Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence

Being a thesis submitted for the degree of Doctor of Medicine at the Hull York Medical School

By

Abduraheem Mohamed

MBChB, MRCS, PGCert Vascular Ultrasound

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Prizes

- North Trent Vascular meeting 2019 - Best oral presentation prize
- Royal Society of Medicine Venous Forum Annual Meeting 2019 – Oral Presentation First Place prize

Publications

- Mohamed AH, Leung C, Wallace T, Pymer S, Harwood A, Smith G, Carradice D, Chetter IC. Mechanochemical ablation for the treatment of superficial venous incompetence: A cohort study of a single centre's early experience. Phlebology. 2019 Aug;34(7):466-473. doi: 10.1177/0268355518818339. Epub 2018 Dec 30
- Mohamed AH, Leung C, Hitchman L, Wallace T, Smith G, Carradice D, Chetter IC. A prospective observational cohort study of concomitant versus sequential phlebectomy for tributary varicosities following axial mechanochemical ablation. Phlebology. 2019 Oct;34(9):627-635. doi: 10.1177/0268355519835625. Epub 2019 Mar 13.
- Mohamed AH, Leung C, Wallace T, Smith G, Carradice D, Chetter IC. A Randomized Controlled Trial of Endovenous Laser Ablation Versus Mechanochemical Ablation with ClariVein in the Management of Superficial Venous Incompetence (LAMA Trial) – Ann Surg. 2020 Jan 21. doi: 10.1097/SLA.0000000000003749. Online ahead of print. PMID: 31977509

Abstract

Background

The routine management of venous incompetence has undergone considerable changes in the last two decades led by the introduction of minimally invasive endovenous techniques. At the heart of these changes has been a drive to offer patients effective symptomatic relief whilst minimising disruption to patient quality of life and periprocedural pain. Endovenous thermal ablation (EVTA) has been the main mode of treatment in this minimally invasive era, however, non-thermal methods are challenging this established order and include mechanochemical ablation (MOCA) which is an exciting new technique that combines liquid sclerotherapy with mechanical damage to vessel intima.

Aims

The studies contained within this thesis aim to assess the evidence supporting the use of MOCA for the treatment of venous incompetence, to independently validate these results, to optimise a strategy of performing MOCA, and to test the efficacy and clinical effectiveness of MOCA against EVTA.

Methods

Study 1 is a systematic review of the current literature of MOCA, focusing on objective assessment of clinical success including duplex ultrasound (DUS) measurements and health related patient reported outcomes (PROMS). Study 2 is a cohort study of symptomatic patients with superficial venous incompetence (SVI), treated with MOCA and 1.5% Sodium tetradecyl sulphate (STS). Outcomes included clinical examination, DUS, health related PROMS at baseline and weeks 1,6,26 and 52. Study 3 compares the approach of treating varicose tributaries with phlebectomy at the time of performing MOCA (MOCAP) against sequential treatment of tributary varicosities at a later date (MOCAS). A similar outcomes assessment and follow up strategy to study 2 was adopted. Study 4 takes forward the results of the previous studies and compares endovenous laser ablation (EVLA) to MOCA in a randomised controlled study comparing the clinical and technical outcomes of each intervention at baseline and weeks 1,6,26 and 52.

Results

Study 1: MOCA is a safe and effective method of treating SVI in the short-term, however, the evidence for the longevity of its results beyond 6 months is poor. Moreover, the data on anatomical occlusion rates is questionable and may not match those of EVTA.

Study 2: Thirty-two patients were recruited to the study. Complete target vein occlusion at one year was achieved in 21 (75%) patients. Six patients (21.4%) required secondary procedures, of which three had axial EVLA and three required ambulatory phlebectomy with perforator ligation. There was a significant improvement in the median (interquartile range) Venous Clinical Severity Score (VCSS) from baseline 6 (5–8) to a score of 1 (0–2) at one year (p<0.001). There was also a significant improvement in health-related quality of life (HRQoL), both generic (p<0.001) and disease specific (p<0.001). One patient (3.1%) had a post-procedural non-fatal pulmonary embolus.

Study 3: Fifty patients underwent MOCAP and 33 patients MOCAS. The two groups were comparable at baseline. MOCAP was associated with lower (better) AVVQ scores at six weeks (3.4 (0.5–6.0) vs. 6.1 (1.8–12.1); p=0.009) and at six months (1.6 (0.0–4.5) vs. 3.34 (1.8–8.4); p=0.009) but by one year the difference was no longer statistically significant (1.81 (0.0–4.5) vs. 3.81 (0.2–5.3); p=0.099). MOCAP was associated with longer procedural duration (45 min (36–56) vs. 30 min (25–37); p<0.001) and higher maximal periprocedural pain (31 (21–59) vs. 18 (7–25); p<0.001). VCSS at all time points was lower in MOCAP group compared to MOCAS (0 (0–1) vs. 1 (0–3); p<0.001). MOCAP was associated with fewer episodes of clinically significant thrombophlebitis (6 of 50 (12%) vs. 10 of 33 (30%); p=0.039) and lower numbers of secondary procedures (2 (4%) vs. 6 (18%); p=0.032)

Study 4: One hundred and fifty patients were randomised equally between MOCA and EVLA. Both groups reported low intraprocedural pain scores; on a 100 mm visual analogue scale, pain during axial EVLA was 22 (9-44) compared to 15 (9-29) during MOCA; p=0.210. At 1 year, duplex derived anatomical occlusion rates after EVLA were 63/69 (91%) compared to 53/69 (77%) in the MOCA group; p=0.020. Both groups experienced significant improvement in VCSS and AVVQ after treatment, without a significant difference between groups. Median VCSS improved from 6 (5-8) to 0 (0-1) at one year; p<0.001. Median AVVQ improved from 13.8 (10.0-17.7) to 2.0 (0.0-4.9); p<0.001. One patient in the MOCA group experienced DVT.

Conclusion

MOCA with 1.5% STS is safe, effective and leads to significant improvement in patient health related quality of life (HRQoL) outcomes up to 1 year follow up. However, the anatomical occlusion rates achieved with MOCA are lower than has been previously reported in the literature and do not match EVLA results. Patient HRQoL gains are better when MOCA is combined with concomitant phlebectomy

of varicose tributaries and using this approach HRQoL gains following MOCA are equivalent to those achieved by EVLA. Long-term follow up is needed however to ascertain the effect of the increased recanalisation following MOCA on disease recurrence and progression.

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Glossary

AASV	Anterior Accessory Saphenous Vein
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	Body Mass Index
BTLA	Buffered Tumescent Local Anaesthesia
CEAP	Clinical aEtiologic Anatomic Pathophysiologic Score
CT	Computed Tomography
CVA	Cerebrovascular accident
CFV	Common femoral vein
DUS	Duplex Ultrasound
DVI	Deep venous incompetence
DVT	Deep Vein Thrombosis
EHIT	Endovenous heat-induced thrombosis
EQ5D	Euro-Qol 5-dimension
EVLA	Endovenous laser ablation
EVTA	Endovenous thermal ablation
GA	General Anaesthetic
GSV	Great Saphenous Vein
ICAM	Intercellular adhesion molecule
J	Joules (unit of energy)
L	Litre: unit of volume (may be prefixed to denote different magnitudes)
LA	Local Anaesthetic
LMWH	Low molecular weight heparin
LEED	Linear Endovenous Energy Density (Jcm-1)
LDS	Lipodermatosclerosis
M	Meter
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MMP	Matrix metalloproteinase
NaHCO3	Sodium bicarbonate
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
PE	Pulmonary Embolism
PROMs	Patient-reported outcome measures
QoL	Quality of Life
QALY	Quality-adjusted life year

REC	Research ethics committee
RCT	Randomised Clinical Trial
RFA	Radiofrequency ablation
s	Second: unit of time
SF-36	Short Form -36
SFJ	Sapheno-Femoral Junction
SPJ	Sapheno-Popliteal Junction
SSI	Surgical Site Infection
STD	Sodium tetradecyl sulphate: sclerosing agent
SVI	Superficial Venous incompetence
TIMP	Tissue inhibitor of matrix metalloproteinase
TLA	Tumescent Local Anaesthesia
UGFS	Ultrasound guided foam sclerotherapy
UK	United Kingdom
VAS	Visual analogue score
VEGF	Vascular endothelial growth factor
VCSS	Varicose Clinical Severity Score
VTE	Venous Thromboembolism
W	Watt: unit of power

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I would like to thank my family and friends for their patience and support during these years of research. My mother, Muxubo who is true to her name, aabo Xuseen, my wife Karolina and all my siblings.

Author's Declaration

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

Contributors to the studies within the thesis

Study 1: A Systematic Review of Mechanochemical Ablation

Ian Chetter (ICC) conceived the idea. I, Abduraheem Mohamed (AHM) designed the search strategy, data collection spreadsheets and analysis methods. Review of study manuscripts was independently performed by AHM and Clement Leung (CL) with Daniel Carradice (DC) arbitrating disagreements. Data collection was carried out by AHM and CL independently. AHM performed all analysis and wrote all the content.

Study 2: A Cohort Study of Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence

ICC and DC conceived and designed the study. ICC and CL recruited and treated all patients. ICC and CL collected all data up to six months. CL, AHM and TW collected one year data. AHM performed all data analysis, interpretation and writing of the study.

Study 3: A Cohort Study of Mechanochemical Ablation with Concomitant Phlebectomy (MOCAP) Versus Sequential Phlebectomy (MOCAS) in the Treatment of Superficial Venous Incompetence

ICC and DC conceived and designed the study. ICC and CL recruited and treated all patients. ICC and CL collected all data up to six months. CL, AHM and TW collected one year data. AHM performed all data analysis, interpretation and writing of the study.

Study 4: A Randomised Clinical Trial of Endovenous Laser Ablation Versus Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence (LAMA Trial)

ICC, DC, TW and CL conceived, designed and established the study. ICC and CL recruited patients from 001 to 080 and AHM recruited patients 081 to 150. All MOCA procedures were performed by ICC or CL. EVLA procedures were carried out by ICC, CL or AHM. Phlebectomy were carried out by two of ICC, CL or AHM at any one time. For patients 001 to 060, CL and ICC collected data from recruitment to one year follow up. For patients 090 to 150, AHM collected all data from recruitment to one year follow up. Patients 061 to 089, CL, TW and AHM collected data from recruitment to one year follow up. AHM performed all data analysis, interpretation and writing of the study.

Chapter 1: Introduction

1.1 Opening Statement

Great developments have taken place in our understanding of superficial venous incompetence (SVI) in the last half a century. Health related quality of life (HRQoL) research has demonstrated the significant morbidity associated with this disease, and increasingly health systems are recognising the financial impact of treating the complications of venous incompetence. But perhaps the largest development in this field has been the endovenous revolution at the turn of the twenty first century, which introduced minimally invasive treatment methods that are now used instead of or in conjunction with open surgical options. Robust evidence has developed to support the use of these methods, but evidence gaps still exist, particularly with the newer non-thermal non-tumescent (NTNT) methods such as Mechanochemical ablation (MOCA). This chapter aims to set the scene for the studies that follow by discussing current knowledge of SVI as a disease, and its modern management methods.

1.2 History of venous disease

Attempts by health professionals at understanding and treating lower limb venous disease can be traced as far back as human civilisations have existed. Perception of the circular flow of blood from the heart to the organs of the body and back can be independently traced to ancient Indians, ancient Chinese and Greeks in the fifth century before Christ (BC)[1]. Ten centuries prior to that, the Ebers Papyrus of pharaonic Egypt also depicts the heart as the centre of circulation in addition to describing the serpentine appearance of varicose veins and issuing a warning “Thou shall not touch something like this”, due to the risk of exsanguination[1,2]. These ideas however were overshadowed by the Pythagorean teachings of “the four humours” until the fourteenth century Anno Domini (AD), when detailed descriptions of the circulatory system and venous anatomy became widely accepted[1]. Consequently, many of the techniques and principles applied today in treating venous incompetence were described in ancient times but were lost in practice until recently.

Forerunners in the field include the Romans Celsus and Galenus in the first century BC and AD, respectively. Both are believed to have performed venectomy and ligation of varicose veins[1]. Galenus in fact is also credited with inventing the surgical ligature and the vein hook for performing phlebectomy[2]. Surgical ligation and stripping of the great saphenous vein (GSV) is later described by the Byzantine Paulus Aegineta in the seventh century AD and the Andalusian Albucasis of Cordoba in the tenth century AD; the latter being credited with the invention of the stripper[1,2].

Another seven centuries would follow before recorded attempts at minimally invasive treatment in the seventeenth century. Daniel Zolliker is credited with the first attempt at sclerotherapy; he performed injections of acidic solutions into varicosities in order to cause them to thrombose. A few years prior, Sigismond Elsholz used a needle and syringe fashioned from chicken bone and a pigeon's bladder to inject distilled water and "essences from plants" intravenously to irritate venous ulcers[1]. These fledgling practices led to the development of sclerotherapy which gained particular popularity in France by the nineteenth century. It is unknown how successful these early attempts were, but perhaps unsurprisingly, injections of caustic and poisonous substances lead to widespread serious complications in these patients, leading the Medical Congress in Lyon to ban sclerotherapy in France in 1894[1,3]. Meanwhile, surgical greats of the nineteenth and twentieth centuries such as Freidrich Trendelenburg, Charles Mayo and William Babcock rediscovered and refined open surgical techniques, which became the established standard of care for treating SVI until the endovenous revolution in the twenty first century.

1.3 Anatomy and nomenclature

The lower limb venous system is more variable than its arterial counterpart, and its study was historically unduly complicated because of the use of contradicting and confusing terms in the literature. Current nomenclature separates lower limb veins into a deep venous system and a superficial venous system connected by two formal junctions at the groin and knee levels. Additionally, communicating veins connect veins of the same system with one another whilst perforator veins connect the superficial system to the deep system. In health, the deep venous system transmits 90% of venous flow from the lower limb back towards the heart. Most flow through the superficial venous system drains into the deep veins via perforators and axial junctions.

An international committee in 2001 formulated a consensus document updating and standardising the nomenclature of the literature[4]. Controversially, it resulted in the replacement of sound terminology such as the saphenofemoral junction (SFJ) with strange new terms such as "confluence of the superficial inguinal veins" leading to some resistance to the committee document. Following some revisions and refinements in 2005 however, the consensus document was accepted almost universally and the SFJ was reintroduced into official terminiolgy[5]. This thesis will adhere to current international terminological consensus.

Histologically, vein walls consist of three distinct layers - intima, media and adventitia. These are not as well defined as their arterial counterparts, particularly in the smaller veins. Valves are present in all the lower limb veins and venules, increasing in number from proximal to distal, and from superficial to deep[6-8]. They are generally bicuspid and are formed by a thin layer of connective tissue lined on both sides with intimal cells. The intima consists of a single layer of endothelial cells, elastic lamina and a basement membrane[9]. The media is composed of three layers of smooth muscle cells (SMCs); the inner and outer layers are arranged longitudinally, and a middle layer arranged circumferentially[9-12]. These three layers are scaffolded together by an extracellular matrix of collagen, proteoglycans and elastin. The medial layer is key to the capacitance function of veins as it allows relaxation and recoil of the vein as required[10,13,14]. The adventitia is made of longitudinal SMCs, fibroblasts, collagen and vasa vasorum[9,12,15].

1.3.1 **Superficial venous system**

The superficial venous system consists of all the veins superficial to the muscular fascia. This includes the subpapillary reticular plexi of the skin and subcutaneous tissue, the superficial tributaries under the skin and several axial veins that can vary from patient to patient. The two main axial veins of this system are the GSV and the small saphenous vein (SSV). The GSV begins anterior to the medial malleolus ascending medially along the calf, the knee and thigh until it enters the deep compartment at the fossa ovalis 2-3cm inferolaterally to the pubic tubercle, draining into the common femoral vein (CFV) at the SFJ. The median number of tributaries joining the GSV before draining in the CFV is four[16]. Figure 1 is a diagram of the classical SFJ[16]. The SSV starts posterior to the lateral malleolus at the ankle ascending along the posterior aspect of the calf lateral to the Achilles tendon then between the heads of gastrocnemius[1,17]. Usually, at the level of the knee crease the SSV pierces the muscular fascia and joins the popliteal vein at the saphenopopliteal junction (SPJ). Both the GSV and SSV travel enclosed in their own saphenous compartment, formed by a thin saphenous fascia superior to the axial vein and a muscular fascia inferiorly. The saphenous nerve is closely associated with the GSV below the knee, sometimes with a connective sheath joining the perineurium to the venous adventitia[18]. The SSV in turn is closely associated with the sural nerve in the calf[19].

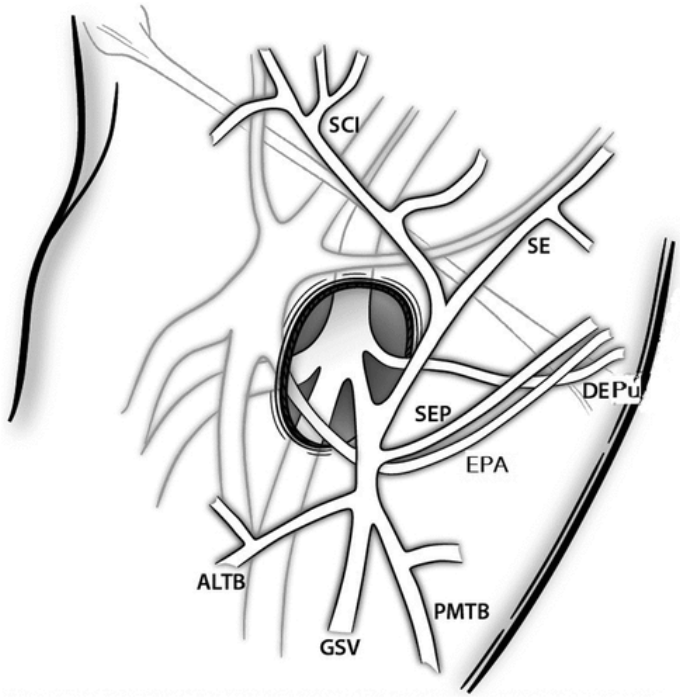


Figure 1 - The classic appearance of the saphenofemoral junction (original drawing by Emma Wray and electronically processed into digital images by Andrea Thompson). SCI: superficial circumflex iliac; SE: Superficial Epigastric; SEP: superficial external pudendal; DEP: deep external pudendal; EPA: external pudendal artery; ALTB: anterolateral thigh branch – more commonly known as Anterior Accessory Saphenous Vein (AASV); PMTB: posteromedial thigh branch; GSV: great saphenous vein.

1.3.2 **The deep venous system**

The deep venous system consists of all veins deep to the muscular fascia, these veins are often duplicated and travel alongside their named arteries. Two main deep veins drain the foot, the deep venous arch drains into the medial and lateral plantar veins, which in turn form the posterior tibial veins posterior to medial malleolus. On the foot dorsum, the digital veins drain into the dorsal metatarsal veins, then the dorsal pedal veins which form the anterior tibial veins. The anterior and posterior tibial veins travel cranially to join the popliteal vein. The other deep tributaries of the popliteal vein are the peroneal vein, soleal veins, and the gastrocnemius veins[1]. Embedded in the calf muscle bellies are venous sinuses that are connected to the deep veins. The popliteal vein becomes the femoral vein as it travels through the adductor hiatus and cranially within Hunter's canal; at this level, there is frequently a large communicating vein connecting the femoral vein to the profunda femoris vein. The profunda femoris drains into the femoral vein forming the common femoral vein, which in turn becomes the external iliac vein when it passes under the inguinal ligament.

1.4 Physiology

Circulation in the venous system is one of low pressure, low velocity, low resistance but high volume. The main function of the venous system is to provide a conduit for return of deoxygenated blood back

to the heart. Three factors are central to this role, the pressure gradient between the right atrium and the capillary bed, the calf muscle pump and the venous valves. The lower limb venous system also plays a key role in cardiovascular homeostasis by providing a reservoir for blood, with around half of the body's total volume of venous blood being contained in the lower limb veins and venules at any one time[20,21]. The lower limb venous system also plays a role in temperature homeostasis by providing a large surface area for heat exchange through the rich network of dermal veins and venules[22,23].

In the supine position the main factor contributing to venous return to the right atrium is the difference in pressure between the right atrium and the venous aspect of the capillary bed[24]. Pressure at the right atrium measures 4-7 mmHg, compared with 12-18 mmHg at the venous side of the capillary bed[24], leading to antegrade flow of blood towards the heart. In the upright position, hydrostatic pressure is generated by the force of gravity on the column of blood below the right atrium, increasing pressure by 0.77 mmHg cm^{-1} below the level of the right atrium[25]. Hydrostatic pressure can reach 95 mmHg in veins at the ankle of an adult of 175cm height. Leg muscles and venous valves work in concert to generate positive pressure to overcome this hydrostatic pressure and maintain adequate venous return to the heart. Whilst foot and thigh muscles contribute to this action; it is primarily the calf muscles that act as the bellows propelling blood cranially towards the heart. The role played by the calf muscles and their corresponding veins and sinuses is commonly termed "calf muscle pump", generating up to 200 mmHg of pressure during contraction[24,26].

At rest venous flow is phasic with respiration and valves open to allow antegrade flow with inspiration and close to prevent retrograde flow with expiration. Similarly, during ambulation the action of the muscle pump relies on competent valves to prevent retrograde flow when they contract; a normal valve can be expected to resist up to 300 mmHg without allowing reflux[22]. Muscular contraction empties the deep venous system creating a stream of venous flow travelling cranially and opening valve leaflets. In the open phase, valve leaflets oscillate with venous flow and do not touch the vein wall. Flow through the valve separates into a cranially directed jet and vortical flow into a sinus pocket behind the valve cusps as shown in Figure 2[27]. Flow is laminar within the central jet and increases in velocity, this is thought to facilitate return towards the heart. Whereas the vortical stream behind the valve cusps prevents stasis inside the valve pocket and later joins the forward jet stream[27]. Muscular contraction leads to emptying of the deep venous system and creates a relative pressure gradient from the superficial venous system to the emptied deep system during the relaxation phase. The perforator valves thus open to allow flow through the superficial system to drain into the deep system. The

muscle pump and valves together dramatically decrease venous pressure at the ankle from approximately 90-120 mmHg to 25 mmHg on ambulation. This is termed the ambulatory venous pressure (AVP) and is an important marker of the health of the venous system. Dysfunction of the pump system is associated with significant rises in the AVP, which consequently is strongly associated with venous ulceration at AVPs of >90 mmHg[28].

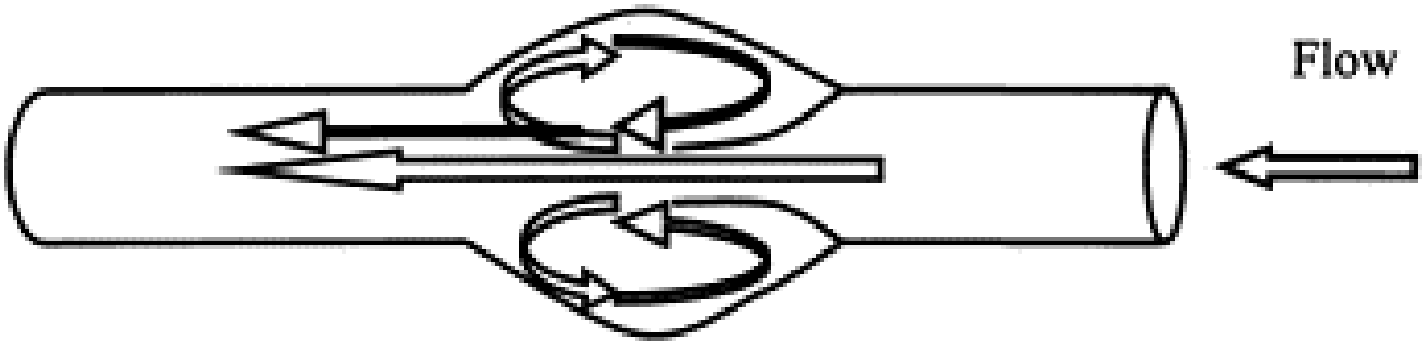


Figure 2 - Flow through open valve leaflets

1.5 Chronic Venous Disease

Chronic venous disease (CVD) is the umbrella term that describes the long-term effects of a malfunctioning venous system failing in its role as a conduit for transporting blood directly and efficiently back to the heart. It is characterised by morphological changes in the lower limb veins including dilatation, valvular incompetence and mural thickening, in addition to further changes in the skin and connective tissues, which can ultimately lead to skin ulceration. The most widely used classification to delineate the underlying cause of CVD is the Clinical aEtiological Anatomical Pathophysiological (CEAP) classification[29] (see1.6.3). This classification categorises underlying pathology into reflux, obstruction, a mixture of both, or an unknown cause[22]. Reflux can be congenital, idiopathic, or secondary. Congenital conditions leading to reflux are rare and include vein valve aplasia and Klippel-Trenaunay Syndrome[30,31]. Secondary reflux is usually due to a form of obstruction; which can be physical such as in May-Thurner Syndrome[32,33], or functional as can happen in neurodegenerative conditions leading to muscle pump failure[28,34].

Idiopathic venous reflux also termed primary venous incompetence – where no underlying cause for reflux is seen – is the commonest cause of CVD accounting for more than 80% of the disease[29]. Superficial Venous incompetence (SVI) is the commonest type of primary venous incompetence and is the focus of this thesis. A study of women with primary venous incompetence showed isolated reflux in the GSV territory was present in 60%, isolated SSV reflux in 3%, with another 17% having mixed reflux

in both superficial axial veins. Only 3% had isolated deep venous incompetence (DVI), with the remaining patients showing mixed reflux of perforators, superficial and deep veins as Figure 3 shows [35].

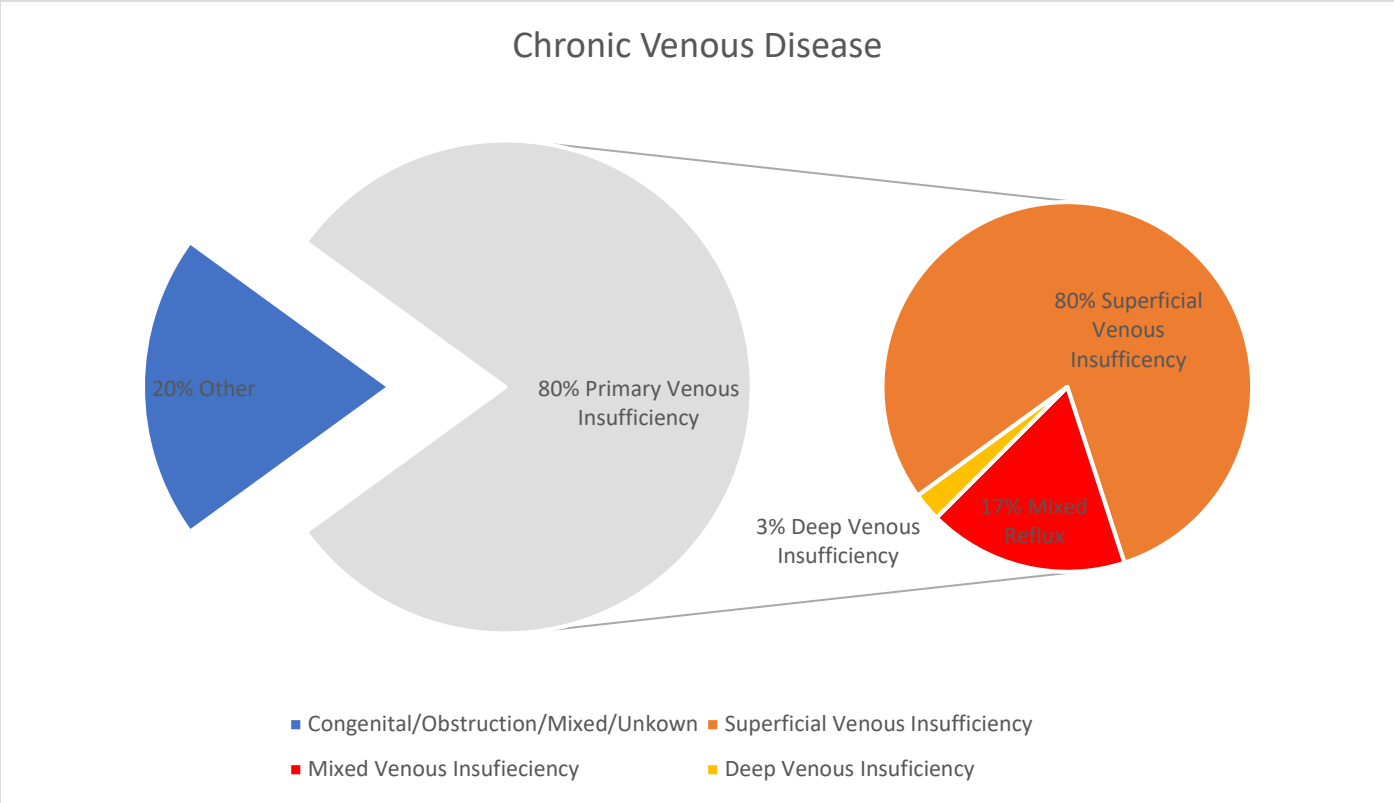


Figure 3 - Pie of pie chart of chronic venous disease

1.5.1 **Pathophysiology of SVI**

Historically, the dominant theory influencing the management approach when treating SVI has been the Descending Theory of pathogenesis. It was popularised by Trendelenburg and can be traced as far back as Paulus of Aegina in the 7th century AD[36,37]. The theory argues that the disease process begins with the failure of the valves at the saphenofemoral junction leading to reflux of blood from the cava and iliac veins down the proximal GSV. This is followed by progressive failure of valves in the superficial system in a cranial to caudal direction; ultimately leading to the appearance of varicose veins and the commonly seen pattern of reflux in the GSV and its tributaries.

Detractors of the Descending Theory have pointed out that many patients with SVI have normal saphenous veins or indeed have competent proximal saphenous valves with incompetence distal to that[36,38-41]. Cadaveric and duplex ultrasound (DUS) studies were key in demonstrating this finding and led to the more current Multifocal Theory of disease progression. This theory states that the disease

can start at different areas in the superficial system and then progress into other superficial veins and trunks; here the disease ascends and descends simultaneously at different sites.

A complete understanding of the pathological processes leading to SVI remains elusive. However, modern understanding has highlighted the interplay between chronic inflammation, venous hypertension, vein wall remodelling and reflux that leads to a vicious cycle of further inflammation and disease progression Figure 4. The apparent macroscopic disease changes in the structure of vein wall, vein valves, venous haemodynamics, skin and soft tissues of the leg are now understood to be the result of microscopic dysregulation affecting immune cells, endothelium, connective tissue and skin cells.

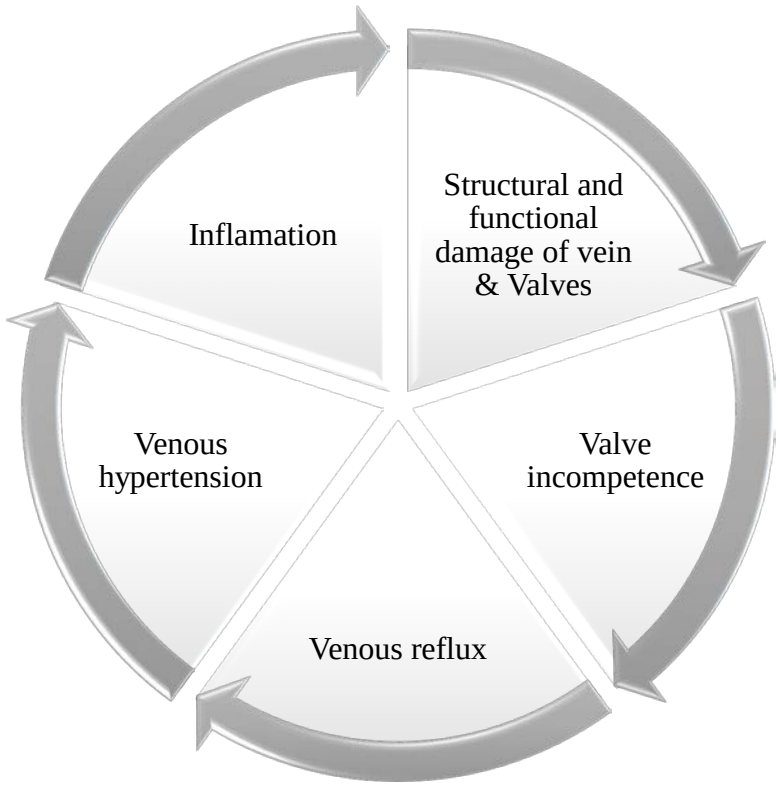


Figure 4 - SVI pathophysiology cycle

1.5.1.(a) SVI venous changes

Consequences of increased pressure on venous valves have been demonstrated in rat models. Researchers created an arteriovenous fistula in the femoral vessels of rats increasing the pressure within the vein from 11mmHg to 90mmHg. Changes within these veins over time were examined, with the contralateral veins as controls[42-44]. Within weeks the hypertensive veins were dilated with reduction in valve width, height and numbers. Increased expression of adhesion molecules and leukocyte infiltration was also detected in these veins[42-44]. The venous changes in these studies are

similar to those observed in patients with CVD leading the authors to conclude that venous hypertension and inflammation may lead to reflux[42-44].

Though rat model studies and others like it provide a perspective into the events that lead to CVD changes, they are unlikely to explain the early pathophysiology involved in SVI that lead to disease progression into symptomatic CVD. These early changes are likely to begin long before symptoms and signs are detected and therefore are difficult to distinguish when analysing tissue showing late phases of the disease. Nonetheless, we now have a good understanding of the changes that occur once the cycle of CVD is initiated that lead to the development of varicosities, stasis dermatitis and venous ulcers.

The role white blood cells play in the development of SVI was first highlighted with the observation that blood from patients with venous disease had a lower concentration of white cells when compared to healthy individuals. This formed the bases for the Leukocyte Trapping theory[17]. The authors hypothesised that the white cells became trapped in capillaries due to stagnant blood flow then activated causing an inflammatory cascade of events[45]. More recent studies show that the process is multifactorial and involves inflammatory endothelial cell activation and plasma proteins[46,47]. When activated, endothelial cells begin to express increased endothelial leukocyte adhesion molecule-1 (ELAM-1), intracellular adhesion molecule-1 (ICAM-1) and other molecules that lead to adhesion and migration of immune cells into the mural layers of the vein[48]. These are in turn activated and begin an inflammatory cascade leading to valvular and vein wall remodelling which involves all components of the vein wall including, endothelial cells, SMCs, fibroblasts, and all components of the extracellular compartment.

Intimal inflammatory changes include areas of thickening and fibrosis as well collagen deposition below the endothelial lining[9,11,12]. In the media, circular and longitudinal arrangements of muscle fibres become disrupted and disorganised, the muscle cells themselves enlarge and appear to change phenotype from contractile to synthetic[49-52]. In the adventitia, areas of increased numbers of SMCs, fibroblasts and collagen are seen, with organised thrombi in the vasa vasorum[15]. In other areas dystrophic mural changes are seen with little cellular content, where the vein wall is comprised of thickened intima, disorganised collagen and atrophic adventitia[9,53]. Interspersed with these, are areas with normal venous architecture[9,53].

The delicate balance in the organisation and proportion of elastin, collagen, SMCs and proteoglycans in the extracellular matrix (ECM) is crucial to the capacitance function of veins. Inflammatory changes affect this balance leading to a loss of venous tone[54,55]. In SVI, activated neutrophils release free radicals that degrade the elastin and collagen components of ECM[56-59]. The inflammatory process also alters the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs)[47,60,61]. The net effect of these events is one of increased matrix deposition[62,63]. However, the matrix proteins are degraded and disorganised. Overall collagen content is increased but with a proportional reduction in the elastic type III collagen and an increase in type I collagen[63-65]. Elastin content within the matrix is lost with fragmentation of the elastic tissue of the wall[66]. These changes in combination with the SMC changes in the media are thought to give varicose veins their classical dilated serpentine appearance.

1.5.1.(b) SVI skin changes

Dependant skin oedema and stasis dermatitis are again manifestations of sustained venous hypertension and inflammation. The role venous hypertension plays was shown in studies of patient's post ambulatory venous pressures[28,67]; where a linear correlation towards more severe stasis dermatitis was seen with increased post ambulatory venous pressure and skin ulceration was present in all patients with >90 mmHg[28,67]. The precise sequence of events leading to skin changes remains unclear but is thought to begin with endothelial cell activation leading to extravasation of macromolecules and red blood cell products into the dermal interstitium[68]. Extravasation of ferric iron compounds are particularly problematic, causing oxidative stress, activating MMPs, in addition to causing the skin pigmentation classical to stasis dermatitis[69-71]. Fibrinogen is another important molecule; once extravasated, it polymerises to form a fibrin cuff which contributes to dermal inflammation and fibrosis[72]. This proinflammatory environment attracts immune cells leading to a secondary inflammatory response with neutrophil infiltration and ECM alterations where disorganised collagen is deposited, and perivascular tissue fibrin cuffs are seen histologically.

Attempts at tissue repair are impaired in CVD. Transforming growth factor beta-1 (TGF-β1) is a cytokine released by activated endothelial cells among other cells. TGF-β1 influences all immune cells, fibroblasts, platelets and stimulates matrix protein production[73,74]. It induces TIMP-1 and collagen production while inhibiting MMP activity thereby favouring deposition of collagen by fibroblats[74]. There is uncertainty as to whether raised levels of TGF-β1 are a cause or a co factor; however, in CVD dermal collagen deposition by fibroblasts is irregular and leads to further dermal fibrosis[75]. Biopsies of

skin from patients with CVD also show elevated levels of other growth factors such as platelet-derived growth factors α and β, and vascular endothelial growth factor[76]. Of note, biopsies of healthy areas of skin from patients with CVD also show altered collagen synthesis by dermal fibroblast, which implies that the problem maybe intrinsic to fibroblasts rather than the inflammatory environment in the lower limb[77].

Further evidence of CVD fibroblast disfunction comes from in vitro studies of venous ulcer fibroblasts which show disfunction in cellular motility, proliferation, and synthetic function. Motility of dermal fibroblasts from patient's skin ulcers was reduced when compared to those of thigh fibroblasts[78]. Interestingly, the same study showed that neonatal fibroblasts also decrease in motility when exposed to venous ulcer exudate, highlighting the multifactorial nature of the process[78]. When comparing collagen production capacity of fibroblast in response to stimulation by proliferative cytokines such as TGF-β1, fibroblasts of patients with venous ulcers did not respond to stimulation, whereas controls increased collagen production by 60%[79]. Similarly, fibroblasts in CVD have a reduced or absent proliferative response to TGF-β1 and other stimulant cytokines that correlates with disease severity. Fibroblasts from patients with active ulcers did not proliferate on exposure to TGF-β1, whereas in earlier disease phases fibroblasts retain an agonist response to stimulation[80,81]. Histologically fibroblasts from venous ulcers appear like fibroblasts undergoing cellular senescence[80,81]. Perhaps fibroblast dysfunction in CVD reflects disease progression and sustained overstimulation rather than being a sign of an in borne primary dysfunction of fibroblasts; however, conclusive evidence is lacking in this matter. In summary, SVI and its subsequent CVD manifestations are the results of active tissue remodelling involving multiple mechanisms and at different stages. Growth factors, cytokines, and proteinases all appear to be involved in this process, but a clear understanding of the process remains elusive.

1.5.2 **Risk Factors for SVI**

Evidence for the risk factors of SVI comes from pathophysiological and epidemiological studies. Pathophysiological studies demonstrate that SVI development and progression is complex and multifactorial (see1.5.1). While epidemiological studies consistently show that SVI is very common. However, much of the epidemiological research carried out in the past now seems dated as our thinking about the science of epidemiology has moved on as well as our understanding of SVI. In terms of epidemiology, modern literature uses accepted terms such as prevalence and incidence, which were not universally accepted in the past. Similarly, the CEAP classification system which underpins much of

modern venous research is a historically recent development. Therefore, older epidemiological studies should be interpreted with caution.

Age

Age is the strongest risk factor associated with SVI and CVD. Studies across different continents, socioeconomics, ethnicities and timepoints consistently show disease prevalence and severity to increase with age[82-98]. The Edinburgh vein study reported a CVD prevalence of 12% in adults aged under 25, compared with 56% in those over 55[82]. In the San Diego Population study, increasing age was associated with worsening CVD severity. Severe disease was reported in 12% of patients aged under 50, which increased to 25% above the age of 70[99]. This positive correlation between increasing age and disease severity is unique among CVD risk factors and is one of the arguments for early treatment of SVI, in the hope of preventing severe venous ulceration in older age.

Gender

Most people hold the belief that SVI and CVD are commoner in women than men; however, the relationship between venous disease and gender is not that clear. Many epidemiological studies indeed report higher prevalence of varicose veins in women[40,88,100,101], and that women report symptoms and seek treatment more frequently than men[94,96,102-104]. On the other hand, a small number of studies show no difference between genders such as the Edinburgh vein study or indeed report higher prevalence of varicose veins in men[87,105,106]. It may seem easy to dismiss these studies as outliers; however, a closer look at the data is warranted. CVD trophic skin changes are reported more frequently in men, even in studies that report higher overall prevalence in women[87,88,92,100]s[101], and DUS studies show more DVI in men[40,87]. Whereas venous ulceration is 2 to 3 times more common in women than men[91]. Therefore perhaps, different pathophysiological factors influence disease progression between men and women.

Pregnancy

Hormonal effects are thought to increase the risk of developing SVI in women particularly with pregnancy. Prevalence of varicose veins in multiparous women is reported to be greater than nulliparous women[95,100,102,107,108]; with an increase in incidence with each full term pregnancy[96,97,109-111]. Again however, a few population level studies do not show such an association[112-114]. Our understanding of pathophysiology however supports the theory that pregnancy plays a role. Firstly, varicose veins in pregnancy develop at an early stage, coinciding with the increased plasma volume,

which is likely to place a strain on venous capacitance and change flow dynamics[115,116]. Secondly, hormone levels of oestrogen and progesterone increase rapidly in early pregnancy both of which mediate venodilation and may contribute to valvular dysfunction[117-120]. Of note, hormonal contraception and replacement therapy do not seem to be associated with varicose veins development despite their strong association with deep vein thrombosis (DVT) [111,121,122].

Family History

Literature evidence suggests that a positive family history of venous disease is one of the strongest risk factors for SVI[89,92,100,123,124]. Two large population studies in fact suggest that heredity is the strongest risk factor for SVI[95,100]. However, these two studies were conducted by telephone consultation or written questionnaires and this can lead to an overestimation of the risk due to patients being more aware of relatives with disease compared to healthy controls; in addition to the possibility of falsely positive reports which cannot be verified without examining relatives. Another study attempted to address this by examining patients and their parents, comparing them to control families[125]. It suggested a 90% risk of varicose veins if both parents had varicose veins and a 20% risk if neither parent was affected[125].

Genetic studies have not so far been able to identify genes that lead to SVI, but they do support the role of genetics in the development and progression of SVI. The FOXC2 gene mutation in lymphoedema-distichiasis for example is associated with early development of varicose veins[126,127]. At the other end of the disease spectrum, some Factor XIII gene variants and haemochromatosis C282Y (HFE) gene mutations have been associated with severe forms of CVD with venous ulcer that are refractory to treatment[128-130].

Ethnicity

Literature evidence of geographical variations in incidence and prevalence of varicose veins is well documented though some of the evidence is quite poor[131]. Overall, the evidence suggests a lower burden of disease in developing countries [131-133]. Genetics aside, lifestyle factors such as toilet habit, dietary fibre content, loose garments and time spent standing were all proposed as mechanisms[107]. In one study comparing cotton worker women in Egypt and the U.K. found higher incidence in the U.K. (32% v 6%), and concluded that tight undergarments were a factor after controlling for other factors [134]. Another study of patients in New Zealand and South Pacific Islands found highest prevalence in native Māori women with the lowest incidence in Tokelau island women[103,135]. In New Zealand, the

western settlers (Pakeha) had a lower prevalence of varicose veins than the native Māori. The large difference between the Rarotonga and the Pukapuka in the Cook Islands is perhaps the strongest evidence for ethnic variation as environmental factors were likely very similar (see Table 1).

Table 1 - Percentage of age standardised prevalence of varicose veins by ethnicity, (total number of patients) [103,135]

Location	Ethnicity	Men% (No.)	Women% (No.)
New Zealand	Māori	33% (366)	44% (355)
	Western Settler	20% (173)	38% (183)
Cook Islands	Rarotonga	16% (219)	15% (198)
	Pukapukan	2% (199)	4% (178)
Tokelau Islands	Tokelauan	3% (347)	1% (439)

Further evidence comes from Israel and San Diego, the Israeli study compared immigrants from North Africa to those from Europe[102]. The San Diego study categorised participants into Hispanic, non-Hispanic Whites, African American and Asian. SVI was observed to be lowest in Asians[101].

Body Mass Index

There is a link associating increasing height and increasing BMI with varicose veins, but the exact mechanisms are uncertain[97,100,111,136]. Perhaps the added weight of the column of blood in tall people is an additional factor that would cause a susceptible individual to develop SVI. As for BMI, the hormonal effect of added circulating oestrogens due to adiposity as well as the mass effect of added fat impairing venous return have been proposed as factors[137,138]. The Bonn vein study and The DIANA project both reported increased odds ratio of having varicose veins with high BMI[111,139]. However other studies have not been able to replicate these results[93,113,114,140]. Interestingly, signs and symptoms of CVD have been reported in obese patients without evidence of reflux[141,142], and in addition to that, overweight patients have been reported to present more frequently with varicose veins[143,144]. Therefore, perhaps obesity does not just affect prevalence of disease but may worsen the symptoms of the disease, thereby increasing the likelihood of attendance for treatment. Alternatively, high BMI may cause symptoms that mimic SVI therefore causing obese patients with SVI to present more frequently.

1.5.3 Epidemiology

SVI is very common with a significant impact on patient quality of life and health care systems[145]. National health survey questionnaires are one method of estimating disease epidemiology. The earliest mention of varicose veins in such a national survey was from 1935, where 2.8 million U.S. citizens

completed questionnaires; this suggested a point prevalence of 1.4% for simple varicose veins[146]. In 1961, another survey reported that 2.25% of the U.S. population were affected by "severe" disabling varicose veins[107]. Assuming that simple varicose veins are far more common than severe disease, the 1961 survey would imply an enormous rise in disease incidence and prevalence compared to the 1930s. Another three decades later, the health survey from 1992 suggested a point prevalence of 3% for simple varicose veins in the USA[147], which implies another enormous change over these decades. These swings in disease epidemiology are highly unlikely and mean that population surveys are not an accurate method of studying venous disease epidemiology. Furthermore, terms such as "disabling" and "severe" carry little clinical information pertaining to the clinical severity of the disease, rendering any conclusion drawn from this information of little clinical value.

Population based observational studies are perhaps a more accurate method to ascertain disease epidemiology. A number of these have been carried out over the last century. Their results vary in terms of reported prevalence and incidence of the disease; however, these literature variations are probably a reflection of methodological differences between studies in addition to geographical variations. Table 2 shows point prevalence estimates for varicose veins across different studies.

Table 2 - Reported varicose veins point prevalence estimate across genders

Year	**Author**	**Location**	**Sample size**	**Prevalence (%)**	
				Male	Female
1942	Lake[148]	United States	536	40.7	73.2
1958	Arnoldi[149]	Denmark	1684	18.4	38.0
1966	Bobek[150]	Bohemia	15060	6.6	14.1
1966	Weddell[151]	United Kingdom	289	31.0	36.0
1969	Mekky[134]	Egypt	504	-	32.1
		England	467	-	5.8
1970	Prior[152]	New Zealand	232	25	42
1972	Malhotra[153]	India (North)	354	6.8	-
		India (South)	323	25.1	-
1973	Coon[123]	United States	6389	12.9	25.9
1973	Guberan[113]	Switzerland	610	-	29
1974	Da Silva[154]	Switzerland	4376	57.0	68.0
1975	Beaglehole [103]	Cook Island (Rarotonga)	417	15.6	14.9
		Cook Island (Pukapukan)	377	2.1	2.0

		New Zealand (Māori)	721	33.4	43.7
		New Zealand (Pakeha)	356	19.6	37.8
		Tokelau	786	2.9	0.8
1975	Stanhope[106]	New Guinea	728	5.1	0.1
1977	Richardson[155]	Tanzania	1259	6.1	5.0
1981	Abramson[102]	Israel	4802	10.4	29.5
1981	Ducimetiere[156]	France	7425	26.2	-
1986	Maffei[96]	Brazil	1755	37.9	50.9
1988	Novo[157]	Italy	1122	19.3	46.2
1989	Leipnitz [158]	Germany	2821	14.5	29.0
1990	Hirai [159]	Japan	541	-	45
1991	Stvrtinova [160]	Slovakia	696	-	60.5
1992	Franks [93]	England	1338	17.4	31.6
1993	Laurikka [161]	Finland	5568	18.4	41.7
1994	Komsuoglo [108]	Turkey	856	34.5	38.3
1995	Sisto [97]	Finland	8000	6.8	24.6
1997	Krijnen [162]	Netherlands	387	58.0	-
1998	Canonico[104]	Italy	1319	17.0	35.2
1999	Evans[82]	Scotland	1566	39.7	32.2
1999	Preziosi[163]	France	3065	10.8	18.1
2000	Kontosic [164]	Croatia	1324	18.9	34.6
2003	Criqui[165]	Unites States	2211	15.0	27.7
2003	Rabe [166]	Germany	3072	12.4	15.8
2003	Jawien[167]	Poland	40095	28.0	35.0
2004	Carpentier[100]	France	8000	30.0	51.0
2007	Sam [168]	United Kingdom	100	33.0	-
2008	Pospisilova [169]	Czech Republic	319	36.0	54.0
2008	Maurins [40]	Germany	3072	-	31.4

The largest U.K. based epidemiological study has been the Edinburgh vein study, which looked at an age stratified random sample of people. The study sample was 1556 patients representing all socioeconomic classes in the city. Age adjusted prevalence of simple varicose veins was 40% for men compared to 32% in women[82], whereas trophic skin changes were present in 9.4% of men and 6.6% of women. Another large population study based in Germany and Latvia, reported simple varicose veins in 12% of men and 16% of women, with trophic changes in 3.1% or man and 2.7% of women[111]. Similar studies have been carried out in France, Belgium, Russia among others[90,100,170], point prevalence amongst these studies for varicose veins is 20-64%, with skin changes affecting 5-10% and venous ulceration in 1-2% of the population[22,171]. Study sample selection plays an important role in studies of this type and often researchers make pragmatic decision to increase the likelihood of participation that

can limit external validity of the study, such as in the San Diego Study where university staff and their partners were the invited participants[101]. Furthermore, those that complete a study after recruitment are a self-selecting cohort that may not resemble the wider population. The cumulative effects of this process likely explain a large part of the differences between epidemiological studies.

A few studies have attempted to estimate the incidence rate of varicose veins. The Framingham study suggested an incidence rate of 51.9 per 1000 and 39.4 per 1000 for women and men respectively over a 24-month period[89]. In the Bonn vein study, incidence of new simple varicose veins was 14% over a six year period[172]. A longitudinal study followed pupils from the age of 10 to the age of 20, noting that none had varicose veins between the ages of 10-12, however, follow up at 18-20 years showed that 5% had visible varicose veins[173].

1.5.4 **Financial burden of SVI**

UK Annual health-care costs have been increasing dramatically over the last two decades. The Office for National Statistics estimated UK health care expenditure at 197 billion in 2017, some 10% of GDP[174]. In this climate of austerity, where the NHS is required to make health savings it becomes increasingly important to provide cost effective care for patients. As previously stated, SVI is a very prevalent disease that increases in severity if not treated and can recur after treatment, it is therefore critical to make cost effect therapy choices when managing this disease. Additionally, consequences of not treating SVI can be high at all stages of the disease from a socioeconomic perspective. One consequence of not treating SVI is venous ulceration which affect 3% of adults at a great financial burden on individuals and healthcare systems worldwide[175]. In the UK, 2% of the annual NHS budget is spent on managing venous ulcers alone[176]. On an individual level, lost working days annually due to venous ulceration have been calculated to cost 6.4 million and 2 million per annum in France and the USA respectively[177,178]. These costs do not include the decreases in mobility and work capacity, patients' out-of-pocket expenses, and adverse psychological effects related to venous disease short of ulceration.

1.5.5 **Quality of life impairment**

SVI seldom threatens patient life, therefore treatment decisions need to be based on an objective measurement of the impact of symptoms on patient lifestyle and livelihood. Consequently, the development of tools that measure said impact accurately is of paramount importance in order to understand the impairment brought about by the disease, how intervention alleviates this impairment

and how this benefits patients overtime. The range of nonspecific symptoms that patients with SVI present with makes objective clinical assessment with history and examination challenging to reproduce, particularly in research where accurate, reproducible measurement are needed. In order to tackle this issue, several health questionnaires or "instruments" have been developed and validated for the assessment of Health-Related Quality of Life (HRQoL) of patients with SVI.

A suitable HRQoL instrument must be easy to administer, reproducible, valid (tests what it intends to test) and responsive (sensitive enough to identify small but important differences)[179]. These instruments or "tools" fall into two broad categories. Namely disease specific such as the Aberdeen Varicose veins Questionnaire, and generic tools such as the EuroQol-5 Dimensions instrument[180,181]. It is recommended that both generic and disease-specific instruments are used together in order to obtain a full assessment of HRQoL in patients with SVI[182] (see1.6.4).

Studies using these instruments have demonstrated the pervasive deleterious impact of SVI on patient lives which includes physical, emotional, psychological and social domains[183-186]. Figure 5 and Figure 6 are from a study modelling the effect of increasing SVI disease severity on patient HRQoL[187]. Figure 5 shows deterioration of bodily function and vitality with increasing severity of SVI, while Figure 6 shows the significant deterioration in patient HRQOL associated with increasing SVI severity. Studies like these highlight the significant HRQoL impact of simple varicose veins, which is indistinguishable from SVI with skin changes[187]. Additionally, generic HRQoL tools demonstrate that SVI symptoms are predominantly physical rather than cosmetic, debunking a commonly held misconception on the predominance of cosmetic symptoms in SVI[187]. Furthermore, the impact of venous ulcer disease on physical function and role limitation is on par with sever chronic conditions such as congestive heart failure and obstructive pulmonary disease[188,189].

Another important role for HRQoL tools is in ascertaining cost effectiveness of interventions. Quality Adjusted Life Year (QALY) is a tool derived from HRQoL questionnaires that is the basis of cost effectiveness analysis when comparing treatments within and across diseases. The two main instruments that can generate values for QALY calculations are the EuroQoL 5 domain (EQ5D) and Short-form 6 dimension (SF6D) generic HRQoL instruments.

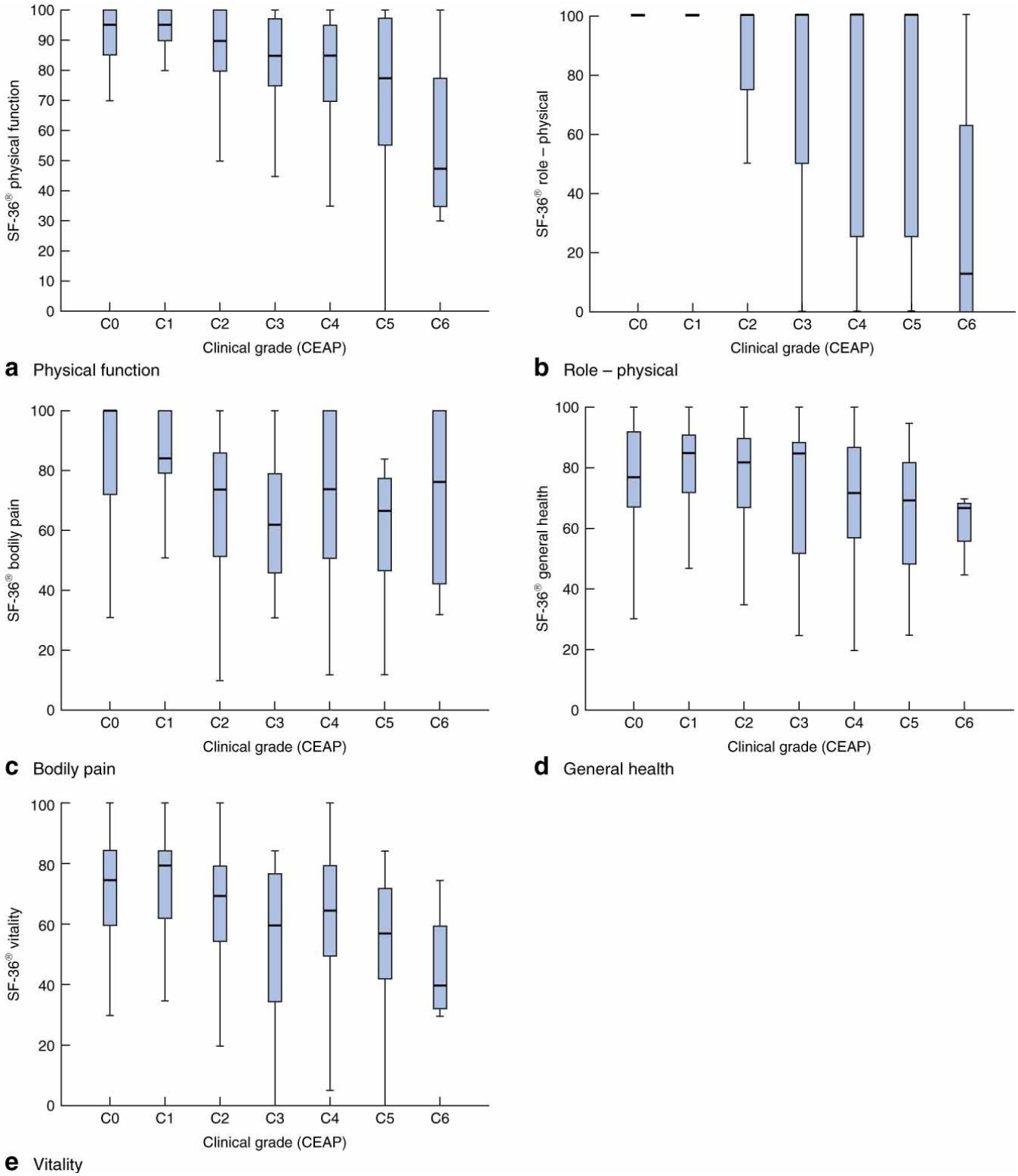


Figure 5 - Short Form 36 (SF-36®) domain scores by Clinical Etiologic Anatomic Pathophysiologic (CEAP) clinical grade. Median (horizontal line within box), interquartile range (box) and range (error bars) are shown. p = 0·012[187]

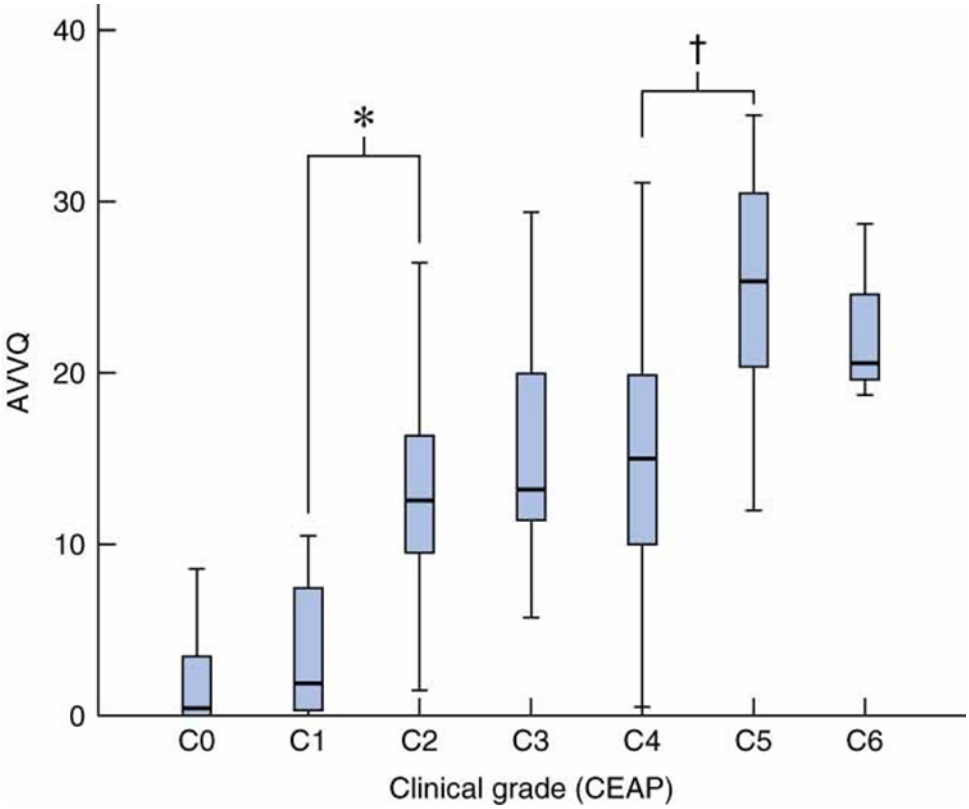


*Figure 6 - Aberdeen Varicose Vein Questionnaire (AVVQ) scores by Clinical Etiologic Anatomic Pathophysiologic (CEAP) clinical grade. *p < 0·001, † P = 0·006*[187]

1.5.6 **Symptoms and Signs**

Leg symptoms related to SVI include heaviness, aching, itching, burning, throbbing and swelling[190]. Muscle cramps, restless and tired legs have also been reported[83,144,190]. These symptoms typically are felt unilaterally in the affected leg or foot. Occasionally bilateral disease is present, but one leg is frequently more symptomatic. Classically, SVI symptoms are exacerbated by heat and prolonged dependency during daily activities and are in turn relieved by elevation, wearing compression garments and massaging[191]. Several conditions can mimic these symptoms and it can therefore be difficult to establish a diagnosis based on history alone. A focused history, clinical examination and DUS imaging are all needed to establish diagnosis. Specific complications that should be enquired about are ulceration, thrombophlebitis and bleeding varicosities. The latter in particular can be perfuse and can lead to death if not treated[192-195].

The clinical signs of SVI and CVD lie on a spectrum of severity which is neither linear nor continuous. Clinical classifications such as CEAP attempt to organise these signs in order of severity however patients often present with severe features of disease such as lipodermatosclerosis in the absence of

the less severe finding of varicose tributaries [196]. This again highlights the importance of wholistic assessment with history, examination and DUS imaging to fully assess SVI. Table 3 is a summary table of the clinical signs of SVI according to international consensus definitions. These were drawn up in order to standardise terminology and avoid confusing terms that were previously used in literature[197,198].

Table 3 - Clinical signs of CVD/SVI

Clinical sign	Synonyms	Description
Telangiectasia	spider veins, hyphen-webs, thread veins	Confluence of dilated intradermal venules less than 1 mm in diameter.
Reticular veins	blue veins, subdermal varices, venulectasies	Dilated bluish subdermal veins, usually 1mm to less than 3mm in diameter. Usually tortuous. Excludes normal visible veins in persons with thin, pale skin.
Varicose veins	varicosities, varices, varix	Subcutaneous dilated veins 3mm in diameter or larger, measured in the upright position. May involve saphenous veins, tributaries, or non-saphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose
Corona phlebectatica	malleolar flare, ankle flare	Fan-shaped pattern of numerous small intradermal veins on medial or lateral aspects of ankle and foot. Commonly thought to be an early sign of advanced venous disease.
Oedema	n/a	Perceptible increase in volume of fluid in skin and subcutaneous tissue. Characteristically indents with pressure. Venous oedema usually occurs in ankle region but may extend to leg and foot.
Pigmentation	haemosiderosis	Brownish darkening of skin, resulting from extravasated blood. Usually occurs in the ankle region but may extend to leg and foot.
Venous Eczema	Stasis dermatitis, Stasis eczema	Erythematous dermatitis, which may progress to blistering, weeping, or scaling eruption of skin of the leg. Most often located near varicose veins but may be located anywhere in the leg.
Lipodermatosclerosis	LDS, “champagne bottle leg”	Localized chronic inflammation and fibrosis of skin and subcutaneous tissues of lower leg, sometimes associated with scarring or contracture of the Achilles tendon. May be preceded by diffuse inflammatory oedema of the skin, sometimes painful, often referred to as

		hypodermitis. Must be differentiated from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features
Atrophie Blanche	white atrophy	Localized, circumferential whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Sign of severe CVD, and not to be confused with healed ulcer scars.
Venous ulcer	stasis ulcer	Full-thickness defect of skin, most frequently in ankle region, that fails to heal spontaneously and is sustained by CVD

1.6 Assessment of SVI

In the UK, most patients with symptomatic SVI should be referred to a vascular specialist unit after consultation with their General Practitioner (GP) as recommended by the National Institute for Health and Clinical Excellence (NICE), guidelines for referral are outlined in Table 4[199]. When assessing these patients careful medical history, clinical examination and DUS imaging are all essential components. Leg symptoms are common amongst the general adult population; therefore, it is important to ensure that the presenting symptoms are directly related to SVI, otherwise any subsequent intervention will be ineffective.

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. • Symptomatic** primary or symptomatic recurrent varicose veins. • Lower-limb skin changes, such as pigmentation or eczema,	** Veins found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness and itching)

	thought to be caused by chronic venous incompetence. • 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.	

Table 4 National Institute for Health and Clinical Excellence (NICE) Referral guidelines for varicose veins[199]

1.6.1 **History**

Most UK vascular surgical units offer dedicated venous clinics for patients referred from primary care [200]. Common symptoms that should be directly sought in the history are aches or leg cramps, itching, limb swelling, heaviness and uncomfortable[201]. The symptoms typically worse with prolonged periods of standing[191]. Limb swelling history is particularly useful, as most patients with SVI will have unilateral disease or will report worse swelling in one limb over another. Important past medical and surgical history should include previous venous treatment, deep vein thrombosis (DVT), leg trauma, periods of prolonged immobility in a cast, parity in ladies, thrombophlebitis, bleeding varicosities and leg ulceration. Family history of SVI or VTE should be ascertained. Social history should include employment status and the effect of disease on work. Drug history should include allergy status, use of hormone replacement therapy, combined oral contraceptive pill or anticoagulants.

1.6.2 **Examination**

The physical examination should be undertaken in a warm, well-lit environment. The presence of a chaperone is highly desirable and at all times patient privacy and dignity should be safeguarded. Inspection starts with the patient in the upright position with the legs fully exposed. Features of SVI should be noted (see Table 3 - Clinical signs of CVD/SVI), any atypically located varicosities traveling cranially towards the abdominal wall or reproductive organs should also be noted as they indicate complex proximal disease or obstruction[202]. Palpation in the upright position is then performed, assessing for fascial defects which may indicate the presence of incompetent perforators. The patient is then examined supine, again beginning with inspection of the abdomen for atypical varicosities, followed by abdominal palpation. Peripheral pulses should also be palpated with ankle brachial pressure index measurement when necessary.

Several eponymous techniques can also be performed, such as Trendelenburg, Fegan and Perthes tests, but these are now generally regarded as antiquated, and are unlikely to alter the patient's management and are seldom performed[203,204] .

1.6.3 **Clinical classification**

CEAP

The clinical signs of CVD were defined by international consensus in 1994, and subsequently revised in 2004[197,198]. The revised CEAP system was the result, which is a physician generated classification tool. The basic form of CEAP is now the commonest clinical classification system used in the assessment of CVD, as shown in Table 5 [176]. CEAP is divided into four parts that aim to classify the severity of venous disease, its underlying causes and the pattern of venous involvement. There are some obvious limitations to the system however; firstly, CEAP cannot discriminate between a limb with extensive superficial varicosities and one with few. Both would be classified as C2 disease, making CEAP insensitive to differences within the same clinical class [205-208]. Secondly, the CEAP is relatively insensitive to change, where once a patient develops ulceration, they can only improve to C5 disease. This makes CEAP a poor measurement for assessing response to treatment and not a good tool for research and audit purposes[196,209].

Table 5 - CEAP classification

	CEAP	Description
Clinical classification	C_0	No visible or palpable signs of venous disease
	C_1	Telangiectasis 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
a**E**tiologic 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

VCSS

To complement CEAP and address some of its limitations, the committee on Venous Outcomes Assessment of the American Venous Forum developed the Venous Clinical Severity Score (VCSS) system, with further refinement in 2010[210,211]. As shown in Table 6, the VCSS consists of ten descriptors and is scored out of three by degree of severity. The ten are pain, varicose veins, oedema, pigmentation, inflammation, induration, number of ulcers, duration of ulcers, size of ulcers, and use of compressive therapy. These escalate in severity with the increased area of the limb involved and are graded 0 to 3 (absent, mild, moderate, severe). Additionally, The VCSS has been shown to be responsive to change in disease severity, such as after treatment or with disease progression over time[211-215]. The VCSS is therefore an excellent assessment outcome both in clinical practice and in research to assess response to treatment over time.

The main criticisms of VCSS are regarding the compression and pain scoring aspects of the tool. Compliance with compression stockings is known to be poor. Some patients find it uncomfortable whilst others, such as the elderly are unable physically to apply it[216,217]. Further, compliance with compression can be affected by unit practice where clinical advice on its usage can vary. Similarly, pain scoring can be subjective and again prone to bias. Therefore, the same patient can score significantly differently using VCSS depending on their ability to comply with compression and how they perceive pain. Nonetheless, VCSS remains an important tool in the wholistic assessment of CVD and is recommended by international guidelines in venous research[182].

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 peri malleolar area	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 of calf
Inflammation	None	Limited to peri malleolar area	Diffuse over lower 1/3 of calf	Wider distribution above lower 1/3 of calf
Induration	None	Limited to peri malleolar 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 6 Varicose Clinical Severity Score (VCSS)[211]

1.6.4 **Assessing quality of life impairment**

As previously discussed, CVD is almost entirely a disease of HRQoL, with very little mortality associated with the disease. However, said HRQoL deterioration is significant and carries consequences to individual patients, healthcare systems and society[187,218-221]. Therefore, the principle aim of any treatment should be to improve patient HRQoL. This is in line with national and international recommendations on the assessment of interventions on SVI[182,199]. Furthermore, NICE in the UK relies on HRQoL tools when carrying out health economic evaluations[222,223]. The tools used to measure this are collectively called patient reported outcomes (PROMS) and will be discussed in this section.

1.6.4.(a) Disease Specific HRQoL measures

The Aberdeen Varicose Vein Questionnaire (AVVQ) is a disease specific HRQoL measurement tool that has been validated for SVI assessment[181,220,224]. The first question of the AVVQ asks the patient to draw the location of their varicosities on a simplified diagram of the legs. a visual representation of their venous disease on diagram (which is later scored using a transparent grid). Then there are 13 questions which employ Likert-type scales scoring the severity of disease impact on patient's life for the preceding two weeks[224]. Disease in both legs can be assessed simultaneously to a maximum score of 50 in each leg and a 100 overall, as shown in Figure 7. uncomplicated SVI patients typically score between 10 to 30 and those with venous ulcers typically score between 30 to 60[187].

Disease specific instruments such as the AVVQ focus on the health aspects most relevant to the illness of interest, and on aspects of disease that are that are most relevant to patients with the disease[179]. Therefore, these are more sensitive to small changes in disease states than their generic counterparts

and indeed the AVVQ has been shown to be sensitive to changes in SVI state even at the milder end of symptomatic disease[225].

Appendix
Clinical varicose veins questionnaire

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

Legs viewed from front | Legs viewed from back

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

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

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

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

4 During the past two weeks, on how many days did you take painkilling tablets for your varicose veins?
(Please tick one box)

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

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

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

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

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

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

- No ☐
- Yes ☐

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

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

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

	Right	Left
No	☐	☐
Yes	☐	☐

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

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

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

No	☐	☐
Yes	☐	☐

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

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

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

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

14 During the past two weeks have your varicose veins interfered with your work or housework or other daily activities?
(Please tick one box)

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

15 During the past two weeks have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)?
(Please tick one box)

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

Instructions for scoring the clinical questionnaire are freely available from the authors on request.

Figure 7 - Aberdeen Varicose Veins Questionnaire (AVVQ)[181]

1.6.4.(b) Generic HRQoL measures

As previously discussed, generic instruments assess global health state and wellbeing across a variety of conditions and diseases, providing an overall sense of HRQoL limitations associated with the disease and measuring the effect of treatment on the disease. Importantly, generic HRQoL tools form the basis that health authorities use to calculate cost-effectiveness of interventions and prioritise health targets. The Short Form 36 instrument (SF-36) (QualityMetric, Lincoln, Rhode Island, USA) is one of the most popular and comprehensive instruments used in healthcare today[188,226-231]. It was developed based on the Medical Outcomes Study and the RAND health insurance study[227,232]. It has been shown to be responsive and sensitive across a wide range of diseases, in addition to SVI where it has also been validated[188,219,220,226,228,229,233]. The SF-36 evaluates patients from a physical and a mental health aspect; each in turn being measured on four domains, as shown in Table 7. There is a total of 36 questions, which are scored and weighted to give a maximum score of 100 representing optimal health, as shown in Figure 8- 11.

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 7 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	☐	☐	☐

Figure 8 - SF-36 questions 1-12

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
☐	☐	☐	☐	☐	☐

Figure 9 SF-36 questions 13-21

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
☐	☐	☐	☐	☐

Figure 10 - SF-36 questions 22-32

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	☐	☐	☐	☐	☐

Figure 11 - SF-36 questions 33-36

The EQ-5D™ (EuroQol Group, Rotterdam, NL) is another popular generic HRQoL. It was developed by a European multidisciplinary team, with the aim of creating a standardised simple and generic tool for measuring HRQoL that can also be used to appraise health economics[234]. The first component (Figure 12) consists of five questions with three weighted responses, which are then used to generate a single index between 0 representing "worse imaginable health" and 1 representing "best imaginable health". Statistical modelling with a Time Trade Off model was used to develop the tool, based on a sample of 3000 adults from the general population in the UK[235,236]. The second component is a visual analogue scale (VAS) scored from 0 – 100, again on a scale from worst to best health state (Figure 13). The main criticism levelled at the EQ-5D questionnaire is that it can be unresponsive to moderate changes in HRQoL [237,238]. However, it has been validated an endorsed by NICE in the UK for calculating cost effectiveness[223].

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	☐

Figure 12 - EQ-5D questionnaire

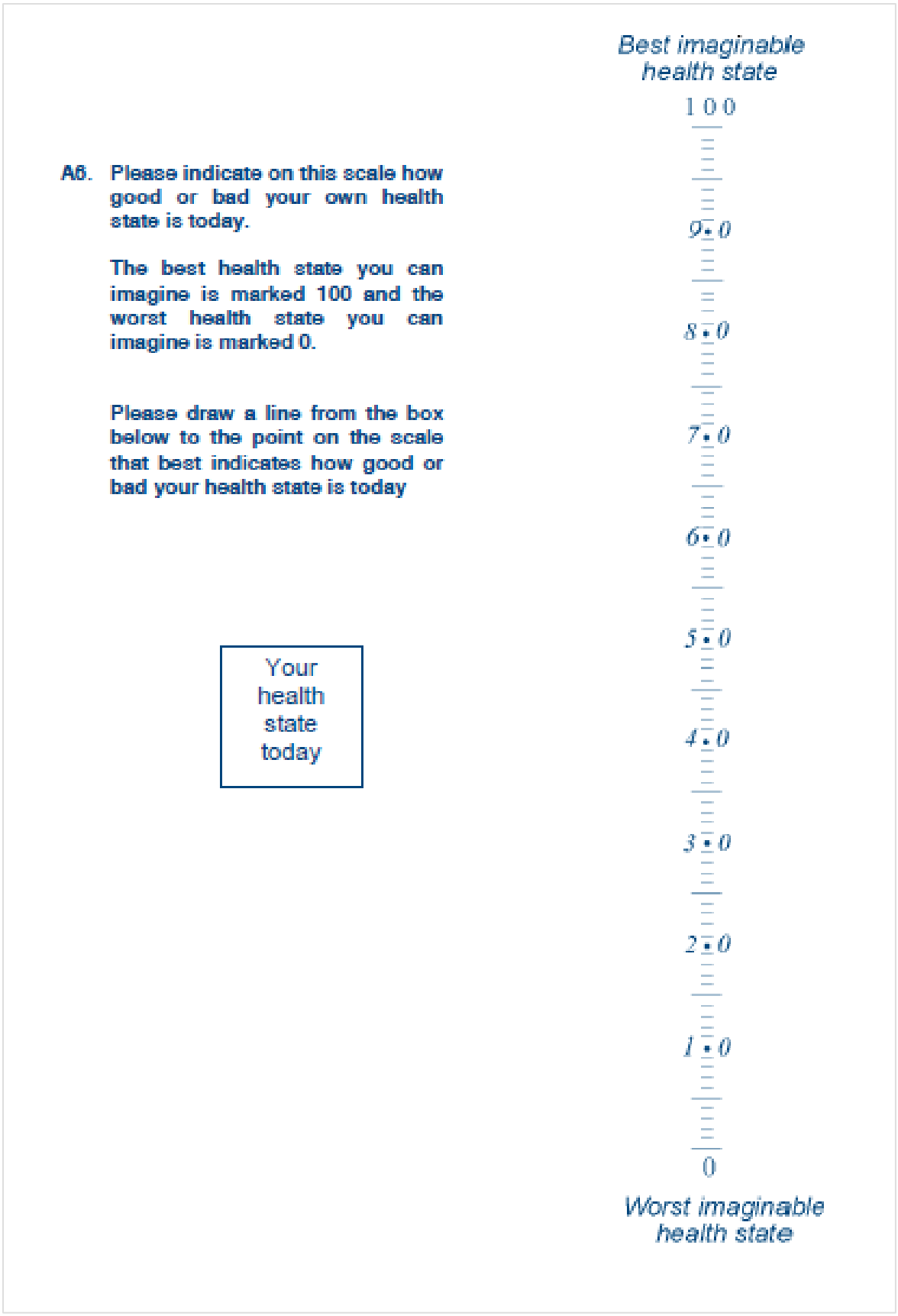


Figure 13 - EQ-5D VAS

1.6.5 **Investigations**

Several investigative options are available to assess patients with SVI including, ultrasound, CT, Magnetic Resonance Imaging (MRI), plethysmography, venography and volumetry. DUS is currently the recommended first line investigation of choice for lower limb SVI/CVD nationally and internationally, based on level 1A evidence (strong evidence from randomised studies and/or meta-analysis) [22,199,209]. Other imaging modalities such as CT and MRI continue to have a role in CVD investigation especially when supra-inguinal disease is suspected or vascular anomalies[22]. Similarly, venography is mainly used to investigate and treat vascular anomalies or obstructive disease[22]. Handheld doppler ultrasound assessment has been supplanted by DUS, and has no role in the assessment or management of CVD[22,239,240]. Plethysmography and volumetry's roles have been largely reduced to research studies[22].

1.6.5.(a) Venous Duplex Imaging

DUS is an ideal tool for investigating CVD as it is widely available, inexpensive, safe and accurate in establishing the pattern of disease. It can be used to establish diagnosis, plan and perform minimally invasive intervention. In addition to this, DUS can be used for follow-up to determine treatment success or presence of recurrence. Of note however, DUS findings on the presence and duration of valvular incompetence should always be viewed in the context of patient symptoms as DUS can identify valvular incompetence on imaging in the absence of clinically significant symptoms [198,241,242].

A venous duplex ultrasound examination relies on reflected ultrasound waves to generate a two-dimensional image of the underlying anatomical structures. Changes in the frequency of the reflected ultrasound waves are also used to generate information about blood flow direction and velocity in underlying vessels. This combined anatomical and haemodynamic assessment is what constitutes DUS. In a standard venous DUS examination, the anatomy is first interrogated to assesses for signs of acute venous thrombosis or obstruction, as well as changes associated with chronic venous occlusive disease. Next, haemodynamic assessment is performed looking at direction and pattern of flow at rest, followed by provocation manoeuvres to test for the presence of valvular incompetence and reflux.

International guidelines have been developed to standardise the performance of venous DUS imaging to ensure accuracy and reproducibility of results[243]. Ideally, the examination is performed with the patient standing, in a relaxed position, bearing most of their weight on the non-index leg. The cut off

point for haemodynamically significant reflux in the deep venous system is set at > 1s, compared with >0.5s for the superficial system and >0.35s for perforators[244,245]. In addition to interrogating all the deep and superficial axial veins for patency and reflux, measurements should be taken of any axial vein to be treated. GSV measurements for example should be obtained at 3cm below the SFJ, at mid-thigh, at the knee and the calf, noting tortuosity and relationship to fascia[246].

While DUS is the only imaging modality needed for most patients with CVD, it has limitations and occasionally other imaging modalities are required to investigate patients. One limitation common to all ultrasound based imaging studies is user dependency, where skilled experienced operators are needed to accurately delineate disease pattern. High operator skill is particularly required when assessing recurrent disease with complex patterns. Another limitation common to ultrasound studies is loss of quality with depth. When assessing CVD, distance to vessels of interest is a particular problem in the calf and pelvis which is why DUS accuracy diminishes when assessing deep veins in the calf and pelvic vessels[22,247]. An alternative emerging technique for pelvic venous disease is to combine transvaginal ultrasound with abdominal DUS, though further studies are needed to establish the role of this technique in the management of CVD[248].

1.6.5.(b) Venous CT and MRI

Both CT and MRI venography can provide accurate detailed three dimensional reconstruction of the lower limb venous system, both coming to the fore when considering ilio-caval pathology as a source of CVD such as in May-Thurner syndrome or Nutcracker syndrome[249-252].[253-255]. However, neither has a role in the routine assessment of most CVD patients. Both techniques are limited by an inability to provide haemodynamic information regarding reflux and by the risk of contrast nephropathy and allergic reactions. Additionally, CT venography carries the risks of radiation whereas patients can find MRI intolerable due to the noisiness and confined space within the machine.

1.7 Treatment of SVI

SVI is a chronic progressive disease leading to HRQoL impairment in addition to complications associated with significant morbidity such as skin ulceration, phlebitis and venous bleeding. The following section will discuss the various treatment options for patients with SVI and the available evidence to support their role in the modern management of this disease. There is great heterogeneity in the outcomes used in the literature to judge successful treatment of SVI, despite international consensus standardising reporting of outcomes[182]. This consensus puts patient symptoms at the centre

of any measurement of success, and HRQoL tools are the standardised validated tools to measure changes in symptomatology of the disease.

1.7.1 Conservative therapy

1.7.1.(a) Exercise

To date, no peer reviewed study has demonstrated that exercise alone is an effective treatment method for SVI. The physical and mental benefits of regular exercise apply to SVI patients in general, and in particular cases, strengthening the calf muscle pump may theoretically benefit patients with SVI. For example, decreased ankle joint movement is an independent parameter inhibiting leg ulcer healing despite compression therapy[256]. Therefore, physiotherapy to improve calf muscle pump action or a supervised exercise programme may be beneficial as an adjunct to compression therapy in C6 disease[257]. Exercise has also been shown to reduce the recurrence rate of venous ulceration when combined with compression therapy [258]. Another consequence to venous ulceration is a significant reduction in patient functional ability when compared to their age matched counterparts[259]. Therefore, perhaps a supervised exercise programme would benefit these patients as has been shown in their counterparts with post thrombotic syndrome by improving their functional ability and consequently their HRQoL [260].

A recent and worrying finding within NHS healthcare provision, has been the use of a trial period of non-supervised exercise as a way of rationing treatments for patients with SVI[261]. This practice is not supported by evidence and has no role in the modern management of SVI.

1.7.1.(b) Leg Elevation

SVI symptoms are characteristically relieved by leg elevation, as this aids venous return to the heart. While this establishes a role for leg elevation in symptom control, there is currently no evidence to support leg elevation as a primary method of SVI treatment. There is however some evidence to support regular limb elevation as an adjunct to compression therapy in preventing venous ulcer recurrence[262,263].

1.7.1.(c) Compression therapy

Compression therapy has been an essential part of CVD management since antiquity. Compression aims to counteract reflux induced venous hypertension by supporting and augmenting venous drainage

of the limb[264-269]; it works by reducing the radius of the lower limb veins and according to Laplace's law (pressure = tension/radius). Therefore, by reducing the radii of the lower limb veins gradually from distal to proximal, a pressure gradient driving venous return up the limb can be created[269]. There is a limit however to how much external compression can be applied to the veins, as pressures >60mmHg have been shown to occlude superficial veins[270].

An overwhelmingly high number of products are available to provide compression therapy. They are generally divided into either bandaging or hosiery based systems, and these can be further subdivided depending on elasticity, antimicrobial property, number of layers, adhesiveness and other categories[271-273]. Graduated elasticated compression hosiery/stockings for example are graded according to the maximal pressure they can generate into different classes. Different international standards exist for the same "class" of compression as shown in Table 8 - International class standards for compression stockings[270]. It should be noted that the British standard compression classification refers to maximal pressure at the ankle[271],however other systems may not. In fact, several European studies have been conducted comparing graduated stockings where maximal compression is applied at the ankle to those where maximal pressure is applied at the calf[274-276].

Table 8 - International class standards for compression stockings[271]

Class	USA standard	German standard (RAL)	French standard	British standard
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	-

Regarding SVI short of ulceration (C2-C4), cohort studies, expert consensus and a Cochrane review of the literature agree that patient symptoms and HRQoL improves when using compression therapy compared to no treatment [22,277,278]. Some authors also argue that compression hosiery that applies maximal compression at the calf may be better than at the ankle[274-276]. These studies are however limited by the use of subjective methods for measuring symptomatic improvement as opposed to the recognised and validated HRQoL tools. As such they have little external validity and are of low level of evidence. In fact, the Cochrane review concluded that the evidence to support the use of compression as the main treatment method for C2-C4 SVI is poor[278].

The REACTIV trial was a three-arm multicentre RCT of the management of varicose veins comparing compression therapy, sclerotherapy and conventional surgical ligation. Some 1000 patients were recruited into the study and both clinical efficacy and cost effectiveness were tested. At 2 year follow up, HRQoL and patient satisfaction were significantly higher in the surgical group compared to compression[221]. Markov economic modelling also showed surgery to be highly cost effective when compared to compression therapy over 10 years.

Aside from the lack of strong evidence on clinical efficacy and its comparatively low-cost effectiveness, compression therapy is very unpopular with patients. In the REACTIV trial, 57% of patients allocated to conservative therapy were dissatisfied with their treatment at 1 year and 50% opted for surgery afterwards[221]. Moreover, compliance with compression therapy is poor with some studies reporting it to be as low as 21%[279], Patients often complain that they feel too hot or itchy or that the compression is too binding[279-281]. It can be argued therefore that patients do not find compression therapy as a viable long-term solution[282]. For some patients, compression therapy is not a viable option due to a lack of dexterity or mobility as can happen with elderly patients. In others, compression is contraindicated altogether as in the case of patients with peripheral arterial disease where it can worsen limb ischaemia[283]; and even in patients without arterial incompetence, poorly applied compression can still compromise arterial supply, damage skin or underlying soft tissues[283,284]. Over and above these limitations, compression garments and hosiery require replacement – typically every three to six months – to maintain efficacy which is something patients and clinicians overlook.

Given these limitations and the poor evidence to support its use a primary treatment method for (C2-C4) SVI, national and international guidelines advise that compression therapy should only be considered a treatment method for patients who decline interventional treatment or are not suitable for any of the available interventions[22,176,199]. Compression should also be offered for a short duration to patients following interventional treatment of SVI as it reduces post procedural complications, pain and increases efficacy[22].

For venous ulcers disease (C5-C6), a convincing body of evidence exists to show that compression therapy reduces healing time and chance of ulcer recurrence[285-289]. Compliance is crucial however as ulcer recurrence is much higher in those who discontinue compression[285]. This is of particular importance in the elderly population where C5-C6 disease is more common, as measures need to be in place to assist with application of compression[290]. The optimum type and length of compression for

venous ulcers is still uncertain, however, multicomponent compression systems with an elastic element perform better than single component systems and those without an elastic element[287]. More recently, the VenUS IV trial showed that ulcer healing rates were similar when comparing two layer compression hosiery and four layer compression bandaging[291].

Combining compression with early interventional treatments seems to be the best method for healing venous ulcers and reducing recurrence. The ESCHAR trial compared compression therapy alone to conventional surgery combined with compression therapy. It showed that ulcer healing was similar between the two approaches, however, at one year, ulcer recurrence rate was lower following the combined treatment method[292,293]. The ESCHAR study was limited by the fact that 25% of those randomised to conventional surgery were not fit to undergo the intervention; this combined with delays in delivering surgical intervention in the interventional group meant that the study was not able to show the benefit of venous intervention in expediting venous ulcer healing. More recently the EVRA trial compared early treatment of SVI in combination with compression therapy against compression therapy alone with delayed treatment of SVI in C6 disease. It showed that compression with early SVI treatment reduced ulcer healing time and increased ulcer free time when compared to delayed treatment[294].

1.7.1.(d) Pharmacological therapy

Medications used to treat venous disease are common and have a long-standing history, often being based on traditional remedies. They are referred to as phlebotropic, phlebotonic or venoactive drugs in the literature. There are many drugs in this class but some of the more known remedies can be categorised into four groups: coumarins (α-benzopyrones), flavonoids (γ- benzopyrones), saponosides (horse chestnut seed extracts), and other plant extracts[295]. The precise mechanisms by which these medications produce their effects are not clearly understood but they are thought to increase venous tone and reduce capillary permeability through adrenergic pathways[295,296]. Flavonoids for example decrease inflammation and vascular permeability by acting on leukocytes and endothelial cells. Micronized purified flavonoid fraction (MPFF) - Daflon (Servier Hong Kong Ltd, Hong Kong) - MPFF consists of 90% micronized diosmin and 10% flavonoids[297] inhibits granulocyte and macrophage infiltration of venous parenchyma[297]. When tested in an animal model of venous hypertension, MPFF attenuated venous valvular degeneration endothelial cell apoptosis[298].

Despite promising animal studies, the role of phlebotonics in the modern management of C2-C4 SVI is questionable. A recently updated Cochrane review looked at the efficacy of many phlebotonics including hidrosmine, diosmine, calcium dobesilate, rutosides, centella asiatica and French maritime pine bark extract[299,300]. The authors reported significant heterogeneity in the evidence available, but importantly there was no strong evidence to show that HRQoL improved with these remedies[300]. However, there was moderate evidence to show a reduction in oedema[300]. A separate Cochrane review on horse chestnut extract reported some symptomatic improvement in relation to leg pain and oedema, but again did not report significant HRQoL improvement[301]. Side effects are frequently reported with these remedies, often they are gastrointestinal but serious adverse events such as agranulocytosis have also been reported[299,302].

Given the low level of evidence on clinical efficacy and the presence of proven interventional treatments for SVI, phlebotropic remedies are not recommended by NICE for C2-C4 SVI[199]. On the other hand, the European Society for Vascular Surgery guidelines on venous disease advises that they should be considered for symptom relief[22].

In the context of C6 SVI, there is considerable evidence to show that some venoactive drugs offer an advantage when used as an adjunct to compression therapy[303]. Compression therapy in addition to Pentoxifylline for example has been shown to expedite venous ulcer healing when compared to compression and placebo[304]. Similarly, MPFF and sulodexide also reduced ulcer healing time[305,306]. Based on this, MPFF and sulodexide are both recommended as adjuncts to compression by the European vascular society, whereas the American Society for Vascular surgery gives venoactive drugs including diosmin, hesperidin, rutosides, sulodexide, MPFF, horse chestnut seed extract gives a Grade 2B recommendation as adjuncts to compression in C6 SVI[176]. It should be noted however that interventional treatments carry an advantage over these medications as an adjunct to compression as they reduce recurrence rates and are proven to be cost effective, which is not the case for venoactive medication.

1.7.2 **Conventional surgery**

Surgical ligation and stripping were popularised and refined by surgical greats such as Friedrich Trendelenburg (1844-1924) and Charles Mayo (1865-1939). Throughout the twentieth century, surgery became the established treatment for SVI[307]; and until the recent development of minimally invasive techniques, surgery remained the most popular interventional treatment for SVI[308]. In keeping with the descending theory of SVI pathophysiology, surgical treatment aims to abolish reflux by removing the incompetent saphenous trunk along with its tributaries, and is usually accompanied by concomitant phlebectomy of superficial varicosities[309].

For the GSV, a 3-4cm incision is made at the groin crease, medial to the femoral pulse. Dissection continues through the cribriform fascia towards the SFJ. Care is taken to preserve the external pudendal artery where possible. After dividing all SFJ tributaries, the GSV is identified and stripped down to the knee level. Recurrence rates are unacceptably high when the GSV is preserved or not stripped to the knee level, whereas stripping to the calf and beyond is associated with high rates of saphenous nerve injury[310-314]. For the SSV, ligation is usually performed at the level of the knee crease, and it is recommended to mark the SSV and SPJ under ultrasound guidance. This method allows for easy ligation of the SSV at an accessible location. Due to the high risk of sural nerve injury with SSV surgery, ligation is not performed flush at the junction and stripping is not usually performed.

Surgical interventions for SVI are now performed as day case procedures under general anaesthesia, and this has been shown to be safe and effective[315]. These operations carry an initial detrimental effect on HRQoL in the perioperative period, mainly due to pain[316,317],but after this initial period patient symptoms and HRQoL gains are superior to those achieved by conservative therapy, as demonstrated in the REACTIV trial and others like it [221,311,318,319]. These HRQoL gains can last up to ten years and are comparable to those gained by other elective surgical procedures such as cholecystectomy[318,320]. More recently, the CLASS trial showed that HRQoL gains following surgery were better than foam sclerotherapy at 6 months and five years follow up[315,321].

Clinical recurrence following surgery has been frequently reported and is associated with HRQoL impairment[313,322-325 326]. Predominantly, recurrence is due to three factors which are not mutually exclusive. These are neovascularisation, progression of underlying venous disease and inadequate primary technique[327]. Technical inability to ligate the junction or incomplete stripping of the axial vein are both possible and lead to high rates of recurrence[310-312,328,329]. Traditionally, surgical ligation of the SFJ was often performed by non-vascular trainees and this is thought to contribute to technical failure

issues. As for SSV surgery, flush ligation and stripping are not advisable, and this may again contribute to the high rates of clinical recurrence following surgery[323,330].

Perhaps the most significant of the frequently reported complications after conventional open surgery is saphenous or sural nerve injury. It can be troublesome for some patients and is the commonest source of litigation for vascular surgeons[331,332]. Surgical site infections are another common complication after surgery. Infections rates of up to 16% have been reported following venous surgery[333-338]. Antibiotic prophylaxis significantly reduces infection rates, however it is probably not possible to abolish infection in groin surgery [339,340]. Bruising and haematoma are common after surgery and contribute to procedural pain, which is one of the reasons why compression is recommended following surgery [341-345]. Venous thromboembolism (VTE) is very rare after surgery but can be serious with an incidence rate of 0.5%[346,347].

Various technique modifications have been attempted to try to reduce the chance of neovascularisation, from suturing the cribriform fascia to biological or synthetic barrier grafts[348-354]. 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.

1.7.3 **Sclerotherapy**

Sclerotherapy for SVI was first popularised in France in the 1850s by Édouard Chassaignac. Due to frequent and serious adverse events in addition to poor long-term outcomes it fell out of favour by the beginning of the twentieth century[355]. It's safety profile and popularity improved half a century later due to the works of pioneers like Fegan who popularised liquid sclerotherapy[356-358]. However, whilst the short-term outcomes appeared encouraging, the long-term results of liquid sclerotherapy were disappointing when compared to conventional surgery[355,359]. Ultrasound guided foam sclerotherapy (UGFS) was the next step in the development of this technique, and it has been shown to be superior to liquid sclerotherapy in terms of technical success and rates of recurrence[360-362]. There are three broad types of sclerosing agents commonly used: detergent sclerosants such as Polidocanol and Sodium Tetradecyl Sulphate (STS), Osmotic agents such hypertonic saline and caustic chemicals such as chromated glycerine[363-365]. The detergent type sclerosants are the most popular in the literature and in the UK, however, only STS is a licenced detergent sclerosant for use in SVI treatment.

Sclerosants in general work by initiating inflammation and mural cell death in the target vein, leading to its subsequent occlusion and abolition of reflux. Detergent sclerosants form micelles and lipid layers that attach to and disrupt the cell membrane's own lipid bilayer. This denatures the cell membrane proteins and ultimately leads to cell death[366]. In the liquid form, these chemicals are easily diluted in the circulation and are not present in high enough concentrations at the vessel wall to denature and kill endothelial cells, especially with larger veins. Foam however displaces and doesn't mix easily with intraluminal blood, increasing the contact surface area of the sclerosant and the time period contact is maintained with intimal cell, thereby potentiating cellular injury[365]. Another advantage gained when using foam is that lower volumes are needed to achieve the same results as the foam isn't washed away as easily as liquid, therefore, the same dose of foam sclerosant can treat more targets in the same session compared to liquid.

Liquid sclerotherapy for its part has been shown to be superior to placebo in treating superficial varicosities[367,368]. The REACTIV trial showed that liquid sclerotherapy was superior to conservative treatment in terms of patient symptoms at 1 year, this difference however was not maintained at 2 years[221]. Tessari's method of creating foam for injection is perhaps the most popular method used today in practice[365]. Comparing liquid and foam sclerotherapy is difficult to do directly due to the large variations in the techniques for both methods however foam is thought to produce better occlusion rates than liquid sclerotherapy[365], and no direct HRQoL comparisons were available in the literature. In experienced hands, UGFS can be a highly successful treatment with success rates of 80% to five years[369-371]. A meta-analysis of technical success rates for minimally invasive techniques including UGFS estimated initial success with UGFS at 82.1% (95% C.I 72.5 to 88.9%), and at one year 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%)[372]. The authors concluded that UGFS was not inferior to conventional surgery (OR 0.15 (95% C.I -0.49 to 0.80) [372]. More recently, the CLASS trial compared foam sclerotherapy to thermal ablation and conventional surgery in a multicentre RCT and showed that both UGFS was not as effective or cost effective as those two options[315,321].

Despite the comparatively less favourable results, UGFS remains a highly versatile treatment method. It can be applied to compromised skin or at ulcer bases where surgical methods are contraindicated. It is inexpensive and can be performed quickly, conveniently and with little infrastructure as a clinic-based procedure. It offers faster recovery than other methods, and when needed can be repeated easily. It does however come with some risks and complications. Commonly reported early complications

include thrombophlebitis at 15%, skin matting 8% and skin blistering or ulceration 7.1%[221,373]. In the class trial, a 7% complication rate was reported for foam sclerotherapy which was significantly higher than EVLA at 1%. Most of these complications were neurological including visual disturbance, vasovagal events and headaches[315]. Rarer but more serios complication of sclerotherapy include cerebrovascular events at 0.1%[373] - and it should be noted that a known right to left shunt is an absolute contraindication for this technique. Other serious adverse event rates vary in the literature, PE is reported at 0.04% and DVT rates range from 0.02%-2%[373].

1.7.4 **Endovenous thermal ablation**

Endovenous thermal ablation (EVTA) techniques have been revolutionary in the management of SVI since their introduction at the end of the 1990s, and have now become the established first line treatment according to NICE guidance[199]. EVTA aims to deliver sufficient thermal energy to cause vein wall cell death resulting in durable non-thrombotic occlusion of the incompetent vein, abolishing reflux[374]. The remaining tissues heal by fibrosis. The concept of using heat energy to treat varicose veins can be traced back to the 1960s[375]; initial results were very poor however technological advances and combination with tumescent local anaesthesia (TLA) have allowed this technique to flourish[375]. There are now several established methods of delivering intraluminal heat energy to varicose veins including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), steam ablation (EVSA) and microwave ablation (EMA). Of these techniques, RFA and EVLA are the most established and have the strongest evidence supporting their use[22]. The technique of EVLA is described in detail in 2.4.3 (120-85) but in general thermal ablation techniques all share standard principles. After correctly positioning the patient, the target vein is cannulated under ultrasound guidance. This allows the operator to place a thermal ablative catheter device into the target vein carefully positioning the tip close to the incompetent junctional source, again under ultrasound guidance. TLA is then infiltrated into the surrounding perivenous space and EVTA can then be safely delivered to the target vein according to manufacturer advice.

1.7.4.(a) Tumescent Anaesthesia

Local anaesthesia was first reported and described in Vienna in the 1880s beginning with topical cocaine[376,377]. It gained popularity very quickly and was adopted by surgical pioneers such as Halsted (1852-1922)[378]. A safer local anaesthetic agent than cocaine continued to be sought leading to the development of novocaine and subsequently lidocaine which is now the main local anaesthetic used in tumescent anaesthesia[379,380]. The next two steps to the development of tumescent anaesthesia were dilution using a large crystalloid volume and the addition of a vasoconstrictor. Vasoconstriction facilitated through alpha adrenergic stimulation reduces the rate of absorption or removal of the locally infiltrated agent into systemic circulation, thereby increasing its bioavailability locally. This in turn means that the local anaesthetic action is maintained for longer and that the risk of systemic side effects is reduced. Both of these steps were described independently by German and Soviet doctors in the early 1920s[381,382]. This method had different names at the time including massive and hard infiltration[383,384]. In more modern times, this technique came to be known as tumescent anaesthesia and gained popularity as a safe anaesthetic method in cosmetic surgery, and subsequently venous surgery and thermal ablation[317,385-394]. Whilst the resultant TLA is effective for thermal ablation, its infiltration is uncomfortable for patients during EVTA, primarily due to the acidity of the solution. Therefore, buffering of the solution to physiological pH termed buffered tumescent anaesthesia (BTLA) has become commonplace, and has been shown to reduce procedural discomfort[395,396]

TLA has several functions during EVTA, its anaesthetic function allows for effective analgesia intra and peri procedurally. The large volume of liquid infiltrated in addition to water's high specific heat capacity allows it to function as an effective heat sink protecting nearby tissues and skin from thermal energy[394,397,398]. TLA is infused under pressure allowing it to hydro-dissect tissues away from the target vein, again protecting them from direct injury during thermal ablation[399]. Finally TLA compresses and vasoconstricts the target vein around the endovenous catheter; which facilitates effective ablation by increasing contact and energy delivery to the vein wall[400]. Vasoconstriction also has the additional benefit of emptying blood from the target vein and its tributaries, which decreases postoperative bruising and discomfort.

1.7.4.(b) Endovenous laser ablation (EVLA)

EVLA was developed at the end of the last century and was first reported in the treatment of SVI 1999[392]; the same publishers then reported a case series two years later[393,401]. Laser itself was

developed in the 1960s and stands for Light Amplification by Stimulated Emission of Radiation (LASER). Although light is specified in the acronym, any wavelength on the electromagnetic wave spectrum can be used. The emitted light beams must be the same wavelength and for the purposes of EVLA this falls at the near infrared part of the spectrum. These light photons are collimated and coherent, meaning that they travel parallel and are in the same phase both in relation to space and time as shown in Figure 14 [402].

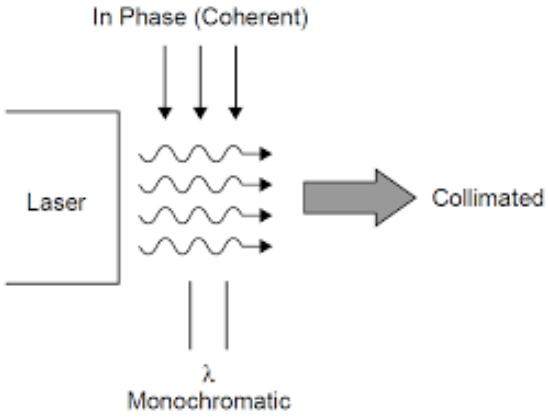


Figure 14 - LASER photons

There are several proposed theories on the mechanism by which heat energy is transferred to the vein wall, and these are by no means mutually exclusive. The histopathological evidence for these theories is based on older, shorter wavelengths however and may not apply accurately to longer wavelengths. One theory argues that the chromophores in the vein wall absorb electromagnetic energy and then releases it as heat energy causing cell damage[391,403]. Another theory is based on an ex vivo observation that steam bubbles are created in the blood as the laser fibre is fired which in turn travel away from the fibre and towards the vessel wall heating it up[404,405]. Diffusion of heat directly from the laser fibre tip has also been implicated as the temperature of the laser tip can rise up to 1000 degrees Celsius when being fired continuously, and finally direct contact between the hot fibre tip is also thought to play a role [406-408]. While these theories are of experimental interest, clinical studies suggest that the amount of energy delivered in J/Cm^2 is a reliable measure of predicting technical success[409,410]. In practice, this is reported as linear endovenous energy density (LEED), with most practitioners recommending around 80 J/cm to achieve successful ablation with the shorter older wavelengths [411].

EVLA technology has undergone several developments since its introduction. The emitted wavelength is designed for preferential absorption by a particular chromophore, which is usually haemoglobin or water [412]. Once absorbed the electromagnetic energy is converted to heat energy causing cell death.

Older designs used shorter wavelengths (810 nm, 940 nm and 980 nm) for which the target chromophore is haemoglobin, but newer designs have longer wavelengths (1319 nm, 1320 nm, 1470 nm and 1500nm) and target water. Longer wavelengths are thought to be better absorbed by the vein wall; therefore ablation can be achieved with lower energy output[403,413,414]. Moreover as less heat energy is inputted and a higher proportion of it is selectively absorbed by the target vein wall, procedural discomfort and morbidity is lower as other leg tissue is not damaged by excess energy[415]. Another development in the delivery of EVLA has been the change from pulsed laser to continuous[416]. More recently, the laser fibre tips that emit laser have undergone changes in their design in order to facilitate better delivery of energy to the vein wall. Initial designs had a forward firing bare tipped fibre [417]; however newer designs are gold-jacketted[418], radial firing[419] and tulip centring [420] fibre tips, Figure 15.

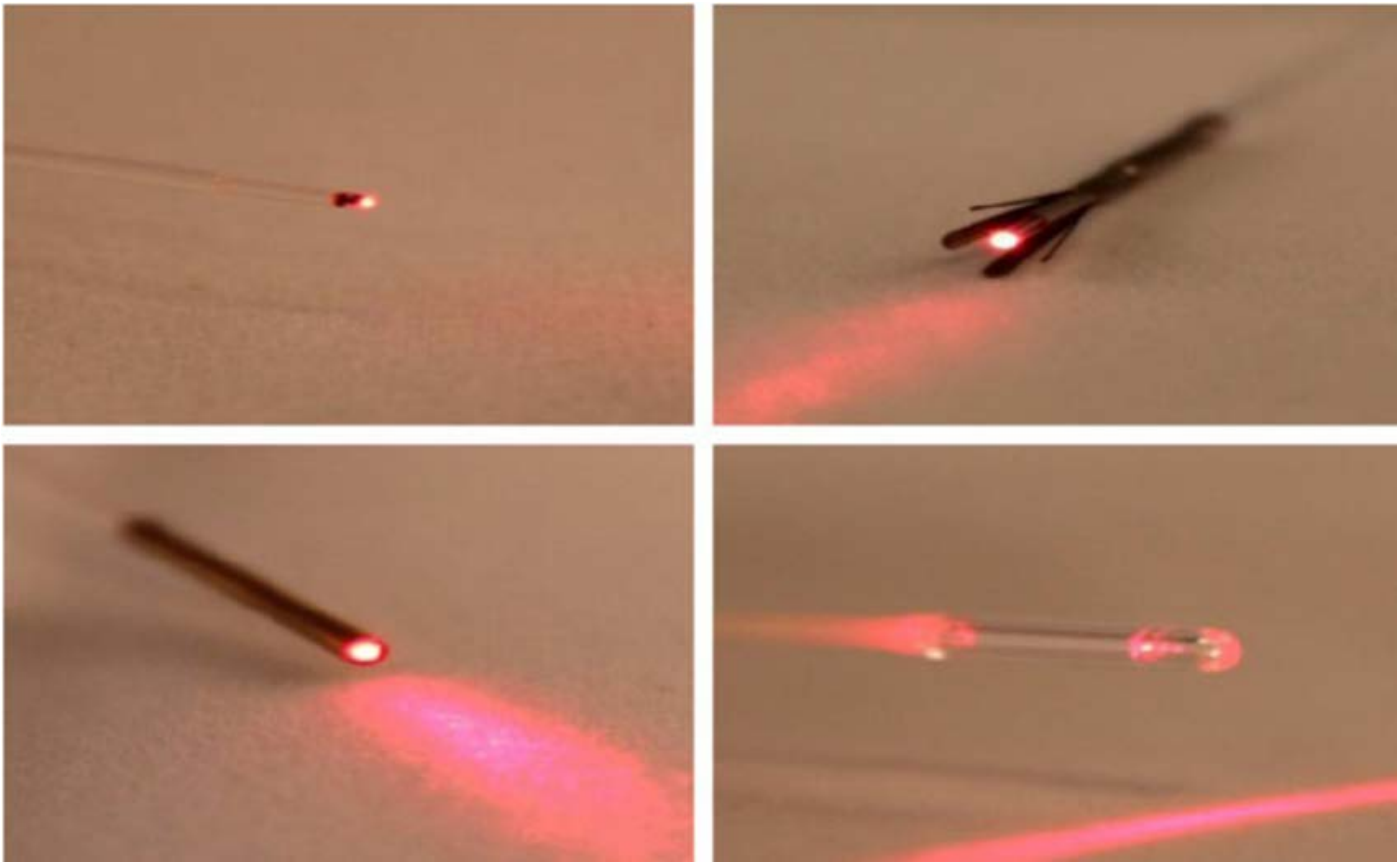


Figure 15 - EVLA fibre tips - bare tip (top left), tulip (top right), gold-jacket (bottom left), radial (bottom right)

Anatomical occlusion rates following EVLA are high which makes it one of the most effective methods of treating SVI[372,421-423]. A meta-analysis of clinical studies using older EVLA technology showed initial success rate of 92.9% (95% C.I. 90.2 to 94.8%)[372], Long-term outcomes remained also high, with success at a year of 93.3% (95% C.I. 91.1 to 95.0%), and at five years 95.4% (95% C.I 79.7 to 99.1%). This was significantly more effective than conventional surgery (OR 1.54 (95% C.I. 1.02 to 2.07)[372]. A more recent Cochrane review of RCTs also showed better technical outcomes following EVLA when compared to surgery (OR 0.29, 95% CI 0.14 to 0.60; p<0.001) [421]. Long-term outcomes at 5 years 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) based on one study only. More recent studies suggest that 5 year results of EVLA are better than surgery[424] or equivalent[321].

Several randomised clinical trials comparing conventional surgery and EVLA have investigated clinical and HRQoL outcomes[425-430]. Five studies found no difference in VCSS improvement between conventional surgery and EVLA at 1 year[317,425,426,431-433], and at long-term follow up, two studies showed no difference in VCSS[321,434] and one showed better results with EVLA[424]. HRQoL results when comparing EVLA to surgery showed similar results at six months to 5 years[425,430-432,435]; however recovery post EVLA is better than post surgery which is reflected in the superior HRQoL following EVLA outcomes compared to surgery[315,317,433]. Because of this earlier recovery and the fact that EVLA doesn't require general anaesthesia or regional anaesthesia, EVLA is more cost effective than surgery and recommended as first line treatment ahead of surgery[22,176,199,315].

The main limitation of EVLA as a minimally invasive technique is that it cannot be carried out as a clinic-based procedure. This is due to the necessary safety precautions needed to operate a laser device. Reported complication rates vary in the literature and those from older EVLA technologies may not apply to newer ones. Common complications include bruising (5%), phlebitis (7%), hyperpigmentation (5%) and paraesthesia (1%)[22]. VTE risk following EVLA is very rare, more commonly however, patients can develop thrombus extension into the deep venous system. The condition is called endovenous heat induced thrombosis (EHIT) and usually carries a benign course compared to a DVT, its incidence rate is 0.5%[436].

1.7.4.(c) Radiofrequency ablation (RFA)

Radiofrequency energy has seen uses in healthcare prior to its adoption for EVTA, including in ablating cardiac arrhythmic circuits[437] and in treating solid tumours. RFA was first reported as a method of treating SVI in 1998 [438]. It works by passing a current through an electrically insulated coil to generate heat energy, achieving temperatures of up to 120 Celsius when triggered. Like EVLA, RFA device technology has undergone several updates in the last 20 years. These forms included the ClosurePLUS system in 2003, which was updated to the VNUS (now Covidien) ClosureFast™ (VNUS Medical Technologies, San Jose, California, USA). This latest system uses a resistive heating system to close the circuit and generate heat, as opposed to the older systems that relied on contact with the vein wall to close the circuit.

As with EVLA, RFA is regarded as a highly efficacious treatment for SVI[372,421] initial success rates of 88.8% (95% C.I 83.6 to 92.5%) compare favourably against conventional surgery[372]. Long-term recurrence rates are also comparable to surgery from a DUS assessment perspective and in terms of clinical recurrence.

Studies comparing RFA to surgery in terms of clinical and HRQoL outcomes report similar improvement in VCSS in the mid to long-term[431,439-441]. Similarly, HRQoL gains offered by RFA are comparable to surgery and just as durable[431,442]. However, like EVLA, periprocedural pain, recovery time and early HRQoL gains are all better with RFA when compared to surgery[431,443]. These similarities with its sister thermal technique EVLA have lead most international bodies to recommend them equally as first line treatment methods for SVI[22,176,199].

EVLA and RFA both share a similar profile in terms of most complication rates including bruising, paraesthesia and skin staining[22,444]. However, phlebitis rates appear to be significantly higher following RFA when compared to EVLA; though it should be noted that this is based on older RFA technology[445]. Similarly, the reported incidence of EHIT with RFA seems ten times higher than for EVLA[446].

1.7.4.(d) Endovenous steam ablation (EVSA)

Endovenous steam ablation (EVSA) is a relatively new EVTA technique which uses steam to ablate veins[447]. The EVSA device is designed to deliver pulses of pressurised steam heated to 120 Celsius via an endovenous catheter. Histological studies of veins that have undergone EVSA suggest that it is

comparable in both thermal damage and temperature profile to RFA and EVLA[405,447,448]. However, unlike RFA and EVLA, vein wall contact is reduced during EVSA, and this may decrease the pain and postoperative ecchymosis[448,449].

In clinical studies EVSA has been shown to be both safe and effective[450,451]. Two recent randomised clinical trials involving EVSA have been published, one versus conventional surgery[452] and one versus EVLA[453] and both reported EVSA to be less painful than their comparator arm. However, while clinical outcomes were similar between EVSA and conventional surgery[452], at one year EVSA was reported to be inferior to EVLA[453]. As reported by Van den Bos et al, [453] 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[452,453]. While only one study measured HRQoL, no significant difference was detected between EVSA and EVLA in generic HRQoL (SF-36, EQ5D) or disease specific HRQoL (AVVQ) [453].

1.7.5 **Ambulatory phlebectomy**

Phlebectomy is the oldest treatment method for SVI and can be traced back to ancient Romans. It seems the technique however was lost to time and modern hook mini-phlebectomy practice is credited to Robert Muller[454]. Its commonly performed as a concomitant adjunct to axial treatment of SVI with surgery or EVTA. Alternatively, several authors have reported the technique as the primary treatment method and showed it to be safe and effect in the treatment of SVI[455-458]. Still others stagger the two treatments by performing axial interventions first then only follow through with phlebectomy if tributary incompetence remains symptomatic[459].

Phlebectomy is versatile and can be performed in a clinic or theatre setting, with local anaesthetic or TLA giving rise to the term “ambulatory phlebectomy”; and on the rare occasion that general anaesthesia is used, patients can still go home on the same day. The technique of phlebectomy involves marking all varicose tributaries in the upright position. Then in the Trendelenburg position, small incisions are made over the pre marked tributaries. The underlying vein is then grasped and avulsed using gentle traction in order to remove as much varicose vein as possible. A retrospective study of 195 legs in 151 patients with SVI showed improved patient signs and symptoms up to 2 years following ambulatory phlebectomy with preservation of the axial vein (ASVAL)[460]. Similar results were

seen in another larger multicentre retrospective study for up to 4 years[454]. The same study showed that after four years 66.3% of previously refluxing axial veins (>0.5s) had reverted to competence, and clinical recurrence was 11.5%. Notwithstanding the glaring limitation that some patients did not report significant symptoms at baseline, this study supports early but limited treatment of SVI. One RCT comparing AASV treatment with either phlebectomy or liquid sclerotherapy, showed significantly higher clinical recurrence rates following sclerotherapy at 1 and 2 years, respectively (1/48 vs. 12/48 and 1/48 vs. 18/48 $p<0.001$)[456].

The main limitation of phlebectomy is that it is contraindicated in compromised skin areas (C4b-C6). Complication rates of phlebectomy alone are difficult to ascertain as it is usually combines with an axial treatment method, but they include infection, bleeding, adverse scarring and paraesthesia. One P.E. has been reported in the literature following ASVAL[454].

The role of tributary treatment in the modern management of SVI has been contentious with strongly held views by different authors, reflected in the aforementioned practices where some argue that tributaries can be initially treated alone with axial reflux addressed later[454,460] and others arguing that all incompetence should be treated concomitantly[461,462] and a third camp arguing for delayed tributary treatment only when necessary[459,463]. Despite these differences in practice, it's worth noting that all three positions are in agreement from a theoretical viewpoint; all three approaches fit with the multifocal theory of SVI development, where tributary disease can be a focal point from which disease can progress in an ascending and/or descending fashion leading to symptoms. They only diverge when applying this theory into practice, however RCT evidence shows that concomitant treatment is clinically more effective and probably more cost effective[462].

1.7.6 Mechanochemical ablation

Endovenous mechanically assisted chemical ablation (MOCA) is a non-thermal non-tumescent (NTNT) method of treating SVI[464,465]. The first and most popular method of performing MOCA is to use the Clarivein® (Vascular Insights, Madison, CT, USA) device. It employs a rapidly rotating motor-powered wire to abrade the vein wall, the tip of this wire simultaneously disperses liquid sclerosant into the vein lumen. Using this method, the sclerosant agent's action is potentiated by allowing it to penetrate deeper into the vessel wall layers through the gorges created by the rotating wire[466]. An alternative device Flebogrif (Balton, Poland) has also been developed but there is so far limited data on its efficacy in the literature[467]. Case report histological evidence of Clarivein® at 1 year supports ex-vivo studies

showing transmural injury and fibrosis confirming the effectiveness of combined physical and chemical ablation[468 469].

Early clinical results of MOCA showed it to be safe and effective in treating SVI. Initial anatomical success rates at 6 weeks were >95% and were maintained up to 1 year[470-472]. Reported procedural pain was also low with one non-randomised study showing lower procedural pain with MOCA compared to older EVLA and RFA technology[473]. The same study also suggested that MOCA had a shorter procedural time than EVTA. More recently, an RCT comparing MOCA and RFA confirmed that MOCA had a lower procedural pain profile than RFA with similar procedural times[474]. Anatomical occlusion rates dropped from 93% at 1 month to 87% at 6 months[475].

Clinical and HRQoL outcomes were also promising following MOCA. A systematic review of patient VCSS following MOCA showed a significant improvement from mean VCSS of 5.78 (± 1.7) at baseline to 2.04 (± 1.4) up to mean follow up period of 46 weeks (p=0.001)[476]. HRQoL tools also significantly improved following MOCA with one RCT showing MOCA to be comparable to RFA at 6 months; median AVVQ for MOCA was 11.8 (7.2–20.5) compared to 9.4 (3.6–21.4) for RFA at six months (p=0.511)[477]. Long-term outcomes are lacking however, and only one cohort study reported results beyond 1 year, showing a deterioration in VCSS and HRQoL measures at 2 and 3 years following MOCA following the initial success[478].

Complication rates following MOCA have also been low. A recent systematic review including 10 studies and 1294 patients reported commonly occurring minor adverse events of thrombophlebitis (5.0%), bruising (2.2%), indurations (1.8%), haematoma (1.4%), and skin staining (0.6%)[476]. The reported rate of both DVT and PE incidence rates were 0.2%[476]. In contrast to EVTA, the risk of nerve injury following MOCA appears to be very low as the mechanical and chemical energy is contained within the veins. To date, the only case of nerve injury attributable to MOCA has been to aggravate pre-existing saphenous nerve neuropraxia[479].

Conceptually MOCA carries the flexibility of sclerotherapy and combines it with the clinical efficacy of EVTA. This shows in its versatility where it can be used retrograde to ablate GSV reflux in ulcer beds and compromised skin[480,481]. However there remain some unanswered questions regarding its long-term efficacy[482], and how to best utilise it. The optimal sclerosant preparation and concentration are

still unknown and one RCT has so far ruled out foam as an option for infusion into the Clarivein® Catheter[483].

1.8 Summary

The twenty first century has seen revolutionary changes in our understanding of SVI and our ability to manage it. Epidemiological studies have demonstrated the burden of disease in the general population. Generally held misconceptions regarding SVI and its cosmetic nature have been cleared away with HRQoL showing shown the impact of disease on patient lives and allowing comparison with other chronic conditions. Moreover, HRQoL tools have put patient symptoms at the centre of assessment and management planning, enabling the production of evidence that puts patient priorities first. The diagnosis and management of the disease have also been changed by the universal adoption of DUS as the standardised tool to establish disease pattern and guide its treatment.

DUS has facilitated the transition towards minimally invasive treatments which are now the established first and second choice treatments ahead of open surgery. EVTA has led the way in this transition, by offering lasting symptomatic resolution whilst improving on the perioperative morbidity and operational costs of open surgery. The progressive recurrent nature of SVI means that interventional treatments alone are unlikely to improve on current long-term results. This has meant that newer developments have been mostly aimed at improving perioperative outcomes while maintaining these long-term results. To that end EVTA technology has improved to reduce procedural pain, while non-thermal ablative methods have also developed and are now challenging this new established order. Besides MOCA, catheter directed foam is another method of chemical ablation in addition to cyanoacrylate venous occlusion. Together, all current endovenous methods offer safe, reliable treatments for SVI, the challenge however is to recognise their various strengths and limitations and to be able to offer treatment that best suits each patient. This thesis will attempt to tackle some of these challenges regarding optimising MOCA.

1.9 Objectives

As of the start of this thesis project, EVTA with concomitant phlebectomy is the established first line treatment method for symptomatic SVI with a considerable body of evidence to support this approach. MOCA on the other hand is an exciting NTNT treatment option contending to become an alternative standard treatment option for SVI. Several studies have shown it to be safe and effective in the short-term, however much of this evidence is sponsored by the manufacturers and warrants independent

scrutiny. Moreover, there are gaps in the literature on MOCA particularly regarding the optimal strategy to deal with tributaries when performing MOCA as well as the durability of the resultant technical and HRQoL outcomes.

In recognition of these gaps, the objectives of this thesis will be to:

- Scrutinise and review the current evidence on the use of MOCA
- Independently assess its safety, efficacy and durability of effects.
- Optimise the technique of MOCA and test the need for adjunctive treatment when performing axial MOCA
- Compare the clinical, technical and HRQoL of MOCA against the current first line treatment of EVTA with concomitant phlebectomy.

2.1 Study Aims

The literature evidence so far has established MOCA to be a safe treatment for SVI associated with low complication rates and significant clinical improvement in patients post treatment. This has culminated in NICE approving MOCA for use in the NHS, with the recommendation of collecting data on safety and efficacy[484]. Much of this literature however has been limited to short-term outcomes such as procedural pain[485]. Additionally, objective assessment of clinical improvement using validated HRQoL tools is often replaced with subjective assessment of disease state using VCSS or CEAP[485]. For example, a systematic review of MOCA assessing efficacy and safety has recently been published[476]; the authors of the review measured clinical success by VCSS improvement and accepted homemade measurements of technical success not matching consensus definitions. Perhaps this was a pragmatic decision reflecting the quality of studies available for review and a consequence, the findings of this review cannot be directly compared to studies of other endovenous modalities. Nonetheless this review offers a contemporary review of the MOCA literature and a similar review in this thesis is unlikely to carry additional utility.

An alternative approach would be to carry out a review of the MOCA literature that applies recommended reporting standards of endovenous ablation. This will offer a fair and reproducible assessment of the literature that facilitates comparison with other treatment modalities. Clinical consensus categorises short-term outcomes post SVI treatment as those obtained within the first year post intervention[182]. Study 1 is a systematic review of the current literature evidence on MOCA with a focus on clinical outcomes for throughout the short-term period, including assessment of technical success rates using consensus criteria and quantitative assessment of symptomatic improvement with HRQoL tools.

2.2 Methods

This systematic review was performed in line with Cochrane and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[486-488].

2.2.1 Study Eligibility Criteria

Prospective studies published in English in a peer reviewed journal were considered if they compared MOCA versus another treatment for adults with symptomatic SVI from a saphenous source, in a

randomised controlled trial or non-randomised cohort study. Data from cohort studies using more than one treatment method were included if data on MOCA patients was separately obtainable. A minimum patient follow-up period of 6 months was required. Studies were included in meta-analysis only if they adhered with international consensus criteria on the reporting of outcomes of interventions for venous incompetence [182].

2.2.2 Outcome Measures

The first outcome measure was DUS derived anatomical occlusion rate, defined as complete occlusion of the treated vein segment, evidenced by disappearance of the vein or complete lack of flow in the treated vein on colour Doppler and incompressibility[182]. The second outcome measure was objective improvement in patient reported HRQoL using validated measures (e.g. AVVQ, SF-36).

2.2.3 Search Strategy

A combined structured literature search was performed using the NICE Healthcare Databases Advanced Search (HDAS) engine. The search was carried out on 4th June 2017. Included databases were EMBASE, PubMed and Medline. Searched phrases were “ClariVein”, “mechanochemical ablation”, “endovenous mechanochemical ablation”, “mechano-chemical endovenous ablation” and “mechanical chemical ablation”. Duplicates were electronically identified and removed using the HDAS engine. The remaining non-duplicated results were amalgamated into a pdf document for manual screening. A similar search was then performed in the Cochrane Library and on Google Scholar to find any additional papers. Titles, abstracts, and full text articles were reviewed for selection and inclusion in the review.

2.2.4 Data collection and analysis

Two reviewers independently assessed titles and abstracts of the studies identified by the initial search, systematically excluding irrelevant studies. Full paper copies of potentially eligible studies were assessed independently against the inclusion criteria. Disagreements about inclusion were resolved by discussion. The same reviewers independently extracted data from the published manuscripts using a standardised data extraction form on to a secure database.

Prior to meta-analysis, clinical homogeneity with respect to patient demographics and the nature of the outcomes reported was to be performed. Only homogenous studies were to be combined for meta-analysis, with heterogenous studies being described separately. Additionally, Cochran’s Q test was to be used to examine for statistical homogeneity; $p<0.10$ was the set cut off point indicating significant statistical heterogeneity.

For anatomical occlusion or its reciprocal (recanalisation) a metanalysis was planned to chart the results of each included study on a forest plot as point estimates with risk ratios (RR) and corresponding 95% confidence intervals (CI). HRQoL measures (e.g. AVVQ) were to be reported as mean difference (MD) with 95%CI.

Where data were missing or unclear from the trial reports, study authors were contacted. No assumptions or imputations were made for missing data.

2.2.5 Bias and Quality Assessment

Methodological quality was measured against the American Venous Forum and Society of Interventional Radiology recommended reporting standards for endovenous ablation for the treatment of venous incompetence[182]. Risk of bias for RCTs was assessed using the Cochrane Risk of Bias Tool[487]. Bias in Cohort studies was assessed using the ROBINS- I (Risk of Bias in Non-randomised Studies of Interventions) tool[489].

2.3 Results

2.3.1 Search results

The literature search was conducted on 4/7/17 and identified 346 papers of which 115 were duplicates. These duplicates were removed electronically, leaving 231 articles remaining for title and abstract review. A further 215 articles were excluded based on title and abstract, the remaining 16 were retained for full text review. This revealed that these 16 manuscripts reported the results of 13 original studies. After full text review of these manuscripts, 12 manuscripts reporting the results of 11 original studies were excluded and 4 manuscripts reporting the results of 2 original studies were included. Figure 16 is a flow diagram showing the study selection process.

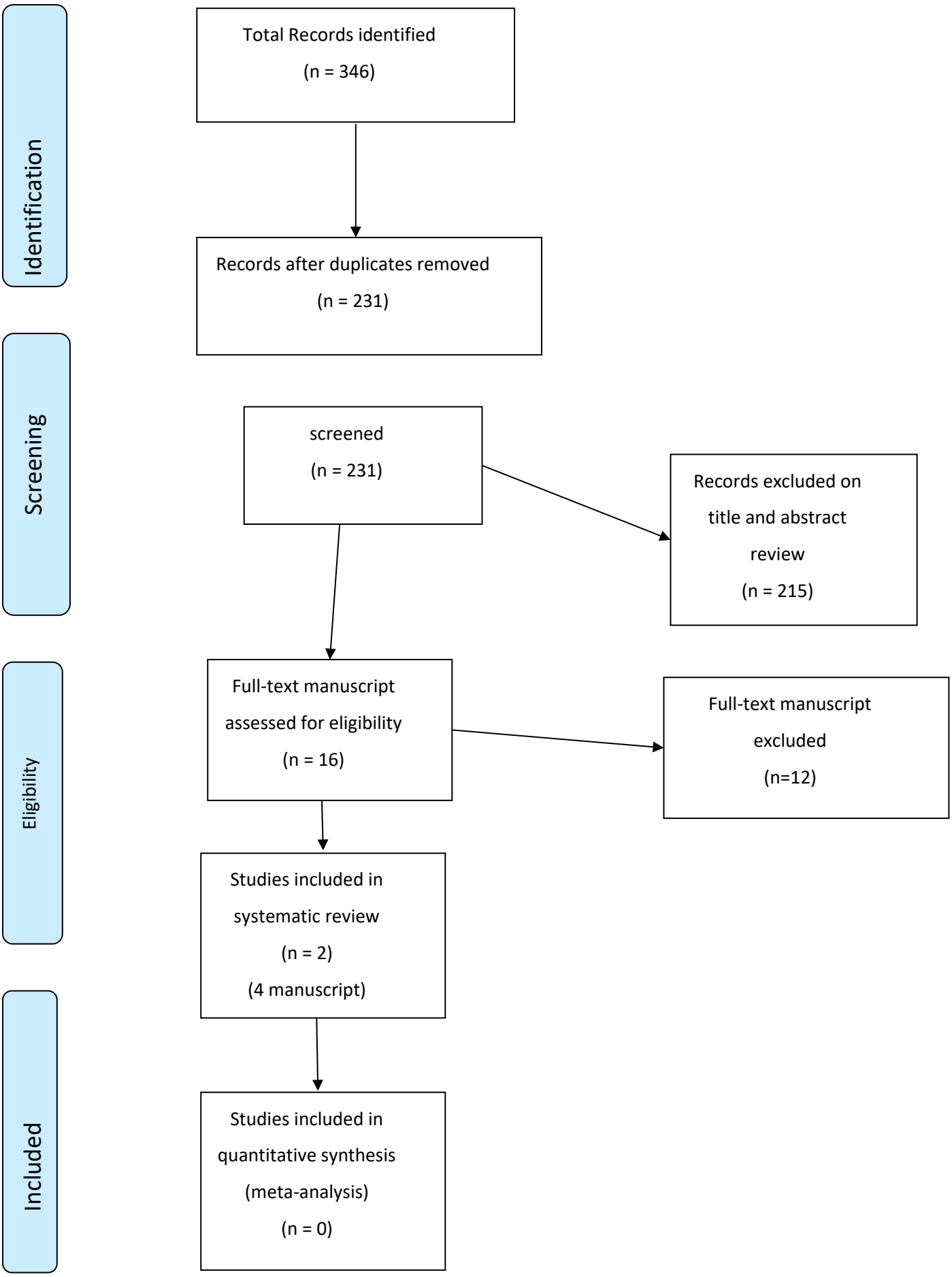


Figure 16 – Literature review study selection flow diagram

2.3.2 Included Studies

- Anatomical occlusion: none of the 16 full text articles reported occlusion according to consensus criteria > 6 months follow up and thus none were included for this outcome
- HRQoL: 2 studies (reported in 4 papers) fulfilled criteria for inclusion in the review for this outcome, a RCT (Venefit™ versus Clarivein® for varicose veins trial)[474,477] and a cohort study "Mechanochemical endovenous ablation for the treatment of great saphenous vein incompetence"[478,490]. Table 9 shows the characteristics of the included studies:

Table 9 – Literature review study inclusion table

Study name	**Venefit vs Clarivein RCT**	**MOCA for GSV Incompetence Cohort**
Methods	Design: multicentre RCT Setting: UK Funding: NIHR & Vascular Insights	Design: consecutive cohort Setting: Netherlands Funding: independent
Participants	Patients randomised: 87 Limbs treated: 83 LTFU 6 months: 29% LTFU 1 year: n/a Median age: 55 Female gender %: 57%	Patients recruited: 92 Limbs treated: 105 LTFU 6 months: 2% LTFU 1 year: 3% LTFU 3 years: Median age: 52 Female gender %: 62%
Intervention	MOCA: Clarivein & 2% STS Adjuncts: conc. phlebectomy in 68%	MOCA: Clarivein & 2% Polidocanol Adjuncts: sequent. Foam sclerotherapy in 22%
Outcomes	Primary: truncal ablation pain Secondary: HRQoL, occlusion rates, VCSS, recovery times, complications	Primary: occlusion rate, VCSS, Secondary: HRQoL, procedure pain, recovery times, complications
Additional notes	- The definition of anatomical occlusion definition did not fit with consensus criteria	- The definition of anatomical occlusion definition did not fit with consensus criteria - Discrepancy in the number of limbs treated between earlier and later publication - Discrepancy between reported LTFU and Survival curve figures - Authors contacted and did not respond to queries

2.3.3 Excluded studies

Twelve of the 16 full text papers reviewed were excluded: 6 papers were excluded as they had a shorter follow up duration than 6 months[483,491-495]; 1 paper was excluded as it did not appear to be published in a peer reviewed journal (the authors were contacted but did not respond)[496]. Regarding anatomical occlusion where study follow up did reach 6 months, all full text papers that were reviewed were excluded from analysis. The commonest reason for exclusion was nonadherence to consensus criteria[471,477,490]. Most papers did not report HRQoL. Table 10 is a summary table of excluded studies:

Table 10 – literature review study exclusion table

Author (year)	Design	Reason for exclusion
Van Eekeren 2011	Prospective cohort	<6 months follow up
Van Eekeren 2013	Prospective cohort	<6 months follow up
Elias 2012	Prospective cohort	No HRQoL outcomes reporting and did not specify outcome occlusion criteria used in study – was contacted and did not respond
Boersma 2013	Prospective cohort	No HRQoL outcomes reporting and did not adhere to consensus criteria on occlusion
Bishawi 2014	Prospective cohort	No HRQoL outcomes reporting and did not adhere to consensus criteria on occlusion
Ozen 2014	Prospective cohort	Not peer reviewed
Sullivan 2014	Prospective cohort	Did not report HRQoL outcomes or anatomical occlusion
Vun 2015	Retrospective	Retrospective
Lam 2016	RCT	<6 months follow up
Deijen 2016	Prospective cohort	<6 months follow up
Tang 2016	Prospective cohort	<6 months follow up
Kim 2016	Prospective cohort	No HRQoL outcomes reporting and did not adhere to consensus criteria on occlusion

2.3.4 Methodological Assessment

The two included studies met most of the recommended reporting standards criteria as shown in Table 11. However, neither study reported on the characteristics of the patient population they recruited from during the study recruitment phase. Specifically, the numbers of patients screened or treated outside the study were not reported, nor the type of treatments routinely offered in their centre.

Table 11 – Literature review methodological assessment

Study name	**Bootun 2016/ Lane 2016**	**Van Eekeren 2014/Witte 2016**
Pre MOCA evaluation		
Patient population	×	×
age, gender	✓	✓
Clinical indication for EVA	✓	✓
Anatomic location of treated vein	✓	✓
CEAP staging	✓	✓
inclusion/exclusion criteria	✓	✓
Comorbidities	×	×
pre-treatment imaging	✓	✓
primary complaint	✓	✓
MOCA description		
method of vein access	✓	✓
intraprocedural imaging	✓	✓
chemical agent description	✓	✓
energy source	n/a	n/a
total dose	✓	✓
adjunctive technique	✓	✓
Anaesthesia	✓	✓
length and vein diameter	✓	✓
Post MOCA		
Complications	✓	✓
follow up imaging	✓	✓
follow up clinical status	✓	✓
need for additional procedures	✓	✓
primary outcome	✓	✓

2.3.5 Risk of Bias Assessment

Selection:

The RCT by Lane et al reported adequate methods for random sequence generation and allocation concealment; it was deemed at low risk of selection bias[474]. The cohort study by Van Eekeren et al had a high risk of selection bias due to the lack of randomisation[490].

Performance:

Due to the nature of the interventions blinding of surgeons or participants was not possible therefore performance bias risk was thought to be high in the included studies.

Incomplete outcome data:

Risk of bias from missing outcome data was deemed high in Lane et al's RCT as it reported 29% LTFU at 6 months. Eekeren et al reported 5% LTFU at 1 year, which puts this data at low risk of attrition bias[490]. However, later analysis at 2 and 3 years are at high risk of bias with a reported LTFU of 15%[478].

Detection:

Both included studies were at high risk of detection bias in terms of anatomical occlusion rates. This is due to the use of occlusion criteria outwith recommended reporting standards that were likely to lead to an over estimation of success rates when compared to standard occlusion criteria. In the cohort study by Eekeren et al , a patent treated vein segment would only register as a failure of occlusion if it was >10cm in length[490].

Selective outcome reporting

Van Eekeren's cohort study is at high risk of selective outcome reporting due to unexplained censoring and inconsistency of some reported data. At baseline 105 limbs were successfully treated, but survival analysis of occlusion data starts with 101 limbs at risk. The later publication reports an occlusion rate of 92% at 1 year compared to 87% that was reported in the older publication. Moreover, LTFU was reported at 15%, however the number of limbs at risk reduces progressively due to censoring without an explanation provided; for example, survival analysis shows 76 limbs are at risk at 24 months, which reduced to 48 limbs at 36 months. Furthermore, HRQoL analysis was carried out using parametric tests in the later manuscript which is an inaccurate method of hypothesis testing of non-normally distributed HRQoL data in addition to inconsistencies when presenting figures, for example 4 different figures are

given for the baseline mean AVVQ (13.1±6.2, 11.6±5.6, 14.0±7.5, 13.1±7.6) and all are used in the analysis at different times.

Reported figures in the RCT by Lane et al are at high risk of bias for selective outcome reporting with regards to anatomical occlusion. This is because the reported figure for successful anatomical occlusion includes “proximal occlusion” which the authors define as “>5 cm proximally occluded, with >5cm open distally”[477]. This means that a 30cm treated segment with an occluded 10cm proximally and a recanalised 20cm segment distally would be regarded as a success.

2.3.6 Outcomes

Anatomical occlusion or anatomical success:

No study met the inclusion criteria for this outcome.

HRQoL:

Both studies used the AVVQ as the disease specific PROM for HRQoL. Lane et al reported a median (IQR) AVVQ score at baseline of 19.3 (13.2–28.7), which improved significantly to 11.8 (7.2–20.5) at 6 months; $p<0.001$ (Friedman)[477]. AVVQ reporting in the study by Van Eekeren et al was inconsistent between the two papers that reported on their cohort of patients. The first paper reported a median AVVQ (IQR) score of 11.1 (8.0-19.2) at baseline 6.6 (4.0-11.0) at 6 months and 2.4 (0.5-6.2) at 1 year; ($p<0.001$)[490]. The later paper reported a median baseline AVVQ (IQR) of 8.8 (2.5, 29.4), 4.1 (0, 17.3) at 6 months, 2.3 (0, 22.4) at 1 year, 2.3 (0, 22.4) at 2 years and 5.6 (0, 35.4) at 3 years[478]. They also found that AVVQ showed significant improvement at all time points when compared to baseline, however, the statistical tests to determine this were parametric tests based on the mean.

The high risk of selective outcome reporting in the cohort study precludes meaningful meta-analysis of the results of the two studies.

2.4 Discussion

Since the first published trial on MOCA in 2011[493], the Clarivein® device has seen increasing popularity as a treatment method for SVI. As of 2018, over 120 000 devices have been sold for use world wide[497]. SVI is a chronic condition significantly impacting upon patient HRQoL. Accepting the progressive recurrent nature of the disease, this review aimed to evaluate the evidence for the use of MOCA in SVI in the short-term – up to 1 year post intervention. The results of this systematic review highlight limitations in the quality of available evidence on the use of MOCA. These limitations are perhaps a result of MOCA being in the early stages of its life cycle as a treatment method for SVI, competing against established EVTA methods. The literature search identified a total of 12 original studies, comprising of case series, cohort studies and two RCTs. Chronologically, the earliest published trials aim to establish the safety and feasibility of MOCA[470,493]. Aims then move towards anatomical success and clinical success in the next group of publication[471,490]. Later, studies focus on procedural and periprocedural pain as well as procedural duration; occasionally comparing MOCA to thermal ablation retrospectively[498] or prospectively[474,477].

Due to their design focusing on early outcomes such as feasibility, safety and periprocedural pain, most studies did not have sufficient duration of follow up to be able to provide evidence on outcomes at 6 months and beyond, which was the focus of this systematic review. In fact, the main reason that six of the 13 original studies were excluded was that their follow up period was less than 6 months[483,491-494,498].

2.4.1 HRQoL

SVI is a chronic and frequently recurring condition and the durability of the benefits of treatment with MOCA therefore is an important factor influencing the decision making of patients and clinicians. The accepted tools used to measure SVI disease burden and patient response to treatment are HRQoL measures[182,374]. By and large, the studies identified in this review overlook the use of HRQoL measures. In fact, the two studies included in the review are the only ones to report patient HRQoL out of the original studies identified by the literature search. Lane et al's RCT provides good evidence that HRQoL benefits following MOCA are non-inferior to RFA at 6 months[477]. Van Eekeren et al's cohort study supports this evidence and demonstrates that HRQoL benefits are sustained up to one year[490]. However, the same study suggests thereafter, that HRQoL decreases after one year with evidence of clinical recurrences at two and three years[478]. The results of this cohort study are significantly limited

by reporting and attrition biases. Therefore, corroborative cohort or RCT level evidence is needed to determine the longevity of results following MOCA.

Based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group guidelines, the quality of evidence for HRQoL data at 6 months is based on one RCT and one cohort study. This evidence is therefore of moderate GRADE quality[499,500], signifying that at 6 months the true effect estimate of the benefit of MOCA is likely to be close to that reported in these studies. Beyond that however, only one cohort study offers data on the benefits of MOCA, signifying very low GRADE evidence. Therefore, it is likely that the true effect estimate of benefit in terms of HRQoL following MOCA is substantially different to that reported in the cohort study[500].

2.4.2 **Anatomical occlusion**

Several studies identified in the search strategy did not report how they measured this outcome in their manuscripts[470,496,501,502]. Attempted contact with these authors to ascertaining these details was ultimately unsuccessful, resulting in their exclusion from the review. Furthermore, there was significant heterogeneity identified in the definition of anatomical occlusion used among the studies on MOCA that did report how this outcome was to be measured[471,474,477,478,490,493,494]. The various definitions employed introduce bias in favour overestimating the true anatomical occlusion rate when compared to consensus criteria. They included ignoring recanalised segments of <10cm in one study[471]. Another study invented a new term called “proximal occlusion” where any segment of recanalisation distally was ignored providing a proximal segment of >5cm was successfully occluded. This was then pooled with the anatomically occluded veins and reported as one result[474,477]. Due to these limitations, none of the studies identified in the literature search were included in an analysis for anatomical occlusion. Based on this finding, it is likely that the figures reported in the literature so far are an overestimation of the true occlusion rates and further studies are needed to measure this outcome in line with recommended standards criteria.

2.4.3 **Other findings**

Of the available sclerosants in the market, the most frequently used drugs are Polidocanol and STS. So far it seems that there is no consensus on whether one sclerosant performs better than another. However, one RCT by Lam et al was identified which is investigating the ideal form and concentration of Polidocanol when performing MOCA[483]. An interim analysis has shown that Polidocanol foam

performs poorly compared to liquid with increased incidence of early recanalisation post treatment. A similar issue which remains undetermined is the role of adjunctive treatments of tributaries when performing MOCA. Further studies are needed to determine the optimum sclerosant preparation and strategy for dealing with tributary varicosities when performing MOCA.

2.4.4 **Limitations**

The findings in this review are limited by the quality of available evidence in the literature. The studies identified in the literature search were not designed or powered to provide evidence on anatomical occlusion rates or patient HRQoL. The two studies included in the review were severely limited by detection bias, selective outcome reporting and attrition bias and therefore any evidence derived from this data is of moderate to low GRADE. However, the literature search did identify protocols of ongoing studies that should shed further light on the issues raised in this review once published[503,504]. therefore, a further review of the literature is warranted in due course.

The risk of publication bias is unknown. Despite a meticulous search of journals in English, it is possible that articles in other languages were missed given the fact that MOCA has been used worldwide and the current literature search already identified one study that was excluded due to it not being published in a peer reviewed English language journal.

2.4.5 **Summary**

Anatomical occlusion is a surrogate measure of clinical success but is strongly associated with a reduction of clinical recurrence rate with EVTA[424,505], this is likely to be true with MOCA. Therefore, accurately measuring this outcome is of clinical importance to clinicians and patients as it can influence their decision making on treatment modality. Moreover, precise understanding of anatomical occlusion rates post MOCA will allow for identification of positive and negative factors influencing technical success, thereby facilitating the refinement of the technique, and ultimately benefitting patients. This outcome has not been accurately assessed in the identified studies on MOCA, highlighting a gap in the literature that can be bridged by later studies in this thesis.

Study 1 has also identified that objective assessment of patient symptoms in studies on MOCA has also been deficient, limiting the generalisability of most studies. The two included studies provide moderate evidence that symptomatic improvement following MOCA is significant and non-inferior to EVTA, up to

six months. But the evidence beyond that is weak and again this is another gap in the literature that can be cleared in later studies within this thesis.

Chapter 3: Study 2, Procedure Refinement - A Cohort Study of Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence: One Year Outcomes

3.1 Study Aims

Considering the paucity of independent high-quality assessment of clinical and technical outcomes following MOCA, study 2 is a cohort study of symptomatic SVI patients being treated with MOCA using the Clarivein® device and 1.5% STS. The study aims to assess the technical efficacy of MOCA using consensus definitions of anatomical occlusion, clinical tools such as VCSS and quantitative measures of disease severity such as HRQoL measures. This will provide a reproducible and fair assessment of MOCA efficacy that is of equal rigor to assessments of other SVI interventions.

3.2 Methods

3.2.1 Study Design and Ethics

This prospective non blinded cohort study was set in a tertiary vascular surgical unit in the UK serving a population of 1.2 million people. The Hull and East Yorkshire Hospitals Quality, Governance, Assurance, Compliance and Audit Administrator approved this study in line with NICE recommendations[506]; project number 2018101. The methods described below are in line with the Strengthening the Reporting of Observational Studies (STROBE) Guidelines[507].

3.2.2 Patient Selection

Consecutive patients presenting to the research team with symptomatic SVI were assessed for inclusion in this prospective study of MOCA. There were three pathways for patients to present to the research team. Firstly, direct referral from primary care to the research team with suspected SVI. Secondly, onward referral from a colleague vascular surgeon with patient consent after seeing the patient, diagnosing SVI and informing the patient of current ongoing studies within the vascular surgical unit. Thirdly, confirmed SVI patients awaiting treatment in the pooled vascular surgical waiting list were contacted in writing with information regarding the study and offered assessment for participation in the study. Once patients attended in clinic, they were assessed and counselled for potential study participation by a Consultant Vascular Surgeon or Clinical Research Fellow with a special interest in venous interventions. Assessments included a focused history and examination using

the CEAP[198] classification and VCSS[210], followed by a detailed venous duplex ultrasound assessment. These were all performed by surgeons qualified and accredited in diagnostic vascular ultrasound. In order to maximise applicability and external validity of the study, no upper limit was set for maximal vein diameter, or length of refluxing segment. Additionally, anticoagulation was not considered an exclusion criterion.

- Inclusion criteria:
  - Consenting adult
  - Symptomatic unilateral C2-C6 CEAP SVI
  - Suitability for any endovenous treatment
  - Incompetent SFJ or SPJ with reflux of >0.5s duration
  - Reflux in the corresponding saphenous vein of >0.5s duration

- Exclusion criteria:
  - Age <18
  - Active thrombophlebitis
  - Deep venous thrombosis in the last 3 months
  - Deep venous reflux in the CFV or POPV of the index leg
  - Bilateral reflux or reflux in more than one axis in the index leg (unless accessory saphenous reflux was originating from the GSV)
  - Pregnancy or Puerperium.
  - Peripheral arterial disease (PAD) with an ankle brachial pressure index (ABPI) of <0.8
  - Known allergy to the sclerosing agent STD
  - Known allergy to dressings materials used post intervention

3.2.3 Interventions

Interventions were carried out in a theatre suite or clean room, under ultrasound guidance using the ClariVein® device with 1.5% Sodium Tetradecyl Sulphate (STS) (STD Pharmaceutical Products Ltd, Hereford, UK) by a vascular consultant or clinical research fellow with a special interest in the management of venous disease and formal qualification in vascular ultrasound.

Pre-treatment:

After patient entry into the theatre suite, a DUS was performed in the upright position to confirm previous duplex findings and to mark the lowest site of saphenous reflux. All varicose tributaries were then marked, following which the patient was positioned in the reverse Trendelenburg position.

Operative method:

Skin prep was carried out with 10% povidone iodine in water or 2% chlorhexidine gluconate in 70% isopropyl alcohol (in case of iodine allergy). Draping was then applied, and the previously marked cannulation site is confirmed. 1ml of 1% lidocaine was used to anaesthetise the cannulation site under sterile conditions. Vein micropuncture and insertion of a 5Fr sheath was performed under ultrasound guidance followed by insertion of the MOCA catheter through the sheath. The patient was then positioned horizontally and the tip of the MOCA wire placed 2cm from the saphenofemoral junction (SFJ). The wire was then activated for 10 seconds to elicit vein wall spasm followed by catheter withdrawal at a rate equivalent to 1.4mm per second (achieved in practice by constant withdrawal of the catheter by 1cm every 7seconds) with simultaneous infusion of sclerosant at a rate of 0.2mls/cm15. Concomitant ambulatory phlebectomy was then carried out on patient request under TLA constituted of (100mls of 1% Lidocaine + 1:200000 Adrenaline and 10mls of 8.4% $NaHCO_3$ added to 900mls of NaCl 0.9%)[395]. This was infiltrated in the perivenous space starting from the already anesthetised cannulation site. When adequate anaesthesia is achieved, small 4-6mm incision were made over the varicosities through which an Oesch Hook was used to pull the tributaries out. Surgical clips were then used to tease out as long a segment of vein as possible proximally and distally. Other incisions were then targeted to maximise the number of varicose tributaries removed whilst minimising the number of skin incisions and anaesthetic skin punctures.

Post treatment:

After treatment completion, skin was dressed in 3M Steri-strips™ (3M Health Care, MN, USA), cotton balls, gauze, and Clinistretch® (Hadden Healthcare Ltd, Bucks) bandaging for one week. Neither analgesia nor anticoagulation were routinely prescribed; patients were risk-assessed for venous thromboembolism (VTE) using a standard proforma widely utilised in UK NHS practice and any that were deemed to be at high risk received 5 days of prophylactic dose subcutaneous low-molecular weight heparin (LMWH)[508]. At one week, patients were seen in the clinic, wound dressings were removed, and patients were advised to wear Anti-Embolic Stockings.

Venous DUS assessments:

All Examinations were performed by vascular surgeons qualified in vascular sonography working to agreed international consensus on the use of ultrasound in the investigation, treatment and reporting of outcomes of SVI in research[182,243,246,374,509]. DUS assessment was performed in a warm room, with dimmed ambient lighting using a Toshiba Aplio MX machine or a Toshiba Aplio 500 machine (Toshiba Medical Systems Ltd, Crawley, UK) and a 6-12 MHz linear array transducer.

B-Mode images were dynamically altered to optimised viewing of the structure of interest by modifying image depth, focal zone, tissue gain and time gain compensation. Tissue harmonics and compound imaging were standardised to optimise imaging of vascular structures by the machine pre-sets. Colour Doppler Pulse Repetition Frequency scale was set to 5-10cms^{-1}. Other colour and spectral Doppler parameters were dynamically optimised by changing colour box size, depth, beam steering, colour gain and sample window as necessary. The angle of insonation was maintained at 45-60^{o} to the direction of blood flow. Manual compression augmentation was carried out at the calf when interrogating thigh veins and at calf site more than 10cm distal the site of interest when interrogating calf veins.

Venous DUS assessments were performed with the patient in the standing position on a raised platform. At first, patients were examined facing the examiner with the index leg rotated externally at the hip and flexed at the knee to maximise access to the groin and the entire medial leg. At this stage, the patient's weight was borne on the healthy leg, ensuring the index foot remained in contact with the platform and the calf of the index leg remained relaxed. Scanning started at the groin in B-Mode, identifying the presence of the SFJ, CFV, FV, GSV and all other SFJ tributaries. The deep veins were then interrogated first ensuring the patency and competency of the CFV and FV using colour and spectral Doppler waveforms. Then, SFJ competency was tested and the pattern of any reflux originating from the junction determined, mapping the full length of all identifiable axes and testing for the lowest point of reflux. Care was also taken to identify all perforator veins and test them for competence and ascertain their anastomosis with any axial vein. Anteroposterior measurements were then taken of the refluxing axial vein using the system's callipers, to the nearest 0.1mm, measuring from the most anterior echo of the anterior wall to the most posterior echo of the posterior wall. For the GSV, these were measured at 2-3cm distal to the junction, mid-thigh, above knee, below knee and mid-calf levels. AASV measurements were taken at 2cm distal to the junction, mid-thigh and above knee when applicable. Care was taken to avoid any localised dilatations during measurement.

The patient then turned 180^{o} facing away from the examiner with both feet forward facing. The patient's weight remained on the healthy leg, with the index leg slightly flexed at the knee. Again, with maintained index foot platform contact and relaxation of index leg calf muscles. Then in B-Mode, the POPV, SSV, SPJ and all its tributaries are identified, followed by interrogation of the POPV's patency and competency. The entire SSV is then interrogated and when incompetent, anteroposterior size measurements were taken 2cm distal to the SPJ and at mid-calf level. When present, the thigh extension vein or Giacomini vein was followed to its termination and care was taken to identify any incompetent posterior thigh or calf perforators.

3.2.4 Outcomes

Patient outcomes in this study were assessed by members of the research team at baseline and weeks 1, 6, 26 and 52. In terms of timing, outcomes were divided into baseline outcomes, immediate outcomes at 1-6 weeks, and short-term outcomes at weeks 26-52[246]. Outcomes were further categorised into clinical, technical, HRQoL or DUS outcomes.

Clinical outcomes were:

- CEAP at baseline only
- VCSS at weeks 1,6,25 and 52
- Complications on examination or imaging: P.E., infection, phlebitis, neuralgia, paraesthesia and skin staining at weeks 1,6,25 and 52
- Recurrence of varicosities on clinical examination – defined as new varicosities detected at 6 months or 1 year that were absent at 6 weeks follow up, irrespective of symptoms.
- Need for further procedures - Reintervention was offered after six weeks if the patient had symptomatic incompetent recannalisation of the treated vein, new axial reflux in the treated leg or if there were symptomatic residual or new varicosities in the treated leg

Technical outcomes were:

- Length of vein treated to the nearest cm – measured to the nearest 0.5cm using the marking on the MOCA catheter.
- Completion of procedure
- Total infused volume of sclerosant – to the nearest 0.1 ml
- Rate of sclerosant infusion in $mlcm^{-1}$

- Procedure duration – timing started from patient entry into the operating theatre, and finished on completion of application of bandaging
- Pain during axial ablation - scored by the patient on a 100mm VAS immediately after axial ablation
- Post operative pain during the first week post procedure – completed each evening independently by the patient in a pain diary sheet containing 7 unmarked 100mm VAS
- Patient satisfaction with cosmetic outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Patient satisfaction with overall outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Time to return to normal activity to the nearest whole day
- Time to return to work to the nearest whole day

HRQoL outcomes were:

- Disease specific: AVVQ at weeks 1,6,25 and 52
- Generic: EQ-5D at weeks 1,6,25 and 52

These were given to the patients by clerical staff on arrival to clinic and completed independently by the patient prior to any clinical interaction with research staff on the day of follow up.

DUS outcomes were:

- GSV diameter to the nearest 0.1mm
- Technical success (immediate occlusion of vein) – on day of treatment and at 1 week.
- Recanalisation – measured at 6 weeks, 6 months and 1 year, the primary study outcome was freedom from recanalisation at 1 year. This was assessed at each visit according to the American Venous Forum consensus criteria[18]; a vein was successfully ablated if it was either absent or incompressible with no detectable flow in the entire treated length.
- Complications: DVT (regardless of symptoms)

3.2.5 Data handling

Collected data were uploaded onto a secure hospital database and analysed using IBM SPSS version 24 (IBM Corp, Armonk, New York). Normally distributed data are presented as mean (standard deviation)

and non-normally distributed data are presented as median (interquartile range). Comparative hypothesis testing was conducted using Friedman's test with significance level set at $p<0.050$.

3.3 Results

3.3.1 Patient Recruitment

Over a 9 month recruitment period (October 2014 - June 2015) 101 patients were screened, of which 94 patients were eligible and 32 consented to participate. The most common reason for non-participation was a patient preference for endothermal ablation (62 patients). Figure 17 is a flow chart of the patients involved at each stage of the study and shows the low rate of attrition during follow up. In the same vascular institution, some 1178 patients underwent thermal ablation, 94 patients underwent open surgery, and nine patients had foam sclerotherapy during the same recruitment period. Table 12 summarises the baseline characteristics of included patients.

Figure 17 - Study 2 flow chart

Table 12 – Study 2 patient baseline characteristics

Number of patients	32
Male: Female	14:18
Mean age (sd)	50.75 (+/-14.6)
Mean BMI	27.10 (+/-4.9)
CEAP 2:3:4:5:6	10:13:6:1:2
Median VCSS (iqr)	6 (5-8)
Median AVVQ (iqr)	13.50 (10.00-18.65)
Median EQ-5D (iqr)	0.877 (0.807-0.877)
Mean saphenofemoral junction vein diameter (sd)	7.97 mm (+/-2.83 mm)

Data is presented as mean with standard deviation (sd) if normally distributed or median with interquartile range (iqr) when not normally distributed

3.3.2 Procedural outcomes

All 32 patients received the planned MOCA and completed 1 week follow up with no protocol violations. The pattern of reflux in all patients bar one was SFJ incompetence with reflux into the GSV axis. The remaining patient had AASV reflux and an incompetent SFJ. Median length of ablated vein was 45cm (37-48). The Mean total volume of sclerosant used was 11 (±3) ml per patient, infused at a mean rate of 0.26 (±0.08) ml/cm. Eight patients opted to have concomitant ambulatory phlebectomy. In those patients where axial ablation only was carried out, median procedure time was 30min (22-35), increasing to 35min (27-40) when phlebectomy was performed.

3.3.3 Periprocedural pain

All pain data was non-normally distributed as shown in Figure 18. Median reported pain during axial ablation was low at 20 (7-47) on a 100mm VAS. Post procedural pain in the first 7 days post treatment was also low as shown in Table 13. One patient did not return a completed pain diary and was excluded from this analysis. Of the remaining patients, 26 completed the pain diary for all 7 days and 28 patients completed the diary up to Day5. Figure 19 outlines the changes in pain scores day by day in the 26 patients that completed their pain diaries.

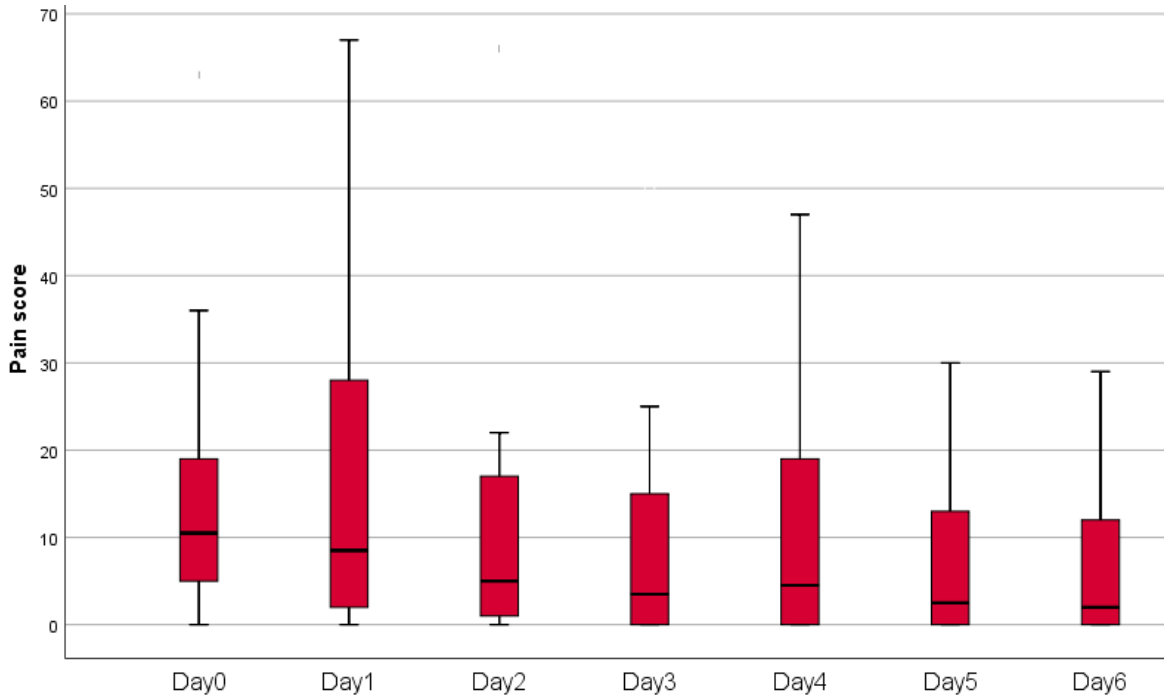


Figure 18 - Study 2 pain box plot

Table 13 - Study 2 pain scores table

Pain score								
		Truncal pain	Day0	Day1	Day2	Day3	Day4	Day5	Day6
N	Valid	31	31	31	31	31	31	28	26
	Missing	1	1	1	1	1	1	4	6
Mean		26.39	14.74	16.23	11.45	9.45	9.84	8.64	8.46
Std. Error of Mean		3.747	2.764	3.825	2.903	2.898	2.500	2.431	2.573
Median		20.00	10.00	8.00	5.00	3.00	4.00	2.50	2.00
Std. Deviation		20.86	15.39	21.30	16.16	16.14	13.92	12.86	13.12
Variance		435.19	236.80	453.65	261.19	260.39	193.81	165.42	172.18

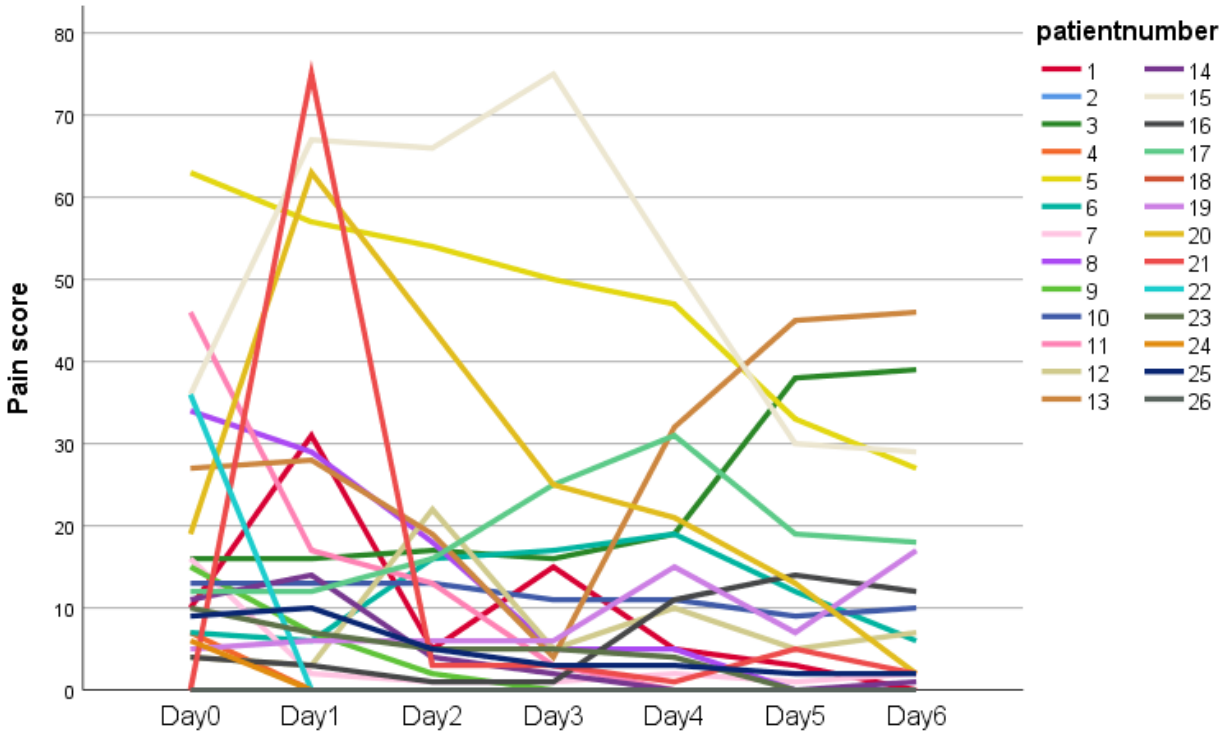


Figure 19 - Study 2 individual day by day pain scores

3.3.4 Anatomical occlusion

All procedures were initially successful with a 100% occlusion rate immediately post MOCA. This remained the case at 1 week (32/32), 6 weeks (30/30) and 6 months (29/29) follow up. However, by 1

year anatomical occlusion on DUS was reduced to 75% (21/28). Recanalisation of the treated GSV was observed in seven patients. One patient had complete recanalisation whereas the other six had partial recanalisation. This occurred in the proximal part of the treated GSV segment (in continuity with the SFJ and deep system) in four patients, whereas distal recanalisation (discontinuous with the SFJ) was observed in another two patients. All recanalised segments showed reflux of greater than 0.5 seconds duration.

3.3.5 Clinician reported outcomes

VCSS scores significantly improved at 1 week, 6 weeks, 6 months and 1 year compared to baseline and are shown in Figure 20; (p<0.001, Friedman).

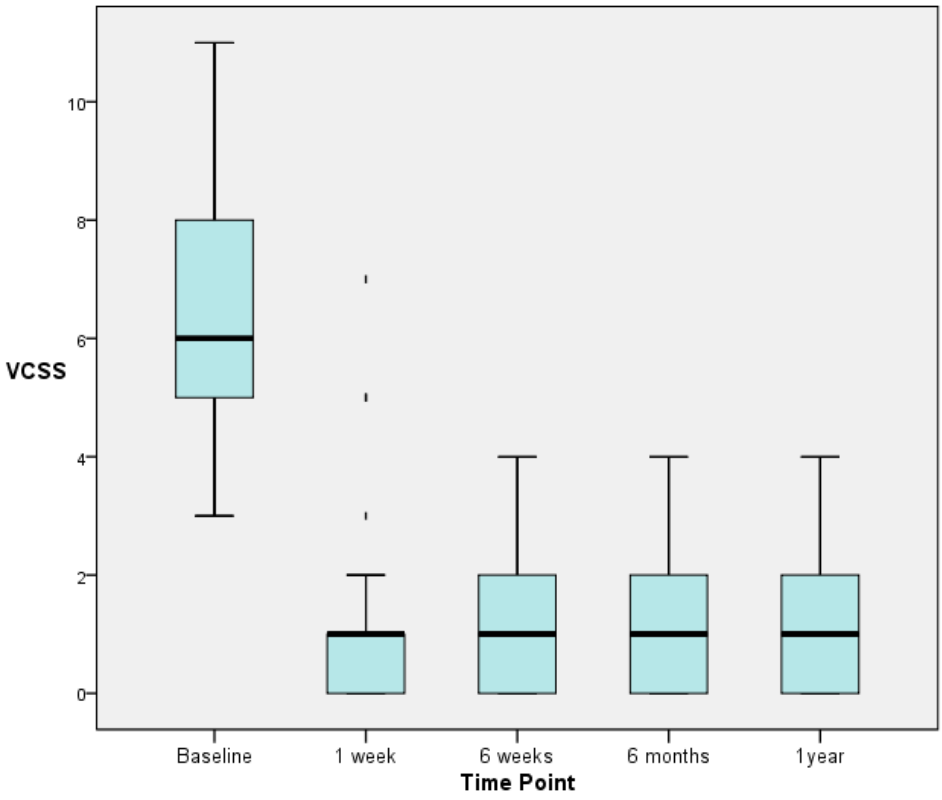


Figure 20 – Study 2 VCSS changes

3.3.6 Patient Reported Outcomes

Disease specific HRQoL as measured by the AVVQ demonstrated significant improvement at 1 week, 6 weeks, 6 months and 1 year compared to baseline as shown in Figure 21; (p<0.001, Friedman). Generic HRQoL as measured by the EQ-5D demonstrated significant improvements at 6 weeks, 6 months and 1 year when compared to baseline as shown in Figure 22; (p<0.001, Friedman). Patient reported

satisfaction was high; median overall satisfaction was 100mm (100-100) at 1 year and median cosmetic satisfaction on VAS was also 100mm (80-100). Median time to normal activity was 2 days (1-7) and time to work was 5 days (2-10).

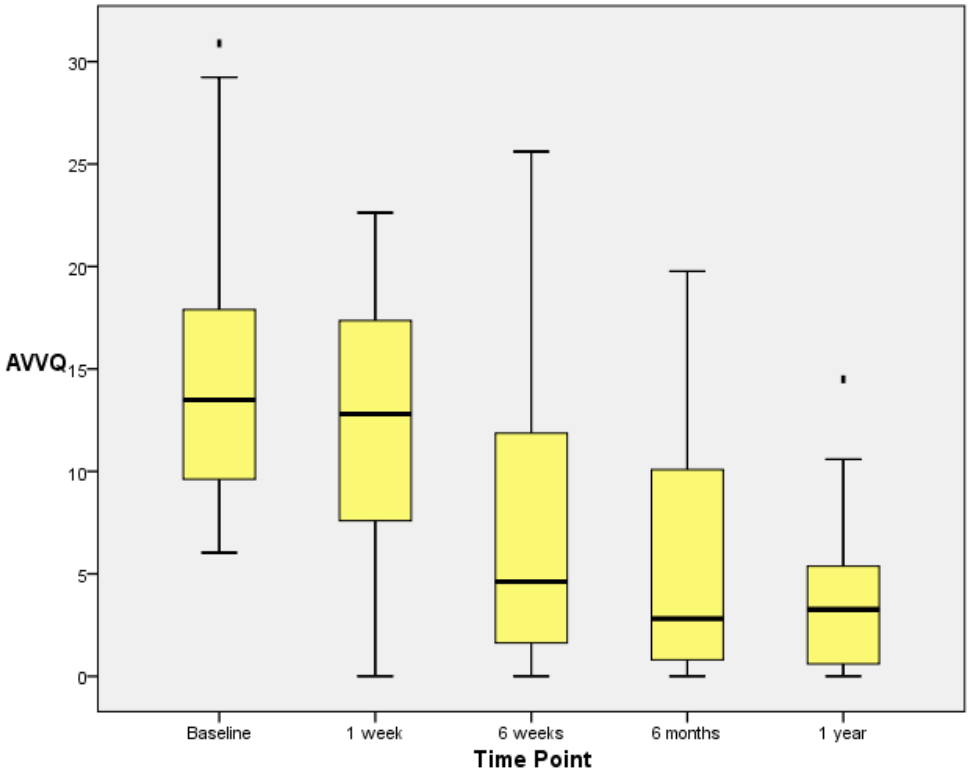


Figure 21 – Study 2 AVVQ changes

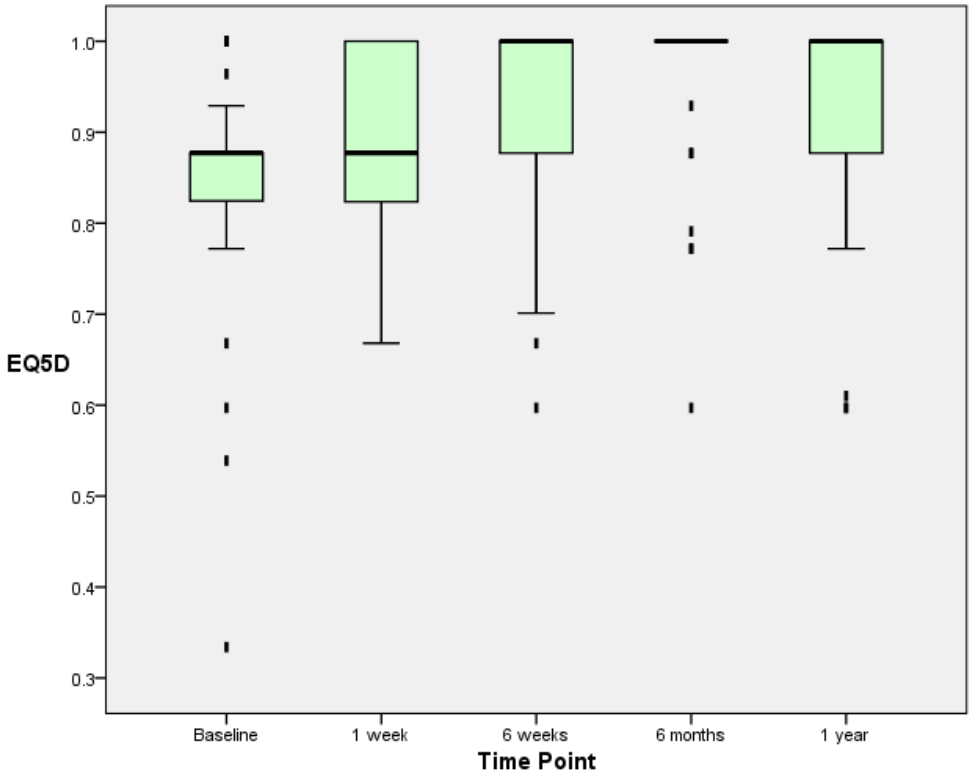


Figure 22 – Study 2 EQ5D changes

3.3.7 Complications

None of the patients in the study were deemed to be at increased risk of VTE therefore, none received prophylactic LMWH. One patient (3.1%), a 46 year old lady, suffered a major adverse event in the form of pulmonary embolism (P.E.), presenting 5 days following GSV MOCA with chest pain and acute shortness of breath. Computed Tomography Pulmonary Angiogram confirmed P.E. but no lower limb DVT was identified on two separate venous duplex scans. She was treated with 6 months of Apixaban and made a full recovery. Minor complications included thrombophlebitis lasting up to 6 weeks in (10/30) 33.3% of patients and skin staining lasting up to one year in (2/32) 6.3% of patients. There were no cases of nerve injury or infection.

3.3.8 Secondary Procedures

Ipsilateral secondary procedures were carried out in six patients (21.4%), all taking place after 6 months follow-up. Three patients underwent ambulatory phlebectomy and perforator ligation for residual symptomatic superficial varicosities. Endovenous laser ablation was performed for new reflux in a previously competent small saphenous vein in one patient, and in the AASV in another. Lastly, one

patient underwent laser ablation for symptomatic recannalisation and reflux of the treated GSV in the proximal segment.

3.3.9 Other results

Notably, patients with recanalisation reported statistically similar AVVQ (Figure 23) and VCSS (Figure 24) scores to those with complete anatomical occlusion during follow up. Similarly, there was no statistically significant difference in satisfaction levels between those with and those without recanalisation (Figure 25).

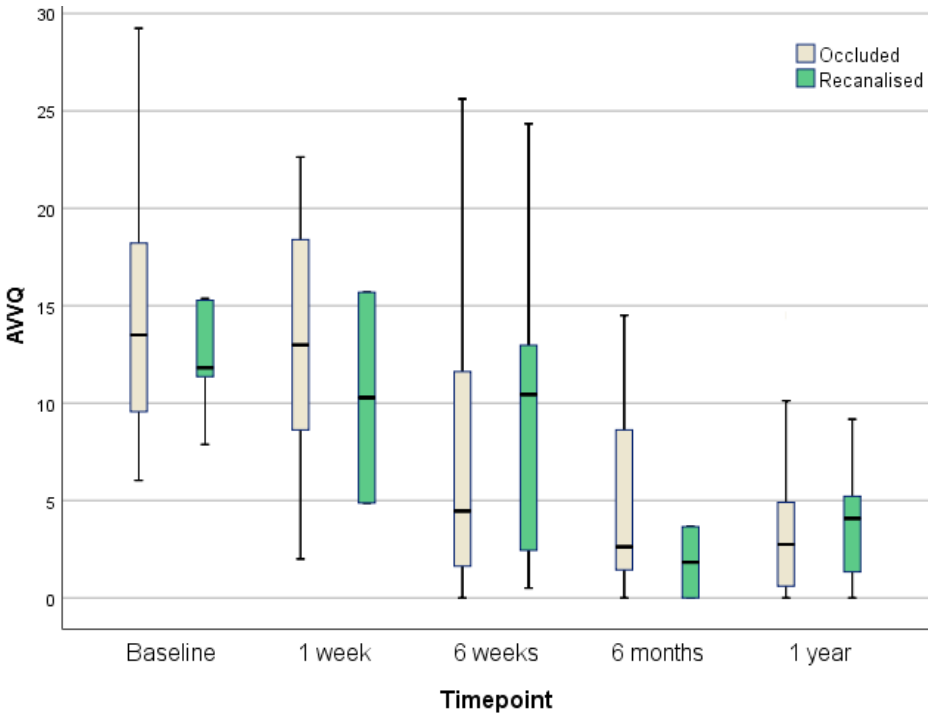


Figure 23 – Study 2 AVVQ comparison

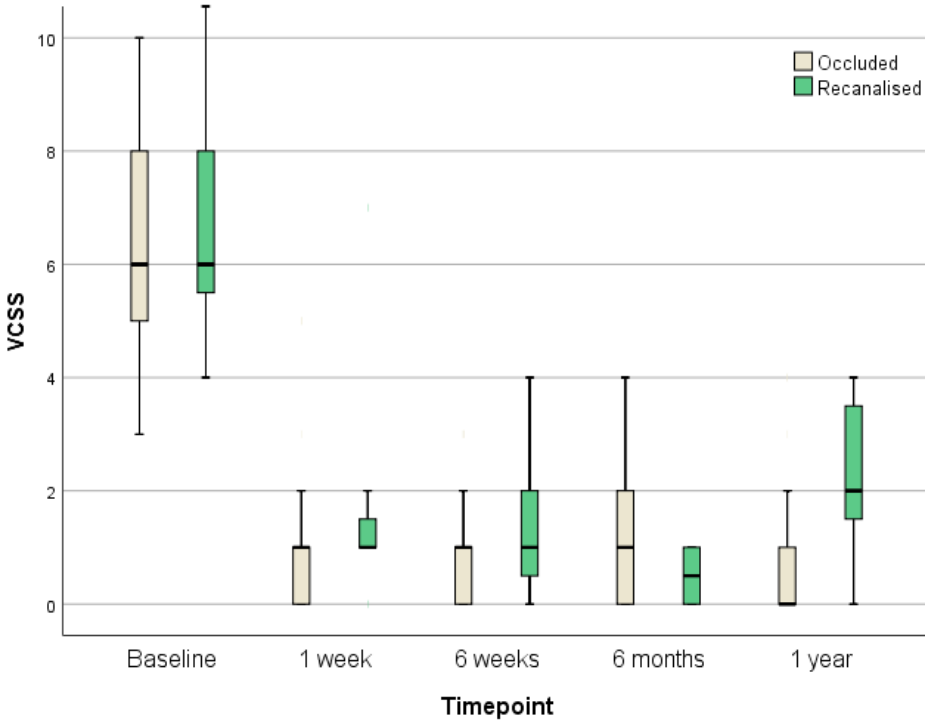


Figure 24 – Study 2 VCSS comparison

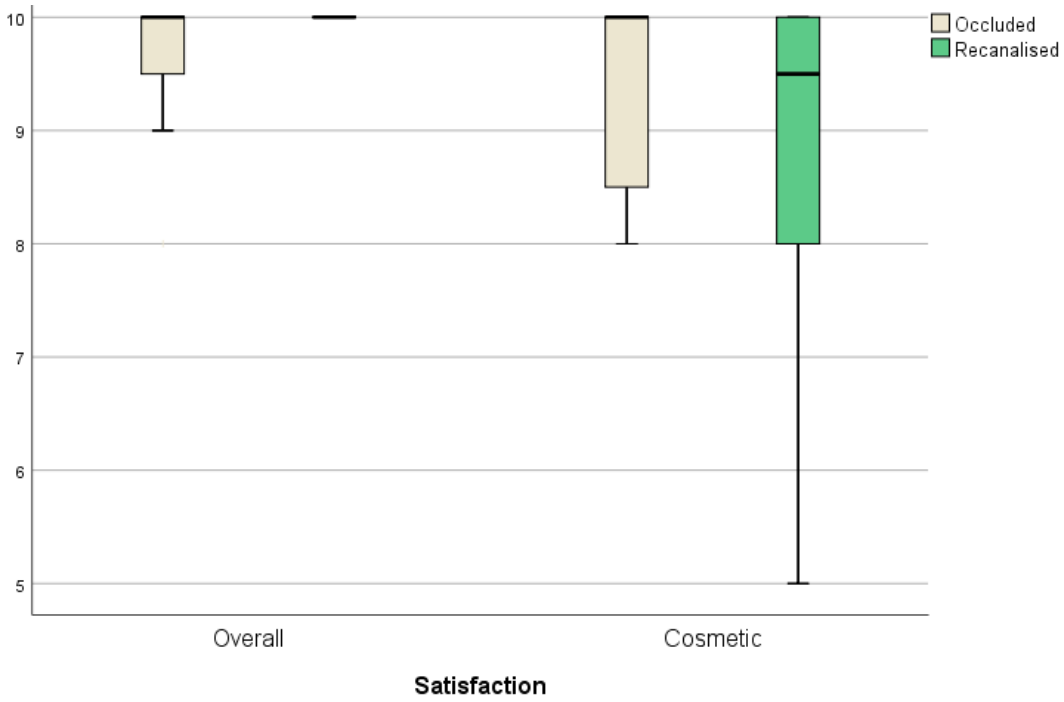


Figure 25 – Study 2 satisfaction comparison

3.4 Discussion

3.4.1 Anatomical occlusion/freedom from recanalisation

Study 1 demonstrated that significant heterogeneity exists in the reporting of occlusion rates following MOCA despite the existence of reporting standards. Other reviews of the literature have also highlighted this issue [476,479,510]. This cohort study (Study 2) is the first study to date, to apply the consensus definition of anatomical occlusion following MOCA, and is defined as "successful ablation of the target vein, as demonstrated by complete lack of flow or disappearance of vein by duplex ultrasound imaging in the entire treated segment"[182]. When applying this consensus definition, the rate of successful anatomical occlusion achieved at 1 year following MOCA in this study is 75%. This is significantly lower than has previously been reported in the literature, which ranges between 93%-96%[470,471,490]. The application of the more stringent consensus criteria for successful occlusion in this study is likely to have highlighted recanalised segments that other criteria would not have identified, leading to a lower occlusion rate.

Following initial technical success, all recanalisations occurred after the 6 months follow up appointment. Higher CEAP disease severity has been associated with an increase in the risk of recanalisation after EVTA[505]. Vein wall remodelling and increased thickening of the media is thought to be the underlying mechanism[511]. In this study, five of the nine patients who had soft tissue damage (CEAP ≥4) at baseline had recanalised during follow up. Perhaps higher CEAP disease severity also affects recanalisation rates following MOCA as these patients with more advanced disease recanalised more frequently compared to those with lower CEAP.

MOCA relies on the synergistic effect of transmural mechanical injury to the vein wall by the device's wire, which allows the sclerosant to penetrate deeper into the vein wall and cause more apoptosis, inflammation and scarring. Perhaps a thicker remodelled vein wall is more resistant to mechanical injury and consequently the chemical sclerosant is less effective. Of note, larger vein diameter size did not appear to increase the risk of recanalisation in this study. Six patients had veins with a proximal diameter >10mm, the largest of which measured 16.7mm. All except for one remained occluded at one year, including the largest vein. This finding is similar to a previous study, which also showed that a larger diameter does not increase the risk of recanalisation following MOCA[490]. Whilst Study 2 was not designed to assess the relationship between vein diameter and occlusion rates, the findings here show

that MOCA can be used on larger veins diameters, which are frequently excluded from other studies of MOCA[471,483,490,493,494,503,504].

3.4.2 Clinical efficacy

Despite the lower anatomical success in this study, the clinical results are similar to other studies on MOCA[477,490]. Patients in Study 2 reported significant improvements in disease specific HRQoL as measured by AVVQ (Figure 21) and reduction of disease severity measured by VCSS (Figure 20). These results were maintained up to 1 year. Amongst patients with recanalised segments, one reported worsening symptoms and underwent thermal ablation one year after MOCA; all the others declined further treatment as they felt their symptoms had improved sufficiently. This again mirrors results following EVTA where recanalisation did not significantly affect HRQoL gains at 1 year[505]. However further follow up is needed as data on MOCA beyond 1 year is very limited as demonstrated in the systematic review. It may be that radiological recurrence after a certain lead-time would lead to clinical recurrence. On the other hand however, Van Eekeren et al's data suggests that between one and three year follow up a deterioration in VCSS and HRQoL scores occurs irrespective of recanalisation status[478], which may be due to residual or progressive symptoms from superficial varicosities as the patients in their study only received axial MOCA.

3.4.3 Perioperative pain

Reported median (IQR) intraprocedural pain 20 (7-47), as well as post procedural pain scores for the first 7 postprocedural days (Figure 18) were low. In keeping with the literature evidence so far that MOCA is associated with low pain scores[476,477].

3.4.4 Complications

The observed incidence of 33% post-operative thrombophlebitis in Study 2 is much higher than the previously reported rate of 10-14% in other studies of MOCA[471,483,502]. Detection bias may have played a role in this finding as no consensus exists on the exact definition of post-operative phlebitis making comparison between studies difficult. However, within this study, the incidence rate of this complication was lower in those patients who opted for concomitant ambulatory phlebectomy, suggesting this may have a protective effect as observed in other studies[462]. Further statistical analysis is not possible here however due to the small sample size.

P.E. is a rare but serious complication of endovenous lower limb interventions. A 2015 meta-analysis of thrombotic events following EVTA identified 6 cases of PE in 14000 interventions[446]. Robust Meta analysis data for VTE rates following foam sclerotherapy are unavailable[512]. A Cochrane review of EVTA, surgery and foam sclerotherapy in 2014 did not give a precise figure for P.E. following treatment of varicose veins but stated that the rates are low[442]. With regards to MOCA however, a recent systematic review found two cases of P.E. out of 1294 patients[476]. The incidence rate suggested by these figures remains small (<1%) but is nearly triple that of EVTA.

However, MOCA is still a new treatment and to date more than 70 000 procedures have been performed[476,497], therefore it is possible that publication bias is affecting current figures. Furthermore, the rarity of this complication precludes an accurate judgement on its incidence rate using current literature.

3.4.5 Limitations

The findings in this study are limited by the small sample size, lack of comparator and potential for selection bias due to the non-random selection of the cohort. These limitations are unlikely to have affected the primary outcome of DUS-determined anatomical occlusion as this was determined in line with consensus occlusion criteria. As previously stated, detection and reporting bias may be affecting phlebitis rates. The occurrence of a serious complication such as a P.E. is of concern here, but is of limited value in isolation given the small sample size, and further data is needed to draw meaningful conclusions.

Chapter 4: Study 3, Procedure Refinement - A Cohort Study of Mechanochemical Ablation with Concomitant Versus Sequential Phlebectomy in the Treatment of Superficial Venous Incompetence

4.1 Aims and Objectives

Dispensing with tumescent anaesthesia is one of the main advantages of MOCA over thermal ablation. Regardless of the axial treatment however, there remains the matter of the optimal strategy in dealing with varicose tributaries following axial ablation. The descending theory of SVI pathophysiology supports the approach of not treating these varicosities in the index procedure as they will likely regress after the axial source is treated; allowing for sequential treatment in a later procedure should tributaries remain symptomatic. Alternatively, tributaries can be treated concomitantly in a single procedure and this approach has been shown to significantly improve patient (VCSS) and reduce the need for reintervention in two RCTs of EVTA with sequential phlebectomy versus EVTA with concomitant phlebectomy[461,462]. Sequential treatment on the other hand, had the advantage of shorter procedural duration[462], while maintaining similar HRQoL improvement[461,462], in addition to avoiding the additional procedural pain of phlebectomy[459].

Both approaches have their merits but in the case of EVTA, it is clear that optimal outcomes are achieved with concomitant treatment of tributaries; this however may not be true for MOCA. The liquid sclerosant used during MOCA may reflux into the incompetent tributaries inducing sclerosis in them, which in turn would lead to a reduction in the need for sequential treatment following MOCA compared to EVTA. If this is however shown to be untrue, then the status quo favouring concomitant treatment would also be true for MOCA, which in turn would have a significant implication on the appeal of MOCA as NTNT if TLA was needed at the end of the procedure to perform phlebectomy. A study comparing MOCA with concomitant phlebectomy (MOCAP) versus MOCA with sequential phlebectomy (MOCAS) is therefore warranted.

Considering the strong evidence in favour of concomitant treatment, an RCT design would be difficult to implement as the researchers would not be in equipoise. A non-randomised cohort study may therefore be a suitable compromise, allowing patients to decide their preferred treatment after informed consent. It would also permit patients to balance their own priorities

Study 3 is a non-randomised parallel arm cohort study aiming to clarify the uncertainties regarding the need for concomitant treatment of varicose tributaries when using MOCA. It compares the clinical and technical outcomes of MOCA with sequential phlebectomy when needed (MOCAS) against MOCA with concomitant phlebectomy (MOCAP).

4.2 Methods

4.2.1 Patients Selection Criteria

This prospective non-blinded parallel group nonrandomised study compares MOCA with concomitant phlebectomy (MOCAP) versus MOCA with sequential phlebectomy when necessary (MOCAS). The study setting was an academic vascular surgical unit in a tertiary hospital in the U.K., serving a patient population of 1.2 million. Consecutive symptomatic patients referred to the research team were offered participation in the study if they met the inclusion exclusion criteria. The referral pathways in this study were the same as those described in Study 2; see section 3.2.2. Prior to clinic attendance, patients were given an information sheet by post briefly outlining the MOCA procedure. In clinic, patients underwent a focused clinical assessment by a vascular surgery consultant or vascular surgical clinical fellow with a special interest in venous disease. This included history, and clinical examination using the CEAP and VCSS classifications[198,210]. A venous duplex assessment was then performed following the protocol outlines in section 3.2.3. All venous DUS assessments were performed by clinicians accredited in diagnostic vascular ultrasound. Reflux was defined as retrograde flow >0.5 seconds following compression augmentation on duplex ultrasonography (DUS).

Patients eligible for participation were recruited into the study and offered a choice between MOCAP and MOCAS while study doctors explained the risks and benefits of both approaches, including reduced incisions, punctures, and procedure time with MOCAs, alongside the increased risk of need for reintervention. Following recruitment, patients were given a date for treatment. All study interventions were completed over a 16 month period from October 2015.

- Inclusion criteria were identical to study 2:
  See 3.2.2

- Exclusion criteria were identical to study 2:
  See 3.2.2

4.2.2 Interventions

Following impartial counselling on the perceived risks and benefits of both the MOCAP and MOCAS treatment strategies, patients were free to choose which treatment group they were included in. All procedures were performed under local anaesthetic in a surgical theatre or a dedicated clean room in the outpatient department. No sedation was used, and no analgesia was prescribed by the research team following treatment, though patients were free to take any routine analgesia that they may normally take. Once in the procedure room, Preoperative marking would take place using a portable EDGE® SonoSite™ (FUJIFILM SonoSite Inc., Nottingham, UK), marking the proposed cannulation site (distal to the lowest point of reflux), followed by marking of varicose tributaries for phlebectomy in the MOCAP group. The patient was then positioned on the operating table.

Skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA); and when iodine allergy was present, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Draping was then applied, and the previously marked cannulation site confirmed. 1ml of 1% lidocaine was used to anaesthetise the cannulation site under sterile conditions. Vein micropuncture and insertion of a 5Fr sheath was then performed under ultrasound guidance followed by insertion of the MOCA catheter through the sheath. The patient was then repositioned horizontally and the tip of the MOCA wire placed 2cm from the SFJ. The wire was then activated for 10 seconds to elicit vein wall spasm followed by withdrawal at a rate equivalent to 1.4mm per second (achieved in practice by constant withdrawal of the catheter by 1cm every 7seconds) with simultaneous infusion of sclerosant at a rate of 0.2mls/cm. After applying MOCA to the most proximal 10cm of the target trunk, the MOCA wire was then repositioned at the SFJ and treatment started again, this time until all the target vein segment is treated. Dressings were then applied in the MOCAS group, completing the procedure.

In the MOCAP group, concomitant ambulatory phlebectomy was carried out following axial ablation using TLA constituted of (100mls of 1% Lidocaine + 1:200000 Adrenaline and 10mls of 8.4% NaHCO3 added to 900mls of NaCl 0.9%)[395]. This was infiltrated in the perivenous space around the varicose tributaries, starting from the already anaesthetised cannulation site. When adequate anaesthesia was achieved, small 4-6mm incisions were made over the varicosities through which an Oesch Hook was used to pull the tributaries out. Surgical clips were then used to tease out as long a segment of vein as possible proximally and distally. Other incisions were then targeted to maximise the number of

varicosities to undergo phlebectomy, whilst minimising the number of skin incisions and anaesthetic skin punctures sites.

After treatment completion, skin was dressed in 3M Steri-strips™ (3M Health Care, MN, USA), cotton balls, gauze, and Clinistretch® (Hadden Healthcare Ltd, Bucks) bandaging for one week. Chemo prophylaxis of VTE was not routinely prescribed; patients were risk-assessed for venous thromboembolism (VTE) using a standard proforma widely utilised in UK NHS practice and any that were deemed to be at high risk received 5 days of prophylactic dose subcutaneous low-molecular weight heparin (LMWH)[508]. At one week, patients were seen in the clinic, wound dressings were removed, and patients were advised to wear Anti-Embolic Stockings.

After a minimum period of 6 weeks all patients with symptomatic residual or recurrent varicose veins were offered a secondary procedure. The decision whether to manage such veins conservatively or have a secondary procedure was left to patients; clinicians aimed to remain impartial.

4.2.3 Outcomes

Patient outcomes in this study were assessed by members of the research team at baseline and weeks 1, 6, 26 and 52. In terms of timing, immediate outcomes were those recorded from the procedure time to the 6 weeks follow up visit, and short-term outcomes were those at weeks 25-52[246]. Outcomes were further categorised into clinical, technical, HRQoL or DUS outcomes.

Clinical outcomes were identical to Study 2:

See 3.2.4

Technical outcomes were:

- Length of vein treated – measured to the nearest 0.5cm using the marking on the MOCA catheter.
- Completion of procedure
- Total infused volume of sclerosant – to the nearest 0.1 ml
- Rate of sclerosant infusion in $mlcm^{-1}$
- procedure duration – timing started from patient entry into the operating theatre, and finished on completion of application of bandaging

- Pain during axial ablation - scored by the patient on a 100mm VAS immediately after the completion of axial ablation
- Total procedural pain score - scored by the patient on a 100mm VAS immediately after the application of dressings
- Post operative pain during the first week post procedure – completed each evening independently by the patient in a pain diary sheet containing 7 unmarked 100mm VAS
- Patient satisfaction with cosmetic outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Patient satisfaction with overall outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Time to return to normal activity to the nearest whole day
- Time to return to work to nearest whole day

HRQoL outcomes were identical to Study 2:

See 3.2.4

- The primary outcome for Study 3 was disease-specific HRQoL measured by AVVQ at 52 weeks

DUS outcomes were identical to study 2:

See 3.2.4

4.2.4 Ethics

See 5.2.7

4.2.5 Data handling

Statistical analysis was performed using SPSS version 24 (IBM Corporation, Armonk, New York, USA). Missing data were labelled as such in the SPSS database; no imputation techniques were employed. Continuous data are presented as mean (standard deviation, SD) when normally distributed or as median (interquartile range) when not normally distributed. Statistical tests for continuous data were Friedman's Test or Mann-Whitney U test, whereas for categorical data, Fisher's exact test or Chi Squared test were used. Statistical significance was set at $P<0.050$.

4.3 Results

4.3.1 **Patient Recruitment**

Eighty six patients elected to undergo MOCA in this centre during the study period of which 83 agreed to take part in the study. Of the patients not taking part, one was missed by the recruitment team and

therefore was not offered participation and the remaining two patients did not wish to take part as they did not want to attend additional follow up. Loss to follow-up was minimal; all patients were reviewed at 1 and 6 weeks. In the MOCAP group, 3 patients did not attend at 6 months and remained lost to follow up at 1 year. In the MOCAS group, 5 patients were not seen at 6 months, but all were seen at 1 year as shown in Figure 26, which is a study flow diagram. The centre treated 758 patients with endothermal ablation, foam sclerotherapy, ambulatory phlebectomy only or open surgery in the same period. The MOCAP (n=50) and MOCAS (n=33) groups were equivalent at baseline in terms of CEAP class, VCSS, and disease impact on quality of life; however, those in the MOCAS group were older. Table 14 lists the baseline characteristics of recruited patients.

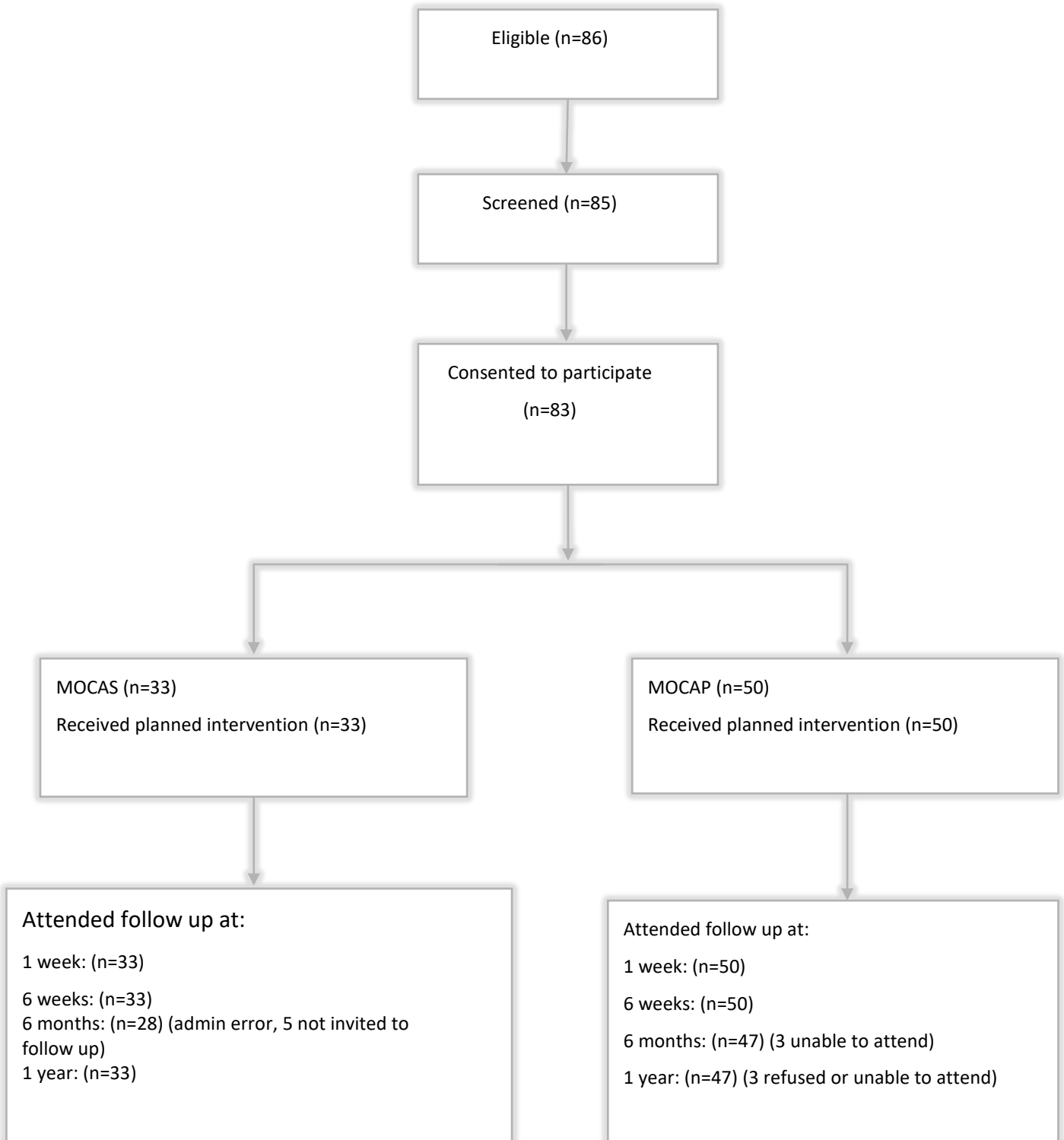


Table 14 - MOCAP vs MOCAP study baseline characteristics table

Characteristic	**MOCAP (n=50)**	**MOCAS (n=33)**	***p* value**
Female	(n=30)60.0%	(n=14) 42.4%	0.178
GSV	(n=44) 88%	(n=31) 94%	0.623
CEAP 3-6	(n=32) 64.0%	(n=26) 78.8%	0.149
Age	48.7 (±14.6)	58.0 (±14.1)	0.005*
BMI	26.6 (23.4-29.6)	28.5 (23.5-30.4)	0.367
VCSS median	6.0 (5.0-8.0)	6.0 (5.0-7.0)	0.695
Mean diameter (mm)	6.1 (5.0-7.2)	6.5 (5.6-7.5)	0.475
Prox. diameter (mm)	8.3 (6.0-10.0)	8.0 (6.5-10.0)	0.887
AVVQ	12.6 (9.8-15.7)	14.4 (8.7-17.8)	0.497
EQ5D	0.877 (0.840-0.877)	0.877 (0.772-0.877)	0.424

4.3.2 Primary outcome – AVVQ

Both groups reported a significant improvement in AVVQ from 6 weeks following treatment up to 1 year follow up Figure 27. Overall median AVVQ was 12.7 (9.6-15.0) at baseline, 12.2 (5.8-17.4) at 1 week, reducing to 3.9 (0.7-6.1) at 6 weeks, 2.1 (0-2.9) at 6 months and 2.1 (0-5.1) at one year; $p<0.001$ (Friedman test). Between groups, AVVQ scores were similar at baseline and 1 week. At 6 weeks the MOCAP group showed greater improvement compared to MOCAS (3.4 [0.5-6.0] vs 6.1 [1.8-12.1]; $p=0.009$) which was replicated at 6 months (1.6 [0.0-4.5] vs 3.34 [1.8-8.4]; $p=0.009$), but not at 1 year MOCAP (1.81 [0.0-4.5] vs 3.81 [0.2-5.3]; $p=0.099$).

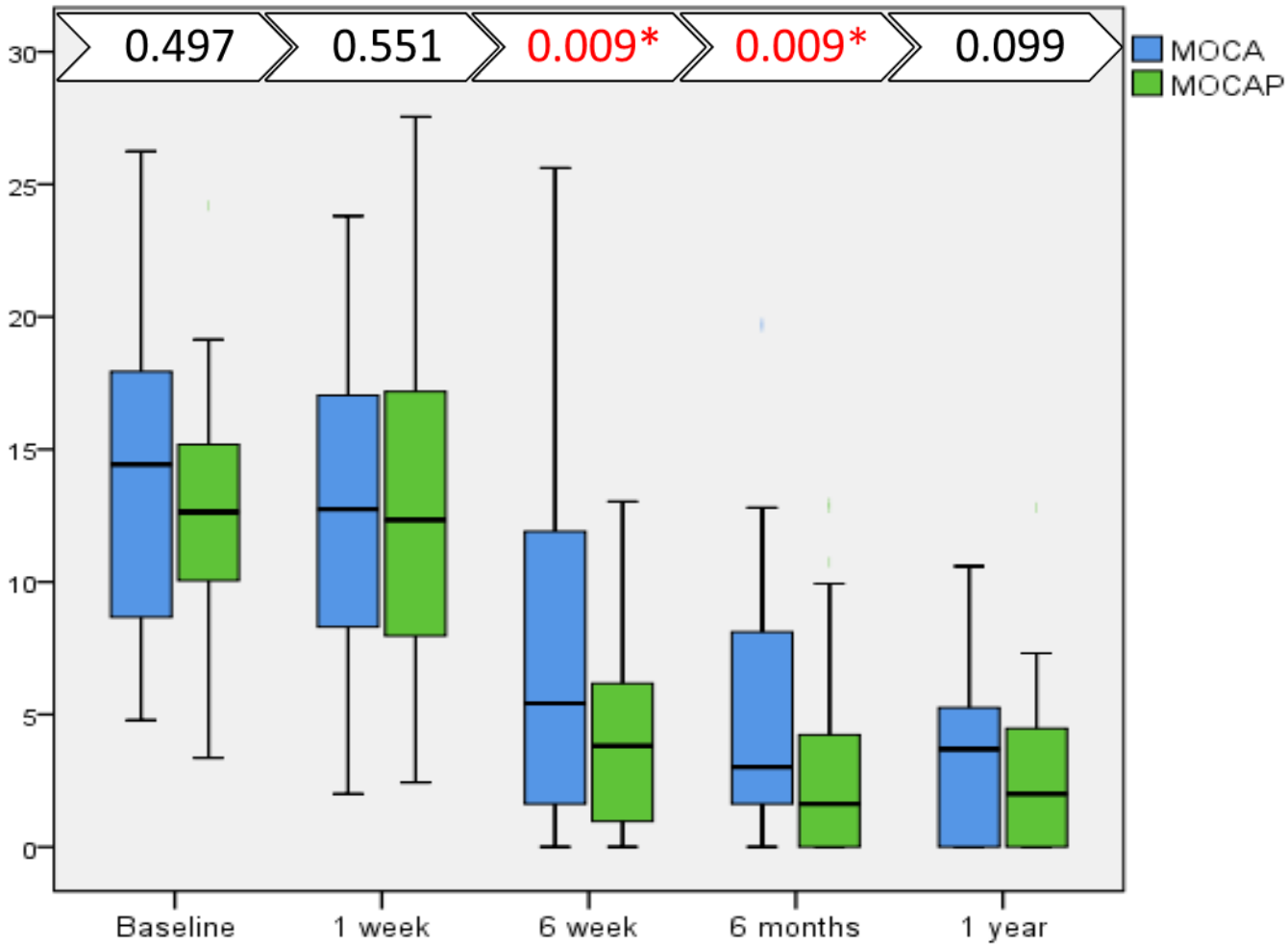


Figure 27 - MOCAP vs MOCAS study AVVQ changes

4.3.3 **Secondary outcomes**

Procedural outcomes

All patients received their allocated treatment without any deviation from protocol. The GSV was the target vein in (44/50) 88% of patients in the MOCAP group, compared to (31/33) 94% in the MOCAS group; *p*=0.623. The overall mean length of ablated vein was 42cm (±1) which was near normally distributed. However, the data for individual groups was not normally distributed. The median length of vein ablated in the MOCAP group was 39cm (33-48), compared with 47cm (45-61) in the MOCAS group; *p*<0.001. Median infused volume per patient in the MOCAP group was 11ml (9-12) compared with 12ml (11-14) in the MOCAS group; *p*=0.002. However, there was no significant difference between the two groups in terms of the mean infusion rate of sclerosant, 0.27ml/cm (±0.1) in MOCAP and

0.27ml/cm (±0.1) in MOCAS; *p*=0.741. Median operative time with MOCAP was significantly longer at 45mins (36-56), compared with 30mins (25-37) for MOCAS; *p*<0.001.

Perioperative pain

Periprocedural VAS pain scores were relatively low in both groups, but significantly lower in the MOCAS group at 18mm (7-25) than in the MOCAP group at 31mm (21-59), *p*=0.001. Daily VAS pain scores were significantly higher in the MOCAP group than in the MOCAS at the end of day 0 (*p*=0.016) and day 1 post procedure (*p*=0.025). There was no significant difference in daily VAS pain scores between the 2 groups thereafter as shown in Table 15.

*Table 15 - MOCAP vs MOCAS study daily pain scores - * = statistically significant difference*

Day	**MOCAP**	**MOCAS**	***p* value**
Day0	20.0 (10-39)	11.0 (5-27)	*0.016**
Day1	16 (6-30)	7.0 (1-17)	*0.025**
Day2	10.5 (2-20)	5.0 (0-15)	*0.184*
Day3	6.0 (1-16)	4.0 (1-11)	*0.384*
Day4	4.0 (0-10)	7.0 (0-13)	*0.828*
Day5	3.5 (0-12)	6.5 (0-13)	*0.706*
Day6	3.0 (0-10)	2.5 (0-11)	*0.699*

Occlusion rates

In all patients, anatomical occlusion was achieved at the end of the procedure. All 83 patients attended for DUS at 1 week and 6 weeks, with an anatomical occlusion rate of 100% in both groups at these timepoints. At 6 months 68/73 (93%) were occluded with no significant difference between the two groups 4/47 (9%) recanalised in MOCAP compared with 1/25 (4%) in MOCAS; *p*=0.645. At 1 year 62/80 (78%) were occluded without a significant difference between groups; 9/47 (19%) recanalisation in MOCAP compared with 9/33 (27%) in MOCAS; *p*=0.414. These 18 recanalisations were segmental (7-

20cm) in 16 patients and in two patients (1 in each group) there was complete recanalisation of the treated segment. Reflux of >0.5s duration was present in 15 cases.

VCSS

Overall VCSS scores improved significantly following intervention compared to baseline (p<0.001; Friedman's test). Between groups, VCSS scores were significantly better (lower) in the MOCAP group than in the MOCAS group at all follow up points (1 week p<0.001, 6 weeks p<0.001, 6 months p<0.001, 1 year p<0.001; Figure 28).

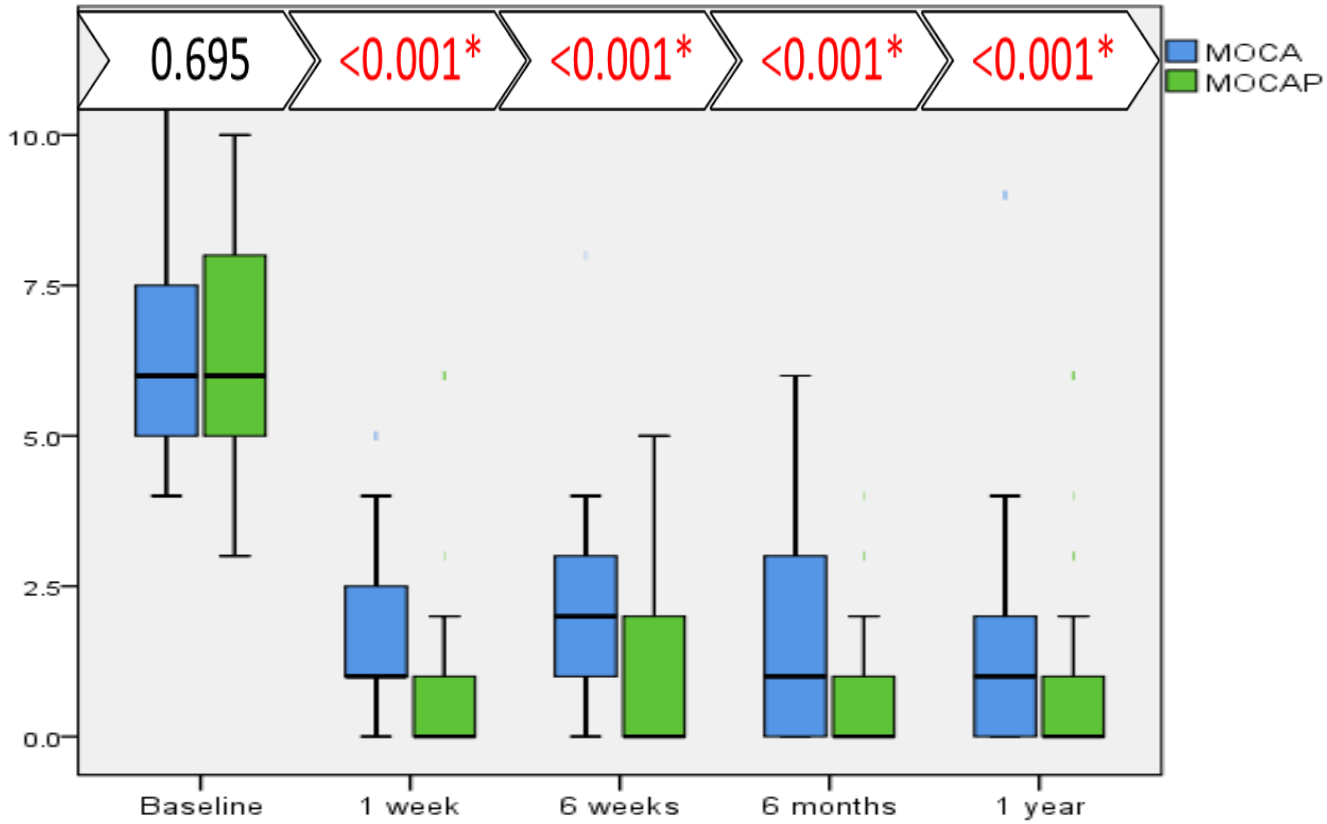


Figure 28 - MOCAP vs MOCAS study VCSS comparison

PROMs

Generic HRQoL measured by EQ-5D improved in both groups after treatment (p<0.001 Friedman's test). Intergroup comparison showed a significant difference in favour of MOCAP at 6 weeks when comparing the two groups but not at any other timepoint (1 week p=0.292, 6 weeks p=0.010, 6 months p=0.870, 1 year p=0.299; Figure 29). There was no significant difference between groups in time to work and to normal activity. Median time to work with MOCAP was 7 days (4-10) compared with 6 days

(2-12) for MOCAS; *p*=0.648. Median time to a normal activity level was 3 days (1-7) in both groups; *p*=0.668. Satisfaction at 1 year was high in both groups, median satisfaction score with overall outcome was 10.0 (9.0-10.0) in both groups; *p*=0.871. Median satisfaction with cosmesis was 9.2 (9.0-10.0) in MOCAP compared with 9.0 (8.0-10.0) in MOCAS; *p*=0.395.

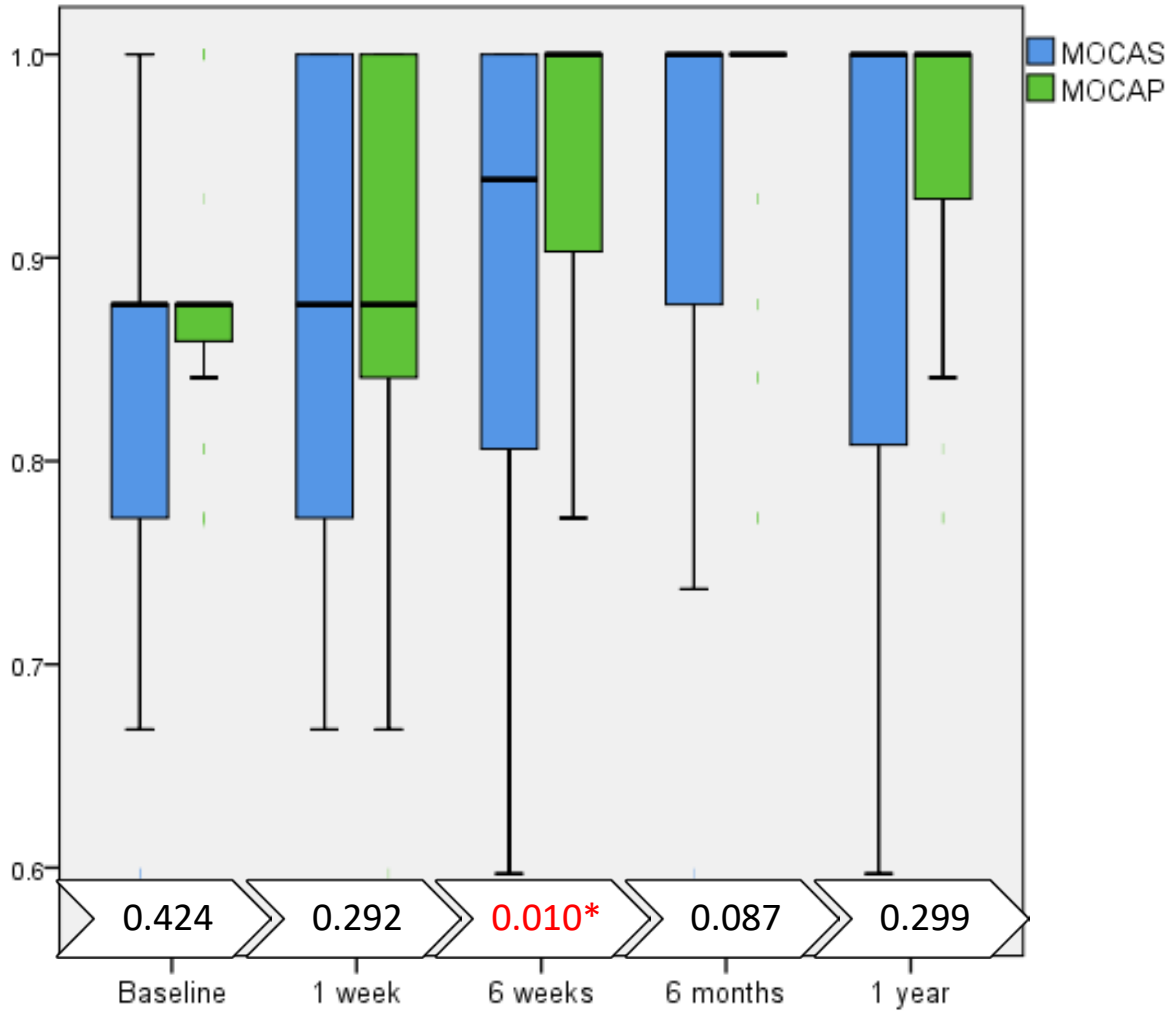


Figure 29 - MOCAP vs MOCAS study EQ-5D comparison

Complications

There were no major complications in this study. Skin staining persisting for the entire duration of follow up occurred in 8/83 (10%) of patients of which 4/50 (8%) occurred in MOCAP and another 4/33 (12%) in MOCAS; *p*=0.707. Thrombophlebitis was significantly less common in the MOCAP (6/50, 12 %) group than in the MOCAS (10/33, 30%) group; *p*=0.039. In each case this resolved prior to the 6 week follow up appointment.

Reinterventions

Secondary procedures were required in a total of 8/83 (10%) of patients, all taking place after 6 months of the index intervention; significantly fewer secondary interventions were required in the MOCAP (2/50, 4%) than in the MOCAS group (6/33, 18%); *p*=0.032. Two patients with GSV recanalisation in the MOCAS group required truncal endothermal ablation, while one patient in the MOCAP group underwent ultrasound-guided foam sclerotherapy for segmental GSV recanalisation, in addition to EVLA for new reflux in a previously competent anterior accessory saphenous vein. All reinterventions and their indications are shown in Table 16.

Table 16 - MOCAP vs MOCAS study reinterventions

Patient	Group	Indication	Procedure
1	MOCAP	New anterior accessory saphenous vein (AASV) reflux + GSV recanalisation	AASV Endothermal ablation + GSV foam sclerotherapy + phlebectomy
5	MOCAP	New small saphenous reflux	Endothermal ablation + phlebectomy
17	MOCAS	Thigh perforator reflux	Perforator ligation + phlebectomy
20	MOCAS	Calf perforator reflux	Perforator ligation + phlebectomy
23	MOCAS	Residual varicosities	Phlebectomy
30	MOCAS	Recanalisation of GSV	Endothermal ablation only
62	MOCAS	Residual varicosities	Phlebectomy
83	MOCAS	Recanalisation of GSV	Endothermal ablation

4.4 Discussion

4.4.1 Clinical efficacy

SVI is a cause of significant morbidity and HRQoL impairment for patients[187,513]. The primary goal patients seek from treatment is symptomatic relief[514]. The results of Study 3 support the findings of Study 2 and the existing evidence to date showing that MOCA either with or without concomitant ambulatory phlebectomy is safe, well tolerated and an effective treatment for SVI[477,491,501]. This is further evidenced by the high level of satisfaction reported by both treatment groups. Patients in Study 3 experienced a significant symptomatic improvement following MOCAS with significant improvement in AVVQ at 6 weeks through to 1 year when compared to baseline. However, the main study finding is that simultaneous treatment of varicose tributaries when undertaking MOCA, while associated with small but significant increases in peri-procedural and early postoperative pain scores, result in greater symptomatic relief and fewer complications (thrombophlebitis) than sequential treatment. In fact, the MOCAS group only reached a similar median gain in AVVQ to the MOCAP group after a sufficient number of patients underwent sequential treatment which was at 6 months (Figure 27). Interestingly, the early difference between the two groups was also detected by the less sensitive generic EQ5D tool highlighting the significant early gains inferred by active tributary management (Figure 29). These findings mirror similar earlier studies of tributary varicosity management following EVTA[461,462]. Collectively these studies highlight that tributaries contribute to the physical symptoms of SVI and therefore warrant active management irrespective of the axial treatment method.

4.4.2 Perioperative pain

Although both groups reported relatively low pain scores intraoperatively and in the first week post operatively. MOCAP was associated with a small but significant increase in VAS reported pain during the procedure 31 (21-59) vs 18 (7-25). Similarly, MOCAP was associated with higher pain at the end of the day of the procedure and the first post-operative day (Table 15). A previous study has suggested that statistical significance when comparing VAS scores doesn't always translate into a clinically significant difference[515]. It suggested that clinical significance between two 100mm VAS reported pain scores is reached when the numerical difference is ≥13mm, regardless of statistical significance[515]. Thus, the reported procedural pain scores are of clinical significance, as median (IQR) procedural pain with MOCAP was 31mm (21-59) compared to 18mm (7-25) for MOCAS. However, the differences between the groups on days 0 (9mm) and 1 (9mm) are likely to be of statistical significance only rather

than clinical. As previously stated however, the primary concern of patients is long-term durable symptom control, therefore most will likely prefer a small increase in procedural pain in favour of improved long-term outcome[182,485].

4.4.3 Secondary procedures

In keeping with findings from previous studies on EVTA, MOCA with concomitant phlebectomy significantly lowered reintervention rates when compared to axial MOCA alone. In contrast to the EVTA trials however, perhaps disease progression was the main driver for further treatment in this study rather than residual disease. In the AVULS and EVLTAP trials, almost all the reinterventions were performed before 6 months follow up using ambulatory phlebectomy to treat residual tributaries[461,462]. However secondary procedures in Study 3 were all after 6 months and greater variety of procedures were performed (Table 16) to treat the disease, which suggests that there is a combination of disease progression and residual disease driving the symptoms.

Interestingly, the reintervention rates for MOCA alone 6/33 (18%) seem lower than endothermal ablation alone 18/50 (36%) in AVULS and 16/24 (67%) in EVLTAP trials[461,462]. This coupled with the fact that phlebitis in the superficial tributaries following MOCA alone was relatively high lends support to the theory that liquid sclerosant in MOCA diffuses into some superficial tributaries and indirectly "treats" them.

4.4.4 Complications

No major complications were detected in this study. Of note however, thrombophlebitis was significantly less common in the MOCAP group, which is another advantage offered by active tributary management.

4.4.5 Anatomical Occlusion

Like Study 2, Study 3 also adhered to consensus criteria on anatomical occlusion. At 1 year only 62 of 80 (78%) of treated vein segments were anatomically occluded, with no difference between the groups. Despite this finding and in keeping with Study 2 findings and similar studies in EVTA, clinical and patient reported measures showed sustained improvements following treatment even in those patients where recanalisation was observed[505,516,517]. The consistency of this finding suggests that endovenous treatment methods including MOCA are technically forgiving and further supports the increasing use of these methods rather than open surgery where historically, technical failure is

associated with high rates of clinical recurrence[518]. Longer term follow up is however needed to ascertain the impact of recanalisation on clinical recurrence and cost effectiveness.

4.4.6 Other

Patients choosing to have MOCAS tended to be older, potentially creating a bias against MOCAP as it may be hypothesised that older patients are less concerned regarding cosmetic outcomes and may report improvements more readily. Acknowledging that patients chose their own intervention group, it may be that many in the MOCAS group were disinvested from pursuing additional treatment. It is therefore noteworthy that this group recorded lower disease specific HRQoL improvement (Figure 27). This is further evidence that SVI is a physical disease causing predominantly physical rather than cosmetic impairment[187,513] and furthermore, highlighting the role tributaries play in the physical symptoms of SVI.

4.4.7 Limitations

The findings in this study are at risk of selection bias due to the lack of randomisation. This was a pragmatic decision based on PPIC feedback, a previous patient survey and the results of the AVULS trial where recruitment targets were not met as screened patients expressly preferred concomitant treatment[461,519]. Blinding was not possible for patients, surgeons, or assessors but this was mitigated using objective, validated patient reported outcome measures and a rigorous DUS protocol based on international consensus. The baseline age difference between the two groups may have been a confounding factor as discussed. Finally, there was an apparent AVVQ difference between the two groups at 1 year, which did not reach statistical significance; this is likely to represent a type II error due to the relatively small sample size. Although attempts were made to keep procedures uniform, several external factors may have influenced patient pain scores including individual stress levels and patient expectations.

Repeated hypothesis tests of related data were carried out for pain, VCSS, AVVQ and EQ-5D without correcting for the resultant potential increase in type I error[520]. Without clinical context, some of these significant findings may be explained by family-wise or experiment-wise error. However, statistical corrections for type I error increase the risk of Type II error and should be introduced carefully. On balance these were not performed in Study 3 with the reasoning that clinical findings on examination that are corroborated by PROMS are more likely to reflect true differences than type I error, especially when these findings replicate previous independent research.

Chapter 5: Study 4; Technique Evaluation - A Randomised Clinical Trial of Endovenous Laser Ablation versus Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence (LAMA Trial)

5.1 Aims and Objectives

Having established optimal MOCA strategy in study 3, the next step would be to compare this treatment against the current first line treatment for SVI which is EVTA. Study 4 compares immediate procedural and post procedural pain scores of EVLA versus MOCA, the resultant anatomical occlusion rates over time and correlates these findings with clinical disease status, HRQoL and patient satisfaction.

5.2 Methods

The methods reported below are in line with CONsolidated Standards Of Reporting Trials (CONSORT) guidelines[521].

5.2.1 Patient selection Criteria

This prospective non-blinded parallel group randomised trial study setting was an academic vascular surgical unit in a tertiary hospital in the U.K., serving a patient population of 1.2 million. Consecutive new symptomatic patients referred to the research team were offered participation in the study if they met the inclusion exclusion criteria. The referral pathways in this study were the same as those described in Study 2; see section 3.2.2. Prior to clinic attendance, patients were given an information sheet by post briefly outlining the nature of trial and the two treatment modalities. In clinic, they underwent a focused clinical assessment by a vascular surgery consultant or vascular surgical clinical fellow with a special interest in venous disease. This included history, and clinical examination using the CEAP and VCSS classifications[198,210]. A venous duplex assessment was then performed following the protocol outlines in section 3.2.3. All venous DUS assessments were performed by clinicians accredited in diagnostic vascular ultrasound. Reflux was defined as retrograde flow >0.5 seconds following compression augmentation on duplex ultrasonography (DUS).

Patients eligible for participation were recruited into the study, randomised, had their baseline outcome measures recorded and were offered a treatment date.

- Inclusion criteria were identical to Study 2:

  See 3.2.2

- Exclusion criteria were identical to Study 2:
  - See 3.2.2

5.2.2 Randomisation and blinding

Following informed consented participants were randomly allocated to one of the two parallel treatments groups. This took place at the baseline visit using an online computerised service (Sealed Envelope, London, UK); using their (Simple randomisation) option which assigns patients at a ratio of 1:1 to either treatment group by random permuted blocks.

- EVLA Group: received EVLA of the incompetent saphenous trunk from the deep-superficial vein junction to the lowest point of truncal reflux, with concomitant phlebectomy of varicose tributaries
- MOCA group: received MOCA of the incompetent saphenous trunk from the deep – superficial vein junction down to the lowest point of reflux, with concomitant phlebectomy of varicose tributaries

The nature of the techniques limited the possibility of blinding in the main part, but every effort was made to be even-handed regarding the surrounding package of information and care. The key outcomes, including the primary outcomes were either independently reported by patients themselves using validated instruments or measured according to standardised international consensus criteria. HRQoL instrument questionnaires were completed prior to clinical and duplex assessment, limiting any investigator induced bias and are validated in the role of assessing a patient's quality of life.

5.2.3 Interventions

All procedures were performed under local anaesthetic in a surgical theatre or a dedicated clean room in the outpatient department. No sedation was used, and no analgesia was prescribed by the research team following treatment, though patients were free to take any routine analgesia that they may normally take. Once in the procedure room, Preoperative marking would take place using a portable EDGE® SonoSite™ (FUJIFILM SonoSite Inc., Nottingham, UK), marking the proposed cannulation site (distal to the lowest point of reflux), followed by marking of varicose tributaries for phlebectomy in the MOCAP group. The patient was then positioned on the operating table in reverse Trendelenburg position.

Skin was prepared with 10% Povidone-Iodine in water (Betadine®, Purdue Pharma L.P, CT, USA); and when iodine allergy was present, 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol (ChoraPrep® Insight Health Ltd, Wembley, UK) was used. Draping was then applied, and the previously marked cannulation site confirmed with USS. 1ml of 1% lidocaine was used to anaesthetise the skin over cannulation site under sterile conditions.

Axial treatments: EVLA

The desired saphenous axis was cannulated using a 0.035" access kit with ultrasound guidance. The Seldinger technique was then utilised to first pass a guide wire, followed by the EVLA sheath. Small-calibre veins were accessed with the additional assistance of a 0.018" 'micro-access' kit. Tortuous GSVs that would not permit passage of the standard 0.035" guidewire were navigated using a hydrophilic guidewire (HiWire®, Cook Medical, Hitchin, UK). The tip of the sheath was sited at the saphenous-deep vein junction under DUS, venous blood aspirated to ensure position, and then flushed with normal saline. The patient was tilted into the Trendelenburg position and perivenous tumescent anaesthesia administered via a spinal needle using a pedal-operated peristaltic pump (Nouvag DP-20, Nouvag, Goldach, Switzerland) along the GSV with the use of ultrasound guidance, at a target of 10ml tumescent per cm length of GSV, aiming to create a halo of tumescent fluid around the saphenous axis. Following tumescent infiltration, a NeverTouch Gold-Tip laser fibre (Angiodynamics, Latham, New York) was introduced so that the tip of the laser fibre lay at the tip of the pre-positioned sheath. The sheath was then withdrawn by 3cm to expose the tip of the laser fibre, thus leaving the fibre tip at the junction, aiming for a flush occlusion. The sheath and laser fibre were then locked together. A VenaCure 1470 nm laser generator (Angiodynamics, Latham, New York) was used to deliver a 10W continuous beam. The catheter and fibre were withdrawn at a rate of $2mmsec^{-1}$, delivering a target LEED of 60Jcm-1. The specific energy delivered, and length of vein treated was then recorded.

Axial treatments: MOCA

MOCA was performed using the Clarivein® device with 1.5% Sodium Tetradecyl Sulphate (STS) (STD Pharmaceutical Products, Hereford, UK) as outlined in 4.2.2.

Tributary treatment: Both groups

Concomitant ambulatory phlebectomy was carried out as described in 4.2.2 and after the axial ablation pain score was recorded.

Dressings and VTE risk assessment: Both groups

After treatment completion dressings and VTE risk assessment were performed per the methods in 4.2.2

5.2.4 Outcomes

Patient outcomes in this study were assessed by members of the research team at baseline and weeks 1, 6, 26 and 52. In terms of timing, immediate outcomes were those recorded from the procedure time to the 6 weeks follow up visit, and short-term outcomes were those at weeks 25-52[246]. Outcomes were further categorised into clinical, technical, HRQoL or DUS outcomes.

Clinical outcomes were identical to Study 2:

See 3.2.4

Technical outcomes were:

- Length of vein treated – measured to the nearest 0.5cm using the marking on the MOCA catheter.
- Completion of procedure
- Total infused volume of sclerosant – to the nearest 0.1 ml
- LEED in Jcm^{-1}
- Rate of sclerosant infusion in $mlcm^{-1}$
- procedure duration – timing started from patient entry into the operating theatre, and finished on completion of application of bandaging
- Pain during axial ablation - scored by the patient on a 100mm VAS immediately after the completion of axial ablation
- Total procedural pain score - scored by the patient on a 100mm VAS immediately after the application of dressings
- Post operative pain during the first week post procedure – completed each evening independently by the patient in a pain diary sheet containing 7 unmarked 100mm VAS
- Patient satisfaction with cosmetic outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Patient satisfaction with overall outcome at weeks 1,6,25 and 52 – completed by the patient on a 100mm VAS at each clinic visit
- Time to return to normal activity to the nearest whole day

- Time to return to work to nearest whole day

HRQoL outcomes were identical to Study 2:

See 3.2.4

DUS outcomes were identical to study 2:

See 3.2.4

5.2.5 Sample size calculation

Calculation was performed based on the joint primary outcomes, which were pain during axial ablation and freedom from recanalisation at 1 year. Regarding axial ablation pain, a previous study found an intraprocedural pain score following MOCA of 19mm on a 100mm VAS with a standard deviation of 19mm, compared to 35mm for Radiofrequency ablation[474]. At 90% power, 5% significance and allowing for 10% loss to follow up, a sample size total of 73 patients was required. For freedom from recanalisation, complete anatomical occlusion following MOCA at 1 month was reported at 83%[474], compared with 99% at 1 year following EVLA[433]. The required sample size to detect a difference based on these figures was 150 allowing for 20% loss to follow up, again at 90% power and 5% significance.

5.2.6 Data Analysis for Study 4

All data was recorded and transcribed onto a secure dedicated Microsoft Excel® database (Redmond, WA, USA) as per international consensus[179,374] (Chicago, IL, USA). All data analyses were undertaken using IBM® SPSS® Statistics versions 24.0 and 25.0 (Chicago, IL, USA). Statistical analysis was performed according to the principle of intention to treat. No assumptions were made at any time as to the direction of any relationships and no imputation of missing data was attempted. Any key assumptions of the statistical techniques used were tested as appropriately.

Continuous data

Normally distributed data is reported as mean (±95% confidence interval for dependant variables) or mean (±standard deviation (SD) for independent variables). Non normally distributed data is quoted as median (inter-quartile range). Graphically, continuous data is presented using standard statistical notation in box and whisker plots. The box indicating the inter-quartile range and the median represented by a line within the box. The whiskers represent the range of data within 1.5 times the inter-quartile range. Data points outside of this are considered outliers and represented by dots.

Prior to hypothesis testing, the distribution of continuous data was tested using histograms; data that appeared normally distributed was then further tested using Shapiro-Wilks test to confirm this, a $p>0.050$ signified normally distributed data[522].

Hypothesis testing was then performed using the appropriate tests based on whether the data was paired or unpaired, normally distributed or not. For single comparisons, the quoted "*p*-value" represents the probability of having observed the data if the null hypothesis were true; *p*-values are quoted to three decimal places and a value of <0.050 was regarded as "significant" and led to rejection of the null hypothesis. Bonferroni correction was performed for repeated measures of pain (adjusted alpha value of 0.006), AVVQ, EQ5D and VCSS scores (adjusted alpha values of 0.01)[523]. Any statistically significant differences were then examined to establish whether they represented clinically significant findings in the context of this research and the existing evidence base.

The tests used for hypothesis testing were:

Normally distributed data:
Paired – paired Student t-test (t test) (2 samples),
Unpaired – unpaired Student t-test (t test)

Non-normally distributed data:
Paired – Wilcoxon signed rank test (WSR test) (2 samples), Friedman's (multiple related samples)
Unpaired – Mann-Whitney U test (MWU test)

Categorical Data

Simple categorical data is presented as percentages (x/y) where the numerator represents the number of cases in a category and the denominator represents the total number of cases under consideration. The primary hypothesis test used in categorical analysis was Pearson's Chi-square test ($\chi 2$ test)[524]. If greater than 20% of expected frequencies were less than 5 or any were below 1, then Fisher's exact test (FET) was used[525]. Freedom from recanalisation was measured using Kaplan-Meier analysis featuring Log Rank significance testing[526].

5.2.7 Ethics for Studies 2,3 and 4

The conduct of these studies on MOCA, the dissemination of findings and drafting of this thesis have all been performed in accordance with the principles of the declaration of Helsinki at their heart[527]. The health of each individual patient included or considered for inclusion was the primary concern of each individual involved with this research. All interventions carried out in these studies have been approved by international and national bodies as suitable treatments for SVI[22,506,528]. Treatments were only offered if the patient felt their HRQoL was significantly impaired by SVI, and the surgeon felt that on balance endovenous treatment of SVI would result in a significant improvement to said patient's HRQoL. Inclusion in Studies 3 and 4 was only considered if both surgeon and patient occupied a position of equipoise over the optimal procedure to be undertaken. All patients were made aware of the additional burden of the assessments associated with the research and were aware that they could withdraw at any stage of the research process, without any cost or prejudice to their existing, on-going or future care.

Protocols were prospectively designed. Ethical approval was sought and secured from both independent ethics committees and the institutional review board. Both prospective cohort studies (2 and 3) were approved by the Hull and East Yorkshire Hospitals (HEYH) Quality Governance, Assurance, Compliance and Clinical Audit Administrator - Project No 2018101. The LAMA trial (Study 4) received approvals from the National Research Ethics Service Committee (15/YH/0207), the Medicines and Healthcare Products Regulatory Agency (21411/0250/001-0001) and HEYH Research & Development (R1788). Additionally, LAMA was sponsored by the HEYH NHS Trust and prospectively registered with ClinicalTrials.gov (NCT02627846).

All hard copy data is kept in a locked room at the Academic Vascular Surgical Unit (based within Hull Royal Infirmary). All electronic data was held on a secure server hosted jointly by the University of Hull and Hull and East Yorkshire Hospitals NHS Trust. This data has an identified Caldicott guardian, and has not been disseminated in any way, such that individual patient's data or involvement in the studies can be identified. All investigators have undergone formal training in "Good Clinical Practice" with regards to the undertaking of clinical research and all investigators involved in the delivery of clinical care were appropriately qualified and experienced in the delivery of that care. The research team did not receive any funding or financial support in carrying out this research; and declare no conflict on interest in the conduct of this body of research.

5.3 Results

5.3.1 Patient Recruitment

Some 271 patients were screened for participation between June 2015 and August 2018, during this period 150 patients were eligible to take part in the study and were recruited. The commonest reason for ineligibility to take part in the study was unsuitable reflux patterns (n=96), the majority of which was due to bilateral reflux disease; other patterns included deep reflux, mixed reflux and unilateral reflux in more than one axis. The main other reason for ineligibility was patient refusal (n=25); cited reasons included geographical distance, high number of follow up appointments, or a patient preference for the established thermal ablation method. Baseline demographics of recruited patients are shown in Table 17.

Some 143 patients underwent treatment as randomised. Of the seven patients that did not receive their allocated treatment, two in each group withdrew consent, one in each group developed severe phlebitis, and one lady became pregnant. These patients were all excluded from the final analysis. Follow up attrition rates were low with 92% of patients attending 1 year follow up. Figure 30 is a study Consort diagram.

Table 17 - LAMA RCT baseline characteristics

Characteristics	**EVLA (n=75)**	**MOCA (n=75)**	***p***
Age (± SD)	51 (± 14)	53 (± 14)	0.278
Female (%)	39 (52%)	41 (55%)	0.870
BMI (± SD)	27 (± 4)	27 (± 5)	0.352
CEAP 2:3:4:5:6	15:29:25:6:0	21:23:26:3:1	0.390
VCSS	6.4	6.5	0.782
Prox. Vein diameter (mm ± SD)	9.0 (± 3.6)	8.6 (± 2.4)	0.380
Mean Vein diameter (mm ± SD)	6.9 (± 2.1)	6.5 (± 1.5)	0.145
GSV:AASV:SSV	66:3:6	61:6:8	0.476
AVVQ (IQR)	15.5 (10.1-20.1)	13.4 (9.7-16.4)	0.050
EQ-5D (IQR)	0.837 (0.772-0.877)	0.851 (0.806-0.877)	0.408

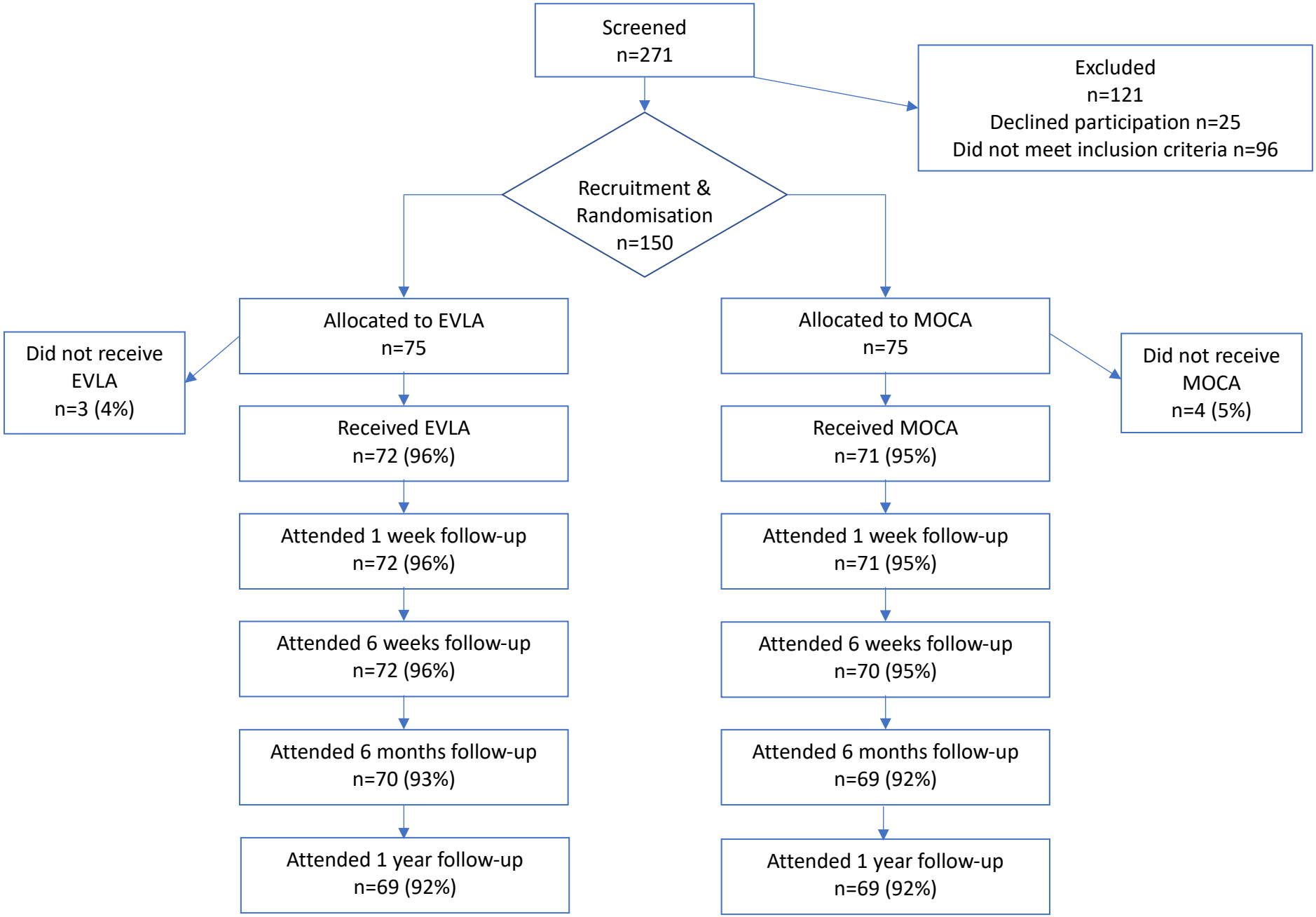


Figure 30 - LAMA consort diagram

5.3.2 Primary outcomes – Axial ablation pain

Axial ablation with both modalities was well tolerated with an overall median pain score of 20 (9-40) for all patients. Median pain during axial EVLA was 22 (9–44) compared with 15 (9-29) during MOCA; *p*=0.210, Figure 31.

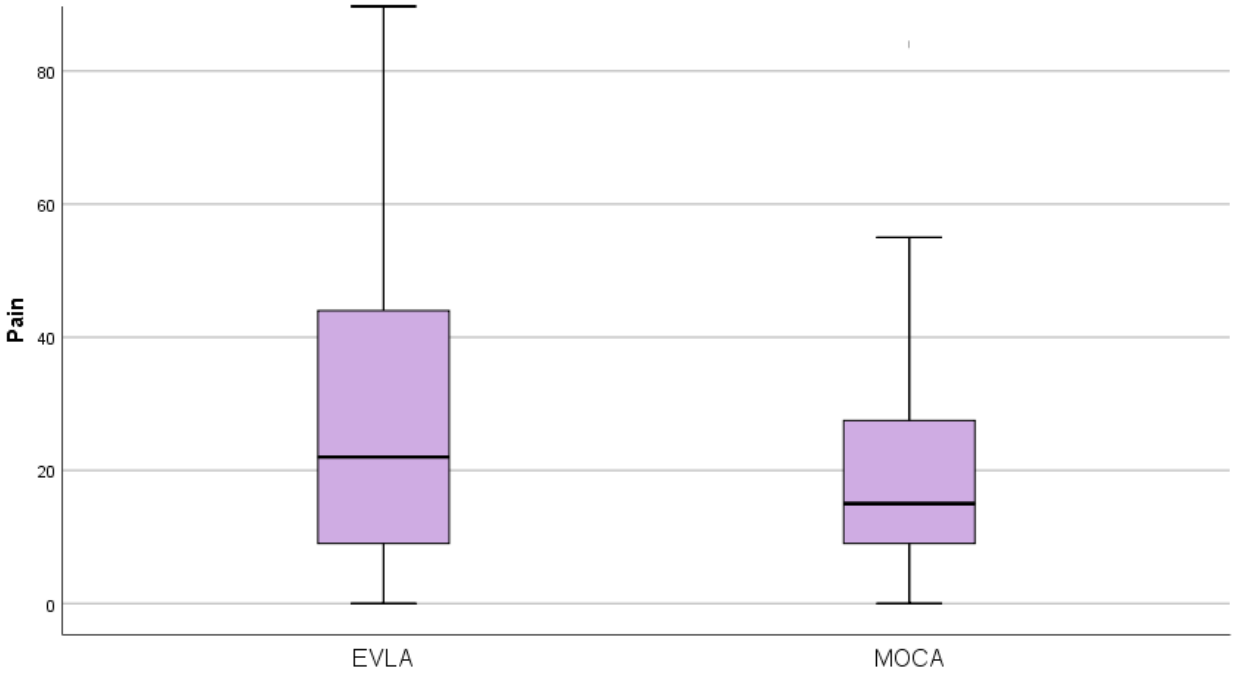


Figure 31 - LAMA axial ablation pain box plot

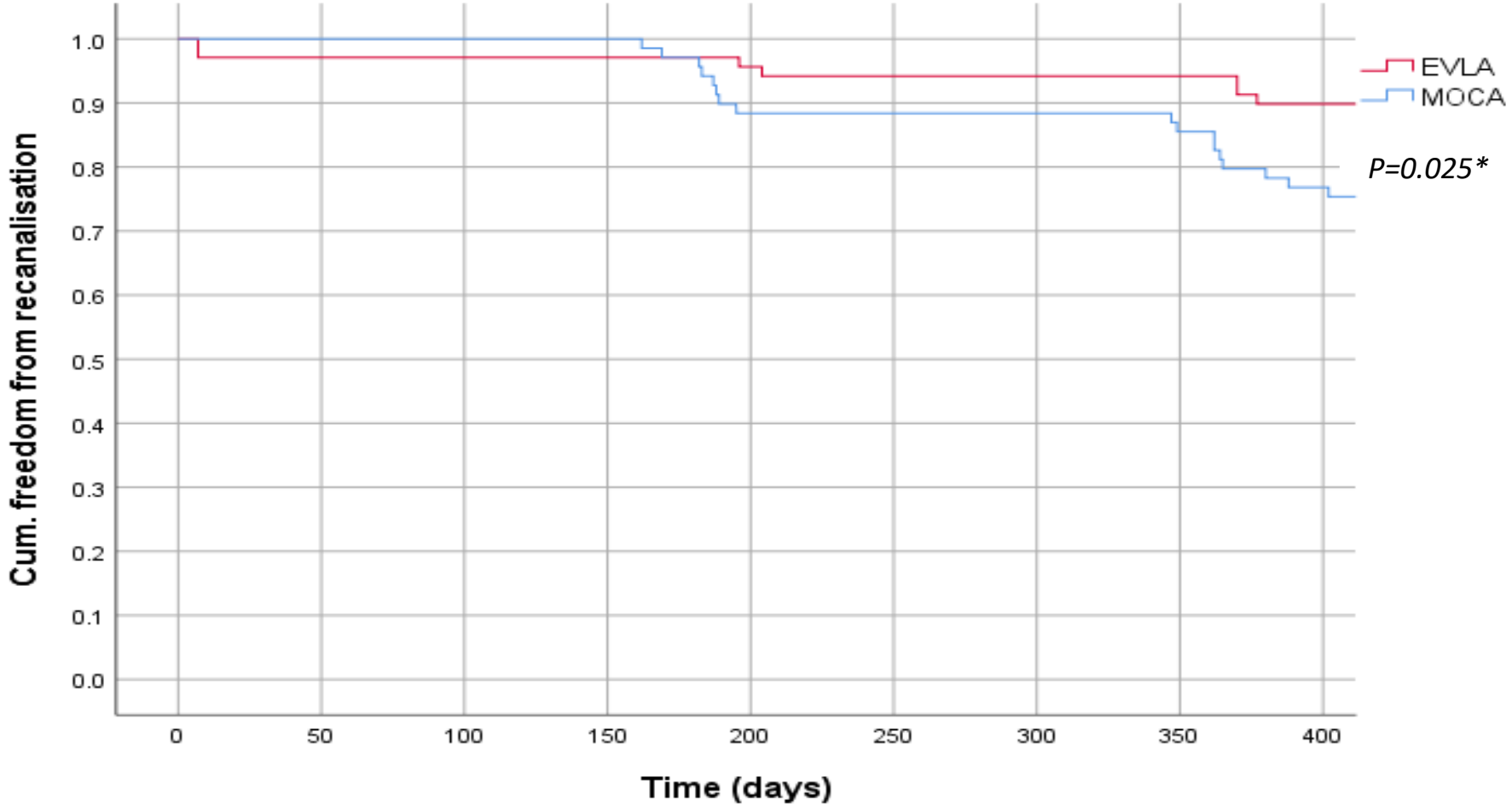
5.3.3 **Primary outcomes – Freedom from recanalisation/anatomical occlusion rate**

In both groups, all procedures were carried out successfully achieving initial anatomical occlusion except for one patient in the EVLA group (1/69) 1%. This was due to user error where the EVLA machine was not set up correctly, and the targeted GSV remained patent at the end of the procedure. At 1 year, anatomical occlusion rate in the EVLA group was significantly greater 63/69 (91%) compared to the MOCA group 53/69 (77%); *p*=0.020 as shown in Figure 32.

In the EVLA group, complete recanalisation was seen in 1/69 (1%) of patients. This patient was on warfarin anticoagulation in addition to having a large calibre GSV (10mm at the knee and 20mm at the groin). In the remaining patients, competent segmental recanalisation of 5-10cm in the proximal thigh occurred in 3/69 (4%), and knee level distal recanalisation with reflux was detected in 1/69 (1%).

Initial technical success was achieved in all patients that underwent MOCA. One patient experienced complete recanalisation with reflux at 6 months, this patient was also anticoagulated with warfarin. In

the remaining patients, segment recanalisation of various lengths (5-20cm) with reflux was detected in 8/69 (12%) with another 7/69 (10%) having no reflux.



EVLA:	69	67	67	67	65	65	65	65	63
MOCA:	69	69	69	69	61	61	61	59	53

Figure 32 - LAMA freedom from recanalisation survival curve
** statistically significant*

5.3.4 **Secondary outcomes - procedural outcomes**

There was no significant difference between the two treatment modalities in terms of the duration of procedure *p*=0.808, this is shown in Table 18 along with other procedural details.

Details	**EVLA**	**MOCA**	***p***
Duration (mins) (SD)	50.9 (16.6)	50.2 (17.4)	.808
Phlebectomy carried out (%)	62/72 (86%)	57/71 (80%)	.303
Treated vein length (cm) (SD)	42.2 (13.7)	41.4 (14.0)	.706
Total Energy (Joules) (SD)	2496 (938)	n/a	n/a
Total Infused volume ml (SD)	n/a	10.2 (2.5)	n/a
Energy density (J/cm) (SD)	58.8 (9.4)	n/a	n/a
Sclerosant rate (ml/cm) (SD)	n/a	0.3 (0.1)	n/a

Table 18 - LAMA procedural details

5.3.5 **Secondary outcomes – periprocedural pain**

There was no significant difference in overall periprocedural pain scores between EVLA and phlebectomy (median 25, IQR 14-46) and MOCA with phlebectomy (median 27, IQR 15-42); *p*=0.868. Post-operative median pain scores remained low in both groups during the first 6 days after the procedure as shown in Figure 33. Intergroup comparison shows a trend of lower pain scores in the MOCA group most days except for day 3 where there is a significant difference between groups even after correcting for multiple testing (adjusted α of 0.006) as shown in Figure 34.

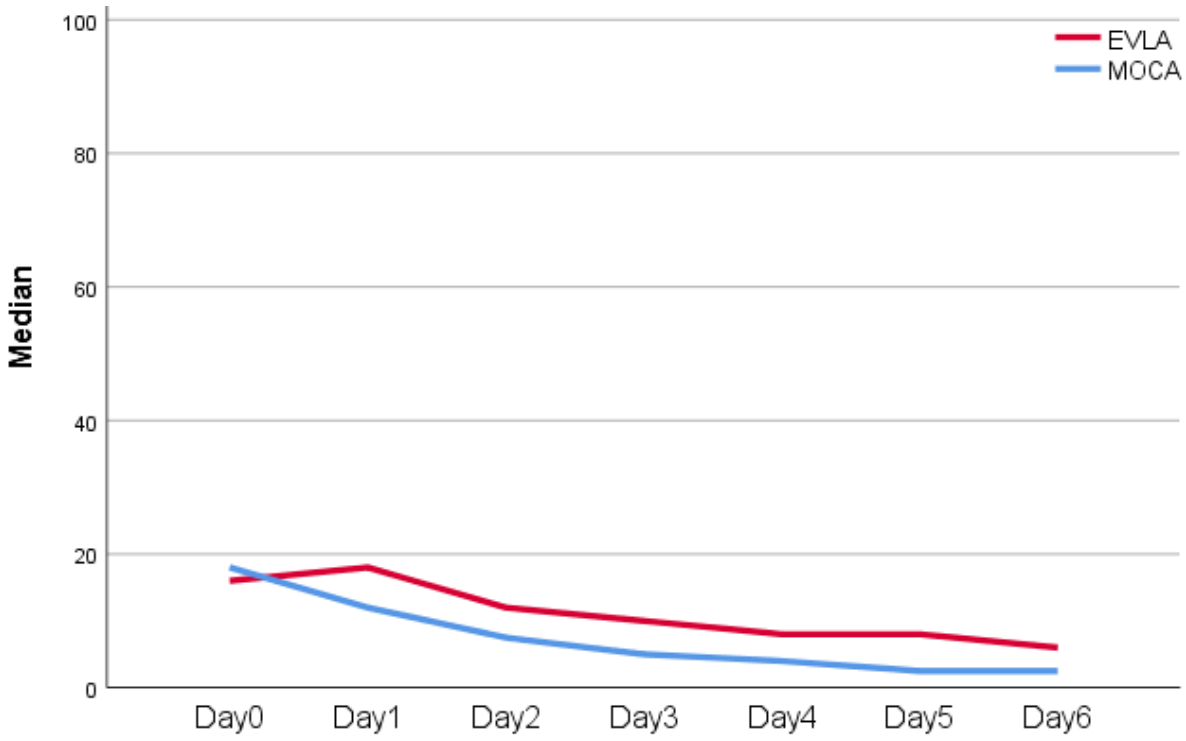


Figure 33 - LAMA post procedural pain scores diagram

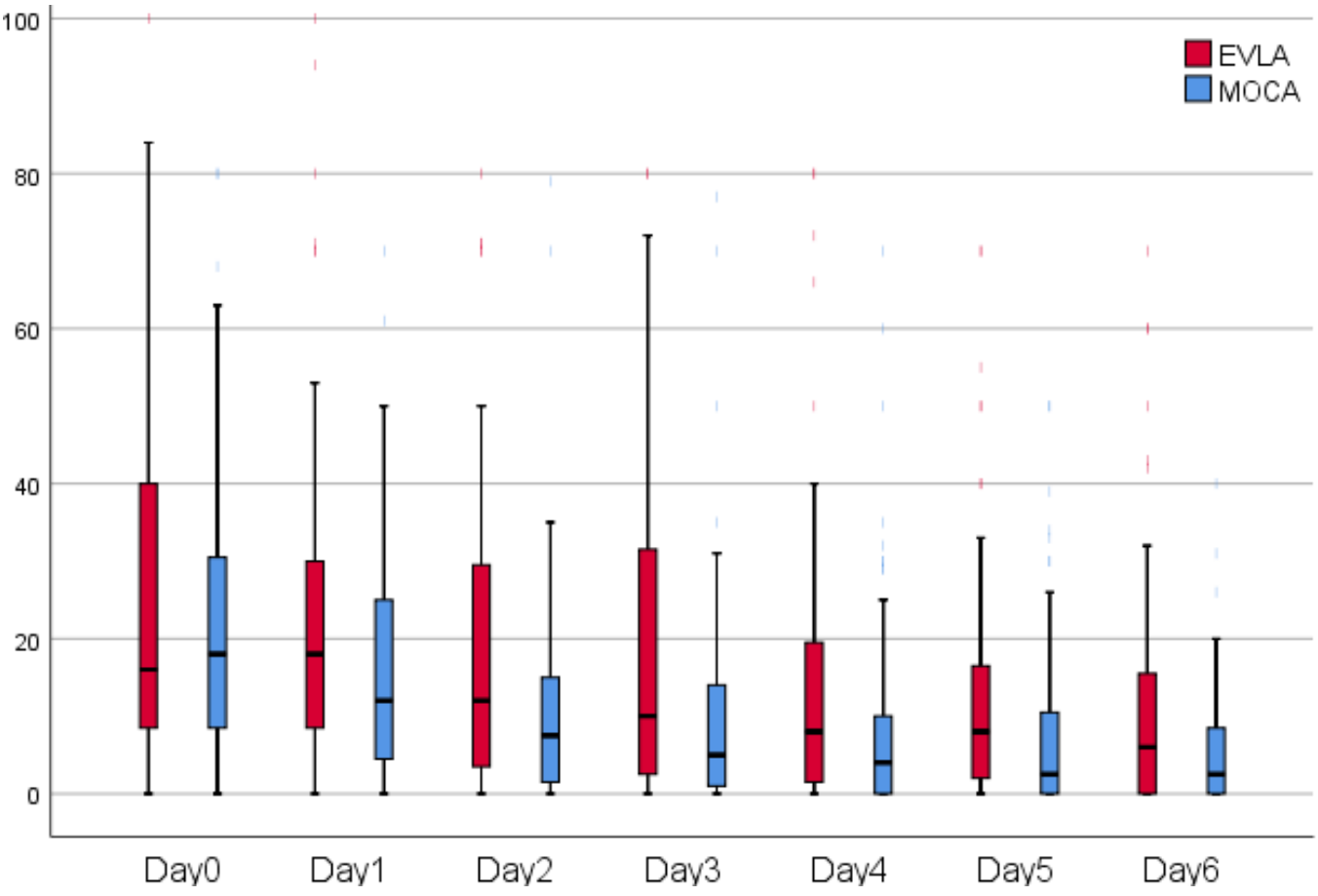


Figure 34 - LAMA intergroup pain comparison

5.3.6 **Secondary outcomes – VCSS**

VCSS improved in both groups following treatment, from a baseline median VCSS of 6 (5-8) to 0 (0-1) at 1 year; p<001 Friedman's test. Figure 35 shows the between groups changes in VCSS at each follow up. There was no significant difference between groups at any time point; *p*>0.010.

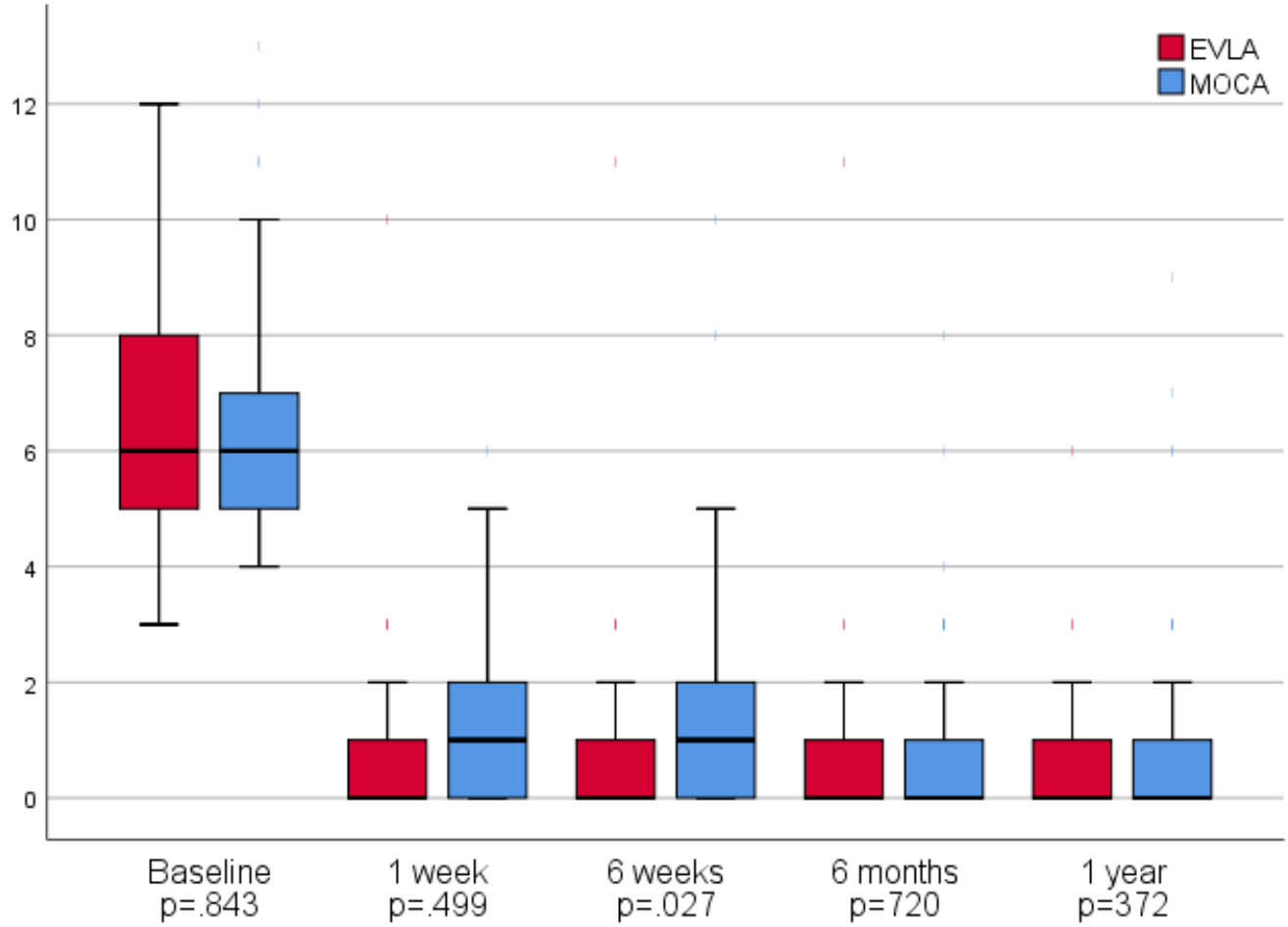


Figure 35 - LAMA VCSS comparison

5.3.7 **Secondary outcomes – PROMS**

At one year, all patients reported improved disease specific HRQoL when compared to baseline. Within group AVVQ decreased from median 13.8 (10.0-17.7) to 2.0 (0.0-4.9); *p*<0.001 Friedman's test. When comparing groups, AVVQ improved from median 15.2 (10.1-20.1) at baseline to 2.0 (0.0-5.3) and from 13.1 (9.8-16.4) at baseline to 2.0 (0.0-4.8) in the EVLA and MOCA groups respectively at one year. There was no significant difference between groups at any time point, *p*>0.010 and this is shown in Figure 36.

Similarly, at one year, generic HRQoL improved in all patients following treatment when compared to baseline. Within group EQ5D improved from a median 0.877 (0.772-0.877) at baseline, to 1.00 (0.877-

1.00) at 1 year; $p<0.001$ Friedman's test. When comparing groups, again there was no significant difference at any time point; $p>0.010$ as shown in Figure 37.

The overall median time to work in days was 5 (3-10), with a median time to normal activity of 3 (1-7) days. Median time to work in days following EVLA was 5 (2-10) compared to 6 (3-10) following MOCA; $p=0.725$. Median time to normal activity following EVLA was 3 (1-7) days compared to 2 (1-4) days following MOCA; $p=0.127$. At 1 year, both groups reported high levels of satisfaction with the overall outcome of treatment. Median overall satisfaction score was 100 (90-100) on a 100mm VAS whereas satisfaction with cosmesis was 95 (88-100). Median satisfaction with the overall outcome in the EVLA group was 100 (90-100) compared with 97 (91-100) in MOCA; $p=0.385$. Median Cosmetic satisfaction in the EVLA group was 98 (90-100) compared with 91 (87-100) in the MOCA group; $p=0.084$.

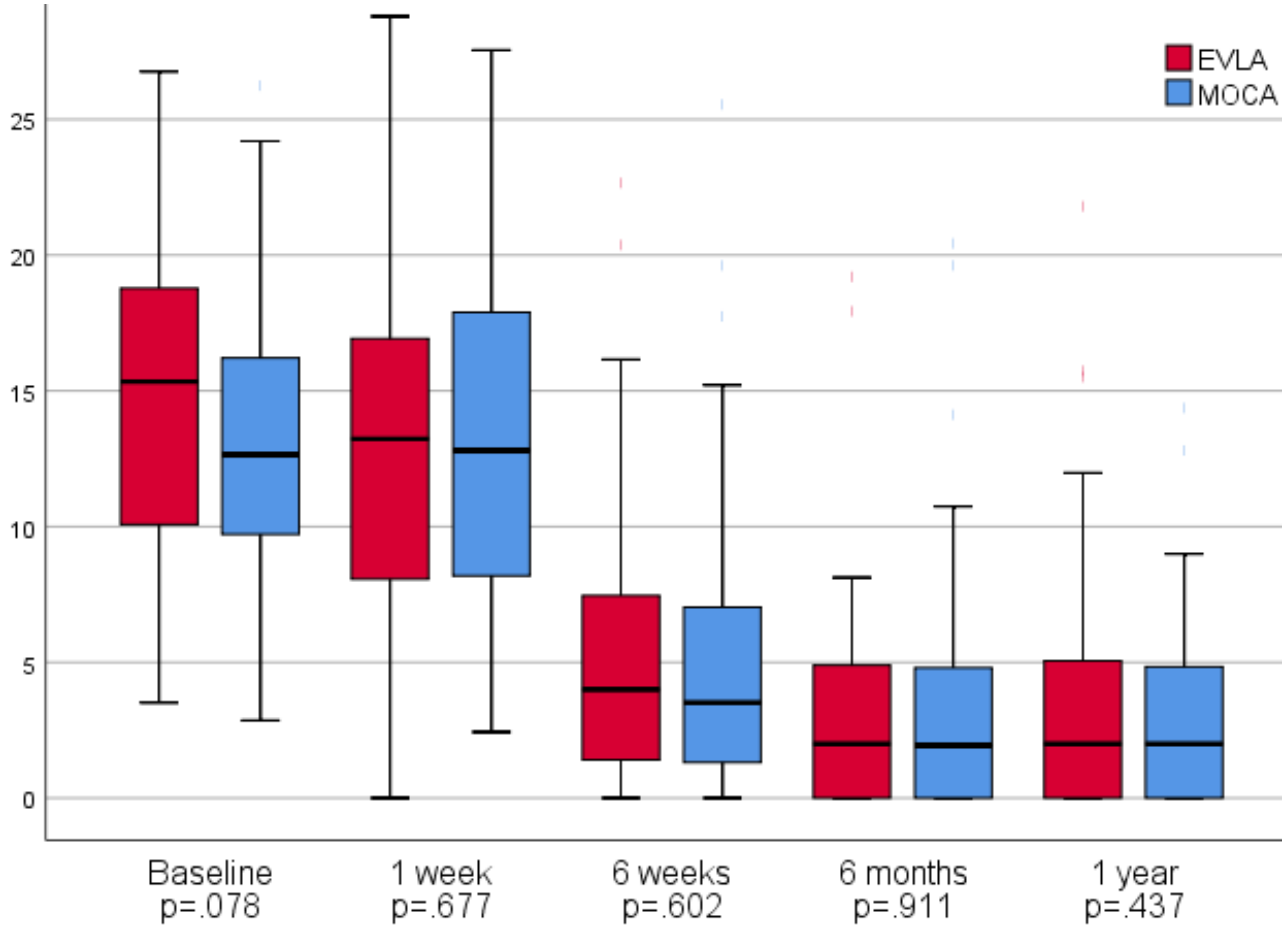


Figure 36 - LAMA AVVQ comparison

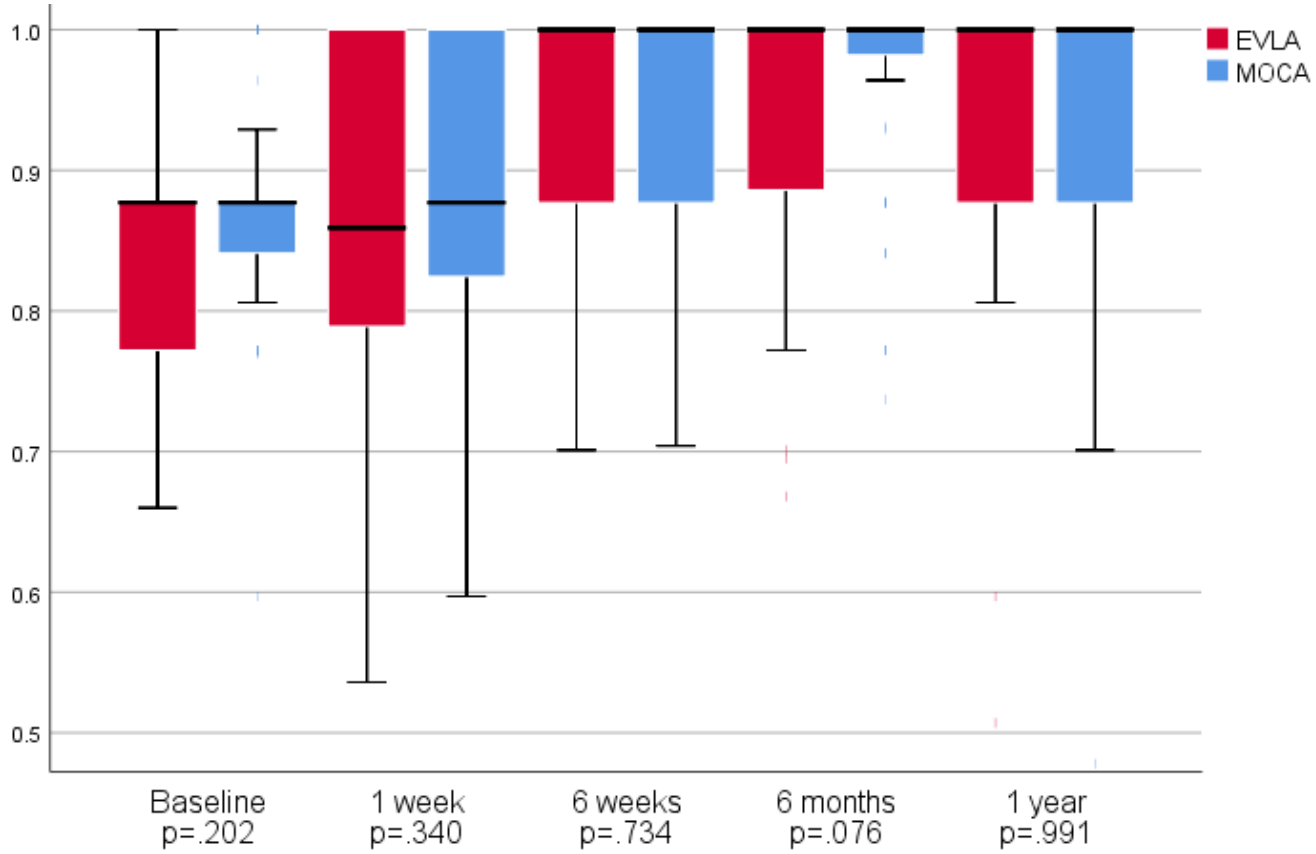


Figure 37 - LAMA EQ5D comparison

5.3.8 **Secondary outcomes – complications**

There were no major complications in the EVLA group, however, one patient in the MOCA group developed an ipsilateral occlusive gastrocnemius vein DVT in addition to a non-occlusive femoral vein DVT. This was detected at 1 week following SSV MOCA and the patient was asymptomatic. She was treated with a 2 week course of LMWH and a repeat duplex 3 weeks post procedure showed a competent deep venous system with complete resolution of the thrombi.

There was no significant difference between groups in terms of minor complications. Phlebitis was detected in 5/69 (7%) of patients following EVLA compared with 9/69 (13%) following MOCA, all resolving before 6 week follow up; *p*=0.262. At 1 week follow up, one patient in each group (1%) was prescribed a 5 day course of oral antibiotics for clinically suspected surgical site infection of a phlebectomy wound; *p*=0.992. Skin staining persisting throughout follow up was seen in 4/69 (6%) patients in the EVLA group compared to 9/69 (13%) in the MOCA group; *p*=0.139. Sensory disturbance from phlebectomy lasting up to the 1 year follow up point was reported by 6 (9%) patients in the EVLA group and 2 (3%) patients in the MOCA group; *p*=0.151.

5.3.9 **Secondary outcomes – reinterventions**

In both groups, the two patients on warfarin anticoagulation experiencing complete recanalisation underwent successful retreatment with EVLA. The EVLA patient where technical success was not achieved felt her symptoms were controlled following concomitant phlebectomy and therefore she declined further treatment. By 1 year follow up mark, all the patients with segmental recanalisation in both groups did not report venous symptoms and therefore no further reintervention were offered to these patients.

5.4 Discussion

5.4.1 Procedural and periprocedural pain

Upon reviewing the literature on MOCA in Study 1, the focus on peri procedural pain reporting is clear, and this is perhaps marketing driven as some of the studies were sponsored by the manufacturers. That aside, Studies 2 and 3 confirm the low pain profile of MOCA as has been demonstrated repeatedly in the literature[477,494,502,529]. On the other hand, EVTA is associated with some periprocedural pain and in particular older EVLA technology which was reported to cause more pain than other endovenous methods[431,530]. However, more recent studies of 1470nm EVLA show a significant reduction of pain with the use of buffered tumescent local anaesthesia (BTLA) and newer laser fibre designs[531,532]. Study 4 is the first adequately powered RCT to compare pain during axial ablation with 1470nm EVLA against MOCA. The study shows that VAS procedural pain scores with both techniques are low without a significant difference between treatments; EVLA 22 (9-44) vs MOCA 15 (9-29); p=0.210. This is in contrast with previous studies comparing MOCA with RFA, where MOCA resulted in a significantly lower procedural pain[474,494,498]. Pain scores for MOCA in the LAMA trial compared to other studies were similar, however, in LAMA the EVLA patients reported lower pain scores when compared to other comparative studies of MOCA and EVTA.

Although maximal procedural pain increased slightly when concomitant phlebectomy was performed, overall pain scores remained low with no significant difference when comparing the two. When concomitant phlebectomy was carried out with EVLA, the mean increase in procedural pain was only 3 points on a 100mm VAS, highlighting the synergy between thermal ablation and BTLA, where axial tumescence in the skilled hands can be used to anaesthetise phlebectomy areas and minimise procedural pain. On the other hand, the mean rise in pain score when phlebectomy was carried out with MOCA was 12 points. This reinforces the argument that carrying out phlebectomy under TLA

somewhat negates the benefits of what is otherwise a tumescentless procedure. However, as Study 3 showed, the clinical benefits of concomitant phlebectomy outweighs this disadvantage.

Post procedural pain scores remained low in both groups for the first postoperative week. In both groups HRQoL was preserved at 1 week when compared to baseline (Figure 36). Previous studies have shown a deterioration in HRQoL due to post procedural pain[317]. However, patient HRQoL was preserved in this study during the first postoperative week, lending further support to the significance of the observed low periprocedural pain scores. Intergroup comparison of post procedural pain in this first week suggested a trend in favour of MOCA, which reached statistical significance on day 3 post intervention. However, this result is unlikely to have been of clinical significance as it fell below the 13 point threshold which is theorised to represent clinical significance[515]. Furthermore, other recovery parameters such as time to return to work and to normal activity were identical for both groups.

5.4.2 Anatomical occlusion/freedom from recanalisation

At 1 year, observed anatomical occlusion rates were significantly higher with EVLA than with MOCA. These findings are representative of the literature for both MOCA and EVLA, when consensus criteria for anatomical occlusion are applied[315,505,529,533]. As observed in Studies 2 and 3, this observed higher rate of recanalisation following MOCA was not linked adversely to any patient outcome at 1 year. Nonetheless, the aim of endovenous treatments of SVI is to permanently abolish flow in the target vein and this has been associated with a lower rate of recurrence and reintervention[534]; and in that sense EVLA carries a technical advantage over MOCA.

5.4.3 Complications

Thrombus extension or formation in a deep vein following SVI treatment is rare with an incidence rate of 0.1% following EVTA and 0.2% following MOCA[446,476]. Endovenous heat induced thrombosis (EHIT) is frequently the cause post EVTA and this usually follows a benign course[436]. A similar phenomenon has not been previously described for MOCA, however, the patient with DVT in this study recovered fully with a short course of anticoagulation as previously observed with EHIT. Therefore, this may represent a similar phenomenon, where thrombus propagates proximally from the junction to the deep vein.

5.4.4 Secondary procedures

Endovenous ablation without cessation of anticoagulants is safe; however it carries a higher risk of primary failure or recanalisation[535]. Previous studies have demonstrated that EVLA is effective in these patients when higher energy is delivered[536]. The effect of anticoagulation on MOCA success rates have

not been reported in the literature. The present study included three patients on warfarin, one of whom was in the MOCA group. This patient underwent MOCA at the maximal dose of STS 1.5% and experienced complete recanalisation with symptoms at 6 months. Of the two patients in the EVLA group, one patient experienced recanalisation in addition to a recurrence of his venous ulcer. Both patients were treated successfully with EVLA at a higher LEED. Study 2 results suggested that higher CEAP classes (C4-6) have a higher risk of recanalisation following MOCA[529]. Therefore, in patients with higher clinical class disease, particularly if they are anticoagulated, EVLA with higher energy density may be a better choice than MOCA.

5.4.5 Limitations

Blinding for both participants and surgeons was not possible in this study due to the nature of the two treatments being studied. This puts the findings in this study at a high risk of performance and detection bias. Steps taken to minimise performance bias included the standardisation of both procedures in a rigorous protocol. Additionally, all the surgeons performing these interventions were experienced in both procedures and a dedicated member of the theatre team was at each patient's side during the procedure to ensure that all patients were put at ease during the intervention. The risk of detection bias was mitigated by using international consensus protocols for DUS assessments and using validated PROMS to assess clinical response. At each visit these questionnaires were completed by patients prior to any interaction with clinicians to ensure patients were not prejudiced by their clinical interaction when reporting outcomes. The risk of attrition bias was low in this study owing to the low loss to follow up. The publication of a rigorous study protocol detailing the outcomes of interest and power calculation ensures that the risk of selective outcome reporting is low.

As with Study 3, repeated measures testing were performed, but unlike Study 3, Bonferroni correction was carried out in Study 4 in order to decrease family-wise Type I error risk. This correction is likely to have increased the risk of type II error, however, conservative hypothesis tests for comparisons other than the primary outcomes were thought to be more prudent considering the number of comparisons performed in the study; with a view to investigating possible clinically significant findings in a future dedicated study.

Chapter 6: Conclusion

6.1 Study Findings and Implications

SVI is a common HRQoL limiting condition. Minimally invasive treatment methods are now the mainstay of treatment and will continue to be for the foreseeable future. Among those, MOCA is a popular, safe, and effective treatment method leading to significant HRQoL improvement that is equivalent to the current leading thermal ablative methods in the short-term as seen in Study 1.

Studies 2-4 showed that anatomical occlusion rates achieved with MOCA are not as high as previously reported in the literature and do not match those of EVLA. Nevertheless, HRQoL gains are equivalent to EVLA for up to 1 year. Periprocedural pain scores and recovery times are similar between the two methods, and patient satisfaction levels are similarly high. As with EVTA, MOCA is best employed with simultaneous phlebectomy in terms of HRQoL gain. This is however associated with a modest increase in procedural pain and duration but importantly reduces the rates of phlebitis and reinterventions.

MOCA is a useful addition to the armamentarium of the modern venous surgeon which should include various techniques. Given the widespread patterns of reflux that SVI patients experience particularly with recurrent disease and with higher CEAP classes, it is important to be able to utilise different tools in order to fit the patient's needs rather than adopt a single method which undoubtedly will not be suitable for all patients. As evidence continues to emerge, the wider role of MOCA among these available options should become clearer. However, the results in this thesis rule out MOCA as a candidate first line treatment within the NHS's Single-Payer healthcare model. Clinically, results following MOCA are no better than EVTA and MOCA's lower technical success rates potentially increase the risk of recurrence and need for further treatment; especially in the long-term and when applied at a large scale.

6.2 Unanswered Questions and Future Research Avenues

Considering the results of all the studies in this thesis, perhaps the most important future research project is the long-term follow up of patients studied here and in similar trials worldwide. For MOCA this would address an obvious gap in the literature regarding its long-term outcomes, which are crucial in establishing the role MOCA will play in SVI treatment going forward. Reporting in these long-term studies needs to be standardised however, to provide accurate, measurable data that maximises external validity and reproducibility.

A similar case can be made for the EVLA technique performed in Study 4 as it differs from the protocols used in classical studies that have established EVTA as first line treatment. For example, the Hull Endovenous Laser Project (HELP) trial employed a 14 Watt continuous power 810nm bare tipped laser fibre with a target LEED of 80-100 Jcm^{-1}, whereas Study 4 (LAMA trial) used a 10 Watt continuous power 1470nm gold tipped laser fibre with a target LEED of 60 Jcm^{-1}. The difference in chromophores and LEED may affect long-term outcomes and recurrence rates. The current trend in the literature is one of lower LEED and higher laser wavelength[22]. This is associated with a low periprocedural pain profile as demonstrated in Study 4, but this approach may need to be revisited should long-term follow up associate it with higher recurrence rate compared to higher LEED ablation.

Economic analysis comparing MOCA and other NTNTs with EVTA would also be a useful future project. This should not be carried out prematurely however as the continuous developments in minimally invasive techniques may render such an analysis worthless. MOCA for example remains in the early stages of its evolution and refinement as a technique; there are still unanswered question regarding optimal sclerosant type, form, concentration and dose. Additionally, the development of the Flebogrif device (Balton, Poland), which doesn't rely on a motor to mechanically score the vessel intima offers a cheaper alternative to Clarivein. Similarly, EVTA technology is likely to become more affordable and therefore a cost effectiveness study comparing NTNTs and EVTA in the next five to ten years would be a worthwhile endeavour.

Venous ulcer disease remains a difficult condition to treat effectively and cost effectively. The results of the ESCHAR and EVRA trials, show that compression therapy with treatment of reflux is more effective and cost effective than compression alone, as it expedites ulcer healing and reduces recurrence rates[293,294,537,538]. The best modality this treatment should take remains unknown and while EVTA is the first line choice, surgeons are often reluctant to use it in compromised skin, which may explain the fact that more than half the patients in the EVRA trial received foam sclerotherapy[294]. MOCA is a flexible technique that offers better occlusion rates than foam sclerotherapy while retaining similar utility to foam. It can be deployed both ante and retrograde, in addition to being safe to use in compromised skin. It is therefore worth exploring if the modality of reflux intervention for C6 patients affects ulcer recurrence rates and ulcer free time and in particular if MOCA offers better results in the long-term than foam sclerotherapy.

On the opposite end of the CEAP scale, there are many unanswered questions on the factors that influence venous disease progression across the CEAP scale. The epidemiology discussed in 1.5.3

highlights our knowledge of the point prevalence at various stages of venous disease however, little is known about the factors that influence disease progression and, whether early treatment has protective effects. Some patients were not eligible for inclusion in Studies 3 and 4 as local NHS Clinical Commissioning Groups (CCGs) restricted treatment of SVI to patients with higher CEAP disease only (C4-6) partway through the recruitment period of said studies[261]. This creates an opportunity to set up a registry to investigate disease progression in patients not eligible for treatment under these rules and compare them to similar patients who did undergo treatment. If early treatment is found to protect against disease progression, then this commissioning restriction policy may prove cost-ineffective, as it may lead to an increase in the prevalence of higher CEAP disease once lower CEAP patients progress. On the other hand, should early treatment not provide protection against progression, then the results from this registry could be used in economic modelling to optimally time interventions and improve cost-effectiveness.

The exclusion criteria for studies 2-4 mean that the findings therein cannot be directly applied to the excluded populations of patients. The injection of a medicinal product such as sclerosant in pregnancy would be unethical and as such pregnancy was an exclusion criterion. Understandably, pregnancy is widely categorised as an exclusion criterion in interventional venous research and therefore there is limited evidence on the best timing to treat symptomatic SVI in pregnancy and puerperium. The vast majority of symptomatic patients can wait until after puerperium; however, occasionally bleeding varicosities present in this population and in those scenarios, treatments requiring injection of sclerosant such as MOCA should be avoided.

To date, lifelong compression therapy has been the principal palliative measure offered to patients with isolated DVI as interventional therapies have been unsuccessful in the long-term[22]. A minority of patients with SVI also have concurrent DVI, and these patients with mixed deep and superficial incompetence were excluded from studies 2-4. Treatment of patients with concurrent SVI and DVI is less well studied compared to isolated SVI. However, SVI should be treated in these patients when symptomatic as it improves HRQoL[22], and in some cases venous haemodynamics improve too; leading to resolution of the deep reflux[539,540]. Nonetheless, patients with mixed reflux are a heterogenous subgroup and their response to SVI treatment may not match those with isolated SVI. Therefore, the decision to exclude them was a pragmatic one that balanced a limitation to external validity with maximising internal validity. EVTA has been shown to be safe and effective in this population of patients and should remain the first line treatment for them.

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8.1 Appendix 1 – PRISMA Checklist for Study 1

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	73
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	5-7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	71-73
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	73
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	73-74
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	74
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	74
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	74-75
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	74
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	73
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	74-75
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	73-75
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	75
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	75
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	76-78
Study characteristics	17	Cite each included study and present its characteristics.	76
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	80-81
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	81
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	82-84
	23b	Discuss any limitations of the evidence included in the review.	84
	23c	Discuss any limitations of the review processes used.	84
	23d	Discuss implications of the results for practice, policy, and future research.	86-140
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	125
Competing interests	26	Declare any competing interests of review authors.	125
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

8.2 Appendix 2 – STROBE checklist for Study 2

	Item No	Recommendation	location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	86
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5-7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	86
Objectives	3	State specific objectives, including any prespecified hypotheses	86
Methods			
Study design	4	Present key elements of study design early in the paper	86
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	92
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	86-87
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	90-91
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	87-91
Bias	9	Describe any efforts to address potential sources of bias	87-91
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	123-124
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	123-124
		(*b*) Describe any methods used to examine subgroups and interactions	-

		(*c*) Explain how missing data were addressed	123-124
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	92
		(b) Give reasons for non-participation at each stage	92
		(c) Consider use of a flow diagram	92
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	93
		(b) Indicate number of participants with missing data for each variable of interest	92-99
		(c) Summarise follow-up time (eg, average and total amount)	92
Outcome data	15*	Report numbers of outcome events or summary measures over time	92-99
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	92-99
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	100-103
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	102
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	100-103

Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	125

8.3 Appendix 3 – Strobe Checklist for Study 3

	Item No	Recommendation	location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	104-105
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5-7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	104-105
Objectives	3	State specific objectives, including any prespecified hypotheses	105
Methods			
Study design	4	Present key elements of study design early in the paper	104-105
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	105
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	86-87
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	108-109
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	90-91
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	87-91
Bias	9	Describe any efforts to address potential sources of bias	87-91
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	123-124
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	123-124
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	123-124

		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	108-109
		(b) Give reasons for non-participation at each stage	109
		(c) Consider use of a flow diagram	109
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	110
		(b) Indicate number of participants with missing data for each variable of interest	108-115
		(c) Summarise follow-up time (eg, average and total amount)	109
Outcome data	15*	Report numbers of outcome events or summary measures over time	108-115
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	108-115
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	116-118
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	118
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	116-118

Generalisability	21	Discuss the generalisability (external validity) of the study results	116-118
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	125

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	119
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	5-7
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	73-119
	2b	Specific objectives or hypotheses	119
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	119
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	119-120
	4b	Settings and locations where the data were collected	120
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	120-121
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	122
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	123
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	120
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	120
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	120
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	120
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	120
	11b	If relevant, description of the similarity of interventions	120-122
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	123-124
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	126-127
	13b	For each group, losses and exclusions after randomisation, together with reasons	127
Recruitment	14a	Dates defining the periods of recruitment and follow-up	126
	14b	Why the trial ended or was stopped	126
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	126
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	127-136
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	127-136
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	127-136

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	135-136
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	138
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	136-138
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	136-138
Other information			
Registration	23	Registration number and name of trial registry	125
Protocol	24	Where the full trial protocol can be accessed, if available	125
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

8.5 Appendix 5 – Study 4 (LAMA) Patient Information Sheet

PARTICIPANT INFORMATION SHEET

Academic Vascular Unit
Department of Vascular Surgery
1st floor, Main Tower Block
Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ
01482 674643

You are being invited to take part in an original research study entitled:

A randomised clinical trial comparing endovenous Laser Ablation and Mechanochemical Ablation (ClariVein®) in the management of superficial venous insufficiency – LAMA Trial.

Before you make a decision, it is important for you to understand why this research is being performed and what it will involve. Please take time to read the following information and discuss it with others if you wish. We will answer any questions you may have.

This sheet is made of two parts

- **PART 1** tells you the purpose of this study and what will happen if you take part
- **PART 2** gives you more information on the conduct of the study

PART 1

What is the purpose of this research and why have I been chosen?

The veins in your legs are responsible for transporting blood upwards back to the heart. You have varicose veins caused by leaking valves inside the veins, which allow blood to flow backward and collect in the vein. As a result, your veins become swollen and enlarged. After discussion with your Vascular Surgery specialist, you have decided to have a procedure to treat your legs.

People who are suitable for treatment in the NHS are offered the "first-line" treatment using a small "hot probe" inserted inside the vein. (Our unit uses a laser fibre to produce this heat and the procedure is called endovenous laser ablation (EVLA)). The heat seals the leaky vein closed and blood diverts itself,

travelling out of the leg through normal veins which are left. This is a highly effective and safe treatment, and is performed with you awake. Local anaesthetic is applied at the site where the probe inserts into the vein. Further local anaesthetic solution is injected along the entire length of the vein which stops any pain you may have during treatment. These injections however do cause some discomfort whilst they are happening.

There is now a new treatment available called mechanochemical ablation (ClariVein®). This new device again involves a "probe" placed inside the vein, but rather than using heat, it has a small rotating hollow wire and releases a medication inside the vein itself. This combination seals the vein closed without the need to apply heat. This avoids the need for some of the local anaesthetic injections and therefore may cause less discomfort. Early studies have shown promising results; however a trial is needed to compare the results directly against the current standard treatment. We do not know whether one of these treatments is better than the other, or whether both are the same.

This new treatment has been approved for use in the UK in the context of a clinical trial by the National Institute of Clinical Excellence (NICE). The results of this research will be used to help guide future treatment and improve the care of patients with varicose veins like yourself.

Do I have to take part?

Involvement in this study is entirely voluntary. We will discuss the study with you and this information sheet is for you to keep. If you would like to take part, we will ask you to sign a consent form to indicate that you understand what is involved and that you agree to this. If you do decide to take part, you will still be free to withdraw from the study at any time, without giving a reason. You will then receive the usual NHS treatment that you would otherwise normally receive.

What will happen to me if I take part?

If you decide to take part, we will record some details about you, including your age, gender, height, weight and severity of your varicose veins. You will have a duplex ultrasound scan, which is harmless and painless, and would be a part of your normal care outside of the study. We will ask you to complete a questionnaire that gives us information about how your varicose veins affect your "Quality of Life".

A random process will determine whether you are to receive either the laser treatment or mechanochemical ablation with ClariVein®. There is an equal chance of you receiving either treatment, but you will not be able to choose, and so you must be happy to undergo either treatment.

What will the visits to the Vascular Lab involve?

You will be asked to attend the Vascular Lab at Hull Royal Infirmary at 1 week, 6 weeks, 6 months and 1 year following your treatment. These visits will last approximately 30 minutes each. Each visit is longer to give us time to do more detailed assessments of your varicose veins, which will tell us whether the treatment is effective. At each visit, we will perform the following:

- Clinical examination to assess the success of treating your varicose veins.
- Duplex ultrasound scan: similar to the one you had before the treatment. This is to ensure the vein has been successfully treated and that you do not have any other problems.
- Questionnaires: the same questionnaire that you completed prior to your treatment in addition to several measurement scales which give your views on your treatment such as pain, bruising and satisfaction with treatment and cosmesis.

The Vascular Lab is like the normal outpatients department, with doctors and nurses available at all times during your visit.

Are there any costs involved?

No costs are involved, but you will need to make your own travel arrangements to attend the Vascular Lab.

What are the potential benefits?

The benefit from completion of this research is that it will provide valuable information to inform the care of patients with varicose veins. This will improve the quality of their care by providing evidence of the very best treatment available and prevent the use of less favourable treatments and the misuse of our precious NHS budget.

Our clinical and research team have a vast experience in the treatment of your condition. We are recognised as international experts and have won multiple awards for our work. You will have time to ask questions about your treatment and condition, and that your leg will be assessed and followed-up

closely. If you have any concerns or problems relating to your treatment, you will be able to contact the team directly

What are the potential risks?

All procedures have recognised complications and all medicines have recognised side effects. The risks of complications and side effects will be no different than if you were undergoing these procedures in normal NHS practice. Your treating surgeon will discuss the risks specific to you at length before treatment as per best clinical practice and national guidelines.

What happens at the end of the study?

After your final visit to the Vascular Lab, 1 year following your procedure, you will be transferred back to standard NHS care. We will contact you in the future to attend for long-term follow-up visits at 5 and 10 years. Hospital records will be checked beforehand to establish the patient status and contact details.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled securely and in confidence. The details are included in Part 2.

What if the treatment doesn't work?

If you still have symptoms of varicose veins after treatment you are welcome to contact us and we will issue you with an appointment to come back for an assessment. If you require any further treatment during your time in the trial, we will arrange for this to be performed.

PART 2

What will happen if I don't want to carry on with the study?

You are free to withdraw your consent to participate at any time and without giving a reason. This will not affect the standard of care you receive. Depending on the time at which you decide to withdraw, we will discuss with you about further follow-up and use of the information we have already collected up to that point.

What if there is a problem?

If you have any problems, concerns or complaints, you should contact the research team in the first instance (details at bottom of sheet). If your issue is not resolved after speaking to us, or you feel that it

would not be appropriate to speak to us, you may contact the hospital Patient Advice and Liaison Service (PALS), which can be contacted through the hospital switchboard (01482 875875).

What if I am harmed?

The treatments used in this research are approved for use in patients with your condition and we will take all known steps to protect you from harm. However, if you are harmed during the course of this research, and that harm is due to negligence, then you may have grounds to take legal action for compensation against Hull University Teaching Hospitals . Further information can be made available to you if required.

Will my taking part in this study be kept confidential?

Yes, If you agree to take part in this research, your medical records will be reviewed by one of the research doctors. All information we keep about you will be coded and kept on a secure electronic database. We will keep your personal details to a minimum and these will be kept in a locked storage area with restricted access. In certain circumstances, the regulatory authorities that ensure the research is being conducted properly, may request participant information. Anyone given access to your details will comply with GDPR rules.

As per standard treatment unless you request otherwise, we will inform your GP about your participation in the study. A note will be made in your hospital records to inform other doctors of your involvement in the research study.

Transparency Information (required by the General Data Protection Regulation (GDPR) introduced on 25 May 2018)

Hull University Teaching Hospitals NHS Trust (HUTH is the sponsor for this study based in the United Kingdom). We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. HUTH will keep identifiable information about you for 5 years after the study has finished.

You can find out more about how we use your information at https://www.hey.nhs.uk/privacy/.

As a NHS organisation we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

Our Data Protection Officer is Carla Ramsay and you can contact her at the address/telephone number/email address below.

Carla Ramsay
Alderson House
Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ
Tel: 01482 477854
Email: information.governance@hey.nhs.uk

What will happen to the results of the research study?

Once the study is complete, the results will be submitted for publication in a scientific journal and a final report written. You should contact your study doctor if you are interested in receiving copies of any resulting publications. You will not be identified in any reports or publications without further written permission from you, but this is unlikely.

Who is organising and funding this research?

The research is undertaken in partnership with the Academic Unit of Vascular Surgery, Hull York Medical School and Hull University Teaching Hospitals NHS Trust.

Who has reviewed the study?

This study has been reviewed and approved by a Research Ethical Committee, Hull University Teaching Hospitals NHS Trust Research and Development Committee.

What happens now?

If you wish to take part in this study, we ask you to contact us. A confidential answer-phone service is provided – please leave your name and contact details if this is activated.

You will then be asked to attend the Vascular Lab at Hull Royal Infirmary, where we can discuss the study in further detail. You will be asked to sign a consent form to say that you agree to involvement in the research study. A copy of your signed consent form will be given to you to keep, with copies placed in your medical records and our research records.

If you decide not to take part, your standard NHS care will continue as planned.

Thank you for taking the time to read this information. If you have any further questions now or during the study, we would be happy to discuss them with you.

Dr Abduraheem Mohamed

Clinical Research Fellow in Vascular Surgery

Mr Daniel Carradice

NIHR Academic Clinical Lecturer in Vascular Surgery

Professor Ian Chetter

Professor of Surgery and Consultant Vascular Surgeon

Academic Vascular Unit
Department of Vascular Surgery
1st Floor, Main Tower Block
Hull Royal Infirmary
Anlaby Road
Hull HU3 2JZ

Telephone 01482 674 643

Academic Vascular unit
Department of Vascular Surgery
Hull Royal Infirmary
Anlaby Road
Hull HU3 2JZ
Tel: 01482 674 643

CLINICAL STUDY PROTOCOL

Laser Ablation versus Mechanochemical Ablation (LAMA) Trial

A randomised clinical trial comparing endovenous laser ablation and mechanochemical ablation (ClariVein®) in the management of superficial venous insufficiency.

Investigators:

Abduraheem Mohamed:	Clinical Research Fellow in Vascular Surgery
(Co-Investigator)	Abduraheem.mohamed@hey.nhs.uk
Mr Daniel Carradice :	NIHR Academic Clinical Lecturer in Vascular Surgery
(Co-Investigator)	d.carradice1@googlemail.com
Professor Ian Chetter :	Consultant in Vascular Surgery
(Principle Investigator)	Professor of Surgery, Hull-York Medical School
	ian.chetter@hey.nhs.uk

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

Signature …… Date ……

Sponsor:

James Illingworth, R&D Manager
Hull and East Yorkshire Hospitals NHS Trust
R&D Department, Office 13,
2nd Floor Daisy Building, Castle Hill Hospital,
Castle Road, Cottingham,
East Yorkshire HU16 5JQ
Tel: 01482 461903

Signature ……

Date ……

Statistician:

Victoria Allgar
Department of Health Sciences
Seebohm Rowntree Building
University of York
Heslington,
York YO10 5DD
Tel: 01904 321321

Signature ……

Date ……

Contents

1. List of Abbreviations and Definitions

AASV	Anterior Accessory Saphenous Vein
AVVQ	Aberdeen varicose vein questionnaire; disease specific quality of life instrument
BMI	Body Mass Index (kgm^{-2})
CEAP	Clinical severity, etiology, anatomy and pathophysiology classification
CIVIQ-20	Chronic Venous disease quality of life Questionnaire; disease specific quality of life instrument
CRF	Case Report Form
CTIMP	Clinical trial of an investigational medicinal product
CVI	Chronic Venous Insufficiency
CVD	Chronic Venous Disease
DUS	Duplex Ultrasound
DVT	Deep vein thrombosis
EQ5D	Euroqol 5-Domain utility index; generic quality of life instrument
EVLA	Endovenous laser ablation
EVTA	Endovenous thermal ablation
FDA	Food and Drug Administration, USA
GA	General anaesthetic
GSV	Great Saphenous Vein
HEY	Hull and East Yorkshire Hospitals NHS Trust
IMP	Investigational medicinal product
J	Joule: unit of energy
LA	Local anaesthetic
LAMA trial	Laser ablation versus mechanochemical ablation trial
MHRA	Medicines and Healthcare products Regulatory Agency
MOCA	Mechanicochemical ablation
$NaHCO_3$	Sodium bicarbonate
NS-SEC	National statistics socio-economic classification
NHS	National Health Service, UK
NICE	National Institute for Health and Care Excellence
PE	Pulmonary embolism
PROMs	Patient-report outcome measures
QALY	Quality-adjusted life year
QoL	Quality of life

R&D	Research and development
RCT	Randomised clinical trial
REC	Research ethics committee
RFA	Radiofrequency ablation
Seldinger technique	Invented in 1952 by the Swedish radiologist Sven-Ivar Seldinger (1921-1998). Means of endovascular access and treatment using guidewires and sheaths.
SF36	Short form 36-item; generic quality of life instrument
SF6D	Short form 6-domain utility index; derived from SF36
SFJ	Saphenousfemoral junction
SmPC	Summary of Product Characteristics
SSV	Small saphenous vein
STD	Sodium tetradecyl sulphate: sclerosing agent
STS	Sodium tetradecyl sulphate: sclerosing agent
SVI	Superficial venous insufficiency
TA	Tumescent anaesthesia
UGFS	Ultrasound-guided foam sclerotherapy
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
VEINES-QOL/Sym	Venous insufficiency epidemiological and economic study to evaluate quality of life and symptoms; disease specific quality of life instrument
VCSS	Venous Clinical Severity Score
VTE	Venous thromboembolism
VVs	Varicose veins

2. Trial Summary

Title	A randomised clinical trial comparing endovenous laser ablation and mechanochemical ablation (ClariVein®) in the management of superficial venous insufficiency.
Short acronym	LAMA Trial
Type of trial	CTIMP, Phase IV
Trial design	Randomised clinical trial
Medical condition researched	Superficial venous insufficiency; varicose veins
Trial Treatment	Endovenous laser ablation; Mechanochemical ablation
Primary Objective	Intra-procedural pain visual analogue scale Technical efficacy at 1 year
Secondary Objectives	Disease specific quality of life, generic quality of life, analgesia use, pain/bruising/satisfaction/cosmesis visual analogue scale, recovery time, clinical severity, complications, surface planimetry of skin changes and complications, duplex ultrasound for recanalisation
Target number of participants	140
Duration participant in trial	12 months
Estimated recruitment period	6 months
Estimated total trial duration	18 months
Planned trial sites	Tertiary Vascular Centre in University Teaching Hospital
Main inclusion criteria	Age 18 or over. Symptomatic SVI which will likely benefit from treatment. Clinical grades C2-C6 on the CEAP system. Superficial axial incompetence with proposed treatment length ≥10cm. Treatment with either endovenous laser ablation or mechanochemical ablation is technically feasible. Patient is willing to participate and give valid, informed consent.
Main exclusion criteria	One of the treatments is thought to be preferable. Patient unwilling or unable to comply with requirements for follow-up. Known allergy to medications and dressings used in the treatment. Known right to left circulatory shunt. Evidence of acute deep venous thrombosis or complete occlusion. Pelvic vein insufficiency. Active or recent thrombophlebitis (within 6 weeks). Impalpable foot pulses with ankle-brachial pressure index < 0.8 Pregnancy or breast-feeding. Active malignancy Immobility Involvement in another CTIMP in the last 4 weeks
Investigations performed	Duplex ultrasound

3. Lay Summary

Veins in the leg carry blood back upward towards the body and heart. Valves within these veins normally open to let blood through and then close to stop it flowing backward. If the valves stop working properly the blood can flow backward and collect in the vein. These leaking valves cause the vein to become swollen and enlarged, called “varicose veins” (VVs). They are a very common problem, affecting more than a third of all adults in the UK. VVs are known to reduce quality of life by causing problems such as pain, aching, swelling, itching, bleeding, skin colour changes and eczema, and can even cause chronic wounds in the leg called ulceration. Aside from this impact upon quality of life, treatment of ulcers is very expensive, with the dressing alone accounting for 3% of the entire NHS budget. VVs and skin ulcers are therefore a significant burden upon patients, their loved ones and society as a whole.

Traditional surgical treatment of VVs, with the patient asleep under a general anaesthetic, involves the removal of the diseased veins, allowing blood to leave the leg via the healthy veins left behind. This method has been clearly shown to improve quality of life. Treatment however has moved on and minimally invasive or “key-hole” treatment under local anaesthetic with the patient awake is now the standard. This has been shown to be less painful and allows an earlier return to normal activities.

These modern treatments involve placing a tube inside the vein through a small incision in the skin (a few millimetres), following injection of local anaesthesia (LA). LA is a medication that blocks the nerves in the skin that carry painful sensation. Current standard treatment then involves further LA injections around and along the entire length of the vein, which typically runs from below the knee to the groin, although sometimes it may run from the ankle to the groin. A “hot-probe” is then passed through the tube into the vein. When laser energy is used to produce this heat, it is called endovenous laser ablation (EVLA). The heat from this laser then seals the leaky vein closed, without the need to remove the vein from the leg. Blood then travels out of the leg through the normal veins that are left behind. This method was found to be superior to conventional surgery and to another minimally invasive treatment (foam sclerotherapy) by the National Institute for Health and Care Excellence (NICE) and was recommended as the first line treatment for suitable patients in the UK NHS.

A new treatment has been developed called mechanochemical ablation (MOCA). Similar to EVLA, a treatment device is placed inside the leaky vein, but rather than using heat to seal the vein, this new device has a rotating hollow wire which simultaneously releases a medication. The device damages the lining of the vein and causes inflammation inside the vein, which seals it shut. The main benefit of MOCA when compared with EVLA is that there is no need for the injections of LA along the entire length of the vein. These injections are typically uncomfortable and so it is hypothesised that patients will find this new procedure less painful. Early studies have shown promising results; however this needs to be confirmed with a well-designed trial and long-term follow up.

A clinical trial will randomly allocate willing participants with VVs to receive either EVLA or MOCA, to establish whether this new treatment will be associated with a significant reduction in the discomfort of the treatment, whilst achieving the same success rates and quality of life improvements, at an acceptable cost. This study will provide information to inform patients, doctors and the wider healthcare service, aiming to achieve the very best outcomes in the management of this disease.

4. Scientific Abstract

• Background

Varicose veins (VVs) or Superficial Venous Insufficiency (SVI) of the leg results from inflammation mediated damage to vein structure, allowing reverse flow. SVI affects 30% of adults and is associated with symptoms causing pain and disability; furthermore 3-10% have soft tissue damage and 1-2% suffer with venous ulcer disease [1-5].

Recent NICE guidelines recommend treatment using thermal ablation such as endovenous laser ablation (EVLA) to occlude the disease vein [6]. This approach has been shown to allow an enhanced recovery, with less pain and disability, allowing superior early quality of life (QoL) when compared with surgical ligation and improved efficacy when compared with foam sclerotherapy [7-11]. A disadvantage however is that it involves the uncomfortable injection of large volumes of tumescent anaesthesia (TA) around the entire length of target vein.

Mechanochemical ablation (MOCA) is a newer treatment aiming to match the enviable efficacy of thermal ablation whilst using a gentle sclerotherapy technique, with no need for TA. A catheter placed within the vein deploys a rapidly rotating hollow wire which causes physical damage to the endothelium and the vein goes into spasm. At the same time a sclerosing agent is injected through the hollow wire into the vein, which results in protein denaturation, endothelial destruction and endoluminal fibrosis [12, 13]. Case series suggest that MOCA has significantly higher efficacy at 6 months than following foam sclerotherapy, with results similar to EVLA [14, 15].

• Aims

The aim of this research is to compare the safety, efficacy, effectiveness and cost effectiveness of MOCA when compared to EVLA in the management of SVI.

• Methods

The sample size is based upon clinically meaningful differences in the joint primary outcomes at 90% power and 5% significance. 140 consecutive consenting participants with symptomatic SVI will be randomised equally to receive EVLA or MOCA. Outcomes will be assessed until 1 year and will include:

- Peri-procedural and post-procedural
    - Pain (joint primary outcome)
    - Analgesia requirement
- Recovery and employment
- Complications
- Generic and disease specific QoL
- Efficacy at 1 year (joint primary outcome)
- Recurrence and disease progression

- Further treatment
- Soft tissue damage caused by SVI
- Satisfaction
- Costs

The patient reported outcomes and clinical data would be checked for completeness and accuracy prior to statistical analysis. The results will then be disseminated via presentations to societies and publication in high impact peer review journals.

A cost-effectiveness analysis will be completed, firstly using the data collected within the trial. This will be followed by a systematic review of the literature available at that time to gather data to inform the structure and parameters of a Markov model allowing estimation of the comparative cost-effectiveness of all available treatments of SVI over the medium to long term. Finally, the uncertainty in model parameters and structure will be explored and the expected value of perfect information analysis will seek to quantify this uncertainty faced by commissioners, surgeons and patients, and will be used to help target and prioritise future research in this area to be of maximum benefit to patients and the NHS.

- ## Benefits of the research

Our Public and Patient Involvement (PPI) group and patients report that one of the major burdens associated with treatment is the discomfort during injections of TA. This trial will establish whether a newer technology results in less discomfort by avoiding additional injections, whilst offering similarly high success rates in the longer term as the current gold standard. An economic analysis will also establish which of these differing technologies is the most cost-effective, allowing the trial to inform decision making discussions between surgeons and their patients, and also strategic decision making in the NHS, where the optimal allocation of resources must be considered in order to maximise the patient and societal benefit from our health service.

5. Introduction

• Superficial Venous Insufficiency (SVI) of the leg

SVI results from inflammation mediated damage to vein walls and valves resulting in reverse flow, which in turn causes a venous hypertension that further propagates the process. Further inflammatory processes result in skin and soft tissue damage, venous eczema, lipodermatosclerosis and ulceration, which is often stubborn, tending towards chronic and relapsing disease.

SVI is one of the most common causes of disease in developed countries. 30-50% of adults have varicose veins, 3-10% have clinical evidence of early soft tissue damage and 1-2% suffer with venous ulcer disease [1-5]. This high prevalence along with the chronic nature of its complications, such as venous ulceration, leads to extremely high costs to society. In 2012/13 over 30,000 procedures were performed by the NHS in England to treat SVI, costing approximately £30 million [16, 17], whilst the direct costs of ulceration accounts for 1-3% of the entire healthcare budget [18-20]. In the USA alone treatment of venous ulcers costs around $3 billion per year [21]. This is aside from the costs to the economy of lost working/carer days, as the disease affects a significant proportion of working age adults.

Aside from the healthcare resources implications, SVI is associated with significant impairment in quality of life (QoL) [22-30]. This is related to physical symptoms such as pain, impacting upon physical function and is frequently associated with role limitation. Cosmetic concern is linked with psychological domains [25] and yet little change in psychological health is seen until the depression and social isolation associated with advance disease [23-25, 28, 29, 31]. Without treatment a patient with uncomplicated varicose veins will experience a loss of 0.7 (0.3-1.2) quality adjusted life years (QALYs) over 10 years. This rises to 1.0 (0.5-1.6) QALYs with skin changes and 2.0 (0.5-3.6) QALYs with venous ulceration [22]. These results are of a clinically significant magnitude [32]. To contextualise this, patients with symptomatic disease can have pain scores comparable to reference patients with recent myocardial infarction, whilst patients with ulceration report physical function and role-limitation comparable to congestive cardiac failure or chronic obstructive pulmonary disease [33]. Such profound QoL impairment provides a clear mandate for the development and application of interventions to increase the health and well-being of the population.

• Treatment

Conservative treatment using compression is available but an intervention to correct venous hypertension by removing or occluding the veins has been shown to correct QoL deficit, whilst being highly cost-effective [34]. Initially the mainstay of intervention involved surgery, typical involving a wound in the groin to tie the varicose vein and then strip it out of the leg.

There has been a revolution in the management of SVI with the development of minimally invasive techniques performed under local anaesthetic, which have been shown to dramatically decrease the pain and disability associated with the procedure when compared with surgery, allowing for rapid recovery [9, 11, 35-38]. These techniques have replaced surgery in NICE clinical guidelines, which recommend endothermal ablation, in preference to foam sclerotherapy, and with open surgery as the last resort [6].

Endothermal ablation involves the placement of a catheter in the main diseased vein under ultrasound guidance, through a tiny incision in the skin (2mm). Following this the vein is surrounded with dilute local anaesthetic solution called tumescent anaesthesia (TA). TA involves multiple injections along the entire

length of the vein the leg under ultrasound guidance. The drawback of TA is that it results in discomfort for the patient, but it performs four functions critical to endothermal ablation. Firstly, it prevents pain during treatment. Secondly, it pushes all of the surround tissues such as nerves and skin away from the vein to prevent any accidental damage. Thirdly, it acts as a heat sink, absorbing thermal energy escaping and preventing collateral damage. Finally it compresses the vein against the treatment catheter, eliminating most of the bloods. This maximises the proportion of energy delivered to the target vein. Two broad types of heat transfer are used. Endothermal laser ablation (EVLA) uses laser energy to rapidly emit heat, which is absorbed by chromophores in the vein. The other passes an electrical current through the tissue or a wire termed radiofrequency ablation (RFA). Heat destroys the cells within the vein wall, which is replaced with a fine band of scar tissue. In experienced hands, occlusion rates following EVLA are 95-100% [8, 10, 39].

Sclerotherapy involves the injection of a chemical agent into the vein. This acts upon the endothelium causing protein denaturation, endothelial destruction and endoluminal fibrosis, occluding the vein. It has several distinct advantages. Firstly there is no need for injections of TA. Secondly the treatment is inexpensive. However the drug is inactivated very quickly after coming into contact with blood. The agent is made into a foam consistency, displacing the blood and increasing the effective volume in contact with the endothelium. In some hands this has led to excellent closure rates [40], however this is far from the norm and major studies have demonstrated disappointing efficacy [6, 7, 10], impacting upon their cost-effectiveness [6, 41].

An "ideal treatment" therefore would combine the efficacy seen with EVLA and the gentle, TA-free treatment of sclerotherapy. Mechanochemical ablation (MOCA) seeks to be this treatment. Similar to EVLA, a treatment catheter is inserted into the vein through a tiny incision. This deploys a rapidly rotating hollow wire which causes physical damage to the endothelium, potentiating it for chemical injury, and the vein quickly goes into spasm around the catheter. At the same time a sclerosing agent is injected through the catheter into the vein and completes the denudation of the vein wall. Optimistic early case series suggest that MOCA has higher efficacy than following foam sclerotherapy, with results similar to EVLA [14, 15], however in a randomised control trial, the efficacy was noted to be lower than in the early studies [42].

6. Aims and Objectives

The aim of this randomised clinical trial is to establish whether mechanochemical ablation (MOCA) is superior to the current first line treatment (endovenous laser ablation (EVLA)). The two main hypotheses are that MOCA may cause less initial pain and disability allowing a more acceptable treatment with an enhanced recovery. The second hypothesis is that this may come at a cost of decreased efficacy, which may lead to increased recurrence and affect longer term QoL, increasing the requirement for secondary procedures.

7. Research Questions

What are the differences between MOCA and EVLA in the management of SVI in terms of:

- **Perioperative period**
    - Intra-procedural pain
    - Post-procedural pain

- Analgesia requirement
- Quality of life (QoL)
- Complications
- Recovery time
- Resource use

- **Longer term**
  - Generic and disease specific QoL
  - Efficacy
  - Clinical status (the presence of residual or recurrent varicosities, skin damage and ulceration)
  - Clinical recurrence
  - Patterns of recurrence
  - The need for secondary procedures
  - Complications
  - Costs and resource use
  - Employment

8. Investigational Plan

• Study design

This is a phase IV randomised clinical trial (RCT) in the setting of a University Teaching Hospital offering tertiary referral services to a population in excess of 1.2 million people ***(see Appendix 1)***. Consenting participants will be allocated to one of the two parallel treatment groups by equal randomisation.

• Target population

The target population for this study are individuals with symptoms of SVI with ultrasound evidence of axial vein reflux and who have agreed to receive treatment for their axial vein reflux.

• Subject recruitment

Each patient referred to the vascular service with symptomatic SVI is assessed. Patients who potentially meet the inclusion criteria will be made aware of this research study and provided with the appropriate information, including the *Patient Information Sheet*. Patients will be given an opportunity to think about the invitation to participate and discuss with family/friends or other healthcare professionals if desired.

Patients expressing an interest in participation will be offered an appointment for a screening visit with a study investigator.

9. Eligibility Assessment

At the screening appointment, the medical history and examination will be reviewed, followed by a detailed duplex ultrasound examination according to a set protocol based upon international consensus [43-45] ***(see Appendix 2)***. If the potential participant meets the required inclusion criteria without any exclusion criteria, subsequent discussion of the study will take place in full.

• Inclusion criteria

- Aged 18 or over
- Symptomatic SVI which will likely benefit from treatment in the opinion of an experienced specialist and the participant
- Clinical grades C2-C6 on the CEAP system
- Superficial axial incompetence with proposed treatment lengths of at least 10cm
- Treatment with either endovenous laser ablation or mechanochemical ablation is technically feasible in the view of an experienced endovenous specialist
- Patient is willing to participate (including acceptance of randomisation to either treatment) and give valid, informed consent in the English language

• Exclusion criteria

- One of the treatments is thought to be preferable by either the patient or an experienced endovenous specialist
- Unwilling or inability to comply with the requirements for follow-up visits
- Known allergy to medications or dressings used in the treatment
- Known right to left circulatory shunt
- Evidence of acute deep venous thrombosis or complete ipsilateral occlusion
- Pelvic vein insufficiency
- Active or recent thrombophlebitis (within 6 weeks)
- Impalpable foot pulses with an Ankle-Brachial Pressure Index of less than 0.8
- Pregnancy or breast feeding
- Active malignancy
- Immobility
- Involvement in another CTIMP in the last 4 weeks

• Withdrawal criteria

- Participant request
- Participant non-compliance with study protocol

If the potential participant meet the inclusion criteria for the study and are willing and able to proceed to enrolment in the trial they will then be consented using a standardised *Patient Consent Form*. The Co-Investigators and Principle Investigator will obtain informed consent. Here the potential participant will be fully briefed on the trial process, the treatments, follow-up, time commitments and that this will be more

detailed than regular follow-up within the non-trial setting. One copy of the consent form will be given to the participant, one copy stored in the patient's case notes, and the original in Trial Master File. To ensure confidentiality and to adhere to the Caldicott and Data protection guidance, the participant will be assigned a unique study number for identification purposes; this will not allow identification of the study arm or any demographic information. No information identifying individuals including the study ID number will be made available to anyone outside of the research group. A letter will be sent to the participant's general practitioner to inform them of their enrolment into the study and its details.

10. Randomisation and Blinding

• Randomisation

Participants will be randomised to one of the two treatments. Randomisation will be conducted by the selection of a sealed opaque envelope. Once enrolled in the study, efforts will be made to assess and manage all participants as outlined in the allocated treatment protocol until the pre-determined end-point of the study or until participant withdrawal. Following randomisation the participant's GP will be informed of the intended treatment plan as per usual practice.

• Blinding

Due to the nature of the procedures involved it will not be possible to blind the participant or clinical team as to which group the participant is allocated. Where possible, assessor reported outcomes will be performed by an independent assessor who is blinded to treatment allocation. Bias in other outcomes will be limited by the use of predetermined standardised objective measurements, standardised protocols, and the extensive use of patient reported outcomes measures.

11. Power Calculation

The power calculation is based upon the joint primary endpoints with 90% power and 5% significance.

A published comparison of MOCA and radiofrequency thermal ablation found a reduction in intra-procedural pain from 35 to 19 on a 100mm visual analogue scale (VAS) with a standard deviation of 20 [42]. This gives a required sample size of 33 patients per group or 73 in the trial including 10% loss to follow-up. This difference is comparable with differences in patient reported VAS pain which we have previously found to be associated with a difference in physical domains of QoL and associated with changes in recovery time [9], and therefore can be judged to be clinically significant. Previous comparisons of radiofrequency ablation with EVLA have suggested that EVLA may be more painful [46-49], however older EVLA technology and general anaesthesia were used and many question the applicability of these findings today.

The same study reported complete target vein occlusion in 83% of patients following MOCA at 1 month. Our previous RCT found target vein occlusion in 99% at 1 year following EVLA [8]. A difference of this magnitude is likely to be clinically significant and have implications towards the long-term durability of the procedure, affecting effectiveness and cost-effectiveness. The required sample size to detect such a difference, if it exists, would be 62 per group or 137 in the trial including a 10% loss to follow-up. Taking into consideration the target sample size is 140.

12. Treatment Protocol

All cases will be performed on a day-case, out-patient basis as per the standard practice in our unit by an experienced endovenous surgeon. For each participant, the investigating team will re-assess the inclusion and exclusion criteria, confirm the consent and undertake the procedure as per the protocol.

Participants judged to be at high risk of venous thromboembolic disease (VTE) due to the use of exogenous oestrogens, immobility, past medical history or a family history of VTE or thrombophilia will be given a single pre-operative dose of prophylactic low molecular weight heparin (LMWH), in the absence of contraindications. All participants will have duplex ultrasound assessment and marking using the same protocol with only the endovenous procedure differing.

The sclerotherapy drug used will be Sodium Tetradecyl Sulphate (STS), also known as STD injection and marketed as Fibrovein™ (STD Pharmaceutical Products, Hereford, UK). STS will be ordered from and supplied by pharmacy from routine stocks and will be stored in the Academic Vascular Unit. Standardised tracing of batch numbers of STS will be undertaken as per our standard operating procedure.

- ### Preoperative procedure

The treatment aim is to eradicate any significant SVI present in the limb. Preoperatively the veins are marked by the surgeon using duplex ultrasound with the patient standing. This will identify the extent and position of the refluxing axial vein alongside any incompetent perforating veins and varicose tributaries. The significant superficial varicose vein (great saphenous vein (GSV), anterior accessory saphenous vein (AASV), short saphenous vein (SSV), Giacomini vein (GV)) to be treated will have its length measured and noted. In addition, the average diameter of the varicose vein will be calculated via three transverse images of the vein (proximal, middle and distal) and noted. The patient will be positioned supine on the operating table and skin disinfectant and sterile draping will be employed. The ultrasound transducer will be prepared with a sterile covering and secured to the sterile drapes to allow sterile intra-operative duplex ultrasound scanning (DUS).

- ### Operative Procedure

All procedures will be performed under local tumescent anaesthesia (TA) in a dedicated clean procedure room within the outpatients department.

a) EndoVenous Laser Ablation (EVLA)

1% Lidocaine with 1:200,000 epinephrine, buffered with 8.4% sodium bicarbonate in a 10:1 ratio (as per a Cochrane review [50]) will be used for skin infiltration where necessary. The target vein will be cannulated under DUS at the lowest point of demonstrable reflux. The surgeon will decide whether to use a direct (sheath and bare back fibre) system or a catheter based system. The treatment catheter or sheath will be introduced into the vein using the Seldinger technique and the tip of the catheter will be accurately positioned under DUS at the site of junctional reflux distal enough to prevent injury to the deep vein. Then tumescent anaesthetic (TA) will be administered. TA will be performed using a solution of 100ml of 1% Lidocaine with 1:200,000 epinephrine in 900ml of 0.9% Sodium Chloride, which is buffered to pH 7.4 with 10ml of 8.4% Sodium Bicarbonate. This will be infiltrated around the axial vein to be treated under DUS using a spinal needle and a pedal-operated peristaltic pump, at a target of 10ml of TA per cm. The same TA will be infiltrated around any tributaries to be treated. If a catheter was positioned then the treatment fibre will be

introduced via the catheter, and positioned accurately as above. Following deployment of the appropriate laser safety precautions, the laser energy will be delivered via the fibre. The wavelength, fibre tip, power and target energy delivery will be left to the discretion of the experienced endovenous surgeon, but clearly noted.

Ambulatory phlebectomy of the varicose tributaries will then be performed through 2mm stab incisions. All phlebectomy sites will be dressed with Steri-Strip ™ (3M), cotton wool and gauze and an elasticated self-adhesive compression bandage applied from foot to groin. This will be exchanged for a full length 15-20mmHg anti-thromboembolism compression stocking for 6 days after 24 hours. Our standard post-procedural advice will be given. Patients will be advised to immediately mobilise within their comfort level, taken analgesia as they see fit and to avoid driving until they can perform an emergency manoeuvre safely without pain or difficulty (usually 24 hours). Additionally patients are advised to go back to normal activities and employment as soon as they feel able.

b) MechanoChemical Ablation (MOCA) with ClariVein®

Pre-procedural preparation will be the same as for the EVLA group. The MOCA treatment device (ClariVein®, Vascular Insights, UK) will be inserted at the lowest point of reflux and positioned as per manufacturer's instructions for use [51] ***(see Appendix 3)***. The chemical ablation agent will be Sodium Tetradecyl Sulphate (STS) (also known as STD injection, marketed as Fibrovein™, STD Pharmaceutical Products, UK). Refer to the *Summary of Product Characteristics* (SmPC) for further details. The concentration used will be 1%, other than in the treatment of GSV or AASV where 1.5% STS will be used. The volume and infusion rate of STS will be calculated using a dosage chart provided by the manufacturer which cross-references the length of vein to be treated to the average diameter ***(see Appendix 4)***. The protocol allows for an additional volume to be added, accounting for dead space within the catheter. The European consensus guidelines recommend a maximum of 12mls of sclerosant STS, can be used at one sitting [541,542].

Study medication will be stored and dispensed by the trial site's pharmacy department in accordance with *Good Clinical Practice* and *Good Manufacturing Practice*.

The catheter deploys a hollow wire from its tip and the motorised base unit will cause this to rotate. This will cause spasm in the proximal vein. No STS is infused for the first 3mm and then the catheter will be withdrawn, wire spinning at a rate of 1.5mm/sec whilst STS is infused at the calculated rate. At 10cm the catheter will be deactivated and the proximal portion of the vein will be checked for closure using DUS. Any open segments will be retreated, if not the treatment will proceed until the entire axis is closed. Total STS volume will be divided by three and the vein treated in thirds to facilitate an even distribution. Any tributaries that can be treated by the catheter will be performed; however symptomatic varicose tributaries which cannot be treated in this way will be treated by ambulatory phlebectomy as in the EVLA group.

- ## Further treatment requirements

The aim is for the venous symptoms to resolve after the initial treatment. However if venous symptoms remain in the presence of residual SVI on duplex at 6 weeks, further treatment will be offered. Further axial treatment should be repeated as per the allocated protocol, unless the participant requests a different

treatment or the responsible clinician feels that this is not in the patient's interest. If symptoms are related to incompetent tributaries, the tributary varicose vein treatment protocol will be used for treatment.

13. Outcomes

- ## Primary Outcome

The joint primary outcomes will assess the hypothesised advantages and disadvantages of MOCA when compared with EVLA, the current first choice treatment of SVI.

The first will be patient reported intra-procedural pain measured on a standardised visual analogue scale (VAS).

The second will be technical efficacy at 1 year, with successful procedure defined as complete occlusion of the target vein segment. This will be assessed using duplex ultrasound.

- ## Complete Study Outcomes

I. Patient reported outcomes

a) Disease Specific quality of life (QoL)

The most commonly used disease specific QoL measure in SVI is the *Aberdeen Varicose Vein Questionnaire (AVVQ)*, which is designed to reflect the QoL impairment associated specifically with venous disease [25, 28, 52]. Patients are invited to complete a diagram representing their perceptions of the surface area of their leg affected, this along with their responses to 14 questions are analysed to produce a single venous specific index score. AVVQ was the instrument chosen for the national patient reported outcome measure (PROM) mandatorily collected during standard NHS treatment.

Chronic Venous disease quality of life Questionnaire (CIVIQ-20) was developed more recently and is becoming more popular in the literature [54]. It addresses some of the concerns in the development of the AVVQ and was designed to be more patient-centred. It is not known yet which of these two instruments will have the best performance characteristics and so both will be included in the study. This will also facilitate comparisons with studies only reporting one of these outcomes.

VEnous INsufficiency Epidemiological and Economic Study to evaluate Quality of Life and Symptoms (VEINES-QOL/Sym) is a 26-item patient-reported disease specific questionnaire to evaluate the quality of life and symptoms across the full spectrum of conditions (e.g. telangiectasias, varicose veins, oedema, skin changes and leg ulcers) related to chronic venous disorders of the leg [54].

b) Generic quality of life (QoL)

Whilst disease specific measures are sensitive to differences in QoL related to SVI, they do not reflect a patient's QoL as a whole or the morbidity of treatment. Generic QoL will be performed to do this and will allow the calculation of quality adjusted live years (QALYs), enabling cost-effectiveness analysis and comparison with other healthcare programmes.

Health profile: *Short Form 36* has become the most widely used generic instrument in the world today [55-57]. It produces a comprehensive profile at eight domains covering the range of physical and psychological well-being (physical function, physical role limitation due to physical disability, bodily pain, general health perception, vitality, social function, emotional role limitation due to emotional problems and mental health). Item scores for 36 questions are coded, summed and transformed on to a scale from 0 (worst health) to 100 (best health) in each domain. SF-36 has been extensively shown to be both valid and reliable [24, 25, 58-61], and used in many patient groups, including those with venous insufficiency. Its global popularity has resulted in it being translated into 130 languages and norm based scores produced for a range of populations based upon population responses, making it a patient centred questionnaire. UK version 2 will be used in the study.

Index utility: Patient preference or utility scoring allows the production of a single generic index utility score, representing a patient's health status on a continuous interval scale from 0 to 1, where 0 represents dead or unconscious and 1 is full health. With some scales utilities of below 0 are possible for states such as intractable pain and disability, considered "worse than death". This index is used in the calculation of the QALY and this common currency is the bedrock of health utility analysis. This single common unit potentially allows the meaningful optimisation of the allocation of health resources, ensuring that these resources are invested in such a way as to maximise the health gained from healthcare programmes whilst addressing the full spectrum of human disease and disability. This will be measured using two instruments. *EuroQol (EQ5D)* is an index scale mapping three available responses to five questions [62]. It is then mapped onto a utility scale of 245 possible health states derived using a time trade off tariff. EQ5D is validated [63, 64] and is the recommended utility measure for cost-effectiveness analysis in the UK [65].

Our previous work has found that EQ5D is relatively insensitive to clinically meaningful differences in the morbidity associated with the treatment of SVI [9] and so a second measure will be also be used. The SF6D is derived by mapping the responses to SF-36 on an interval utility scale containing 18,000 health states derived via the standard gamble method [66, 67].

c) Pain Visual Analogue Scale (VAS)

Patients will record their intra- and post-procedural pain on a 100mm unmarked scale. Results will be from 0 indicating "no pain at all" to 100 "the worst pain imaginable". Patients will complete this immediately following axial treatment and again following tributary treatment. They will then go on to record this in a diary, providing a daily score for the first week.

d) Analgesia use

The type and daily dosage of any analgesia taken by patients will also be recorded in the diary for the first week by the patient.

e) Bruising visual analogue scale

Patients will record their appreciation of the severity of their bruising on a 100mm unmarked scale. Results will be from 0 indicating "no bruising at all" to 100 "the most severe bruising imaginable".

f) Satisfaction visual analogue scale

Patients will record their satisfaction with treatment on a 100mm unmarked scale. Results will be from 0 indicating "not satisfied at all" to 100 "completely satisfied".

g) Cosmesis visual analogue scale

Patients will record their satisfaction with the cosmetic result from treatment on a 100mm unmarked scale. Results will be from 0 indicating “worse result imaginable” to 100 “best appearance possible”.

h) Recovery time

Patients will record in a diary the time taken to work (if employed), driving (if applicable), baseline self-care; baseline social role (e.g. role as a carer/family member); social activities (socialising with friends, hobbies, etc).

II. Clinical assessments

a) Clinical severity

Two validated objective measures will be used to assess and classify the severity of disease. The first is the clinical grading component of the CEAP (Clinical severity, Etiology, Anatomy and Pathophysiology) classification [68] ***(see Appendix 5)***, which classifies severity into 6 grades. This system clearly describes venous severity and is valuable in assessing intergroup differences; however it remains relatively insensitive to intragroup improvement or deterioration [67-72] and is therefore frequently used alongside the Venous Clinical Severity Score (VCSS) ***(see Appendix 6)*** for research purposes [67-71, 73]. The VCSS grades three components from 0-3 with increasing severity. A chart clearly describes the criteria for each grade of each component, which are then summated into a single score.

These measures will be assessed by a member of staff who is experienced in their use and with reference to the scoring charts. This individual will be blinded to the treatment allocation. It is unlikely that there will be any visual clues which violate this blinding.

b) Complications

An experienced clinician will assess participants at each time point to assess for any complications from treatment. If any treatment is required, this will be provided.

c) Surface planimetry of skin changes and complications

The surface area of any skin changes will be estimated by measurement of tracing on acetate pre-printed with 1 cm^2 grids. This will be assessed by an investigator blinded to the patient’s treatment allocation. Skin changes will include pigmentation, eczema, lipodermatosclerosis, atrophy blanche, healed venous ulceration, active venous ulceration. Any bruising or pigmentation related to the treatment or post procedural phlebitis will be considered as skin change as well. Each of these areas will be noted individually at baseline and post-procedurally.

d) Duplex ultrasound (DUS)

DUS has become the gold standard investigation of venous disease below the inguinal ligament, giving both morphological and haemodynamic information of the lower limb veins [74]. All DUS assessments will be performed by or in the supervision of an accredited sonographer with qualification either by a Postgraduate

Certification in Medical Ultrasound or Society of Vascular Technologist. Each scan will be performed and reported using a standardised protocol based upon international consensus [75, 76]. In addition the diameter of the axial vein to be treated will be measured at three points; proximal (1-2 cm from the junction with the deep vein), middle and distal. These measurements will also be used to calculate the estimated mean vein diameter.

The post-procedural DUS will assess treatment efficacy ***(see Appendix 7)***. Initial treatment success will be defined as complete target vein occlusion at 1 and/or 6 weeks. Anything else will be regarded as a technical failure. Recanalisation will be assessed at 52 weeks and is defined as blood flow within the target vein which had been treated. This will be broken down into partial <25% or full ≥25% of the length of the treated vein. Residual disease is regarded as any reflux which was also present at baseline, but not a target for ablation. Disease progression will be defined as any reflux within a vein which was not present on assessment prior to 52 weeks (baseline). In the presence of clinical recurrence, DUS will be used to map out the pattern of the recurrence as this may give insight into techniques to avoid further recurrence and aide understanding of how recurrence comes about after these novel treatments. Post-procedural DUS will also look for evidence of complications such as heat-induced thrombosis, deep vein thrombosis, haematoma and superficial thrombophlebitis.

III. Additional data

The following data will also be recorded.

a) Identification details

Identification details will be recorded on the study patient ID list held in the Trial Master File to facilitate communication between the participant and the investigation team. These can include participant name, date of birth, gender, address, phone number and unique hospital number.

b) General Practitioner details

This will be recorded to facilitate communication between the participants General Practitioner and the investigation team.

c) Medical history

A medical history (per review of the subject's medical records) will be collected during their Baseline Assessment. The participant will also be able to provide a verbal medical history if the medical records are not available or insufficient. The investigator will ensure to document any co-morbidities, known allergies and the mobility of the participant.

d) National Statistics Socio-Economic Classification (NS-SEC)

The Office for National Statistics classification system for socioeconomic class, the National Statistics Socio-Economic Classification (NS-SEC) ***(see Appendix 8)***, is internationally comparable and validated. The NS-SEC "three-class" version has been updated to four classes; "Higher managerial, administrative and professional occupation", "intermediate occupation", "routine and manual occupation" and "never worked and the long term unemployed".

e) Employment status

The participant's employment status and occupation will be recorded (employed, self-employed and retired/unemployed).

f) Abbreviated medical history and clinical examination

An abbreviated medical history and clinical examination at follow-ups is performed to determine if there are any differences compared to the baseline measurements. Any differences are to be reported in the Case Report Form (CRF). The BMI will be calculated following the measurement of height and weight.

14. Study Visits

Baseline measurements will be collected from all participants once consent is obtained and prior to randomisation. Study measurements will be taken on the day of treatment and at the 1 week, 6 week, 6 month and 1 year ***(see Appendix 9)***. At 5 and 10 years patients will also be contacted and offered further follow-up at this time.

- ### Visit 1 (Baseline Assessment)

Information collected will include:

- Identification and Demographic details
- Employment Status and Occupation
- Medical History including
    - Previous investigations and treatments
    - Co-morbidities
    - Allergies and current medications
    - Mobility
- Clinical Examination including
    - Weight and Height
    - Venous Clinical Severity Score (VCSS)
    - CEAP Classification
- Skin surface planimetry
- Duplex ultrasound assessment
- Quality of Life Measurements

- ### Visit 2 (Day of Treatment)

On the day of treatment the participant will undergo their randomised treatment as per the protocol. Technical and non-technical measurements will be recorded during this visit. Participants will also be given a 1-week Visual Analogue Scale Pain Diary and 1-week Analgesia Diary at this visit to be returned completed at visit 3 (1 week).

a) Technical treatment measurements

- Vein axis/axes treated

- Number of tributary veins treated
- Length of axial vein and average diameter of vein
- Total duration of procedure
    - Duration of allocated procedure
    - Duration of tributary treatment
- Total volume and concentration of sclerosant used

b) Non-technical treatment measurements

- Visual analogue pain score (VAS)
    - During procedure (recorded immediately following the procedure)
    - Daily pain record for 1 week post procedure (recorded each evening in a diary)
- Daily analgesia diary for 1 week post procedure (with type and number of tablets)

• Visit 3 (At 1 week post treatment)

- Collection of the 1 week VAS Pain Diary
- Collection of the 1 week Analgesia Diary
- Venous clinical severity
- Quality of Life measurements
- The number, timing and nature of any further treatment required
- Satisfaction visual analogue scale
- Cosmesis visual analogue scale
- Bruising visual analogue scale completed by the patient and evaluated by blinded assessor
- Surface planimetry
- Time to return to normal activities
- Number of primary care calls/visits related to this treatment
- Any additional secondary care costs related to this treatment (e.g. drugs to treat complications / additional clinic visits / days spent in hospital)
- Venous duplex ultrasound

- **Visits 4, 5, 6,7 and 8 (At 6 weeks, 6 months, 1 year, 5 years and 10 years post treatment)**

If patients are also assessed in the future, they will follow this protocol.

- Abbreviated medical history and clinical assessment
- Venous clinical severity
- Quality of Life measurements
- Satisfaction visual analogue scale
- Cosmesis visual analogue scale
- Time to return to normal activities
- Number of primary care calls/visits related to this treatment
- The number, timing and nature of any further treatment required
- Any additional secondary care costs related to this treatment (e.g. drugs to treat complications / additional clinic visits / days spent in hospital)
- Venous duplex ultrasound

15. Data Collection

Data for all outcomes from each participants visit will be assimilated into the participants unique Case Report Form (CRF) and anonymised Microsoft Access Database to allow further analyses. CRF folders will be kept in a secure location with access available immediately in case of emergency.

16. Statistical Analysis

Analysis will be intention-to-treat (ITT) and will be conducted using 2-sided significance tests with a 5% significance threshold. A multilevel model will be fitted to the data for each of the outcomes where patients will be treated as random effects (to allow for the clustering of data within each patient). These models will adjust for time, baseline score, treatment group and the interaction between treatment and time (to assess whether any difference between treatment groups changing over time) and other important covariates. Different covariance patterns for the repeated measurements will be explored and the most appropriate pattern will be used for the final model. Model assumptions will be checked and if they are in doubt the data will be transformed prior to analysis or alternative non-parametric analysis methods will be used. The difference between treatment groups and where appropriate corresponding 95% confidence interval (CI) will be presented as well as the estimated difference in means between groups at each time-point. Similar models will be developed for the secondary outcome measures.

17. Interim Analysis

An interim analysis may be done for safety, efficacy or futility reasons to indicate whether the study should be continued, modified or stopped. The analysis should be conducted by suitably qualified personnel with

no involvement in the conduct of the trial or the final analysis. The investigator team will be informed whether the study should continue, be modified or stopped but should remain blind to the interim analysis results. The Sponsor (HEY R&D) will be sent a copy of the data prior to analysis and will be provided with a copy of the analysis report as well as the decision to continue, modify or stop the study. A substantial amendment will be submitted if the study is to be modified.

18. Economic Evaluation

This will be performed independently of the clinical team and follow published NICE recommendations.

- ### Within trial analysis

The total number of QALYs per patient will be estimated using an area under the curve technique. Resource use will be collected prospectively for each individual patient allowing a ratio of cost per QALY to be estimated for the duration of the trial for each treatment. Following this a Markov model will be constructed.

- ### Model design and assumptions

The analysis will be performed from the perspective of the NHS, and is based upon the management of symptomatic patients with primary unilateral great saphenous vein (GSV) reflux. Markov models will be constructed to compare costs and QALYs for the current treatment strategies performed in the NHS within the NICE guidelines and the experimental treatment. This includes no treatment, conservative treatment with compression, open surgery under GA (in both inpatient and day-case settings), open surgery under GA, EVLA under LA, radiofrequency ablation (RFA) under LA, foam sclerotherapy and MOCA. Endothermal ablation and MOCA will be assessed in association with a policy of concomitant and sequential treatment of tributaries. Time horizons of 5 and 10 years will be studied.

The structure of the model will account for the likelihood of initial technical success, the recurrence rate (by year 1 and 5), and the requirement for secondary procedures (by month 6, year 1 and 5) and the probability of disease progression. Secondary procedures can be for treatment of residual tributaries (with foam sclerotherapy or phlebectomy) or for the axis itself. Secondary procedures are assumed to have the same probability of success as a primary procedure.

Time preference will be represented by the discounting of both costs and QALYs by 3.5% per annum.

- ### Parameter estimation

The probabilities of events and estimated index QoL associated with each state will be estimated from this RCT along with a systematic review of the highest levels of evidence available in the literature [78, 79]. The costs associated with each state and transition will be estimated from NHS healthcare resource group (HRG) reference costs, supplemented by additional information from this RCT, systematic review of the literature, device manufacturers and published list prices.

- ### Economic analysis

The uncertainty in the mean value of each parameter will be represented using a probability distribution and the model analysed by running 1000 Monte Carlo simulations. The mean costs and QALYs will be reported for each strategy by model and their cost-effectiveness compared by estimation of incremental cost-

effectiveness ratios (ICERs) using standard decision rules [80]. Secondly the decision uncertainly will be represented as the probability that each intervention was the most cost-effective for a given cost-effectiveness threshold using a cost-effectiveness acceptability curve [81]. Finally a value of information analysis will be used to produce estimates for the expected value of perfect information regarding the model structure and parameters. This will be used to prioritise future research efforts and funding targeting the topics which will have the largest benefit for patients and the NHS.

19. Benefits of the Research

Our Public and Patient Involvement (PPI) group and patients report that one of the major burdens associated with treatment is the discomfort during injections of tumescent anaesthesia (TA). This trial will establish whether a newer technology results in less discomfort by avoiding additional injections of TA, whilst offering similarly high success rates in the longer term as the current gold standard. An economic analysis will also establish which of these differing technologies is the most cost-effective, allowing the trial to inform decision-making discussions between surgeons and their patients, and also strategic decision-making in the NHS, where the optimal allocation of resources must be considered in order to maximise the patient and societal benefit from our health service.

20. Risk, Burden and Benefits of Participation

Patients will undergo EVLA as per routine, planned NHS care; the protocol will not deviate from that which they would receive during usual NHS treatment. EVLA is proven to be a safe and effective technique.

Sodium Tetradecyl Sulphate (STS) (also known as STD injection, marketed as Fibrovein™, STD pharmaceutical Products, UK) is licensed for use in the UK as both a liquid and a foam preparation in the treatment of varicose veins. There have been “no new or unexpected concerns” and it was judged that the benefit-to-risk ratio be positive; hence Marketing Authorisations have been granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2012 [82]. Further information is provided in the SmPC.

The data on risks associated with the MOCA ClariVein® device, which employs liquid sclerotherapy, is limited but the published safety trial found no evidence of any major complication (deep vein thrombosis, skin necrosis, infection or hyperpigmentation) at 1 year. The only complication recorded were localised ecchymosis (12%), induration around the access site (12%) and transient superficial thrombophlebitis of the treated vein (14%) and pain lasting more than one week (10%) [14, 15, 83]. A NICE review of this interventional procedure approved its use in the context of a clinical trial such as this [84].

The treatments will not differ from what NHS patients outside of the trial could expect; the only difference in the patient pathway will be randomisation to a treatment group and more intensive clinical and ultrasound follow up. Although this follow up does place an additional burden upon patients there are also benefits including ease of access to professional advice and expertise over the phone and in specialist clinics staffed by experienced endovenous surgeons. These services have proven very popular in previous studies and have been highlighted as an advantage by participant groups from our previous studies.

21. Trial Timescales

At the current rate of patients presenting to the unit, relatively wide inclusion criteria and experience from previous trials of this nature, it is anticipated that the recruitment and treatment phase would be complete within approximately 12 months. The primary end point is measured at 1 year and therefore completion of data collection is anticipated in approximately 24 months, follow up data collection carried at 5 and 10 years will be completed by August 2030.

22. Safety Assessments

Participants will undergo more intensive clinical and ultrasound follow up than would be routinely offered to NHS patients, in addition to having ease of access to professional advice over the phone and specialist clinics staffed by experienced endovenous surgeons.

23. Safety Reporting

- ### Definitions

Adverse Events (AE) - An adverse event is any untoward medical occurrence in a subject whom a medicinal product has been administered, or a procedure performed, as part of a research study, including occurrences which are not necessarily caused by or related to that investigational medicinal product (IMP).

Adverse Reaction (AR) – An adverse reaction is any untoward and unintended response in a subject to an IMP.

Serious Adverse Event (SAE) – An adverse event becomes serious if it:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in significant or persisting disability or incapacity
- Is a congenital anomaly or birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

SAE is not related or unlikely to be related to the IMP.

Serious Adverse Reaction (SAR) – A serious event which is suspected (possibly, probably or definitely) to be related to an IMP and expected for the IMP.

Suspected Unexpected Serious Adverse Reaction (SUSAR) – A SUSAR is a serious event which is suspected (possibly, probably or definitely) to be related to an IMP, i.e. not previously documented in any of the IMP information (Investigator Brochure, Summary of Product Characteristics, Product Information Leaflet) or protocol.

- ## Reporting adverse events

Adverse events will be reported in accordance with Hull and East Yorkshire Hospitals NHS Trust Research and Development (HEY R&D) department's Safety Reporting standard operating procedure (R&D GCP SOP 07) to ensure compliance with UK Clinical Trial Regulations.

- ## Reporting period of adverse events

The **AE reporting period** for this trial **begins as soon as patients have consented to the trial** and **ends 30 days** after the patient's treatment visit (Visit 2).

The health status of subjects will be checked at each study visit. The investigator will record all directly observed AE and all AE spontaneously reported by the trial subject. A pre-existing condition is a disorder present prior to the patient entering the trial and does not need to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period. Pre-existing condition will be documented at the screening or baseline study visit.

All AE (serious and non-serious) will be recorded by the investigator in patients' Case Report Forms (CRFs) using R&D's adverse event report form. All adverse events will be recorded by the investigator in patients' medical records/notes. All AE will be followed-up by investigators until the event has resolved or a decision has been taken for no further follow-up. If a clinically significant abnormal laboratory value occurs, this abnormality will be recorded as an adverse event/reaction.

- ## Reporting serious adverse events

Investigators will notify the sponsor (HEY R&D department) of serious adverse events **within 24hours** of becoming aware of the event using the *Serious Event Initial and Follow-up report forms* provided by HEY R&D. The sponsor (HEY R&D department) will report fatal or life-threatening SUSARs to the MHRA within 7 days and follow-up information in a further 8 days. The sponsor will send all other SUSAR reports to the MHRA within a maximum of 15 days. The investigator will report fatal or life-threatening SUSARs to the *Research Ethics Committee (REC)* within 7 days and follow-up information within a further 8 days by following the request on the *Serious Event Initial and Follow up report forms*. The investigator will send all other SUSAR reports to the *REC* within a maximum of 15days.

Any planned surgery and planned hospital admissions prior to consent will not be reported as SAE within 24hours to HEY R&D on the initial SAE form but will still need to be reported on HEY R&D's AE report form.

All SAE that do not require reporting to the HEY R&D will still be reported annually on the *Development Safety Update Report (DSUR)*.

- ## Annual safety reports

Investigators will submit a *Development Safety Update Report (DSUR)* to the MHRA 12 moths after the date of the MHRA clinical trial authorisation and thereafter until the end of the study according to the MHRA website and using HEY R&D's *DSUR form*.

- ### Urgent safety measures (refer to R&D GCP SOP 09)

The investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. These safety measures should be taken immediately and may be taken without prior authorisation from the MHRA, REC, or Trust.

The investigator must alert the sponsor (HEY R&D) as soon as possible of the urgent measures by contacting the R&D office telephone number 461883 or 461903 *(Mon-Fri 8am-6pm)* or the Trust Switchboard 875875 (out-of-office hours) and asking for either the *R&D Director* or the *R&D Manager*. The investigator or sponsor should phone the *Clinical Trial Unit* at the MHRA and discuss the issue with a medical advisor as soon as possible. Contact the *MHRA CTU* via the MHRA Central Enquiry Point on 020 3080 6456 *(weekdays 08:30-16:30)*.

The MHRA, main REC and Trust should be notified by the investigator within 3 days after the urgent measures have been taken by submitting a *Notification of Amendment form*. This form should be sent with a covering letter detailing; the measures taken, the reason for them and the medical assessor contacted, and any supporting documentation.

24. Withdrawal of Participants

Participants will be withdrawn from the study at any stage if they fulfil any of the withdrawal criteria; without prejudice to their rights to receive other appropriate treatment for their disease or follow-up. The study is powered to allow for a 10% drop out/loss to follow-up.

25. Quality Control and Quality Assurance

- ### Monitoring

The study will be monitored in accordance with HEY R&D department's standard operating procedures to ensure compliance with UK Clinical Trial Regulations. All trial related documents will be made available upon request for monitoring by HEY R&D monitors and for inspection by the MHRA.

- ### Ethics, MHRA and R&D approval

The study will be performed subject to favourable Research Ethics Committee opinion, MHRA clinical trial authorisation (CTA), and HEY Trust R&D approval.

- ### Research governance

This study will be conducted in accordance with the *Medicine for Human Use Regulations* 2004 and *Amendment Regulations* 2006 and subsequent amendments; the *International Conference for Harmonisation of Good Clinical Practice* (ICH GCP) guidelines; and the *Research Governance Framework for Health and Social Care* 2005.

- ## Data handling and Record keeping

The Principal Investigator will be responsible for data collection, recording and quality. Data will be collected and retained in accordance with the *Data Protection Act* 1998. As a minimum, the following information will be recorded in patients' Case Report Forms for study visits or telephone contacts:

- Clearly written date of visit or contact, brief study title/acronym and visit number
- Date patient given *Patient Information Sheet*
- Date *Consent Form* signed
- Date of screening
- Medical history, concomitant diseases and medication including study medication, and any changes in concomitant diseases and medication at subsequent visits
- Anything which is relevant to the ongoing care of the subject;
    - Relevant results and study doctor's assessment of these results
    - Brief description of any AEs with start and stop times/dates and any significant test results or a medical summary of events if more appropriate
- Any other relevant information

Electronic data will be stored on a Trust computer within the Vascular Laboratory. The IT Services Department has a backup procedure approved by auditors for disaster recovery. Servers are backed up to disk media each night. The disks run on a 4 week cycle. Files stay on the server unless deleted by accident or deliberately. Anything deleted more than 4 weeks previously is therefore lost. Additional 'archive' backups are taken for archived data, so data should not be lost from this type of system e.g. File Vision which stores Medical Records. Disks are stored in a fireproof safe.

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All essential documents including source documents will be retained for a minimum period of 5 years after study completion (last visit of the last patient). A label stating the date after which the documents can be destroyed will be placed inside the front cover of case notes of trial participants.

- ## Access to source data

The investigators and institution will permit monitoring, audits, REC and MHRA review where applicable and provide direct access to source data and documents.

- ## Protocol deviation / serious breaches

All deviations from the protocol or GCP will be reported by investigators to HEY R&D (as sponsor). HEY R&D monitor will record deviations on the *Protocol Deviation Form* for the trial. A serious breach is likely to affect to a significant degree either the safety or physical or mental integrity of a trial subject or the scientific value of the trial. Major deviations or serious breaches will be reported by investigators to HEY R&D by telephone (tel.461883) or in person **within 24 hours** of the deviation or breach being identified. HEY R&D will notify the MHRA **within 7 days** of becoming aware of a serious breach. Investigators will take into account all protocol deviations and any serious breaches in the final study analysis and publications.

- ## End of trial

This is defined as the Last Patient Last Visit (LPLV) completing their 1 year follow-up assessment.

The end of trial declaration form will be submitted to the MHRA, REC and HEY R&D **within 90 days** from completion of the trial and **within 15 days** if the trial is discontinued prematurely. A summary of the trial final report/publication will be submitted to the MHRA, REC and HEY R&D **within 1 year** of the end of trial. HEY R&D will be notified immediately of any reason to halt the trial. The Chief/Principle investigator and HEY R&D as sponsor will decide if the trial should be halted temporarily. The MHRA, REC and HEY R&D will be notified **within 15 days** of a decision to temporarily halt the trial by submitting a substantial amendment notification.

- ## Finance

The study is funded through the Academic Vascular Surgical Unit at Hull Royal Infirmary. Participants will not receive any financial incentive to take part in this study.

- ## Indemnity

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contract only when the trial has been approved by the HEY Trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. The University of Hull has an insurance policy that includes cover for no-fault compensation in respect of accidental injury to a research subject.

- ## Reporting and dissemination

The trial will be prospectively registered on a freely accessible trial registry. The results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement (www.consort-statement.org) in high impact factor peer-reviewed journals and presented at national and international meeting of learned societies.

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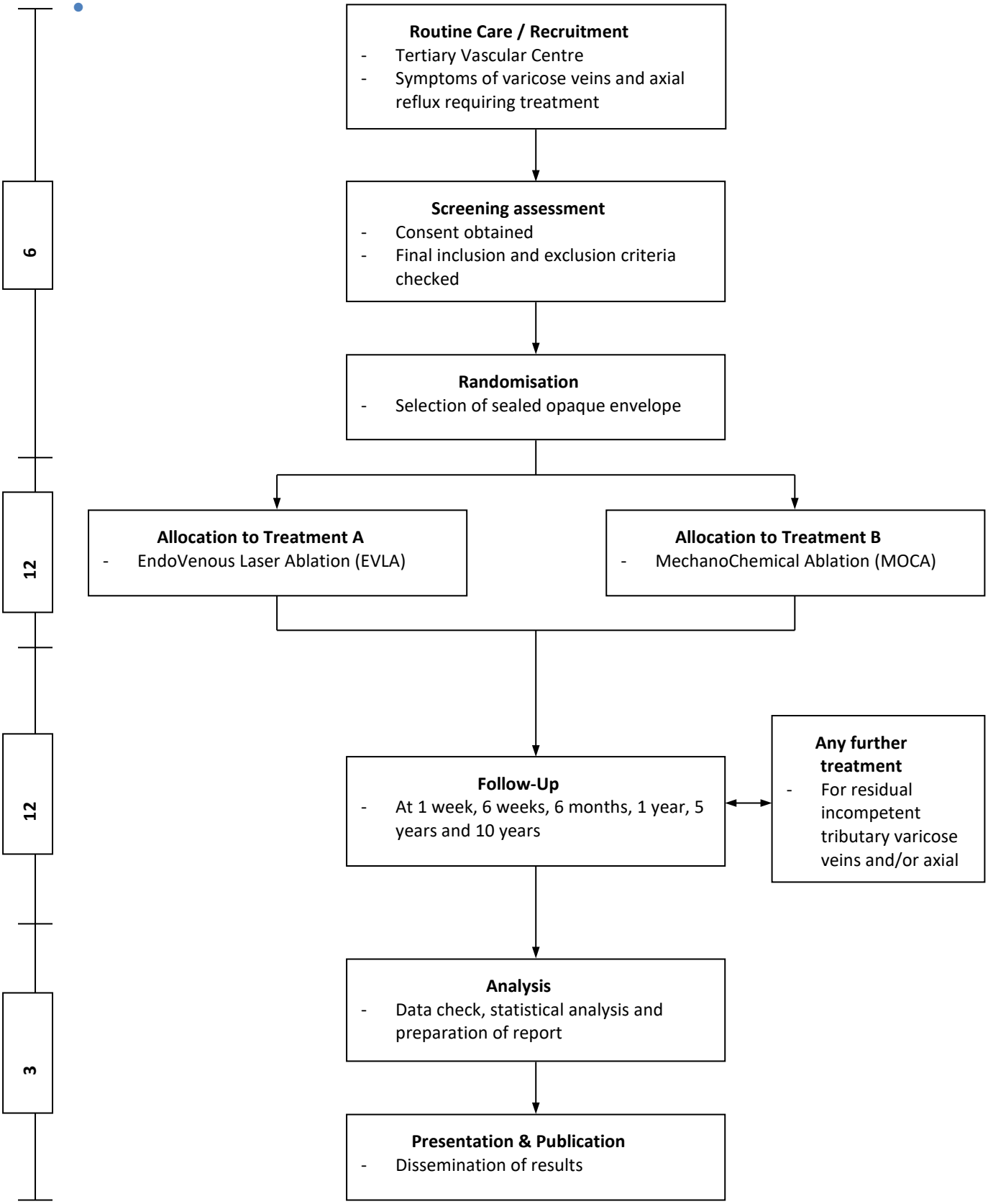
Appendix 1: Study Flow Chart



- **Appendix 2: Clinical severity, Etiology, Anatomy and Pathophysiology (CEAP) Classification**

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

- ## Appendix 3: Venous Clinical Severity Score (VCSS)

	None: 0	*Mild: 1*	*Moderate: 2*	*Severe: 3*
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin		Occasional pain or other discomfort (ie, not restricting regular daily activities)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)
Varicose veins "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position.		Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

- ## Appendix 4: National Statistics Socio-Economic Classification (NS-SEC)

Eight-, five- and three- class versions

eight classes	five classes	three classes
1. Higher managerial, administrative and professional occupations 1.1 Large employers and higher managerial and administrative occupations 1.2 Higher professional occupations 2. Lower managerial, administrative and professional occupations	1. Higher managerial, administrative and professional occupations	1. Higher managerial, administrative and professional occupations
3. Intermediate occupations	2. Intermediate occupations	2. Intermediate occupations
4. Small employers and own account workers	3. Small employers and own account workers	
5. Lower supervisory and technical occupations	4. Lower supervisory and technical occupations	3. Routine and manual occupations
6. Semi-routine occupations	5. Semi-routine and routine occupations	
7. Routine occupations		
8. Never worked and long-term unemployed	*Never worked and long-term unemployed	*Never worked and long-term unemployed

*Presentation of 'Never worked and long-term unemployed' altered on Table 3 in the five- and three-class versions. This corresponds more closely to the cautionary notes in 7.2. Revised 14.01.04.

• Appendix 5: Schedule of Assessments

Visits	1	2	3	4	5	6		
Procedures	Screening, Eligibility, Baseline assessment & Randomisation	Treatment	1 Week Follow Up	6 Weeks Follow Up	6 Months Follow Up	1 Year Follow Up	5 year follow up	10 year follow up
Medication history	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
NS-SEC	X							
Employment status	X							
Informed consent	X							
CEAP	X		X	X	X	X	X	X
VCSS	X		X	X	X	X	X	X
AVVQ	X		X	X	X	X	X	X
CIVIQ-20	X		X	X	X	X	X	X
VEINES-QOL/Sym	X		X	X	X	X	X	X
SF-36	X		X	X	X	X	X	X
EQ5D	X		X	X	X	X	X	X
DUS	X		X	X	X	X	X	X
Surface planimetry	X		X	X	X	X	X	X
Pain VAS		X	X	X	X	X	X	X
Analgesia diary			X	X	X	X	X	X
Satisfaction VAS			X	X	X	X	X	X
Cosmesis VAS			X	X	X	X	X	X
Recovery time			X	X	X	X	X	X
Complications			X	X	X	X	X	X

NS-SEC = National Statistics Socio-Economic Classification, CEAP = Clinical severity, Etiology, Anatomy and Pathophysiology, VCSS = Venous Clinical Severity Score, AVVQ = Aberdeen Varicose Vein Questionnaire, CIVIQ-20 = Chronic Venous Insufficiency Questionnaire, VEINES-QOL/Sym = VEnous INsufficiency Epidemiological and Economic Study, SF-36 = Short Form 36, EQ5D = EuroQol, DUS = Duplex ultrasound, VAS = Visual Analogue Scale