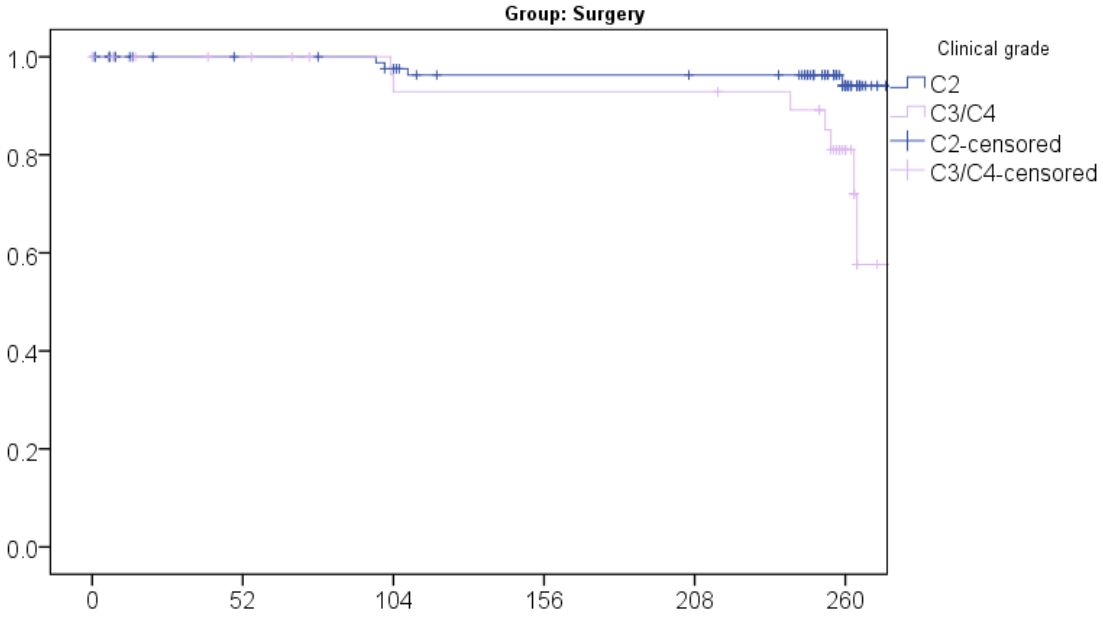


Figure 107 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from AASV and superficial proximal thigh veins after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	83	78	73	72	30
C3-C4	36	31	26	26	26	10

Table 72 Patient numbers at risk at each time point for AASV and superficial proximal thigh veins (Study 5)

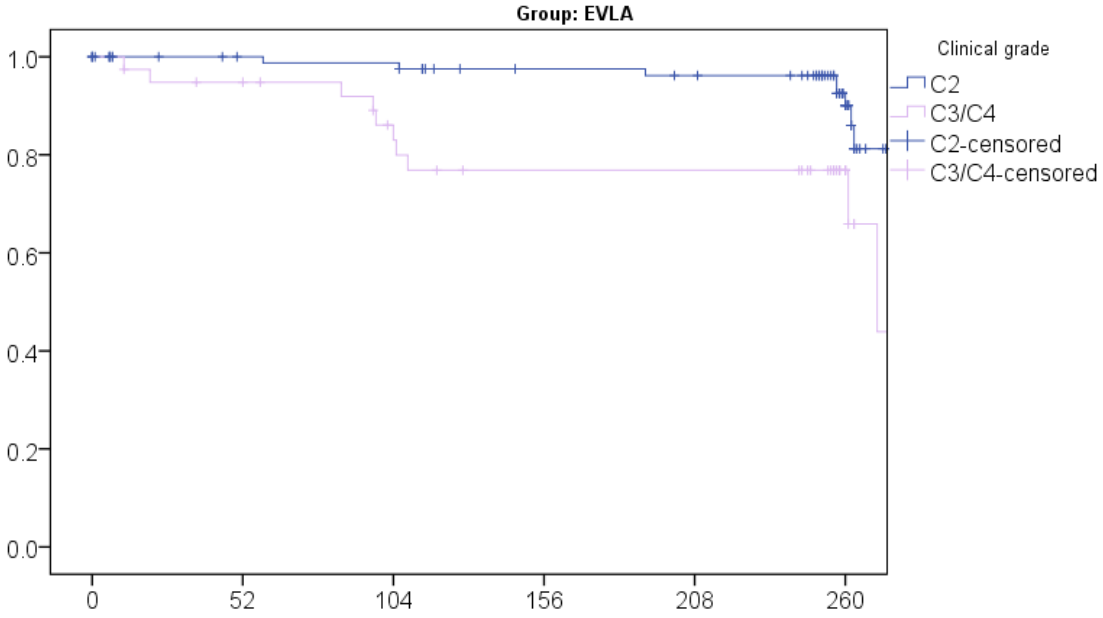


Figure 108 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from AASV and superficial proximal thigh veins after EVLA (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	81	80	72	70	27
C3-C4	40	34	27	23	23	7

Table 73 Patient numbers at risk at each time point for AASV and superficial proximal thigh veins after EVLA (Study 5)

Perforator Incompetence

As shown in Figure 109, those with C3-C4 disease were much more likely to develop incompetent perforators (P<0.001 L.R). This was also observed for those who had undergone Conventional surgery (P=0.001 Figure 110; P=0.001 LR) and EVLA (Figure 111; P=0.004 LR)

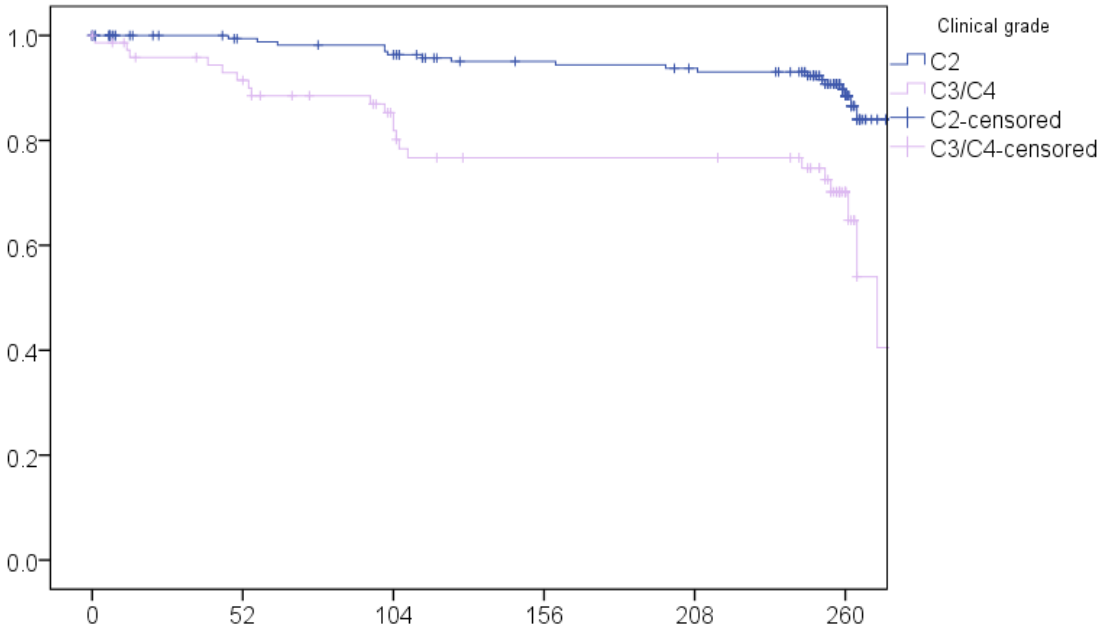


Figure 109 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from perforator incompetence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	163	156	144	140	54
C3-C4	76	62	48	42	42	13

Table 74 Patient numbers at risk at each time point for perforator incompetence (Study 5)

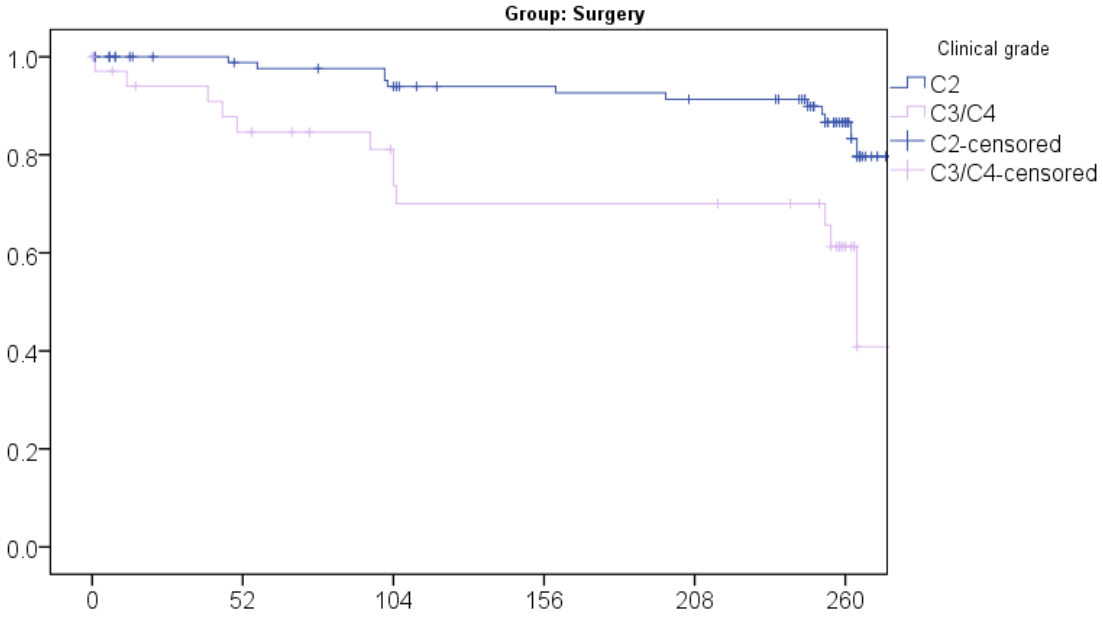


Figure 110 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from perforator incompetence after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	82	76	72	69	30
C3-C4	36	27	20	19	19	6

Table 75 Patient numbers at risk at each time point for perforator incompetence after Conventional surgery (Study 5)

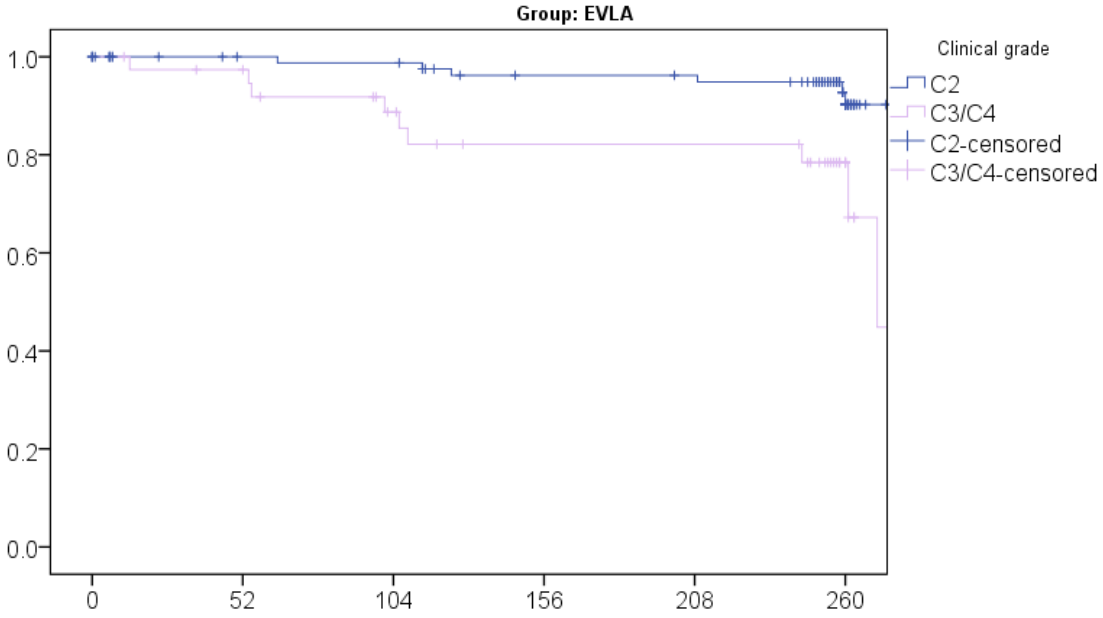


Figure 111 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from perforator incompetence after EVLA (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	81	80	72	71	24
C3-C4	40	35	28	23	23	7

Table 76 Patient numbers at risk at each time point for perforator incompetence after EVLA (Study 5)

SPJ incompetence

As shown in (Figure 112, the development of SPJ recurrence was broadly similar between both disease groups (P=0.089)

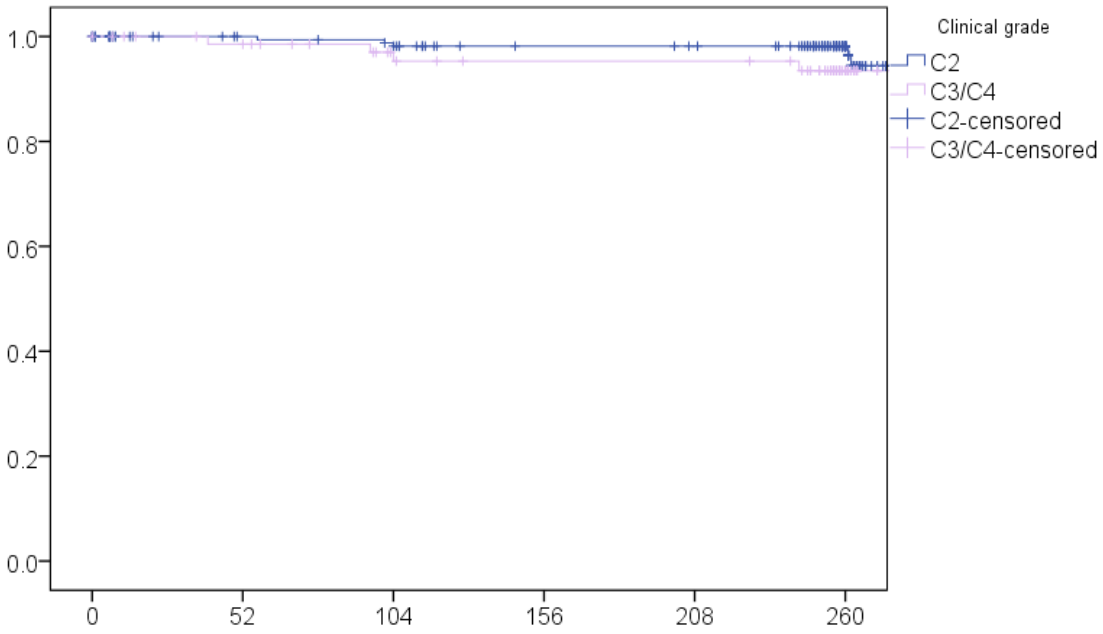


Figure 112 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from SPJ incompetence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	164	158	147	145	56
C3-C4	76	67	57	54	54	18

Table 77 Patient numbers at risk at each time point for SPJ incompetence (Study 5)

SSV incompetence

The development of SSV recurrence was similar between the two disease groups (Figure 113, P=0.154). However it appears more common after Conventional surgery (P=0.019 LR) rather than EVLA (P=0.401 LR)

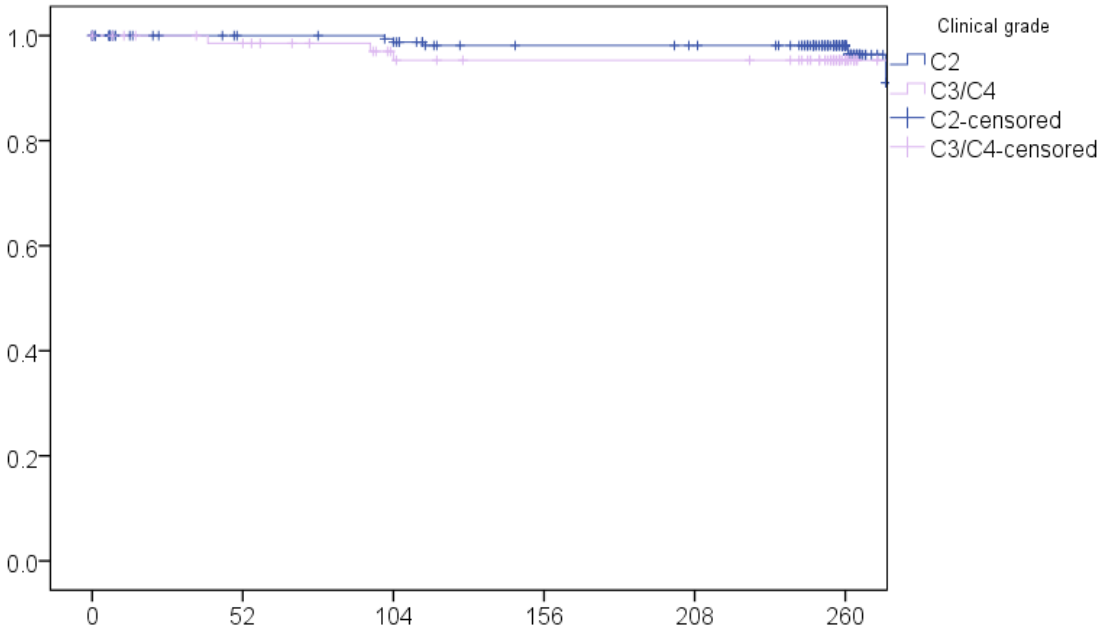


Figure 113 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from SSV incompetence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	164	159	147	145	56
C3-C4	76	67	57	54	54	17

Table 78 Patient numbers at risk at each time point for SSV incompetence (Study 5)

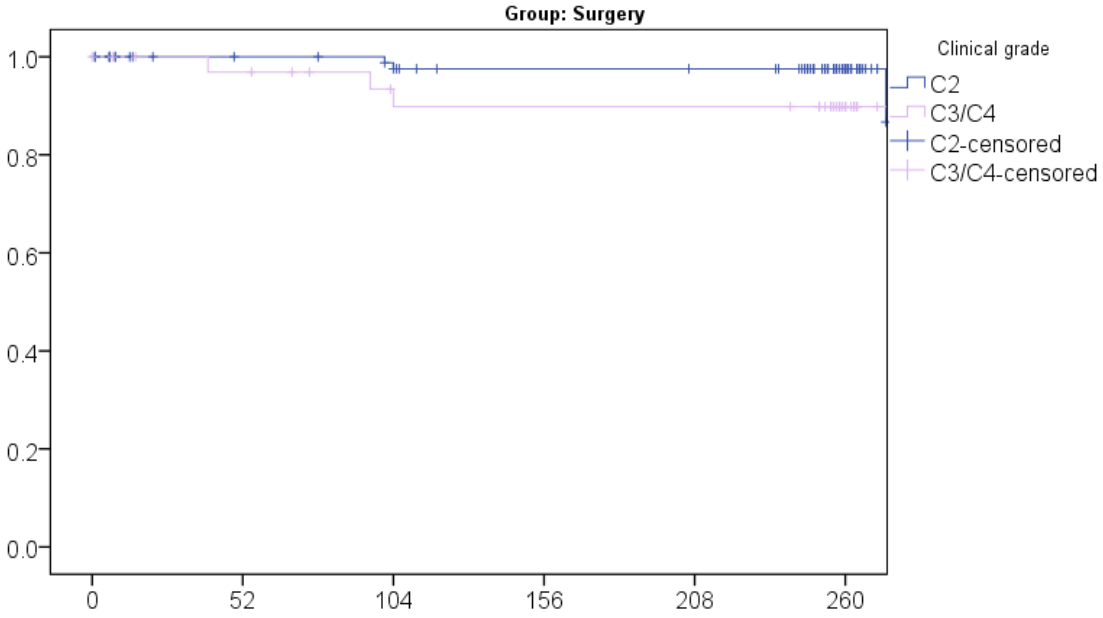


Figure 114 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from SSV incompetence after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	83	78	74	73	30
C3-C4	36	31	25	25	25	9

Table 79 Patient numbers at risk at each time point for SSV incompetence (Study 5)

Recurrence of varicose tributaries

Those with C3-C4 disease were more likely to develop recent varicose tributaries (Figure 115; P<0.001 LR). This was also the case after Conventional surgery (Figure 116; P=0.001 LR) and EVLA (Figure 117; P=0.002 LR)

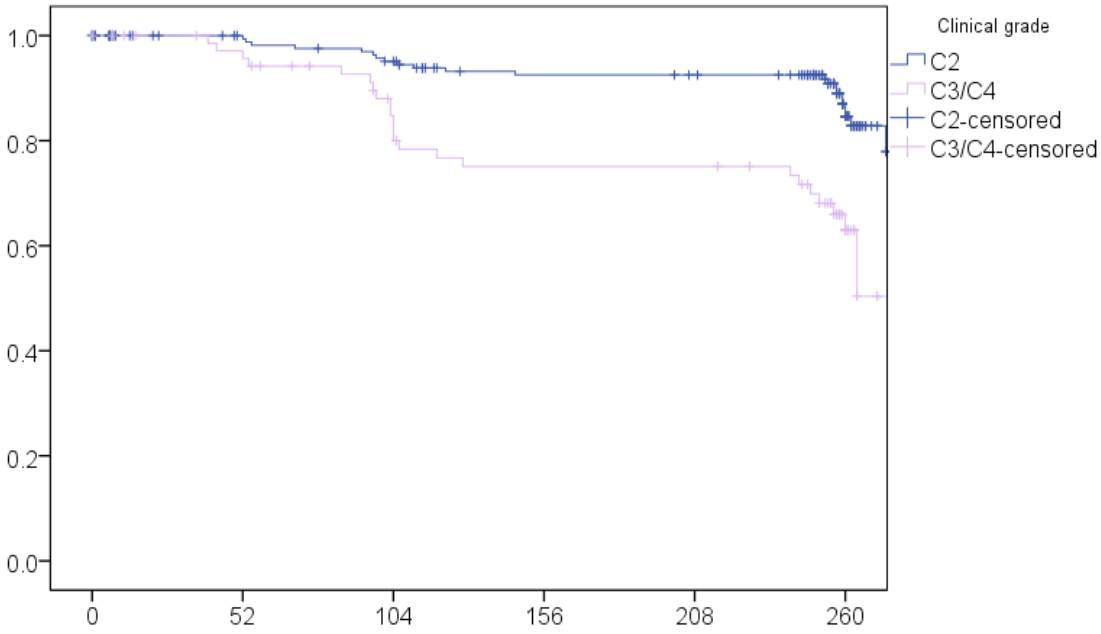


Figure 115 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recurrence of varicose tributaries (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	163	153	139	137	55
C3-C4	76	66	50	46	46	16

Table 80 Patient numbers at risk at each time point for recurrence of varicose tributaries (Study 5)

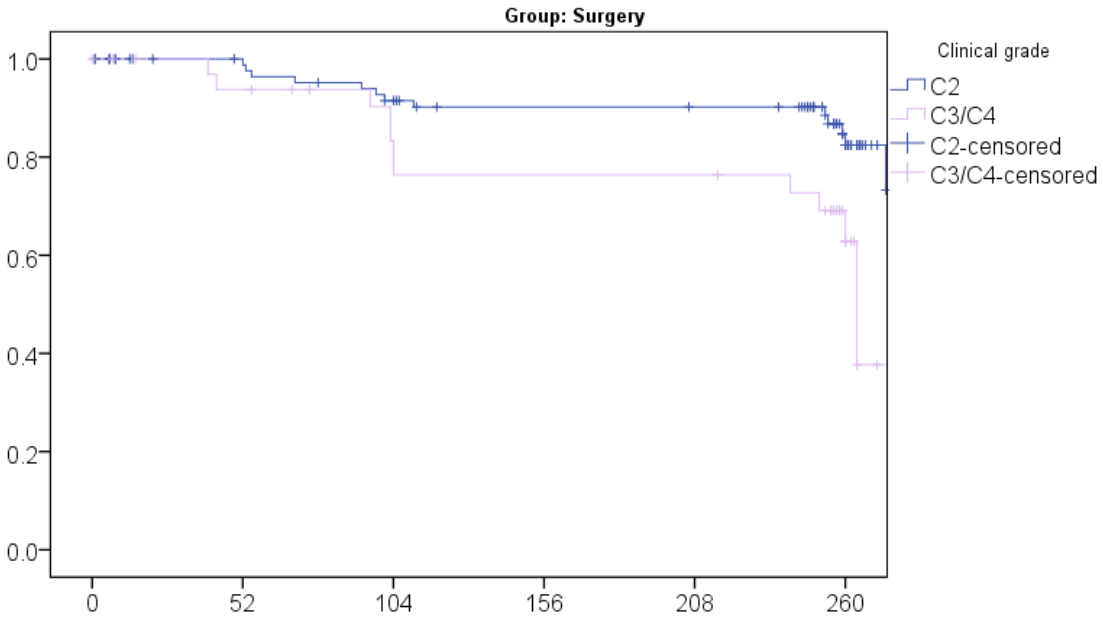


Figure 116 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recurrence of varicose tributaries after Conventional surgery (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	96	82	73	68	67	30
C3-C4	36	30	22	22	22	7

Table 81 Patient numbers at risk at each time point for recurrence of varicose tributaries (Study 5)

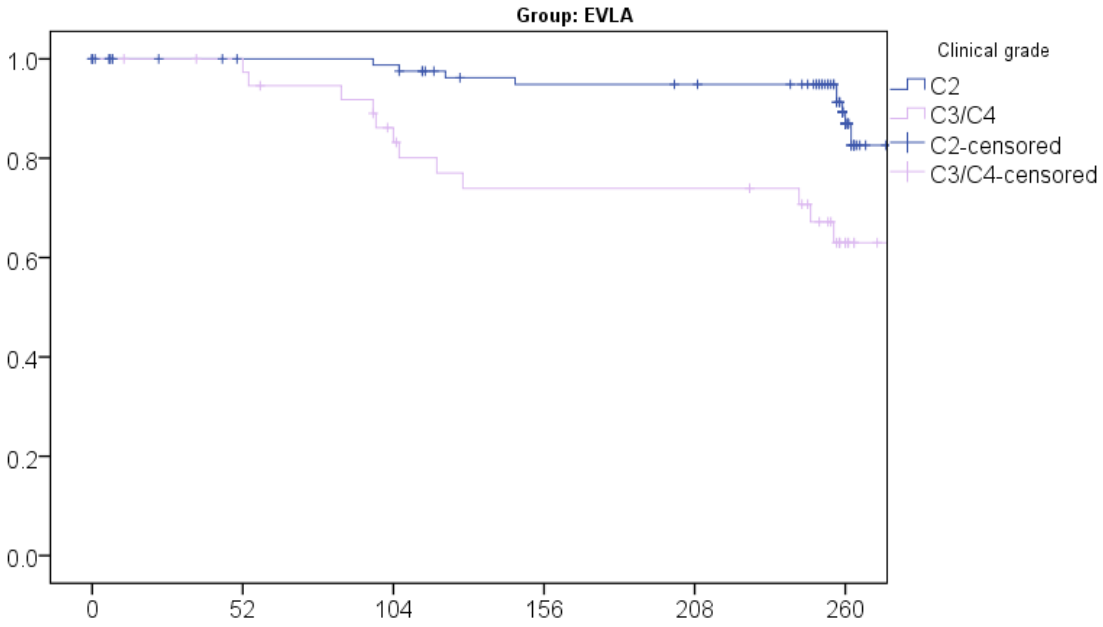


Figure 117 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from recurrence of varicose tributaries after EVLA (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	95	81	80	71	70	25
C3-C4	40	36	28	24	24	9

Table 82 Patient numbers at risk at each time point for recurrence of varicose tributaries after EVLA (Study 5)

Recurrence of incompetent tributaries

Development of incompetent tributaries was observed more often in the C3-C4 group compared to the C2 group (Figure 118; P=0.011 LR)

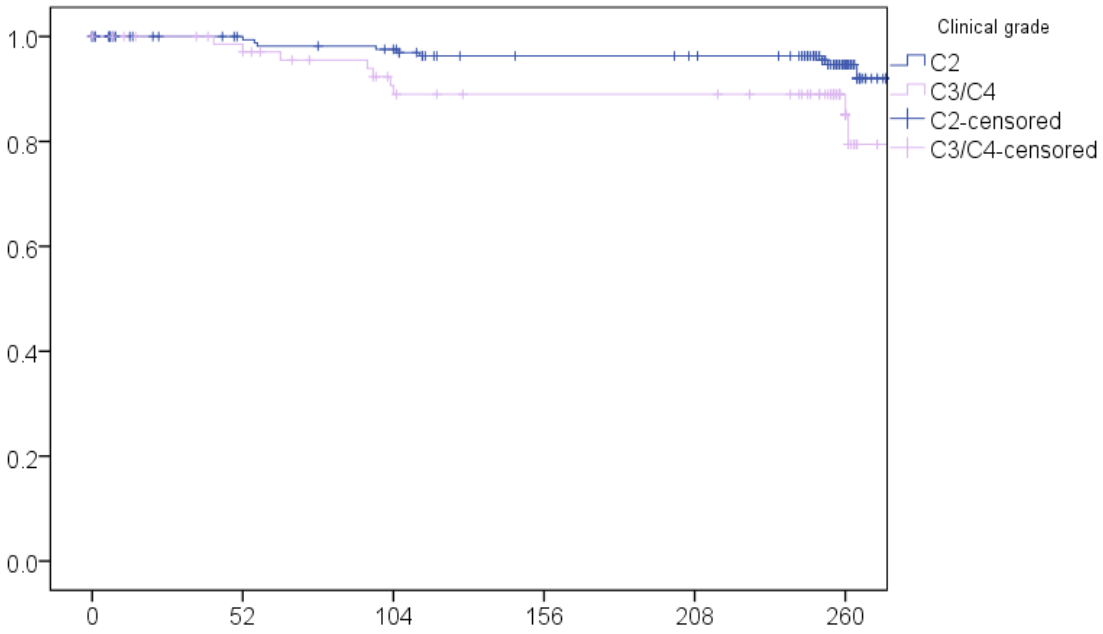


Figure 118 Kaplan-Meier Survival plot showing the proportion of patients in groups C2 and C3-C4 free from tributary incompetence (Study 5)

Number at risk	Baseline	52 weeks	104 weeks	156 weeks	208 weeks	260 weeks
C2	191	163	157	144	142	56
C3-C4	76	65	53	50	50	15

Table 83 Patient numbers at risk at each time point for tributary incompetence

Multi-variable regression analysis

Quality of Life

The improvement in patient QoL was explored further using multivariable linear regression using the independent variables of age, gender, BMI, smoking status, treatment group and clinical grade (C2 and C3-C4).

In holding all other variables constant, benefit in early post-procedural SF-36 impairment among those undergoing EVLA was confirmed in the domains of Physical Function and Role Physical. At one week, despite an overall fall in these domains, those receiving EVLA reported on average 6.2 (95% CI 0.8-11.5) more points in Physical Function (P=0.025) and 17.6 (95% CI 6.4-28.8) more points in Role Physical (P=0.002) than those receiving Conventional surgery. While treatment group did not influence Body Pain at one week, the preoperative clinical status was a significant variable, with those graded at C2 receiving 11.1 (95% CI 3.0-19.2) P=0.007) more points in Body Pain than those graded with C3-C4 disease. Patient age also influenced outcomes, with each additional year on average increasing Physical Function by 0.4 points (95% CI 0.2-0.6) P=0.001), Role Physical by 0.7 points (95% CI 0.3-1.2) P=0.003) and Body Pain by 0.5 points (0.2-0.8) P<0.001) at one week. At six weeks, as both groups improved both the treatment and patient characteristics had little effect on any SF-36 domain improvement.

At one year, most SF-36 domains were not influenced by patient characteristics or treatment group, aside for Body Pain, whereby those graded at C2 reported 12.7 (95% CI 4.8-20.7) P=0.002) more points than those graded at C3-C4. This was also observed at two years, with those graded at C2 reporting 9.8 (95% CI 1.6-18.0) P=0.020) more points in Body Pain than those graded at C3-C4. At two years age

also influenced several SF-36 domains. Each additional year in patient age at treatment typically decreased the number of improvement points in Body Pain (-0.4 (95% CI -0.7 to -0.1) P=0.009), General health (-0.2 (95% CI -0.4 to -0.0) P=0.047), Role Emotional (-0.5 (95% CI -0.8 to -0.1) P=0.011) and Mental Health (-0.2 (95% CI -0.4 to -0.0) P=0.014). As noted previously (page 154) from a lower baseline significant gains were made in the Mental Health domain among those undergoing Conventional surgery. At two years, in holding all other variables constant, those receiving Conventional surgery reported on average 4.6 (95% CI 0.4-8.8) P=0.034) more Mental Health points than those undergoing EVLA.

At five years, neither patient characteristics nor treatment group influenced any change in any measured SF-36 domain.

An early benefit in AVVQ was observed in older patients by one week, with every additional year of age typically improving the typical change in AVVQ by -0.01 (-0.17 to -0.02) P=0.019). Also, SF6D was significantly improved among those older and those receiving EVLA, with every additional year of age increasing SF6D improvement by 0.001 (95% CI 0.000-0.002) P=0.027) and those undergoing EVLA experiencing on average 0.026 (95% CI 0.005-0.047) more points than those undergoing Conventional surgery. However, at any other time point, change in QoL was not influenced by patient characteristics or treatment group. In addition EQ5D did not appear to be affected by any independent variable measured.

Clinical and Patterns of Recurrence

The development of clinical and various patterns of recurrence were further explored using multivariable binary logistic regression using independent variables of age, gender, BMI, smoking status, treatment group and clinical grade (C2 or C3-C4).

In holding all other factors constant, clinical recurrence was less likely in those receiving EVLA (OR 0.551 (95% CI 0.312-0.975) P=0.41) and in those clinically graded with C2 disease (OR 0.289 (95% CI 0.142-0.588) P=0.001). While treatment did not affect the likelihood of symptomatic recurrence, those with C2 disease were much less likely to develop symptomatic recurrence (OR 0.264 (95% CI 0.100-0.699) P=0.007).

Groin recurrence was less likely after EVLA (OR 0.484 (95% CI 0.240-0.980) P=0.044) and those with C2 disease (OR 0.297 (95% CI 0.132-0.667) P=0.003). While it is expected that neovascularisation was more common after Conventional surgery and SFJ incompetence more common after EVLA, neither recurrence was influenced by patient characteristics. Development of AASV and proximal superficial thigh veins were much less common among those with C2 disease (OR 0.323 (95% CI 0.112-0.935) P=0.037) and more likely for each unit increase in baseline patient BMI (OR 1.166 (95% CI 1.059-1.284) P=0.002). Those graded at C2 were also less likely to develop incompetent perforators (OR 0.259 (95% CI 0.110-0.609) P=0.002) and recurrent varicose tributaries (OR 0.296 (95% CI 0.138-0.635) P=0.002). However, neither patient characteristics nor treatment affected the development of recannalisation, SPJ incompetence, SSV incompetence or the development of incompetent tributaries.

Requirement for additional procedures over five years was similar between the two treatment groups, but was less likely in those graded at C2 (OR 0.256 (95% CI 0.103-0.635) P=0.003).

4.6 Study 6 – A cost comparison of treating those with and without the complications of SVI

As detailed above, 191 patients were identified as C2 disease and 76 patients were identified as C3-C4 disease prior to treatment (page 232). The economic analysis of is detailed below.

Primary treatment costs

The costs of primary treatment are detailed in Table 84. The mean operative time was similar between both clinical groups (P=0.948) and therefore primary treatment costs were similar (P=0.633).

Procedure Stage	Cost item	C2	C3-C4
Referral and diagnosis	GP clinic	45	45
	Outpatient visit	169	169
	Diagnostic Venous Duplex	62	62
Intervention	Operation Time (mins)	63 (15)	64 (17)
	Medical personnel	221 (84)	217 (84)
	Nursing personnel	105 (25)	106 (29)
	Procedure costs	381 (48)	379 (46)
After care	Follow up DUS	52	52
	Routine outpatient	142	142
Total cost		**1137 (133)**	**1128 (135)**

Table 84 Primary treatment costs. Values are mean (S.D.) (Study 6)

Additional Procedures

An additional 50 procedures, 25 in each group, were required among 42 patients. The breakdown of the additional mean costs accrued per treatment group at various intervals are detailed in Table 85. Overall, there was no significant difference in the cost of an additional treatment at one year (P=0.562 *t*-test), two years (P=0.694 t-test) nor five years (P=0.756 t-test).

	Procedure time stage	**C2**	**C3-C4**
1 year	DUS	62	62
	Procedure time	48 (12)	38 (7)
	Personnel costs	193 (49)	151 (28)
	Procedure costs	89 (107)	85 (103)
	Aftercare	149 (18)	148 (17)
	Total	**439 (166)**	**391 (165)**
2 year	Referral & diagnosis	240 (23)	226 (32)
	Procedure time	62 (32)	71 (32)
	Personnel costs	268 (140)	302 (134)
	Procedure costs	259 (149)	191 (169)
	Aftercare	187 (20)	175 (27)
	Total	**953 (255)**	**894 (312)**
5 year	Referral & diagnosis	237 (26)	234 (29)
	Procedure time	59 (33)	77 (35)

	Personnel costs	267 (154)	336 (178)
	Procedure costs	260 (163)	245 (183)
	Aftercare	184 (22)	181 (24)
	Total	**948 (311)**	**996 (333)**

Table 85 Costs of secondary treatment (Study 6)

Overall treatment costs

As shown in Figure 119 and Table 86, while treating both groups was of a similar expense at one year, at five years treatment for those with a clinical grade of C3-C4 was more expensive compared to those with C2 disease with a mean difference of £132 (95% CI £22 to £242 P=0.019 *t*-test). This difference was maintained in a sensitivity analysis of discounting with both 0% (P=0.042 *t*-test) and 5 % (P=0.020 t-test).

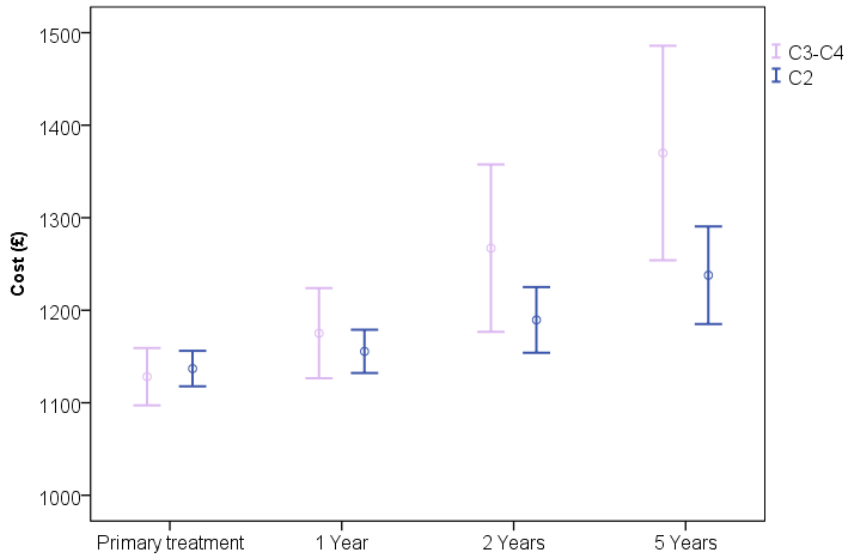


Figure 119 Cost of treatment over five years with 3.5% discounting of costs per annum. Bars represent 95% Confidence intervals (Study 6)

Time point	C2	C3-c4	
Primary treatment	1137 (133)	1128 (135)	0.633
Secondary treatment	1156 (163)	1175 (212)	0.402
1- 2 year	1190 (248)	1267 (393)	0.056
2 - 5 year	1238 (368)	1370 (504)	0.019

Table 86 Mean treatment costs of EVLA alone and EVLTAP (Study 6)

Health outcomes – EuroQol 5 Dimension

As detailed in Table 87 and page 247, at one year the C2 group demonstrated a significantly larger AUC compared to those in the C3-C4 group (P=0.005 *t*-test). This superiority was continued at two years (P=0.001 t-test) and at five years (P=0.020 *t*-test). As detailed in Table 88, a sensitivity analysis of discounting rate variation and different missing value imputations, aside for mean imputation at 0% and 3.5% discounting, was similar to the study results.

Time point	C2	C3-C4
EQ5D Score		
Baseline	0.849 (0.166)	0.831 (0.176)
1 week	0.813 (0.168)	0.765 (0.199)
6 weeks	0.921 (0.130)	0.885 (0.183)
12 weeks	0.931 (0.146)	0.899 (0.161)
1 year	0.933 (0.131)	0.887 (0.185)
2 years	0.917 (0.158)	0.860 (0.220)
5 years	0.906 (0.161)	0.872 (0.211)
AUC		
0 to 1 year†	0.933 (0.111)	0.876 (0.159)

1 to 2 year†	0.936 (0.157)	0.872 (0.185)
2 to 5 year	2.771 (0.524)	2.635 (0.500)
Total		
0 to 5 years†	4.652 (0.573)	4.393 (0.741)

Table 87 EQ5D scores over five years. Values in mean (S.D.) with 3.5% discounting per annum †Significant difference in means at the 5% level (Study 6)

Missing Value replacement	Discount rate	C2	C3-C4
Nil	0%	4.653 (0.573)	4.393 (0.742)
	3.5%	4.034 (0.531)	4.097 (0.684)
	5%	3.937 (0.477)	3.718 (0.610)
Interpolation	0%	4.581 (0.778)	4.293 (0.892)
	3.5%	4.271 (0.720)	4.004 (0.826)
	5%	3.875 (0.645)	3.635 (0.743)
Last result carried forward	0%	4.577 (0.773)	4.330 (0.893)
	3.5%	4.266 (0.715)	4.038 (0.826)
	5%	3.870 (0.642)	3.665 (0.742)
Group mean	0%†	3.699 (1.683)	3.617 (1.498)
	3.5%†	4.059 (0.842)	3.812 (0.932)
	5%	3.690 (0.747)	3.466 (0.830)

Table 88 Sensitivity analysis of different discounting rates and missing value imputations for the five year EQ5D QALY AUC. †Significant difference in means at the 5% level (Study 6)

Health outcomes – SF6D

As detailed in Table 89, at one year the C2 group demonstrated a significantly larger AUC compared to those in the C3-C4 group (P=0.009 t-test). This was continued at two years (P=0.001 t-test) and at five years (P=0.004 t-test). As detailed in Table 90, a sensitivity analysis of both discounting rate variations and different missing value imputations, aside from mean value imputations, were similar to the trial results.

Time point	C2	C3-C4
SF6D Score		
Baseline	0.785 (0.090)	0.775 (0.102)
1 week	0.766 (0.089)	0.748 (0.103)
6 weeks	0.817 (0.077)	0.794 (0.100)
12 weeks	0.824 (0.083)	0.802 (0.092)
1 year	0.824 (0.073)	0.802 (0.098)
2 years	0.816 (0.084)	0.784 (0.106)
5 years	0.789 (0.096)	0.771 (0.091)
AUC		
0 to 1 year	0.827 (0.065)	0.795 (0.092)
1 to 2 year	0.821 (0.072)	0.789 (0.096)
2 to 5 year	2.411 (0.246)	2.347 (0.256)
Overall		
0 to 5 years	4.096 (0.335)	3.902 (0.402)

Table 89 SF6D scores over five years. Values in mean (S.D.) with 3.5% discounting per annum †Significant difference in means at the 5% level (Study 6)

Missing Value replacement	Discount rate	C2	C3-C4
Nil	0%	4.096 (0.335)	3.902 (0.402)
	3.5%	3.819 (0.312)	3.640 (0.374)
	5%	3.706 (0.302)	3.533 (0.362)
Interpolation	0%	4.047 (0.363)	3.899 (0.445)
	3.5%	3.776 (0.337)	3.637 (0.413)
	5%	3.665 (0.326)	3.530 (0.400)
Last result carried forward	0%	4.039 (0.381)	3.910 (0.464)
	3.5%	3.766 (0.354)	3.648 (0.431)
	5%	3.654 (0.343)	3.540 (0.418)
Group mean	0%†	3.575 (0.848)	3.552 (0.752)
	3.5%†	3.334 (0.788)	3.318 (0.695)
	5%†	3.237 (0.763)	3.221 (0.672)

Table 90 Sensitivity analysis of different discounting rates and missing value imputations for five year the SF6D QALY AUC. †Significant difference in means at the 5% level (Study 6)

Cost effective analysis – EuroQol 5 Dimension

A summary of the statistics used in the EQ5D cost effective analysis are detailed in Table 91. Over five years, the C2 group were associated with fewer expenses compared to the C3-C4 group and also experienced a greater increase in QALYs. The mean ICER calculated a reduced expenditure of £510 to achieve one QALY gain.

		C2	C3-C4	Difference
Effect (QALY)	Mean	4.653	4.393	0.259
	Variance of mean	0.00285	0.01250	0.01535
Cost (£)	Mean	£1,229	£1,361	£-132
	Variance of mean	£1,348	£431	£5,564
Cost and Effect	Covariance	-19.110	-115.668	-1.239
	Correlation	-0.085	-0.362	-0.219
Incremental Cost Effectiveness Ratio (£/QALY)				£-510

Table 91. Summary of the cost effective analysis statistics using the EQ5D (Study 6)

Incremental Net Benefit (INB)

The Incremental Net Benefit (INB) of the C2 and C3-C4 groups were calculated. As detailed in Table 92 and shown in Figure 120 the INB increases as the cost effective threshold increases. At the typical NICE threshold value of £20,000 - £30,000 it appears likely that treatment for the C2 group is more cost effective than treatment for the C3-C4 group.

Cost Effective Threshold (£/QALY)	Incremental net benefit	Variance	95% CI lower	95% CI higher
£0	£132	£5,564	-£14	£278
£5000	£1,428	£417,232	£162	£2,694
£10,000	£2,724	£1,596,336	£248	£5,200
£15,000	£4,020	£3,542,875	£331	£7,709

£20,000	£5,316	£6,256,851	£413	£10,219
£25,000	£6,612	£9,738,263	£495	£12,728
£30,000	£7,908	£13,987,111	£578	£15,238
£35,000	£9,204	£19,003,395	£660	£17,748

Table 92 Incremental net benefit of intervention (C2) vs Control (C3-C4) (Study 6)

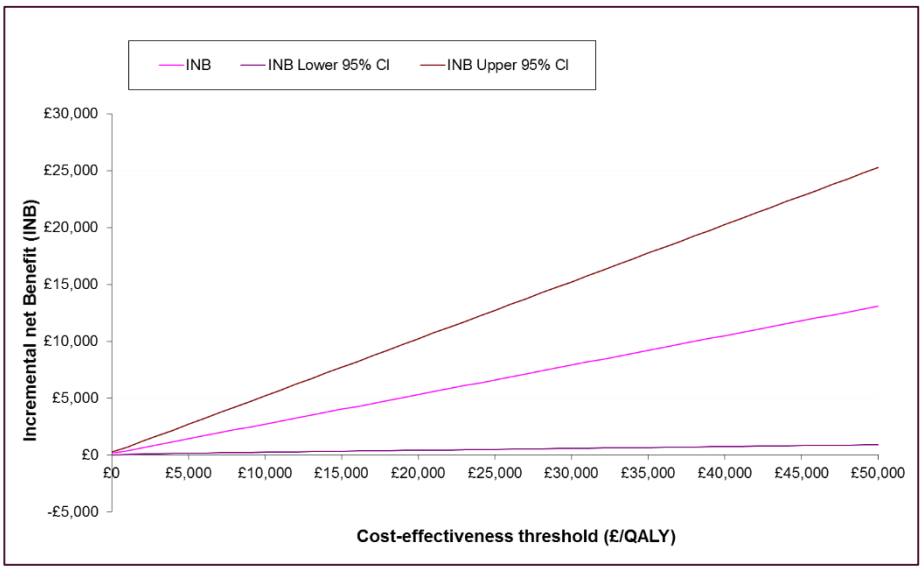


Figure 120 Incremental Net Benefit (IBM) of treating patients with C2 versus C3-C4 disease (Study 6)

Cost-effectiveness acceptability curve (CEAC)

As shown in Figure 121, a CEAC curve was generated to assess if treatment for those with C2 was cost effective compared to those with C3-C4 disease. At the typical WTP threshold of £20,000, the probability of increased cost effectiveness was greater than 90%.

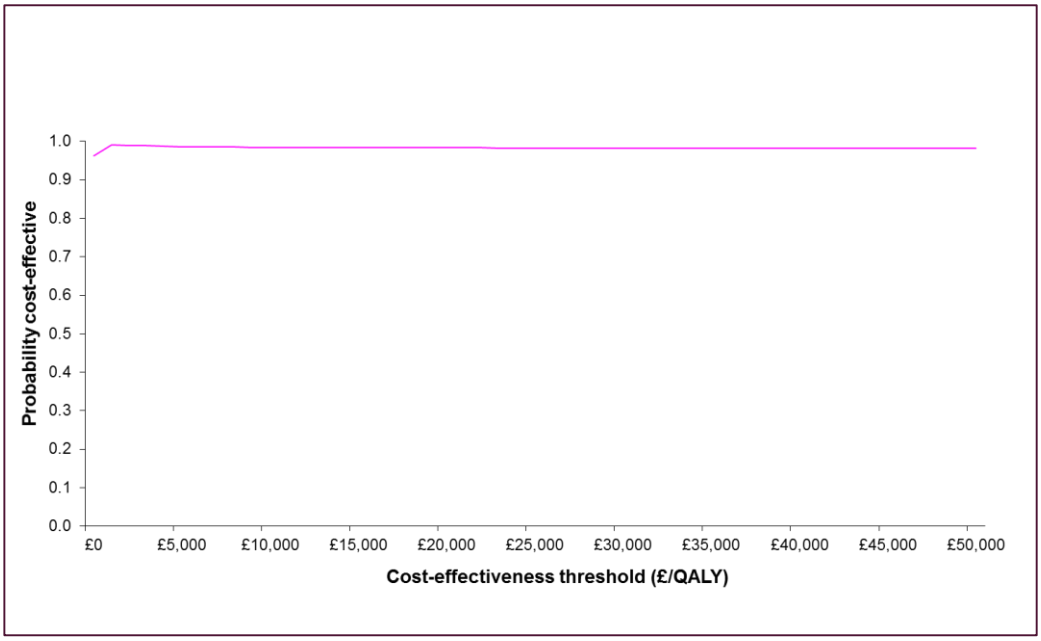


Figure 121 CEAC curve of EVLA vs Conventional surgery using the EQ5D (Study 6)

Confidence ellipses

As shown in Figure 122, uncertainty around the estimated mean difference in costs and effects was explored using a cost effectiveness plane. The point estimate of this study was located in the south-east quadrant, which suggests that treatment of C2 disease "dominates" the treatment of C3-C4 disease i.e. is more effective in both cost and beneficial effect.

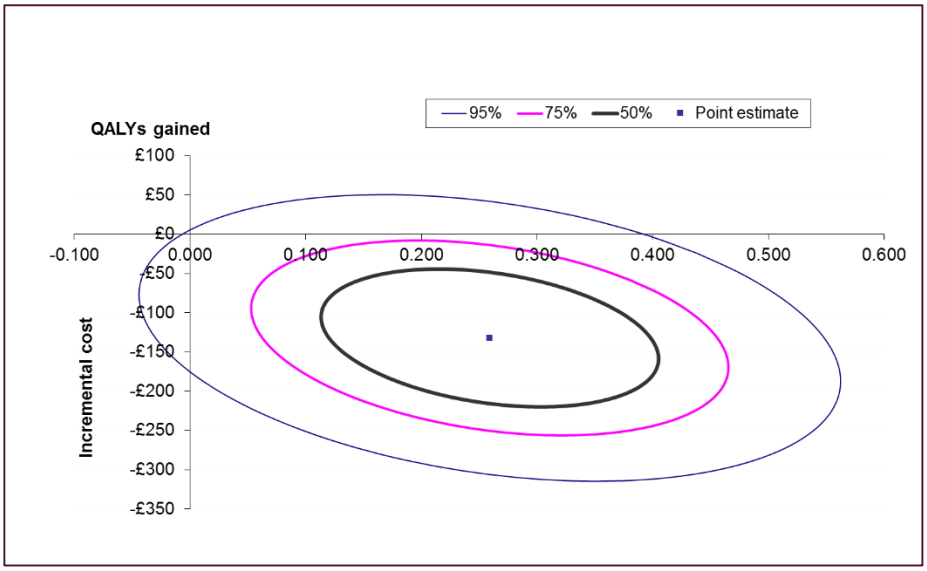


Figure 122 ICER estimates of EVLA vs Conventional surgery using the EQ5D (Study 6)

Cost effective analysis – SF6D

A summary of the statistics used in the SF6D cost effective analysis are detailed in Table 93. Over five years the C2 group were associated with significantly fewer expenses compared to the C3-C4 group, and also gained more QALYs. The mean ICER suggests that one unit of QALY can be gained with £450 less expense.

		C2	C3-C4	Difference
Effect (QALY)	Mean	4.096	3.902	0.194
	Variance of mean	0.00107	0.00425	0.00532
Cost (£)	Mean	£1,231	£1,319	-£87
	Variance of mean	£1,545	£3,658	£5,203
Cost and Effect	Covariance	-10.577	-28.314	-0.846

	Correlation	-0.078	-0.189	-0.161
Incremental Cost Effectiveness Ratio (£/QALY)				-£450

Table 93 Summary of the Cost effective analysis statistics using the SF6D (Study 6)

Incremental Net Benefit (INB)

The Incremental Net Benefit (INB) was calculated. As detailed in Table 94 and shown in Figure 123 the INB increases as the cost effective threshold increases. At the typical NICE threshold value of £20,000 - £30,000, the INB is likely to show treatment of C2 disease as highly cost effective compared to treating those with C3-C4 disease.

Cost Effective Threshold (£/QALY)	Incremental net benefit	Variance	95% CI lower	95% CI higher
£0	87	5,203	-54	229
£5000	1,059	146,730	308	308
£10,000	2,030	554,395	745	571
£15,000	3,002	1,228,197	1,108	829
£20,000	3,973	2,168,137	1,472	1,087
£25,000	4,944	3,374,215	1,837	1,344
£30,000	5,916	4,846,430	2,201	1,601
£35,000	6,887	6,584,782	2,566	1,858

Table 94 Incremental net benefit of intervention (C2) vs Control (C3-C4) (Study 6)

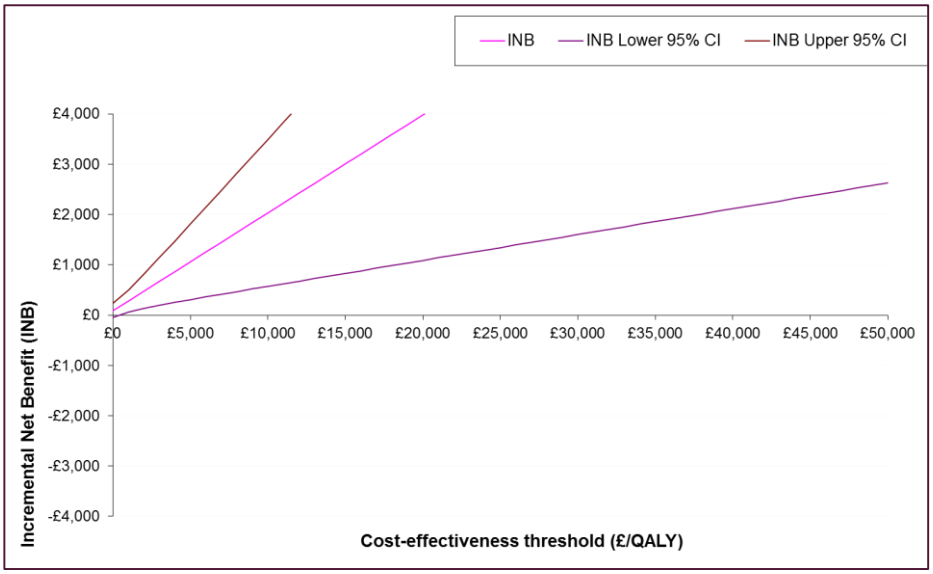


Figure 123 Incremental Net Benefit (IBM) of C2 vs C3-C4 (Study 6)

Cost-effectiveness acceptability curve (CEAC)

As shown in Figure 124, a CEAC curve was generated to estimate the cost effectiveness probability of treating those with C2 disease compared to C3-C4 disease. At the typical WTP threshold of £20,000, the probability was greater than 90% that treating those with C2 disease was cost effective compared to C3-C4 disease.

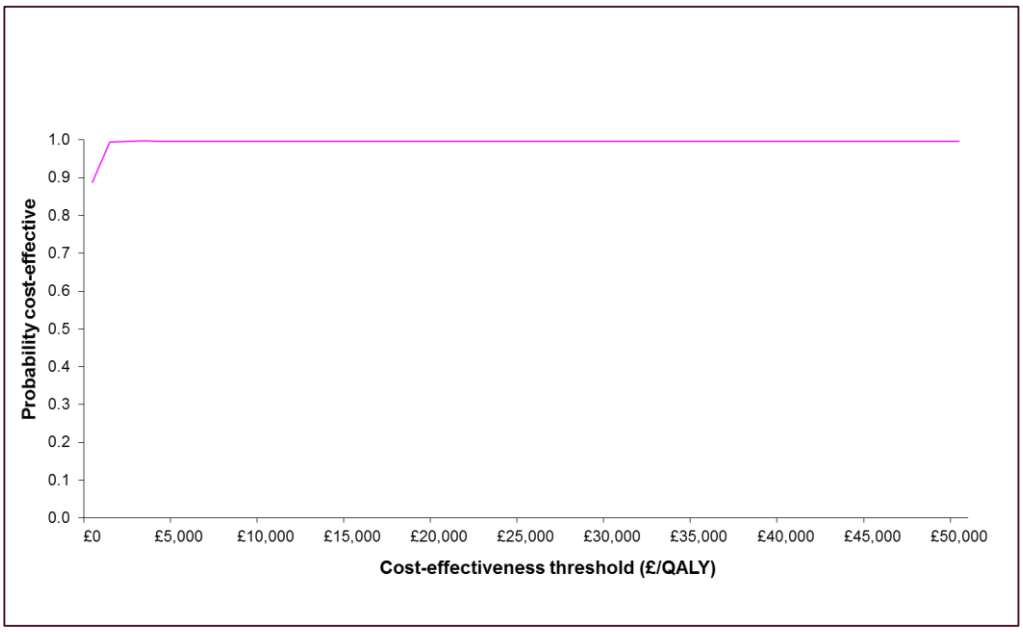


Figure 124 CEAC curve of C2 vs C3-C4 using the SF6D (Study 6)

Confidence ellipses

As shown in Figure 125, the point estimate was placed in the south-east quadrant. Again, this supports C2 treatment as a cost effective option.

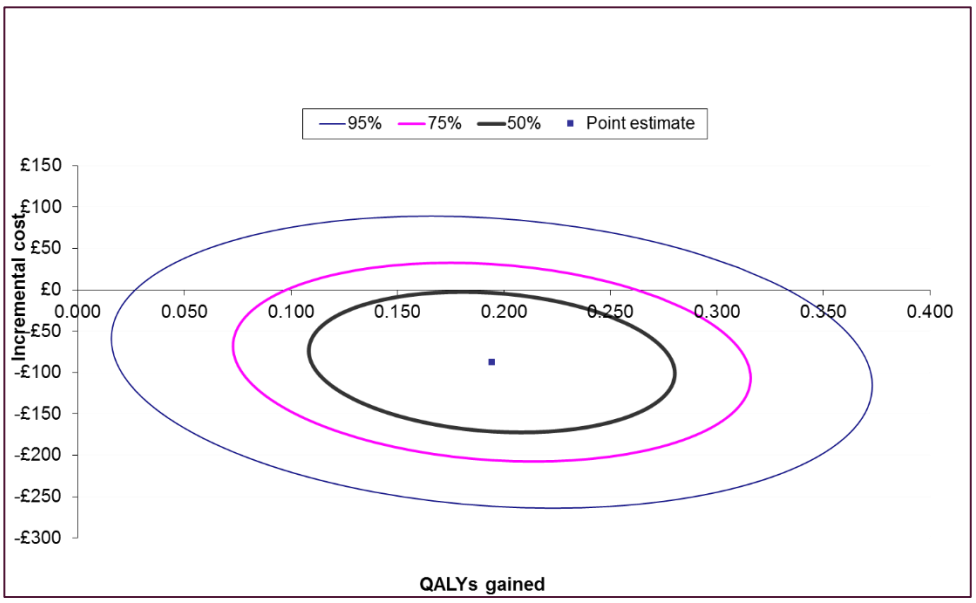


Figure 125 ICER estimates of EVLA vs Conventional surgery using the SF6D (Study 6)

4.6 Study 7 – Comparison of endovenous laser design, technique and clinical outcomes in the treatment of superficial venous insufficiency

The EVLA arms of the HELP-1 (see page 151), EVLTAP (see page 217) and EVLA Watt trial [516], some 255 patients with C2-C4 disease were included for analysis. Aside from the proportion of females, baseline characteristics of the studies (Table 95) and subsequent groups was similar (Table 96).

	HELP-1	EVLTAP	12 vs 14 Watts	P
Patients	135	45	75	
Age	50.0 (13.6)	52.0 (13.7)	49.9 (13.7)	0.418 *
Female	82 (61%)	36 (80%)	45 (60%)	0.046 #
BMI	26.7 (4.9)	26.9 (5.0)	25.5 (3.3)	0.158 *
Left leg	71 (53%)	24 (53%)	39 (52%)	0.990 #
CEAP (C2)	95 (70%)	34 (76%)	50 (67%)	0.587 #
Smoking status				
Current	35 (27%)	12 (27%)	23 (32%)	0.716 #
Ex	33 (25%)	8 (18%)	14 (19%)	
Never	62 (48%)	25 (56%)	36 (49%)	

Table 95 Baseline characteristics (Study 7) * *t*-test # χ^2

	Group 1	Group 2	Group 3	P
Patients	37	197	21	
Age	49.9 (13.7)	50.0 (13.6)	47.7 (13.6)	0.319 *
Female	20 (54%)	124 (63%)	19 (91%)	0.018 #
BMI	25.9 (3.3)	26.5 (4.8)	26.0 (3.7)	0.763 *
Left leg	23 (62%)	98 (50%)	13 (62%)	0.255 #
CEAP C2	25 (68%)	136 (69%)	18 (86%)	0.254 #
Smoking status				

Current	13 (35%)	54 (28%)	3 (14%)	0.550 #
Ex	8 (22%)	42 (22%)	5 (24%)	
Never	16 (43%)	94 (50%)	13 (62%)	

Table 96 Baseline characteristics of study groups (Study 7) * t-test # χ^2 (Group 1 - 12 Watt EVLA with Ambulatory Phlebectomy, Group 2 – 14 Watt EVLA with Ambulatory Phlebectomy, Group 3 – 14 Watt EVLA alone without Ambulatory Phlebectomy)

Generic Quality of Life - Short Form – 36

As detailed in Table 97, the use of the 14 Watt laser was associated with an added benefit at one year in the domains of Physical function (R^2=6.6%), Vitality (R^2=9.7%) and Mental Health (R^2=3.8%). As shown in Table 98, concomitant phlebectomy was noted to have a significant gain at 12 weeks in the SF-36 domain of Physical Function (R^2=4.6%) Thereafter both groups were similar (with a policy of sequential phlebectomy implemented)

SF-36 (Watt)	Time point	Effect size	P
Physical Function	12 weeks	3.7	0.163
	1 year	+7.4	0.023
	2 year	-1.0	0.856
	5 year	3.4	0.773
Role Physical	12 weeks	2.8	0.662
	1 year	+13.5	0.074

	2 year	-4.6	0.704
	5 year	8.9	0.334
Body Pain	12 weeks	-0.2	0.956
	1 year	4.8	0.293
	2 year	-2.9	0.698
	5 year	-4.0	0.537
General Health	12 weeks	-0.3	0.923
	1 year	6.0	0.081
	2 year	-1.0	0.881
	5 year	1.2	0.780
Vitality	12 weeks	3.5	0.287
	1 year	8.7	0.017
	2 year	1.5	0.826
	5 year	5.0	0.327
Social Function	12 weeks	-3.0	0.428
	1 year	3.9	0.308
	2 year	-2.2	0.773
	5 year	9.6	0.424
Role Emotional	12 weeks	2.2	0.652
	1 year	-0.02	0.997
	2 year	3.7	0.722
	5 year	3.1	0.715
Mental Health	12 weeks	2.9	0.303
	1 year	9.0	0.011

	2 year	-8.3	0.125
	5 year	5.4	0.226

Table 97 Results of linear regression model analysing the effect of 14 Watts on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and phlebectomy were controlled

SF-36 (Phlebectomy)	Time point	Effect	P
Physical Function	12 weeks	7.0	0.040
	1 year	6.2	0.132
	2 year	-2.0	0.657
	5 year	6.3	0.660
Role Physical	12 weeks	10.2	0.207
	1 year	5.5	0.562
	2 year	4.7	0.604
	5 year	1.2	0.915
Body Pain	12 weeks	8.7	0.121
	1 year	5.6	0.327
	2 year	0.3	0.957
	5 year	2.5	0.748
General Health	12 weeks	0.6	0.853
	1 year	-0.1	0.982
	2 year	-5.8	0.202
	5 year	-1.0	0.848
Vitality	12 weeks	0.6	0.876
	1 year	-2.5	0.582

	2 year	-5.7	0.257
	5 year	3.4	0.579
Social Function	12 weeks	-3.3	0.500
	1 year	-2.3	0.625
	2 year	-2.5	0.628
	5 year	6.8	0.395
Role Emotional	12 weeks	6.3	0.307
	1 year	1.7	0.825
	2 year	3.0	0.712
	5 year	1.8	0.856
Mental Health	12 weeks	-2.9	0.402
	1 year	-4.7	0.291
	2 year	-2.8	0.457
	5 year	2.1	0.691

Table 98 Results of linear regression model analysing the effect of concomitant phlebectomy on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and Watts were controlled.

Disease Specific QoL - Aberdeen Varicose Vein Questionnaire

As detailed in Table 99 and Table 100, the choice of EVLA Watt did not affect AVVQ improvement but concomitant phlebectomy was associated with a significant fall (improvement) at 12 weeks (R^2=4.0%) A policy of sequential phlebectomy thereafter similar in both groups.

AVVQ (Watt)	Time point	Effect	P
	12 weeks	2.4	0.062
	1 year	1.5	0.242
	2 years	-0.7	0.753
	5 years	0.7	0.638

Table 99 Linear regression model analysing the effect of 14 Watts on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and phlebectomy were controlled

AVVQ (Phlebectomy)	Time point	Effect	P
	12 weeks	-3.6	0.029
	1 year	-0.3	0.831
	2 years	0.5	0.745
	5 years	-0.3	0.878

Table 100 Linear regression model analysing the effect of concomitant phlebectomy on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and Watts were controlled

Utility Index QoL - EuroQol 5 Dimension

As shown in Table 101 and Table 102, no significant influence on EQ5D was detected by EVLA Watt or concomitant phlebectomy.

EQ5D (Watt)	Time point	Effect	P
	12 weeks	-0.025	0.423
	1 year	-0.006	0.831
	2 years	-0.058	0.266
	5 years	-0.063	0.069

Table 101 Linear regression model analysing the effect of 14 Watts on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and phlebectomy were controlled

EQ5D (Phlebectomy)	Time point	Effect	P
	12 weeks	0.056	0.158
	1 year	0.011	0.763
	2 years	-0.023	0.570
	5 years	0.015	0.740

Table 102 Linear regression model analysing the effect of concomitant phlebectomy on change in SF-36 over five years (Study 7). The effects of gender age, BMI, smoking status, baseline CEAP and Watts were controlled

Recurrence and clinical outcomes

As shown in Table 103, the choice of Watts did not appear to affect the chance of additional treatments nor recurrence over five years. In

Table 104, the lack of concomitant phlebectomy is expected to increase the change of sequential phlebectomy, but additional treatment due to axial recurrence are similar between the two treatment policies. Absence of recannalisation among group 3 precluded exploration of the effect of phlebectomy.

Watt		Odds Ratio	P
Additional treatment	Phlebectomy	1.792 (0.207 to 15.546)	0.596
	Axial treatment	1.438 (0.298 to 6.946)	0.651
Recurrence	AASV	0.733 (0.216 to 2.483)	0.617
	Recannalisation	0.492 (0.085 to 2.855)	0.429
	Varicose tributary recurrence	2.706 (0.323 to 22.674)	0.359

Table 103 Results of a binary logistic regression model analysing the effect of 14 Watts on clinical outcomes (Study 7). The effects of gender, age, BMI, CEAP and concomitant phlebectomy are controlled.

Phlebectomy		Odds Ratio	P
Additional treatment	Phlebectomy	0.006 (0.001 to 0.034)	<0.001
	Axial treatment	1.575 (0.186 to 13.355)	0.677
Recurrence	AASV	1.186 (0.230 to 6.130)	0.838
	Varicose tributary recurrence	1.280 (0.149 to 11.015)	0.822

Table 104 Results of a binary logistic regression model analysing the effect of concomitant phlebectomy on clinical outcomes (Study 7). The effects of gender, age, BMI, CEAP and Watts are controlled.

Chapter 5 – Discussion

The short term advantages of minimally invasive treatments for SVI have been shown consistently across several clinical studies[308], but the long term outcomes are only now coming into view. The era of minimally invasive surgery has now arrived and it is essential that the long term effects minimally invasive techniques are fully explored because this is the new "gold standard" treatment for thousands of patients annually and the consequences will be felt for decades. The main significance of this study is that an almost complete picture of the long term outcomes of EVLA treatment for SVI has been captured and documented up to five years with perhaps the greatest detail yet seen.

While some randomised trials have managed to present the long term outcomes of EVLA[481, 482, 486-488, 517, 518], the HELP-1 study is perhaps the first trial of sufficient size to be able to detect small but significant differences in quality of life over five years. In addition, exhaustive DUS examinations undertaken during the course of the trial provide one of the most detailed long term assessments of post intervention limbs following EVLA and conventional surgery. Controversy still remains around the optimum management of varicosities during EVLA. The EVLTAP trial is the first to explore the long term consequences of a policy of concomitant or sequential phlebectomy, and with the economic analysis of study 4, brings level 1 evidence to help settle the debate. The size of the HELP-1 study also allows for an almost unique enquiry into the importance of baseline disease state in the eventual outcomes of SVI treatment, as seen in study 5 and 6. The effect of EVLA settings and procedural technique have also been explored.

Long term outcomes - HELP-1

The results of the HELP-1 study show that both EVLA and conventional surgery are both highly effective treatments for SVI with comparable long term outcomes. In the short term EVLA has several advantages over conventional surgery, such as fewer complications and less early impairment of the SF-36 physical health QoL domains. After a brief postoperative recovery period, both groups improved substantially in both clinical and QoL measurements, with benefit duly maintained for several years. By five years however, significant differences had begun to develop. Improvement in the AVVQ (disease specific) and EQ5D (generic) QoL were sustained for both groups, but at five years the SF-36 (generic) physical health domains had returned to baseline. In clinical outcomes, objective clinical measurement of venous disease (VCSS) were slightly worse amongst the conventional surgery group at five years. However this was not sufficient to greatly affect the overall opinion of cosmesis or satisfaction, which remained equally high. In terms of technical outcomes, as per the REVAS consensus[519, 520], the conventional surgery group were more likely to develop clinical recurrence over five years and, if they did develop a clinical recurrence, it typically occurred earlier than those who had undergone EVLA. Conversely, symptomatic clinical recurrences were overall few in number and not dissimilar in incidence between both groups. In the DUS assessments, patterns of clinical recurrence often appeared related to the nature of their respective intervention. For example, while groin recurrence was largely similar between the groups, after conventional surgery recurrence would typically be related to neovascularisation whereas after EVLA recurrence would be typically related to axial incompetence (SFJ or GSV). Despite such differences the progression of disease was similar both proximally and distally, as seen with local development of

new axial incompetence (AASV, SPJ, and SSV) or superficial tributaries. Nonetheless, if the strict criteria for technical success was maintained it appears that EVLA preserves technical success of treatment longer than conventional surgery.

The importance of different grades of venous disease has seldom been recognised in venous research, but investigation of those with and without complications of SVI (study 5 and 6) have shown that there are significant differences between the two patient groups. At baseline, patients with C3-4 disease were already worse in several aspects, not least clinical disease severity (VCSS) and impairment of the physical and mental health domains of the SF-36. The impact of treatment is less noticeable among those with C3-4 disease due to their pre-existing burden, whereas those without SVI complications (C2) deteriorate to an impairment comparable to those with complications of SVI (C3-4). After the early post-operative period both groups gain significantly in generic QoL, but only those without the complications of SVI at baseline were able to maintain this improvement into the long term. Those with C3-4 disease soon found that any benefit was ultimately momentary, and that by five years generic QoL domains had returned back to baseline levels. However, it should be noted that disease specific measurements of venous disease had improved in both groups regardless. Both clinical severity (VCSS) and disease specific QoL (AVVQ), were still significantly improved at five years, with correspondingly high cosmesis and satisfaction rates. Despite lifting the burden of venous disease, those with advanced disease did not see a global increase in their quality of life afforded to those with C2 disease. It is perhaps also logical to expect that those with more advanced venous disease were more likely to experience deterioration over the long term. Indeed, those with already complicated SVI experienced more clinical and symptomatic recurrence over five years. As well a groin recurrence, other areas of

the limb were also more likely to experience multifocal progression of disease, such new axial incompetence or varicose tributary manifestation. At the proximal aspect it appears that the trauma of conventional surgery is itself the main cause of neovascularisation rather than the underlying venous disease. Conversely, the action of EVLA appears highly successful at producing long term ablation, with areas which not directly treated by EVLA (i.e. the SFJ and its tributaries) more likely to develop recurrence or progression of disease. This raises the question if EVLA is undertreating patients by not ablating the AASV and proximal thigh veins during the index procedure. Conventional surgery, by definition, treats all proximal tributaries, but EVLA often misses tributaries close to the junction (to avoid damage to the deep vein or by technical limitations). Treatment of incompetent tributaries is both logical and necessary to avoid early recurrence, but proximal veins which have yet to show signs of incompetence may be a potential avenue of later recurrence as well. Overtreatment is a concern, as damage to local tissues (skin, nerves etc) is always a risk during any intervention, especially so in EVLA due to the high temperatures involved and the superficial nature of the proximal thigh. Another limitation is the lack of a substantial facial covering of these proximal veins compared to the facial compartment around the GSV which aids tumescent anaesthesia. If avoiding a recurrence is a special concern for the patient, it may be worth discussion the treatment options and potentially treating adjacent veins, however, this may also be in vain if disease progression occurs elsewhere.

Regression of the HELP-1 study data confirmed that EVLA was itself associated with a significant QoL benefit in the early period compared to conventional surgery. However, beyond the post-operative period the direct effects of treatment subsided. Recurrence was also significantly less among those undergoing EVLA and those

with uncomplicated SVI. Compared to conventional surgery, the chance of developing a clinical recurrence was 45% less after EVLA. Compared to those with C3-4 disease, the chance of developing clinical recurrence was 71% less in those with C2 disease.

The HELP-1 study therefore supports the position of NICE that EVLA techniques, should be preferred over conventional surgery, and that referral should not be limited to only those with C3 disease and above[152]

Rasmussen et al[481] reported that those receiving conventional surgery and EVLA both reported significant improvements in VCSS, SF-36 and disease specific QoL (AVVQ) over five years with no differences detected between the groups at any time point. However it should be noted that the study, about half the size of the HELP-1 trial, is unlikely to be sufficiently powered to detect small differences in the SF-36. Clinical recurrence was similar between both treatments and was in keeping with the results of the HELP-1 trial. Almost half developed recurrence, with proximal tributary and ASSV incompetence associated with EVLA more than conventional surgery. This was not statistically significant, again, perhaps due to the study size. Re-operation rates were similar after conventional surgery (37.7%) and EVLA (38.6%) and overall more than the HELP-1 trial, although these procedures were limited to UGFS with or without phlebectomy.

The RELACS study[488] reported that disease specific QoL improved significantly over five years with no difference detected between conventional surgery and EVLA. Long term recurrence was also similar, typically affecting half of the study group. It was also reported that while "nature of the source of recurrence: different site" was more likely after conventional surgery, the "nature of the source of recurrence: same site" was much higher after EVLA. Distal recurrence was however

similar between both groups. Recurrence at the SFJ after EVLA was 28% with 62% of those also demonstrating GSV recannalisation and 48% demonstrating incompetent groin tributaries. These outcomes are significantly worse than the EVLA outcomes reported in the HELP-1 trial. A possible explanation for this may be due to the relatively low EVLA energies used in the RELACS trial, typically around 20 J/cm^2 energy fluency equivalent (EFE). Converted into the Laser Energy Density (LED) this is around 40-50 J/cm[397], well below the energy used in the HELP-1 trial (95 J/cm), Rasmussen et al (73.5 J/cm)[406] and Flessenkamper et al studies (85.4 J.cm)[521] and, indeed, most practitioners today. Further treatments were similar between the groups (Conventional surgery 29%, EVLA 41%) even despite a "wait and see" policy for those in the conventional surgery group. Of the EVLA group, six patients required retreatment of the axis, with four undergoing open surgery and two undergoing re-do EVLA treatment

In a trial comparing EVLA, EVLA with SFJ ligation and conventional surgery, Flessenkamper et al[521] reported that rate of clinical recurrence was similar between all three procedures with almost half developing recurrence by five years. As expected, not ligating the SFJ increased the chance of incompetent proximal tributaries and GSV reflux. This technical advantage had no benefit on long term outcomes however, and any marginal improvement to the EVLA technique, if any, comes with additional costs, such as procedural complications associated with open ligation. Kalteis et al [518] also reported a small study which investigated EVLA with SFJ ligation versus conventional surgery. Both groups reported an improvement in VCSS, QoL and cosmesis, but at five years recurrent varicose tributaries were present in half of the participants of both groups. Even after careful dissection of all tributaries, a fifth of all patients still had incompetent proximal tributaries by five

years. Recannalisation was also seen in 10% of those after EVLA and 5% of those after conventional surgery. In a study by Disselhoff et al[487], rates of groin recurrence were similar between those with and without ligation during EVLA. Rates of complete ablation of the treated GSV segment were also similar, at 98% and 88% following EVLA with ligation and EVLA without ligation respectively. As expected, neovascularisation only occurred in those with ligation during EVLA, whereas recannalisation and incompetent proximal tributaries only occurred in those without ligation during EVLA. Both groups improved substantially in VCSS scores and these differences did not appear to affect any long term outcomes. The long term benefit of junctional ligation with EVLA remains to be established.

A trial investigating the long term outcomes of conventional surgery, EVLA and UGFS was reported in a study by Van der Velden et al[482]. Accordingly, over five years all three treatments improved EQ5D QoL and disease specific QoL. Complete obliteration of the GSV was also high, in 85% of conventional surgery and 77% of EVLA patients. As with the HELP-1 study, disease progression of away from the area of treatment was similar in both groups, but localised to the treatment area recurrence of SFJ incompetence was more likely after EVLA treatment whereas neovascularisation was more likely after conventional surgery. At 10% the further treatment rare was less than the HELP-1 trial although, as with Rasmussen et al[481], treatment were limited to just phlebectomy or UGFS.

The HELP-1 trial therefore appears to be in agreement with other long term randomised trials investigating EVLA. Other EVTA treatments, such as RFA, also appear to have promise in the long term, although level 1 evidence at five years is still awaited[522]. The three year results of a four way trial investigating UGFS, EVLA, RFA and conventional surgery have been reported by Rasmussen et al[517], and so far

appear to correspond with long term results already seen. The long term results of the CLASS trail[487], one of the highest quality venous trials ever conducted, are also eagerly awaited.

Long term outcomes – EVLTAP

The long outcomes of both EVLA groups were highly favourable, with significant improvements in both clinical and QoL measurements over five years. Both groups reported a significant improvement in AVVQ scores, but significant differences were apparent in the early post-operative period. Those undergoing concomitant phlebectomy had shown significant improvement in AVVQ scores by six weeks, however, those who did not receive concomitant phlebectomy had not shown any improvement. At twelve weeks those in the concomitant phlebectomy group improved further still, but those receiving EVLA alone only just started to show moderate levels of improvement from their baseline scores. At one year both groups were similar in AVVQ, however this was after two thirds of the EVLA alone group had received sequential phlebectomy. This was reflected clinically with worse VCSS scores at twelve weeks among the EVLA alone group, whereas both groups were similar at one year. Beyond one year both groups were broadly similar and sustaining improvement into the long term.

The results of this study refute this, instead suggesting that the full benefit of treatment can only be achieved once both the axial and superficial disease manifestations are treated. It has also been shown that patients prefer their treatment to be delivered in one sitting, with early secondary treatments deemed unpopular[523]. The additional costs associated with sequential phlebectomy, as shown in study 4,

supports the argument that it is overall more desirable perform concomitant phlebectomy.

The AVULS trial[524], a randomised trial comparing concomitant and sequential phlebectomy with RFA, found that patients are reluctant to undergo only axial treatment for SVI when burdened with symptomatic varicose tributaries. Of 221 eligible patients, 51% refused to participate as they did not want to be randomised to a group which would not deliver their treatment "in a single sitting". Of those recruited, sequential phlebectomy was required in 36% of those without concomitant phlebectomy and 2% of those with concomitant phlebectomy. As seen in the EVLTAP trial, a significant benefit in disease specific QoL (AVVQ) was detected in those receiving concomitant treatment at six weeks and six months. At one year, only after all patients had received their required phlebectomy, did both groups report similar AVVQ scores. Interestingly, as seen in the EVLTAP trial, the AVULS trial also saw a slightly worse AVVQ score at one year amongst those receiving sequential phlebectomy. This could potentially be a type 2 error, requiring a significantly larger study to elicit if the beneficial effect of phlebectomy is indeed delayed if the phlebectomy is itself delayed. Also hinted at in the EVLTAP trial was a benefit in generic QoL among those receiving concomitant treatment. Accordingly the larger AVULS trial detected a significant improvement in EQ5D in those receiving concomitant phlebectomy up to one year.

Concomitant and sequential phlebectomy are both highly effective long term treatments for SVI. However, concomitant treatment is associated with optimal improvement in both clinical QoL and, ultimately, is a more cost effective treatment.

Cost-effectiveness

This is the first study to explore the actual costs of EVLA treatment for SVI over a five year period. In the first economic analysis, the costs of EVLA and conventional surgery were compared (study 2), in the second, costs of a policy of concomitant or sequential phlebectomy during EVLA (study 4) and in the third, the costs of treating those with and without the complications of SVI (study 6).

In study 1, conventional surgery was significantly more expensive compared to EVLA, even when taking into account the additional expense of the EVLA laser device and kit. In the long term, the requirement and costs of further procedures were broadly similar between both groups, effectively maintaining the relative cost advantage of EVLA. However, health related QoL outcomes were also similar between both groups over five years. In the cost effective analysis the chance that one treatment is more cost effective than the other is rather low. Additional cost and slight benefit in QoL may appear to give conventional surgery superiority, but significant uncertainty in the model suggests that this is unlikely. In fact, due to the similar cost effectiveness of both treatments, the significant short and long term clinical benefits take precedence, again supporting EVLA treatment

In study 2, a clear cost effective benefit is observed amongst those who undergo concomitant phlebectomy during EVLA treatment for SVI. The additional costs of sequential phlebectomy are substantial, potentially making any such a policy of delayed treatment exorbitant even with the highest threshold of re-intervention. However, a policy of sequential phlebectomy also ignores the significant early benefit in QoL which occur after concomitant phlebectomy. It is only after further treatment that the full benefit of intervention is realised.

In study 3, over five years those with more advanced venous disease were more expensive to treat. A higher proportion of those with C3-C4 disease develop clinical recurrence, which subsequently increases the proportion requiring intervention. It was therefore more cost effective to treat those less complicated venous disease as, once the disease had progressed, further costs were much more likely to arise in the long term.

In the absence of long term any long term financial data, several economic models have been developed to estimate long term cost effectiveness of EVLA and conventional surgery[472, 494, 525-527]. One of the highest quality studies in venous research, the CLASS trial[472, 525], used six months of clinical data and expert advice to produce a five year cost-effective Markov model. Comparing against UGFS, the base case analysis calculated that conventional surgery was more expensive by £206 and less effective in QALY by 0.078, whereas EVLA was both more expensive by £431 and more effective in QALY by 0.118. Accordingly, conventional surgery was "dominated" by UGFS (more cost with worse outcomes), but EVLA was shown to be cost effective with an incremental cost per QALY of £3640, well beneath the typically willingness to pay threshold of £20,000 used by NICE. Of the three treatments EVLA was regarded to have the highest probability of cost effectiveness (79%).

Unable to use "raw" clinical and cost data, two studies used systematic reviews of the literature and expert advice to produce economic models[494 526]. A network meta-analysis reported by Carroll et al[494], simulated 10 years of clinical outcomes. Initial modelling suggested that, compared to conventional surgery, EVLA was more successful at avoiding technical recurrence (Hazard ratio 0.70 (95% CI 0.27 to 1.45) and around twice as expensive. Over 10 years, conventional surgery was estimated to

cost £1334 and gain 8.0347 QALY. In comparison EVLA cost £1302 more with a gain of 0.0025 QALY more than surgery. The incremental cost per QALY was therefore £518,462, well beyond any reasonable level of cost effectiveness. Another network meta-analysis model reported by Marsden et al[526], simulated five years of endothermal, conventional surgery, UGFS and conservative care. In this model conventional surgery cost £1,102 and gained 3.55 QALY, whereas endothermal treatments cost £869 and gained 3.72 QALY. Similar to the CLASS trial, the incremental cost was £3,161 per QALY, well within cost effectiveness.

The results of the HELP- economic analysis are surprising in that EVLA produced marginally smaller QALY in the long term, albeit very minor and not statistically significant. Most economic analyses took an optimistic view that minimally invasive treatment would be more benefit in the long term. However, aside from a significant early benefit, over a five year time period differences between the EVLA and conventional surgery are in fact minimal. In health economic terms, both treatments are at a similar level of value, with conventional surgery potentially being a cost effective alternative to EVLA despite its additional costs.

EVLA design and technique

Modifications of the EVLA device are now common, with the 810 nm bare fibre used in this study almost outdated against a wide variety of wavelengths, laser designs and settings now available. Of course these new products are advertised as superior, but long studies are rare.

In this study it was found that there was an early advantage to using ELVA at a higher power (14W) and at continuous energy delivery. At 12 weeks there was an advantage in the SF-36 domains of Physical function, Vitality and Mental Health

versus those using the 12W pulse setting. It was also noted that concomitant phlebectomy was able to enhance early SF-36 Physical function and disease specific QoL in the AVVQ. Beyond these early benefits, the effect of different EVLA settings and techniques was minor, with no difference in long term clinical outcomes or recurrence.

Adjustments to the EVLA tip design, laser wavelength and power have all been suggested as ways of improving the already highly successful EVLA technique[387-390]. While it does appear that the power and firing rate can be altered to improve the short term outcomes, further studies are required to establish if this is also the same for alterations to the wavelength and EVLA tip [371, 391-394]. Intense temperatures associated with EVLA may limit the effect of any such modifications, whereas a clear contrast between continuous and pulse delivery of energy would likely result in two different endovenous environments with different outcomes[394-396]. Pain and discomfort during EVTA is still a pressing concern, even with liberal application of TLA. It is perhaps no surprise that "pain-free" techniques are being sought, such as MOCA or even endovenous glue[528]. Again, long term studies are required. It is also important to note that treatment of varicose tributaries, oft ignored in many trials comparing EVLA devices, was independently associated with a significant improvement in QoL. While marginal improvements may be achieved between different EVLA fibres, early outcomes may depend more on treating the whole limb rather than just one axis.

Study limitations

The ability of a study detect meaningful differences depends on its power. A larger study has more power and is more likely to detect a true significant difference

between two treatment groups when a minimum sample size is met. In the case of the HELP-1 trail, despite its large size, at five years overall follow up was 79%, whereas statistical provision was only made for a loss to follow up of 10%. A risk which is inherently related to an underpowered study (i.e. one with fewer numbers than the *priori* power calculation), is the risk of a type 1 error; a statistically positive result which has occurred by chance rather than a true difference[529]. When lots of outcome measurements are taken, especially with surveys such as the SF-36, there is always a risk that one may become statistically significant by chance alone. Generally, large differences are more likely to be clinically relevant, although these too can be in error, so caution is always needed when interpreting slight differences as a significant result. The HELP-1 study is therefore at risk of such an error, as well as missing statistically important differences which a study with enough participants (i.e. >90% follow up) may have detected (i.e. type 2 error). Overview of the data distribution of most of the outcomes take across the studies above (e.g. AVVQ in the HELP-1 study) does not suggest an underlying type 1 or 2 error and is suggestive that the trial was of a sufficient size at five years to give reasonably accurate impression of the true results. Issues might arise with slight differences observed, such as Physical Function at five years in study 5 (C2 vs C3- C4 disease). While a 5 point difference is said to be a clinically noticeable by the SF-36 authors, in the context of a clinical trial this this really only applies when the study is of a sufficient power. A study with sufficient power therefore warranted to investigate if this is a true difference rather than one which could have arisen by chance. In another example, while QoL data was collected in the EVLTAP trial, the study was powered to detect differences in AVVQ only, the more subtle SF-36 instrument may not be a true reflection of the true outcomes. Conversely, the difference seen in the EQ5D

was so pronounced, that it supports the conclusion that a significant difference had arisen. However, this remains conjecture until a formal study is undertaken which is powered to specifically investigate this hypothesis.

Another limitation is that, due to the very nature of the interventions studied, blinding was impractical at both the time of intervention and during follow up. However, use of objective clinical criteria, QoL questionnaires and validated ultrasound protocols minimised the risk of bias.

One aspect which cannot be answered is what the long term outcomes would be if further treatments were not performed (i..e only the index treatmet). In the EVLTAP trial, sequential phlebectomy appeared to greatly improve patient outcomes but the true long term outcomes of no concomitant phlebectomy are unknown. Indeed, any trial which would deny further treatment could be deemed unethical, especially with the EVLTAP trial showing a clear relationship between QoL improvement and additional treatment. Extent and breadth of additional procedures, such as phlebectomy, could also not be controlled. Any restriction would have likely impaired any potential clinical improvement, but by allowing treatment equally to both groups any bias should be minimised.

In the economic analysis there are some limitations in accurately detailing all costs over five years. Some economic trials have extended costs to society, such as employment losses due to absence leave[513]. This was not done in the above studies as this is often an unreliable measure, not least due to the various types of employment[513] and general variation in recovery times seen in the UK population following vein surgery [160, 530].

The specific inclusion and exclusion criteria may also have limited the generalisability of the study. However, broadening the recruitment pool would have caused significant problems with statistical and clinical comparisons within the trail.

The nature of the scheduled follow up appointments also added a limitation in accurately recording a trend of when incidents were to arise after treatment. In the above studies patients were intensively followed up in the first year and then were reviewed in the long term at two and five years. This left a period of three years when a recurrence could potentially arise undetected, unless the patient was symptomatic and chose to book an expedited appointment. However, a concern is that by booking too many appointments patients may find them onerous and could withdraw from the study, especially if they feel that they are attending unnecessarily as nothing has progressed, and by booking too few important information would be lost. In waiting at two and five years our study was still able to record important long term data with a respectable follow up attendance while still capturing symptomatic recurrences as and when they arose. Other contemporary studies have used annual appointments in their follow up protocols[481-483], whereas others have also omitted the third and fourth year[484, 485]. It appears that regardless of the follow up frequency, final outcomes at five years are generally similar in most studies. However, the observable trend over time is different and of a more gentle linear slope when the follow up is annually. As such, while it can be said that the HELP-1 and EVLTAP studies are accurate at their follow up points at two and five years, caution should be used when approximating the outcomes during these interim periods. In addition, it is also possible that as patients with symptomatic recurrence are encouraged to attend when their symptoms arise, the proportion and time taken to develop symptomatic recurrence is overestimated. While of course a study with more

frequent appointments is more preferable (and will allow more clear interpretation of trends), it may not prove to be logistically viable or indeed statistically necessary, as often the clinical question is not to record annual trends but rather to establish what the clinical outcomes are at certain time points after treatment.

Improvements in further research

Venous disease is a constantly evolving research subject but several areas have yet to be fully investigated. Of course, uncertainty of the outcomes beyond 5 years after EVLA and conventional surgery treatment remains, with only few longer term studies published[322, 531]. The longer follow up of the HELP-1 and EVLTAP trial to 10 years would therefore provide an invaluable contribution of high quality long term data.

Another aspect of venous treatment which warrants investigation is the use of compression and bandages. In its most recent guidelines NICE[152] specifically raised concerns regarding the quality of literature surrounding post treatment compression techniques. During a review of the evidence base much of the published literature was felt to be of poor quality and often not relevant to the new minimally invasive techniques. Indeed most studies had been based on clinical experience after conventional surgery where compression is often used to prevent bleeding and haematoma (common concerns after surgery). Experts in sclerotherapy often suggest that the choice of compression regime is vital to improving patient outcomes. It is therefore possible that the choice of compression may have altered patient outcomes in the studies above. A compression period of 6 weeks is now regarded as excessive after minimally invasive treatment (NICE recommend 1 week). It is possible that compression for too long might increase patient discomfort. It is also possible that

compression applied for too short a period after EVLA may increase the risk of complications and recurrence, or perhaps compression has no effect at all. A study which investigates the role of compression in the era of minimally invasive treatments is therefore urgently warranted, as this is a variable common to all procedures which could drastically alter results and inform any future research trials.

A further question raised by NICE was the role of phlebectomy during and after EVTA. While the EVLTAP and AVULS[524] trials have both supported the practice of concomitant phlebectomy during EVTA, other options, such as sclerotherapy, have been proposed as alternative methods of tributary treatment. A trial of sufficient power to investigate the QoL outcomes (e.g. SF-36, EQ5D) and size to include various tributary treatment option would help establish the ideal intraoperative practice if a similar study was to be repeated.

Study implications

Research is an iterative process and there are certain lessons which can be learned from this study which may help inform later trials. The first is that an expected 10% loss to follow up is too optimistic and, as seen in this study and in others, a typical follow up loss should be expected to be around 20% over five years. A larger study would therefore be more likely to retain its power into the longer term, and perhaps beyond**.** The frequency of appointments did not appear to be a limiting factor in five year attendances. If the burden associated with frequency of follow up appointments can be ameliorated it may be possible to increase the study to annual review, although this will add little additional information. Rather, if the question is the trend between treatment and five years they study should be designed with this as the main hypothesis.

The use of clear and objective measurements was vital in trying to minimise the risk of bias. Unfortunately some instruments have inherent limitations. For example, while satisfaction was measured objectively it could be interpreted quite subjectively, and QoL instruments such as the EQ5D, may not be as sensitive as anticipated. These unexpected limitations may be resolved with further development of the QoL instruments (i.e. five level EQ5D-5L), which themselves may lead to more research.

The clinical and cost outcomes of treating venous disease also raises some important implications. Treatment of less severe venous disease (C2) is often restricted by healthcare commissioners and insurance companies until severe changes start to develop. The additional long term costs of such an approach suggest that delaying treatment is not just a fallacy in terms of saving money, but also causes patients to miss a period of QoL gain which does not occur after treating limbs with severe disease. Potentially treating proximal veins (e.g. AASV) may also save money in preventing recurrence, but this may be unnecessary and risks complications.

In future research is

The ESCHAR trial[277, 278, 532] reported that conventional surgery can reduce ulcer recurrence rates. A trial investigating the role of EVTA, the EVRA trial, in venous ulcer disease is keenly awaited. Optimisation of the EVLA technique will no doubt continue, but new non-tumescent methods have now arrived and may soon challenge the supremacy of EVTA.

Chapter 6 – Conclusion

SVI is a common disease of the adult population and is associated with a significant impairment of QoL. Both conventional surgery and EVLA are highly successful treatments at improving QoL and provide high levels of patient satisfaction over five years. Recurrence in the long term is high, affecting up to half of the study, and does not appear to be greatly affected by either treatment. Requirement for further interventions are low but can be complex, requiring specialist input to ensure optimal treatment. Early benefits of EVLA are significant with reduced complications and enhanced QoL recovery. After one year both treatments are broadly similar.

Concomitant phlebectomy during EVLA is associated with a significant early gain in QoL compared to those only receiving EVLA alone, but in the long term outcomes are similar, as long as a policy of sequential phlebectomy for residual symptomatic tributaries is employed. Use of the 14W continuous laser EVLA fibre was also recognised to provide enhanced early QoL. Long term outcomes were also similar.

Economic analysis found that concomitant phlebectomy and treatment of those with early disease was much more cost effective than sequential phlebectomy and treatment of those with complex disease. Conventional surgery and EVLA are both effective treatments and despite the smaller initial cost of EVLA, are broadly of the same cost effectiveness in the long term.

In conclusion, this study supports NICE guidance that EVLA should be preferred over conventional surgery.

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