

OUTCOMES OF PATIENTS WITH VARICOSE VEINS

Thesis submitted to Imperial College London for the degree of Doctor of Philosophy

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INSPIRATION

"Everyone shines, given the right lighting"

Susan Cain

Quiet: The Power of Introverts in a World that Can't Stop Talking

ABSTRACT

Introduction

Varicose vein disease is a common ailment affecting the population. It is associated with causing an adverse effect on the quality of life of patients, with treatment of the condition known to improve it. The introduction of endovenous ablation has enabled the cost-effective treatment of the condition with procedures being carried out as day cases with an earlier return to normal activities. However, with healthcare expenditure increasingly under scrutiny, newer pathways are needed to continue the evolution of varicose vein management.

Aim

1. To explore and compare the current and newer endovenous methods of treatment
2. To assess patients' views of the current management of the condition
3. To evaluate a new referral and treatment pathway of varicose vein disease
4. To assess possible improvement in the post-procedural management of varicose veins

Methods

1. A randomised controlled trial was conducted to compare radiofrequency ablation to mechanochemical ablation as well as a pilot study evaluating the use of a new cyanoacrylate adhesive sealing system. In addition, a systematic review and cost-effectiveness analysis was undertaken to evaluate the newer endovenous ablation methods.
2. A patient survey was carried out to understand the reasons for their referral as well as exploring a new management pathway.
3. A pilot study was undertaken to evaluate the feasibility of a One Stop Vein Clinic, offering same day diagnosis and treatment.
4. A randomised controlled trial comparing the use of compression stockings following endovenous ablation.

Results

1. (a) With 170 patients recruited, the randomised controlled trial comparing radiofrequency and mechanochemical ablation shows that pain score during the procedure was less with the latter method, and that there were no other major differences between the two techniques.

(b) This pilot study of 20 patients in the use of the new cyanoacrylate demonstrates that it is a safe and effective method, though a larger study would be able to provide further evidence of efficacy.

(c) The systematic review shows that surgery and the endothermal methods seem to have lower re-intervention rates compared to foam sclerotherapy. However, a lack of comparative studies involving the non-thermal techniques meant that this analysis was unable to provide sufficient evidence as to their re-intervention rates and cost-effectiveness.
2. The patient survey of 106 patients revealed that they favoured less waiting time between appointments and their treatment. A high proportion of patients were also keen on attending a One Stop Clinic.
3. The early results of this pilot study of One Stop Vein Clinic shows that patients waited on average 4 weeks from being referred by their GP, but this study was hampered by unavailability of the treatment room for long periods and reduced possibility to add patients to the veins lists.
4. One hundred and nine patients have been recruited to the randomised controlled trial of the use of compression stockings. This shows that patients in the compression group had significantly less discomfort in the first few days following treatment, but there were no major differences by 2 weeks.

Conclusions

This work illustrates that varicose vein treatment is fast evolving. The newer technologies show promise, but currently, there is insufficient evidence to demonstrate their superiority over conventional endothermal methods. The One Stop Vein Clinic also shows potential, but may be difficult to incorporate into current practice without clear protocols between the different departments. The use of compression stockings following endothermal ablation indicates that it might be advantageous in the first few days, but may not necessarily have a long-term benefit.

STATEMENT OF ORIGINALITY

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Roshan Bootun

14th April 2017

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LIST OF ABBREVIATIONS

ABPI	Ankle-brachial pressure index
ARV	Abdominal rectus vein
AVF	American Venous Forum
AMD	Age-related macular degeneration
ASA	American Society of Anesthesiologists
AVM	Arterio-venous malformation
AVULS	Ambulatory Varicosity avUlsion Later or Synchronised
AVVQ	Aberdeen Varicose Vein Questionnaire
BCA	Butyl cyanoacrylate
BMI	Body mass index
CA	Cyanoacrylate
CAE	Cyanoacrylate adhesive
CEAP	Clinical-Etiological-Anatomical-Pathophysiological Classification
CFV	Common femoral vein
CDFS	Catheter-directed foam sclerotherapy
CIVIQ	Chronic venous insufficiency questionnaire
CLASS	Comparison of LAser, Surgery and foam Sclerotherapy
COMETA	COMpression following Endovenous Thermal Ablation
CONS	Conservative
CONSORT	Consolidated Standards of Reporting Trials
CTS	Carpal tunnel syndrome
DVT	Deep vein thrombosis
EHIT	Endovenous heat-induced thrombosis
ESVS	European Society of Vascular Surgery
EVLA	Endovenous laser ablation
EVLV	Endovenous laser therapy
EVOLVeS	Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping
EQ-5D	EuroQoL's 5 domain score
GMC	General Medical Council
GP	General practitioner
GSV	Great saphenous vein
HRQoL	Health-related quality of life

HL/S	High ligation and stripping
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
IASA	Interatrial septal aneurysm
LAVVU	Local Anaesthetic Varicose Vein Unit
MARADONA	Mechanochemical endovenous Ablation versus RADiOfrequeNcy Ablation
MPS	Medical Protection Society
MOCA	Mechanochemical ablation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NRES	National Research Ethics Service
NTNT	Non-thermal, non-tumescent technique
PE	Pulmonary embolus
PFO	Patent foramen ovale
POL	Polidocanol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
QoL	Quality of life
QALY	Quality of life years
RCT	Randomised controlled trial
REC	Research and Ethics Committee
REVAS	Recurrent Varices after Surgery
RFA	Radiofrequency ablation
REACTIV	Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins
RTT	Referral to treatment
QALY	Quality-adjusted life year
SCS	Saphen Closure System
SD	Standard deviation
SEV	Superficial epigastric vein
SFJ	Sapheno-femoral junction
SF-12	Short Form-12 questionnaire
SPJ	Sapheno-popliteal junction

SSV	Short saphenous vein
STS	Sodium tetradecyl sulphate
SVS	Steam vein sclerosis
TED	Thrombo-Embolic Disease stockings
TEP	Total extraperitoneal repair
TIA	Transient ischaemic attack
UGS	Ultrasound-guided sclerotherapy
UGFS	Ultrasound-guided foam sclerotherapy
UK	United Kingdom
USA	United States of America
VAS	Visual-analogue scale
VCSS	Venous clinical severity score
VDS	Venous disability score
VTE	Venous thromboembolism
VVCVV	VNUS Versus Clarivein for Varicose Veins

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CHAPTER 1

VARICOSE VEINS

CHAPTER 1. VARICOSE VEINS

1.1 Varicose veins

Varicose veins are a common affliction of the general population (Bergan, 2007; Robertson et al., 2008). Usually defined as dilated palpable subcutaneous veins with a diameter greater than 3mm, they have a poorly understood aetiology and cause a variety of symptoms (Meissner et al., 2007b). Varicose veins are the commonly recognised part of the chronic venous disease spectrum.

1.1.1 Anatomy

The venous system is an essential part of the human body. Its main purpose is in allowing return of blood from the capillary bed to the heart as well as maintaining haemostasis through changes in capacitance (the relationship between pressure and volume at a given smooth muscle tone in the venous system) (Cronenwett and Johnston, 2010). This process of venous return is aided by the interactions of pressure gradients, muscle pumps and valves (Cronenwett and Johnston, 2010). The recognised muscle pumps in the lower limbs are found in the thigh, calf and plantar aspects of the foot (Cronenwett and Johnston, 2010). They forcefully propel blood from the intramuscular and surrounding veins to the heart. The calf muscle pump has been demonstrated to play a bigger role than the thigh muscles in expelling blood, being able to expel up to 65% of the blood that enter the calf (Cronenwett and Johnston, 2010). This pump is composed of soleal and gastrocnemius muscles, their intramuscular venous sinusoids and superficial and deep veins.

Varicose veins occur in the superficial veins of the legs. The deep and superficial veins are recognised by the fascial compartments they run in, namely, the deep and superficial compartments (Gray, 1918; Bergan, 2007). These compartments are separated in the lower limb by fascial layers.

The superficial compartment consists of all tissues between the skin and the fascia, while the deep compartment includes all the tissues between the fascia and the bones (Bergan, 2007). The superficial veins run in the superficial compartment and deep veins run in the deep compartment. The deep veins are responsible for most of

the venous return of the lower limbs(Bergan, 2007). The two major superficial veins of the lower limb are the great saphenous vein (GSV) and the small saphenous vein (SSV)(Moore and Dalley, 1999).

The GSV takes its origin from the dorsal veins of the foot(Moore and Dalley, 1999; Bergan, 2007) (Figure 1.a.). Lying in the saphenous compartment (part of the superficial compartment), the GSV then ascends anterior to the medial malleolus of the ankle, passing in the medial aspect of the popliteal space and through the anteromedial thigh ends up in the common femoral vein, just below the inguinal ligament(Bergan, 2007).

The SSV starts at the lateral aspect of the foot from the union of the dorsal vein of the fifth toe with the dorsal venous arch and travels subcutaneously behind the lateral malleolus at the ankle(Moore and Dalley, 1999; Bergan, 2007). After ascending in the calf, it enters the deep fascia and goes through the heads of the gastrocnemius muscle to finally empty into the popliteal vein in the popliteal fossa(Moore and Dalley, 1999; Bergan, 2007) (Figure 1.b.).

A third system of veins, the perforating veins, pierce through fascia and connect the superficial and deep systems of veins(Bergan, 2007).

Muscle contraction gives rise to higher pressures within the deep venous system than in the superficial system, but blood is prevented from refluxing to the superficial system by a system of venous valves within the perforating veins(Cronenwett and Johnston, 2010). These venous valves produce a one-way system, preventing retrograde flow of blood, and are found in higher concentration in the lower limb(Cronenwett and Johnston, 2010).

1.1.2 Epidemiology

The prevalence of varicose veins has been estimated to be 10-40% for men and 28-51% for women(Abramson et al., 1981; Maffei et al., 1986; Laurikka et al., 1993; Evans et al., 1999; Criqui et al., 2003; Carpentier et al., 2004)(see Table 1).

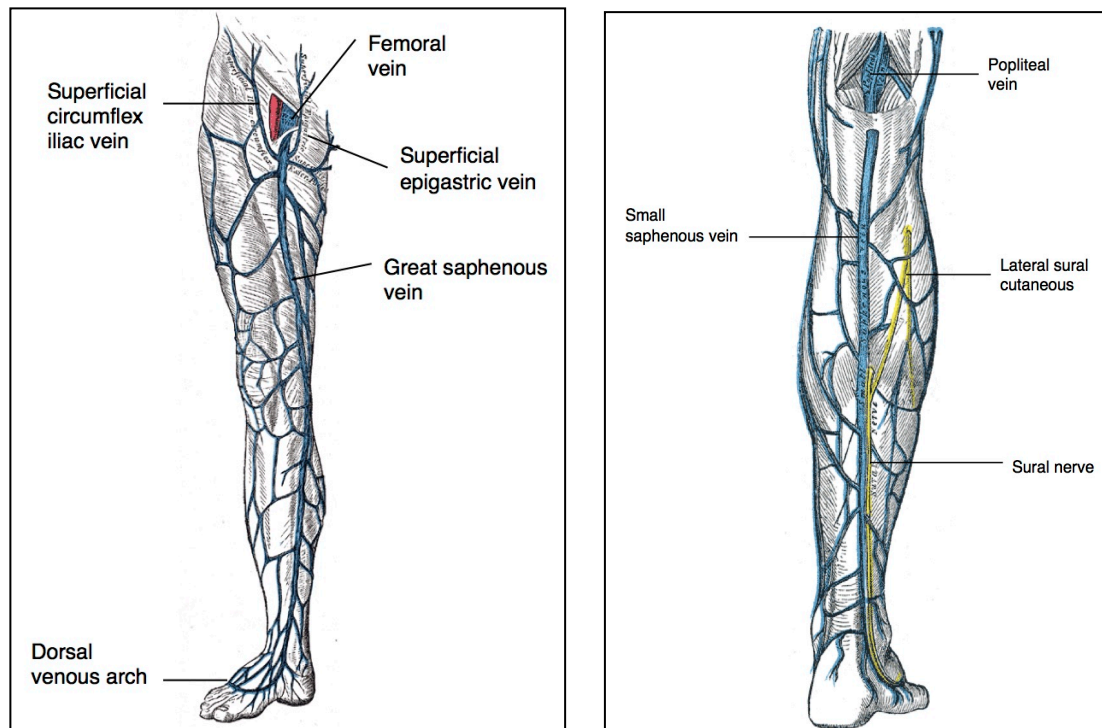


Figure 1. Superficial veins of the lower limb. a. The right great saphenous vein and its tributaries. b. The short saphenous vein and its relations to the sural nerve. (adapted from *Anatomy of the Human Body* by H. Gray(Gray, 1918)).

Table 1 illustrates a number of variations in the age groups, populations selected, study methodology, definition used and diagnostic method used. Except for the studies by Abramson et al. (1981) and Maffei et al. (1986), which had the same age criteria for including patients (above 15 years of age)(Abramson et al., 1981; Maffei et al., 1986), other studies used a variety of other age ranges. Callam (1994) indicated that the prevalence of the condition increases with age(Callam, 1994). It could, therefore, be postulated that studies which include patients from a younger age would tend to underestimate the prevalence (less patients with the condition in the population), while studies with an older lower age limit would be overestimating the prevalence (more patients with the condition in their population). However, from Table 1, it is noted that this expected state of affairs is not actually observed.

Another issue is the heterogeneity of the populations involved. For example, some studies selected patients attending the hospital outpatient clinics(Maffei et al., 1986), while others would use random sections of residents or university staff(Evans et al., 1999; Criqui et al., 2003).

A number of different methods are also used to gather data, with some studies opting for objective assessments by the clinical team, while others preferred using self-assessments. Self-reporting carries the risk of introducing inaccuracies in the calculation of prevalence (e.g., underestimation with patients with asymptomatic varicose veins at the back of the leg)(Beebe-Dimmer et al., 2005). Furthermore, variable definition of varicose veins and different methods of assessment (e.g., use of duplex scanning) also renders it difficult to determine the accuracy of estimates of prevalence.

All these observed discrepancies result in uncertainty as to the real prevalence of varicose veins(Callam, 1994). Indeed, after analysing 24 different studies looking at the prevalence of the condition, Callam (1994) found a prevalence rate of 0.6-56% in males and 0.1-73% in females. This author also noted that factors giving rise to a high prevalence were age range, varicose vein definition, method of assessment and sample used, while factors contributing to a low prevalence included age range and ethnicity(Callam, 1994). After controlling for these factors, Callam (1994) estimated that the prevalence of visible varicose veins in an unselected Western population over the age of 15 years is 10-15% for males and 20-25% for females.

1.1.3 Pathogenesis

The pathogenesis of varicose vein disease is unclear. Venous blood flow in the lower limbs is aided by contraction of skeletal muscles, with valves ensuring that the flow is unidirectional towards the heart and against gravity. In patients with varicose veins, this flow is interrupted, leading to blood stasis and reflux(Lim and Davies, 2009).

The conventional hypothesis for the development of primary varicose veins has been that valvular incompetence causing venous reflux is the initial event leading to vein wall weakness and dilatation(Lim and Davies, 2009). Indeed, blood stasis and reflux gives rise to venous hypertension, which leads to ischaemia, injury and inflammation of the vein wall, surrounding tissues and skin(Lim and Davies, 2009). This ultimately causes the signs and symptoms of varicose veins.

Study	Year	No. of subjects	Prevalence (%)			Age Range (years)	Country	Methods	Definition of varicose veins
			Men	Women	Total				
Abramson et al.	1981	4888	10.4	29.5	-	>15	Israel	Community health survey - Interview at home followed by examination by physician, using standardised criteria	Distended and tortuous subcutaneous veins
	1986	1755	37.9	50.9	47.6	>15	Brazil	Patients attending local hospital - Questionnaire filled by social worker, then clinical examination	Dilated, tortuous, elongated subcutaneous veins
Laurikka et al.	1993	6874	18	42	-	>40	Finland	All city resident born in 1929, 1939 and 1949 - Questionnaire sent in 1989 asking if they had ever had varicose veins (self-reporting)	Clearly visible, dilated, tortuous, and possibly prominent subcutaneous veins
Evans et al.	1999	1566	39.7	32.2	-	18-64	United Kingdom	Random sample of city residents - self-completed questionnaire and examination by a member of the research team	Trunk varices: dilated, tortuous trunks of saphena magna or parva vein and their branches of the first and second order Reticular varices: dilated, tortuous subcutaneous veins not belonging to the main trunk or its major branches
Criqui et al.	2003	2211	15.0	27.7	23.3	40-79	USA	Random selection of current and retired university employees - medical questionnaire - Duplex examination	(No definition of varicose veins provided)
Carpentier et al.	2004	835	30.1	50.5	-	>18	France	Random population sample - phone and medical interview, then clinical examination	Enlarged, tortuous, subcutaneous veins, either visible or palpable clinically

Table 1. Selected studies of the prevalence of varicose veins. This table demonstrates the variability in the criteria used to determine a prevalence level.

New evidence suggesting that vein wall weakness may actually precede valvular incompetence has emerged recently, casting doubt over this theory (Abu-Own et al., 1994; Lim and Davies, 2009). This would similarly result in blood stasis and reflux giving rise to venous hypertension, which, in the end, produces the features commonly associated with varicose veins. The presence of venous reflux below competent valves adds strength to this hypothesis (Abu-Own et al., 1994).

Regardless of the initial cause of blood reflux, a number of cellular mechanisms are thought to interact with each other with the formation of varicose veins as the end result. This is depicted in Figure 2 below.

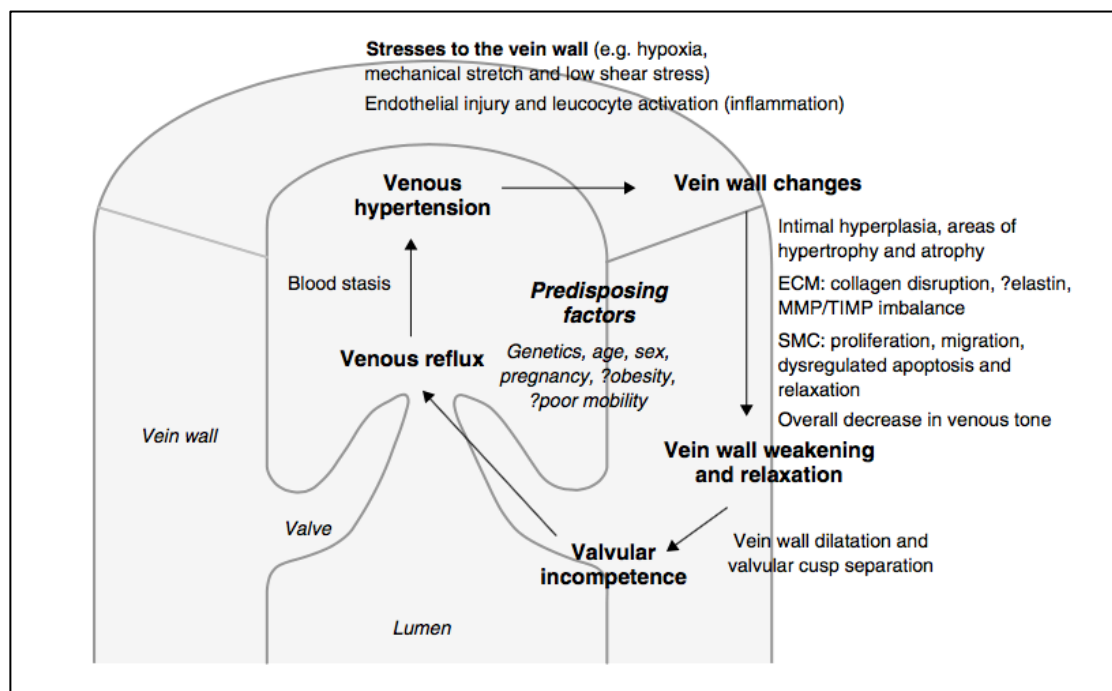


Figure 2. Cellular mechanisms believed to contribute to varicose vein formation (ECM: extracellular matrix; MMP: matrix metalloproteinase; SMC: smooth muscle cell; TIMP: tissue inhibitor of metalloproteinase) (from Lim and Davies, 2009)

Commonly postulated causes for primary varicosis include family history, increasing age, pregnancy, sex, obesity and decreased mobility (Laurikka et al., 2002; Carpentier et al., 2004; Beebe-Dimmer et al., 2005; Robertson et al., 2008). Family history confers a higher risk of developing varicose veins, with a risk as high as 90% if both parents are affected (Cornu-Thenard et al., 1994). When one parent is affected, the risk falls to 25% for males and 62% for females (Cornu-Thenard et al., 1994). A number of related conditions and candidate genes have also been identified

which could provide further insight into the pathogenesis of the condition (see Table 2 and 3 below)(Lim and Davies, 2009; Anwar et al., 2012a; Krysa et al., 2012). Research is, however, still ongoing to determine the exact mechanism leading to the development of varicose vein disease.

Conditions With Chromosomal Defects	Conditions With Gene Mutations or Defects	Single Nucleotide Polymorphism or Gene Mutations
Klippel-Trenaunay syndrome (translocation 8:14, 5:11)	Ehlers-Danlos syndrome (<i>COL3A1</i> gene)	Thrombomodulin
Clonal trisomies (7, 12 and 18) or monosomies (14)	Chuvash polycythemia (Von-Hippel Lindau gene)	Notch3 mutation in pedigree of CADASIL (1279GT)
	Lymphoedema distichiasis (<i>FOXC2</i> gene)	Desmuslin
	Severe congenital neutropenia type 4 (<i>G6PC3</i>)	
CADASIL indicates cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.		

Table 2. Disorders, genes and specific mutations associated with varicose vein development (from Anwar et al., 2012)

Secondary varicose veins arise following weakness of venous valves brought about by thrombosis within the deep venous system(Meissner et al., 2007a; Labropoulos et al., 2009). While reflux is the primary mechanism leading to primary venous insufficiency, secondary venous insufficiency is the result of a combination of both reflux and obstruction(Meissner et al., 2007a). Post-thrombotic syndrome refers to the development of pain, oedema, skin changes and ulceration following an episode of DVT(Meissner et al., 2007a). The CEAP (Clinical-Etiological-Anatomical-Pathophysiological) clinical class was found to progress from year 1 to 5 in 30% of post-thrombotic limbs and this evolution of the condition worsened with recurrent ipsilateral deep vein thrombosis(Labropoulos et al., 2009).

Further research to clarify the pathogenesis of varicose vein is still ongoing.

Type of Genetic Defect	Phenotypic Change	Clinical Effect
F13A1 gene	Factor XIII deficiency	Delay in healing of venous ulcers
HFE gene	Increased iron deposition	Exacerbation of venous ulcers
MTFR gene (SNP C677T)	Reduction in enzyme methylenetetrahydrofolate reductase (MTFR) function	Associated with varicose veins and chronic venous disease (CEAP score 4-6)
SLC40A1 (SNP 8CG)	Possible increased iron deposition	Increased risk of chronic venous disease and primary leg ulcer development
MMP-12 (SNP 82AA)	Functional change	Increased risk of ulcer formation
FGFR-2 (SNP 2451AG)	Possible mRNA instability-reduced mitogenesis	Associated with non-healing ulcers

Table 3. A list of genes associated with poor healing of venous ulcer or venous ulcer progression and chronic venous disease (adapted from Anwar et al., 2012)

1.1.4 Risk Factors

Several factors have been implicated in the aetiology of varicose vein disease. The main risk factors are age, female gender, a positive family history, and parity(Laurikka et al., 2002; Carpentier et al., 2004; Beebe-Dimmer et al., 2005; Robertson et al., 2008).

Even though a rising prevalence of the condition has been demonstrated with increasing age, the absolute percentages vary because of different definitions and populations sampled (Callam, 1994). This is illustrated in Figure 3 below.

Female sex is also regarded to be an important factor, but epidemiological studies have shown high prevalences in both males and females(Evans et al., 1999; Laurikka et al., 2002; Carpentier et al., 2004). An analysis of the sex ratio (male to female) by Callam (1994) found a range from 1:0.6 to 1:4.0(Callam, 1994). Callam (1994) noted that studies showing a higher female preponderance used self-reporting tools and varying samples sizes, but also concluded that females were more likely to have the condition, with a female to male ratio somewhere between 1.5:1 to 5.3:1.

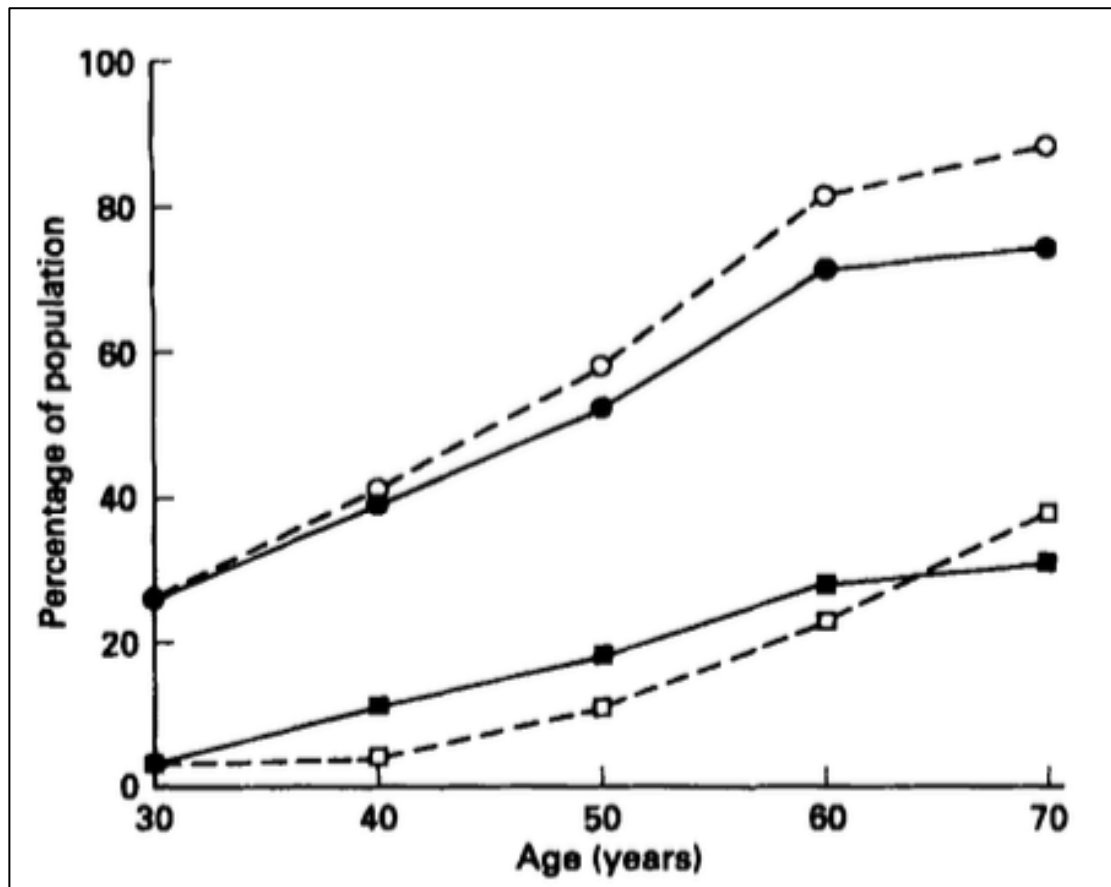


Figure 3. Prevalence of varicose veins according to age (Black circle: men (all veins); clear circle: women (all veins); black square: men (trunk veins); clear square: women (trunk veins)) (from Callam, 1994)

Risk Factor	VV	CVI
Older age	+	+
Family history	+	+
Female gender	+	-/+/0
Standing occupation	+	+
Constipation/Low fibre intake	+/0	0
Obesity	+	+/0
Smoking	+/0	+/0
Oral contraceptive/Hormone replacement therapy	-/0	-/0
Hypertension	+/0	+/0
Physical activity	-/0	-
Injury	+/0	+
History of phlebitis/clot	+	+

Table 4. Established and potential risk factors for varicose veins (VV) and chronic venous insufficiency (CVI) (+: positive association; -: negative association; 0: no association) (from Beebe-Dimmer et al., 2005).

Pregnancy also appears to be a risk factor for the development of varicose veins. It is theorised that valve failure and progression of varices is the result of blood volume expansion as occurs early in pregnancy as well as an increase in abdominal pressure and central venous return resulting from foetal growth and weight gain later in the pregnancy(Beebe-Dimmer et al., 2005). It is also believed that hormonal changes occurring during pregnancy cause vasodilatory effects (relaxin), increase venous capacitance (oestrogen) and weaken blood vessels walls (progesterone)(Beebe-Dimmer et al., 2005).

Mixed results have, however, been obtained from studies looking at the prevalence of varicose veins in parous women. Laurikka et al. (2002) found a prevalence of varicose veins of 32% in nulliparous women compared to 38%, 43%, 48% and 59% in women with one, two, three and four or more pregnancies, respectively(Laurikka et al., 2002). On the other hand, Engelhorn et al. (2010) found that the prevalence of great saphenous vein reflux was not dependent on the number of pregnancies(Engelhorn et al., 2010). A recent meta-analysis estimated an odds ratio of 1.82 of developing varicose veins in women with a history of pregnancy(Ismail et al., 2016). However, the authors noted a high degree of statistical heterogeneity which they have attributed to a disparity between study results as well as differences in study design, age range, geography and diagnostic assessment(Ismail et al., 2016).

Currently, there is uncertainty as to the true effects of weight, standing position at work, fibre intake, smoking, physical activity, oral contraceptive or hormone replacement therapy and history of diabetes, hypertension and traumatic injuries to extremities(Laurikka et al., 2002; Carpentier et al., 2004; Beebe-Dimmer et al., 2005; Lim and Davies, 2009).

1.1.5 Clinical Effects

Symptoms of varicose veins are variable and include pain or ache, itching, restlessness, swelling, tingling, heaviness and cramps(Bradbury et al., 1999; Darvall et al., 2009c). Itching in men and, heaviness, itching and achiness in women, was significantly associated with worsening grade and severity of trunk varicosities on clinical examination(Bradbury et al., 1999). The significantly most common

symptoms in patients with chronic venous insufficiency were heaviness, swelling, aching and itching(Ruckley et al., 2002). They can also cause skin changes such as hyperpigmentation and induration, eventually leading to leg ulceration(Evans et al., 1999).

Increasing severity of the condition has been associated with worsening of the quality of life of patients(Kurz et al., 2001; Darvall et al., 2012).

1.1.6 Classification

The degree of severity of varicose vein disease are classified according to the CEAP classification, which was first introduced in 1994 in a Consensus statement of an ad hoc committee of the American Venous Forum (AVF)(Beebe et al., 1996). The classification was revised in 2004 in a consensus statement of the AVF where the overall structure of the CEAP was maintained but more precise definitions were added (Table 5)(Eklof et al., 2004). This classification is based on the clinical signs of venous disease (C), etiology (E), anatomy (A) and the underlying pathophysiology (P)(Gloviczki et al., 2011). The aim of the clinical evaluation is not only to determine the presenting signs and symptoms and the type of venous disease but also to exclude other aetiologies (e.g., peripheral arterial disease)(Gloviczki et al., 2011).

Following revision of the CEAP classification in 2004, the AVF conducted a National Pilot Screening Program for venous disease and screened 476 persons in 17 different institutions using the CEAP classification(McLafferty et al., 2007). These results are tabulated below (Table 6). Limitations of this screening program included the relatively high inclusion rate of women (78%), abbreviated duplex scans rather than a more comprehensive one, no randomness in patient selection, with patients responding to an advertisement rather than randomly selected. Furthermore, all the sites were advised to screen patients above 40 years of age(McLafferty et al., 2007). The CEAP classification tends to indicate the severity of venous disease at a given point in time and, going from C1 to C6, indicates a progressive worsening of the condition(Rutherford et al., 2000).

The Revised CEAP Classification		
Clinical Classification	Pathophysiologic Classification	
C0: no visible or palpable signs of venous disease. C1: telangiectasiae or reticular veins. C2: varicose veins. C3: edema. C4a: pigmentation and eczema. C4b: lipodermatosclerosis and atrophie blanche. C5: healed venous ulcer. C6: active venous ulcer. S: symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction. A: asymptomatic. <i>Etiologic Classification</i> Ec: congenital. Ep: primary. Es: secondary (postthrombotic). <i>Anatomic Classification</i> s: superficial veins. p: perforator veins. d: deep veins.	<i>Basic CEAP:</i> Pr: reflux. Po: obstruction. Pr,o: reflux and obstruction. Pn: no venous pathophysiology identifiable.	<i>Advanced CEAP:</i> Same as Basic with the addition that any of 18 named venous segments can be utilised as locators for venous pathology: Superficial veins: 1. telangiectasies/reticular veins. 2. GSV above knee. 3. GSV below knee. 4. LSV. 5. Nonsaphenous veins. Deep veins: 6. IVC. 7. Common iliac vein. 8. Internal iliac vein. 9. External iliac vein. 10. Pelvic: gonadal, broad ligament veins, other. 11. Common femoral vein. 12. Deep femoral vein. 13. Femoral vein. 14. Popliteal vein. 15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired). 16. Muscular: gastrocnemial, soleal veins, other. Perforating veins: 17. Thigh 18. Calf

Table 5. The revised CEAP classification

CEAP	Description	Right n (%)	Left n (%)
Class 0	No visible or palpable signs of venous disease	87 (19)	91 (20)
Class 1	Telangiectases, reticular veins, malleolar flare	171 (37)	170 (37)
Class 2	Varicose veins	129 (28)	122 (26)
Class 3	Oedema without skin changes	45 (10)	48 (10)
Class 4	Skin changes ascribed to venous disease	30 (6)	29 (6)
Class 5	Skin changes with healed ulceration	3 (0.6)	3 (0.6)
Class 6	Skin changes with active ulceration	1 (0.2)	1 (0.2)

Table 6. Number (percentage) of extremities in each clinical class of chronic venous disease (adapted from McLafferty et al., 2007)

A pilot study of 102 legs confirmed the practicality of the CEAP classification in venous disease(Kistner et al., 1996). Primary disease was found to be present in 79% of cases while 18% were due to secondary causes (post-thrombotic). These post-thrombotic legs were then found to have more advanced problems and included most of the ulcerated limbs (57%)(Kistner et al., 1996). The authors acknowledged that the CEAP criteria were more thorough and precise compared to previously employed ones.

However, CEAP is not the ideal classification. In a study assessing the 'C' clinical classes of CEAP, Uhl et al. (2001) found that, even though providing a high level of intra-observer concordance (κ -coefficient=0.85), the classification only reached a level of inter-observer concordance of 0.47(Uhl et al., 2001). Indeed, a perfect agreement between observers was only achieved in 33% of cases.

The classification was also found to have greater discrepancy in the lower 'C' classes, but was more accurate in higher classes(Carpentier et al., 2003). Carradice et al. (2011) also noted that the classification was neither cumulative nor additive, with patients in the higher classes not necessarily having any of the features of the lower classes (e.g., patients with C6 disease lacking the characteristics of patients with C2-C4 disease)(Carradice et al., 2011a). Another criticism of the classification is of its rather static nature and ability to change by only very little in response to treatment. For example, healing of an ulcer would 'only' cause an improvement from C6 to C5(Rutherford et al., 2000).

1.1.7 Venous Severity Score

The Venous Severity Score (VCSS) was introduced by the American Venous Forum ad hoc Committee on Venous Outcomes Assessment to quantitatively gauge change in chronic venous disease (CVD) treatment in a meaningful and objective way and to allow for analysis and comparison(Rutherford et al., 2000). It is composed of three elements, namely the Venous Clinical Severity Score (VCSS), the Venous Segmental Disease Score (VSDS) and the Venous Disability Score (VDS).

1.1.7.1 Venous Segmental Severity Score

The Venous Segmental Severity Score is part of the VSS and combines the anatomical and pathophysiological parts of the CEAP classification(Rutherford et al., 2000). Patients are scored according to the pathophysiological findings of reflux and/or obstruction. The maximum possible score is 10 for the presence of reflux and 10 for the presence of obstruction (see Table 7).

Reflux		Obstruction	
Vein involved	Points	Vein involved	Points
Short saphenous vein	½	Great saphenous (only if thrombosed from groin to below knee)	1
Great saphenous vein	1	Calf veins, multiple	1
Perforators, thigh	½	Popliteal vein	2
Perforators, calf	1	Superficial femoral vein	1
Calf veins, multiple (PT alone = 1)	2	Profunda femoris vein	1
Popliteal vein	2	Common femoral	2
Superficial femoral vein	1	Iliac vein	1
Profunda femoris vein	1	IVC	1
Common femoral vein and above	1		
Maximum reflux score = 10		Maximum obstruction score = 10	

Table 7. The Venous Segmental Disease Score

1.1.7.2 Venous Disability Score

The Venous Disability Score (VDS) relates to the effect of CVD onto the day-to-day activities of patients(Rutherford et al., 2000). It also refers to the need to wear compression hosiery and/or limb elevation to be able to participate in normal activities. The maximum score is 3.

Score	Symptoms
0	Asymptomatic
1	Symptomatic, but able to carry out usual activities without compressive therapy
2	Can carry out usual activities only with compression and/or limb elevation
3	Unable to carry out usual activities even with compression and/or limb elevation

Table 8. The Venous Disability Score

1.1.7.3 Venous Clinical Severity Score

The VCSS is predominantly based on the clinical CEAP classification and includes elements of all the six clinical class levels (C1-C6) as well as features pertinent to C4-C6 (e.g., skin pigmentation, duration and presence of ulceration)(Rutherford et al., 2000). Other aspects, such as pain, venous eczema and use of compressive therapy, were also considered. In 2010, the scoring system was revised to reduce ambiguities, update the terminology and simplify its application(Vasquez et al., 2010). It encompasses 9 clinical descriptors as well as the use of compressive therapy (ten in total)(Rutherford et al., 2000; Vasquez et al., 2010). These descriptors are pain, varicose veins, oedema, pigmentation, induration, inflammation, number of active ulcers, duration of active ulceration and size of largest current ulcer. These are characteristics of CVD with potential of change over time. A grading score of 0 to 3 was used (0=absent; 1=mild; 2=moderate; 3=severe) to calculate a final score (see Table 9). The highest possible score is 30.

Meissner et al. (2002) conducted a study to evaluate the clinical application of the VCSS and to compare it with the CEAP classification. The research team wanted to ascertain the relationship between the CEAP classification and the VCSS as well as to determine its intra- and inter-observer reliability (Meissner et al., 2002). Three observers (1 research nurse, 1 research vascular surgeon and 1 clinical vascular surgeon) scored 128 lower limbs and the results analysed. It was found that the VCSS worsened with each CEAP class and had a high correlation with each CEAP clinical class ($R=0.84$; $p<0.001$). It was noted that a VCSS score of ≤ 3 was associated with a sensitivity and specificity of 76% and 90%, respectively, for absence of disease, whereas a score ≥ 8 had a sensitivity and specificity of 70% and 96%, respectively, for the presence of severe disease(Meissner et al., 2002). The correlation co-efficient between the VCSS and CEAP was 0.68 for presence of severe disease and 0.63 for absence of disease. In addition, the agreement between the three observers was good for both absence of disease ($\kappa=0.59$) and for the presence of severe disease ($\kappa=0.65$) (Meissner et al., 2002). In spite of these results suggesting that there was a good correlation between CEAP and VCSS, Meissner et al. (2002) recommended that the CEAP classification should remain as a descriptive tool and VCSS should be used in assessing CVD outcomes(Meissner et al., 2002).

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

Table 9. The revised Venous Clinical Severity Score

Kakkos et al. (2003) investigated the role of VCSS in determining the outcome after varicose vein surgery(Kakkos et al., 2003). A total of 45 patients (48 legs) were examined and each patient was assessed for CEAP and VCSS. It was found that the VCSS increased linearly in advanced CEAP clinical class ($r=0.83$; $p<0.001$). Six months following intervention, the VCSS had reduced by 70% from the pre-operative score. There was only a minimal improvement in the CEAP clinical class and, in clinical class C4-C6, it was found to be rather static(Kakkos et al., 2003). Based on

their findings, the authors suggested using the CEAP clinical class for daily clinical practice and the VCSS for outcome measurement(Kakkos et al., 2003).

Despite seemingly being a good assessment tool for measuring disease severity and being easy and fast to use, the VCSS fails to provide any information as to the impact of the condition on the quality of life of patients (Shepherd et al., 2011). Hence, assessment using quality of life questionnaires have been suggested as a means to obtain a more complete picture of the effect of disease (Shepherd et al., 2011).

1.1.8 Assessment of Quality of Life

1.1.8.1 Definition

Quality of life (QoL) has been described as an elusive concept, as it involves considering the fluctuating well-being of society and the community as well as assessing different individuals or groups in varied situations(Felce and Perry, 1995).

In its position paper on this subject, the World Health Organisation (WHO) defines quality of life as *“individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”*(The WHOQOL Group, 1995). Hence, quality of life is regarded as a subjective measure, incorporating both positive and negative aspects of life and has a number of elements. Six broad domains are recognised, namely: (1) a physical domain; (2) a psychological domain; (3) the level of independence; (4) social relationships; (5) the environment; and (6) spirituality, religion and personal beliefs(The WHOQOL Group, 1995).

Despite this attempt at defining QoL, it remains an obscure concept, having a different meaning to different individuals and also being affected by the area it is being applied to(Fayers and Machin, 2000).

The WHO defines health as “*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*”(WHO, 1946). As such, health-related quality of life endeavours to describe the quality of life of an individual based solely on his/her health status and excludes factors such as income, freedom, and quality of his/her environment, even though they may have an adverse impact on QoL(Guyatt et al., 1993).

1.1.8.2 Quality of Life as an Outcome Measure

A person's degree of health has an objective dimension, but with this person's subjective experience and expectation, this objective assessment is turned into the level of quality of life experienced(Testa and Simonson, 1996). In Vascular Surgery, such reliance on subjective evaluations is viewed with suspicion by surgeons(McDaniel et al., 2000). However, McDaniel et al. (2000) noted that, since patients are the consumers of our treatment methods, only they would be able to report back as to the effect of these interventions on their day-to-day lives.

With regards to venous disease, several tools are available both for objective and subjective assessment of the condition. Shepherd et al. (2011) evaluated the various tools available, which measured the anatomical, haemodynamic, clinical and functional outcomes of patients following varicose vein interventions. They found that a poor correlation existed between the disease-specific quality of life measurements and the other outcome measures used(Shepherd et al., 2011).

Clinical Practice Guidelines from the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) as well as the European Society for Vascular Surgery (ESVS) recommend the use of both a clinical scoring system (VCSS) as well as a quality of life assessment tool in the measurement of outcomes following varicose vein intervention(Gloviczki et al., 2011; Wittens et al., 2015). Evaluating the quality of life of patients can be via using either a generic or a disease specific

instrument. There are advantages and disadvantages to using these tools as shown in Table 10 below.

Generic instruments		Disease-specific instruments	
<i>Pro</i>	<i>Con</i>	<i>Pro</i>	<i>Con</i>
Many already validated	Not sensitive to some clinically important changes	Useful instruments are sensitive to clinically important changes	Cannot compare findings across populations
Allows comparison of health status across groups			Already developed and well validated only in certain disease categories (not applicable to venous disease)
Widely available			

Table 10. Advantages and disadvantages of using generic and disease-specific instruments to assess functional health (adapted from McDaniel et al., 2000).

1.1.8.3 Generic Quality of Life: the EuroQol EQ-5D

The EuroQol group, set-up in 1987 in Europe, is a multidisciplinary and multilingual team of researchers having as primary aim to develop a standardised non-disease-specific assessment tool for describing and scoring health-related quality of life (The EuroQol Group, 1990). The group's intention was to be able to produce international comparisons of health status as well as standardise the collection and reporting of QoL data.

The EuroQol group developed the EQ-5D, which is a generic descriptive system with five dimensions. These are: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression (Rabin and De Charro, 2001). Each dimension has three separate levels (no problems, some or moderate problems, and extreme problems), with 243 health states potentially being defined (Rabin and De Charro, 2001).

The EQ-5D also incorporates a self-rating of health status using a 20cm vertical visual analogue scale (VAS), the EQ-VAS (Rabin and De Charro, 2001). The scale starts at "0" (worst imaginable health state) at the bottom and ends at "100" at the top

(best imaginable health state). The EQ-VAS provides a quantitative measure of an individual's health state and can be used as an outcome measure.

EuroQol EQ-5D Dimensions	
1. Mobility	No problems Some problems Bed bound
2. Self-care	No problems Some problems washing or dressing Unable to wash or dress
3. Usual activities	No problems Moderate Unable to perform
4. Pain/discomfort	None Moderate pain/discomfort Extreme pain/discomfort
5. Anxiety/depression	None Moderate anxiety/depression Extreme anxiety/depression
EuroQol EQ-VAS	Visual analogue scale 0 (worst imaginable health state) – 100 (best imaginable health state)

Table 11. The EuroQol EQ-5D and EQ-VAS

1.1.8.4 Disease-specific Quality of Life Assessment

The use of a disease-specific questionnaire for varicose veins has the advantage of being more sensitive to small, but clinically relevant changes in the health status of patients compared to more generic instruments (Garratt et al., 1993). Moreover, such a questionnaire would be able to differentiate between the varying impact of the condition on patients' health, allow clinicians to incorporate questions related to clinical care, and it will be familiar to patients (Garratt et al., 1993).

1.1.8.4.1 Aberdeen Varicose Vein Questionnaire

Garratt et al. (1993) devised a disease-specific instrument for varicose veins and validated it by comparing the responses to the SF-36 (Short-Form 36, a generic quality of life questionnaire) (Garratt et al., 1993). The SF-36 was again used to

confirm the responsiveness of the measuring tool for patients with varicose veins(Garratt et al., 1996). Thirteen different items were identified for this questionnaire (see Table 12).

The validity of this instrument, later known as the Aberdeen Varicose Vein Questionnaire (AVVQ), was carried out by determining the quality of life of patients with varicose veins and finding out their QoL following surgery(Smith et al., 1999). The final version of the AVVQ is composed of 13 questions (one of them is to draw the distribution of veins on the leg(s))(Catarinella et al., 2015). An online version, without the drawing task, has also been used(Ward et al., 2013). Having been used for more than a decade now, it is considered to be a short, and easy-to-use questionnaire. However, because it is mainly designed for patients with varicose veins, it may be unsuitable for other venous diseases, such as post-thrombotic syndrome (PTS) and deep venous obstruction(Catarinella et al., 2015).

Item
1. Distribution of veins
2. Days with pain or ache
3. Number of painkillers
4. Degree of ankle swelling
5. Use of support stockings
6. Extent of itching
7. Discolouration
8. Presence of rash or eczema
9. Presence of ulcer
10. Degree of concern at appearance
11. Influence on clothing
12. Effect on daily activity
13. Effect on leisure activity

Table 12. The thirteen individual items selected for the Aberdeen Varicose Vein Questionnaire (AVVQ), a disease-specific quality of life instrument(Garratt et al., 1996).

1.1.8.4.2 Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ)

The CIVIQ questionnaire was devised in the 1990s as a disease-specific quality of life instrument(Launois et al., 1996). This assessment tool is composed of 20 questions with points attributed on a 5-point scale and is divided into four dimensions (psychological, physical, pain and social dimensions)(Launois et al., 1996). The minimum score is 0 (very poor quality of life) and the maximum score is 100 (very good quality of life)(Jantet, 2002). Validity of this CIVIQ-20 questionnaire was

undertaken in a study of a micronised flavonoid preparation in 934 patients, while the reliability, responsiveness and validation of the tool was achieved in a prospective, international, multicentre study of micronised purified flavonoid fraction(Jantet, 2002).

The CIVIQ-14 is a shorter version to the CIVIQ-20 questionnaire with 14 items and 3 dimensions present(Launois et al., 2012). Scores range from 0 (excellent quality of life) to 100 (terrible quality of life). Although already validated, CIVIQ-14 is awaiting further evaluation of its responsiveness and sensitivity to change and is being used in the Vein Consult Program, a prospective, international, observational study of patients with chronic venous disease(Rabe et al., 2012).

1.1.8.5 Patient Reported Outcomes Measures (PROMs)

The Department of Health (DoH) initiated the Patient Reported Outcome Measures (PROMs) project in April 2009(Devlin et al., 2010). PROMs have been defined by the Health Services Research Unit (HSRU) as “*measures of health status or health-related quality of life that come directly from patients*”(HSRU, 2007). Comparison of the patients’ self-reported health status at two time points (e.g., before and after an operation) is used to determine the effect of the intervention on the quality of life of the patient(HSRU, 2007). The intention from the DoH is to utilise the PROMs data to assess and manage how the hospitals in England perform with respect to improving the care offered to patients(Devlin et al., 2010). This will allow NHS England to provide the information obtained to patients so that the latter can make an informed decision as to which hospital they would prefer to attend for their treatment(Devlin et al., 2010).

The four procedures selected for the recording of PROMs are unilateral major joint replacement (knee or hip), cataract removal, groin hernia repair and varicose vein surgery. The questionnaires used for varicose vein procedures are the EQ-5D and the AVVQ(HSRU, 2007). The questionnaires are administered on the day of the procedure and are sent by post 3 months later.

Analysis of the PROMs data in the first year since it was started showed that 37,521 varicose vein procedures were performed with variable improvements noted in outcomes(Nesbitt et al., 2012). Patients generally reported an improvement in their symptoms following the procedures (90.3%) and 85% described their results as good or better. The EQ-5D improved from 0.773 to 0.867, the EQ-VAS was nearly static (from 80.40 to 79.96) and the AVVQ improved from 18.75 to 10.76(Nesbitt et al., 2012). It was also found that patients with the worse pre-operative scores received the greatest benefit from intervention.

With time, the PROMs initiative will be introduced to other NHS-funded interventions, enabling NHS England to determine the productivity, resource allocation, cost-effectiveness and demand for each hospital in the country(Devlin et al., 2010). It is envisaged this will eventually lead to hospitals' reimbursement being determined by their performance in terms of PROMs and delivery of NHS services.

1.1.9 Guidelines

A number of guidelines have been made available for the management of varicose veins. In the United Kingdom, the National Institute of Health and Clinical Excellence (NICE) issued guidance for the management of the condition in July 2013(National Institute for Health and Care Excellence, 2013b). Similar guidelines have been developed by the American Venous Forum in the United States and the European Society of Vascular Surgery in Europe(Gloviczki et al., 2011; Wittens et al., 2015). The main focus of the NICE guidelines is to provide evidence-based guidance on the most clinically- and cost-effective management options available (Marsden et al., 2013). The AVF and ESVS also offer recommendations for the evaluation and treatment of patients with venous disease. However, both stress that these guidelines should not be considered as the legal standard of care for all patients, but that each patient should be treated based on their individual and disease-specific characteristics with the recommendations only being used as a guide(Gloviczki et al., 2011; Wittens et al., 2015).

The NICE guidelines make use of the clinical CEAP classification (e.g., C1-C6) in their report, especially to match the outcomes of included randomised controlled trials, but do highlight that the classification was not designed to measure clinical change, nor to provide referral criteria for varicose vein disease (National Institute for Health and Care Excellence, 2013b).

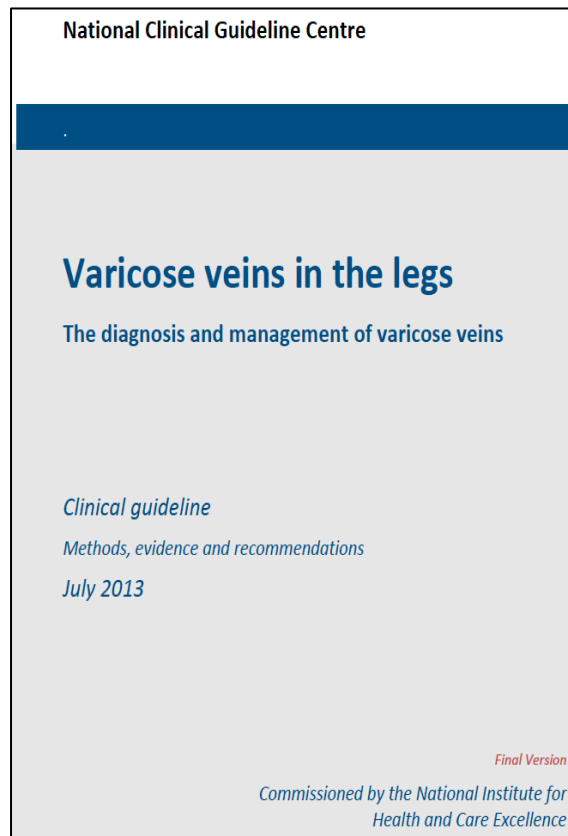


Figure 4. The 2013 NICE Guidelines for the diagnosis and management of varicose veins

1.1.9.1 Referral

The NICE guidelines released in July 2013 recommend patients with the following presentations to be referred to a vascular service (Figure 4) (National Institute for Health and Care Excellence, 2013b):

- Symptomatic primary or symptomatic recurrent varicose veins
- Patients with skin changes suggestive of chronic venous insufficiency (e.g., pigmentation or eczema)
- Superficial vein thrombosis (hard, painful veins)
- Venous leg ulcer
- Healed venous leg ulcer

1.1.9.2 Assessment

The use of a duplex ultrasound is recommended to confirm the diagnosis of varicose veins and to determine the extent of truncal reflux (Gloviczki et al., 2011; National Institute for Health and Care Excellence, 2013b; Wittens et al., 2015). Ultrasound imaging uses sound waves to obtain information about objects and structures. Two modalities are needed for duplex imaging, namely, B-mode scanning (brightness) and pulsed Doppler (Myers and Clough, 2004). B-mode modality enables anatomical visualisation of structures and incorporates a two-dimensional, instantaneous, greyscale image of tissues being scanned. This provides information about the depth, direction and brightness of each echo. Greyscale echoes range from bright to dark depending on the degree of reflection achieved from tissues (Myers and Clough, 2004). Pulsed Doppler provides information about blood flow and movement patterns (Zwiebel and Pellerito, 2005). This method of investigation has been found to be superior to the Trendelenburg tourniquet test (Hoffmann et al., 2004).

With clinical assessment deemed inaccurate, it was believed that increasing use of hand-held Doppler (HHD) would improve the evaluation of varicose veins (Wills et al., 1998). Even though HHD has nearly 100% sensitivity when assessing SFJ incompetence, this falls to 64% for the SSV (Wills et al., 1998).

However, when comparing hand-held Doppler (HHD) to duplex scanning, Campbell et al. (2005) found that the presence of GSV reflux and SSV reflux was missed in 3% and 9% of cases, respectively. There were a number of limitations in this study though, including reflux being considered to be present if venous flow was longer than one second following calf squeeze as subjectively assessed by the examiner and there being no blinding between the findings from the examiner and the vascular scientists doing the scans (Campbell et al., 2005).



Figure 5. A duplex ultrasound scanner

In a randomised controlled trial of preoperative duplex scanning prior to varicose vein surgery, Blomgren et al. (2005) randomised 308 patients and found that in 26.5% of cases preoperative duplex imaging indicated a different procedure to the one initially planned based on clinical grounds. At 2 years, 1.4% of those randomised to preoperative duplex scanning (group 1) were scheduled for reoperation compared to 9.5% in those randomised to no preoperative scanning (group 2) ($p=0.002$) (Blomgren

et al., 2005). After a mean follow-up of 7 years, 12.1% of cases in group 1 needed reoperation, compared to 28.4% of those in group 2 ($p=0.001$)(Blomgren et al., 2011).

With increasing use of duplex ultrasonography, improved definition as to what classes as reflux was needed. Labropoulos et al. (2003) determined that the cut-off for venous reflux in the superficial and deep calf veins should be greater than 500ms, more than 1000ms in the femoropopliteal vein and greater than 350ms in the perforating veins(Labropoulos et al., 2003).

Given its advantages over clinical assessment and HHD, duplex imaging is now considered the 'gold standard' assessment method for patients with varicose vein disease(National Institute for Health and Care Excellence, 2013b). It also has the added benefit of being safe, non-invasive, comparatively inexpensive and reliable(Gloviczki et al., 2011; National Institute for Health and Care Excellence, 2013b; Wittens et al., 2015).

1.1.10 Cost of Varicose Vein Treatment

There have been a drive for rationing in the management of varicose veins, especially as it is considered a low-priority condition(Gohel, 2013). However, as the REACTIV trial demonstrated, surgical treatment of varicose veins is both clinically- and cost-effective for the treatment of varicose veins, with an incremental cost-effectiveness ratio (ICER) well below the threshold normally considered appropriate for the funding of treatments within the NHS(Michaels et al., 2006).

Both radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) performed as day-case or office-based setting using local/tumescent anaesthesia have also been shown likely to be cost-effective methods at the same threshold for the cost per QALY (quality of life years) in the UK(Gohel et al., 2010). Marsden et al. (2015) arrived at the same conclusion when assessing the cost-effectiveness of different varicose vein treatment method (foam sclerotherapy, RFA, EVLA and compression stockings)(Marsden et al., 2015).

A Health Technology Assessment (HTA) funded by the National Institute of Health Research (NIHR) conducted a systematic review, network meta-analysis and exploratory cost-effectiveness model of minimally invasive treatments of varicose veins compared to surgery (Carroll et al., 2014). Thirty-one randomised controlled trials were included in their analysis. They found that the hazard ratio for technical recurrence compared to surgery at 2 years was 0.84 for EVLA, 0.94 for RFA and 0.92 for foam sclerotherapy. Foam sclerotherapy was found to be the cheapest intervention and RFA the most expensive. In addition, foam sclerotherapy had a more than 90% probability of being the most cost-effective option at a threshold of £20,000-50,000 (Carroll et al., 2014). Analysis of the ICER suggests that EVLA and RFA are not cost-effective compared to surgery at the usual threshold.

In another HTA report, this time for the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) trial, foam sclerotherapy was found to be the most cost-effective treatment compared to surgery at a threshold of £20,000-30,000 per QALY gained (Brittenden et al., 2015). EVLA was found to cost £26,107 per QALY gained compared to foam sclerotherapy, but was found to be cheaper with more QALY gained compared to surgery. At a time horizon of 5 years and using the same threshold of £20,000, EVLA had the highest probability of being cost-effective ($\approx 79\%$) compared to foam ($\approx 17\%$) and surgery ($\approx 5\%$) (Brittenden et al., 2015).

1.1.11 Conclusions

Varicose veins are common conditions with a multifactorial pathogenesis and aetiology. They cause a variety of symptoms and have a negative impact on quality of life, and, if untreated, can lead to severe complications such as leg ulcerations. The main diagnostic method is a venous duplex scan, which helps determine patients suitable for intervention. Recently, there has been an increase in the number of patients having endovenous procedures and these techniques have been shown to be cost-effective and safer as well as allowing an earlier return to normal activities.

1.1.12 Aims

The aims of this work are to evaluate potential ways whereby the outcomes of varicose disease management could be improved. This will include:

1. Investigations of innovative new methods of treatment.
 2. Investigations of ways to reduce the delay between assessment and treatment.
 3. Optimisation of post-operative care.
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CHAPTER 2

VARICOSE VEIN TREATMENT

CHAPTER 2. VARICOSE VEIN TREATMENT

2.1 Introduction

Varicose vein has been recognised as an ailment for centuries, with early evidence going back to 1550 BC and visual depiction of a varix dating back to 4th century BC being found at the base of the Acropolis in Athens (Ombrellino and Kabnick, 2005). Further development followed, with Celcus, in first century Rome, proposing the concept of ligation and division of bleeding varicosities and Galen, in the second century, introducing ligation and using specialised hooks to avulse veins (Ombrellino and Kabnick, 2005). These early works, to a large extent, have inspired the current surgical techniques used to treat varicose veins.



Figure 6. Votive relief of Lysimachides (end of 4th century BC) - found at the base of the Acropolis in Athens (Greece). This is believed to be the earliest known illustration of a varicose vein.

2.1.1 Surgery

Contemporary surgical treatment of varicose veins involves the ligation of the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ) with or without stripping of the saphenous vein. The technique enables immediate abolishment of reflux within the truncal veins and is often carried out under general or regional anaesthesia.

Ligation and stripping has been found to be superior to ligation alone. Dwerryhouse et al. (1999) looked at the reoperation rate for patients having surgery for GSV incompetence (Dwerryhouse et al., 1999). This was a randomised study comparing ligation of sapheno-femoral (SFJ) only to SFJ ligation and stripping, and patients were initially followed up for five years. The rate of reoperation at 5 years was found to be 17% in those receiving ligation only compared to 4% in those also having stripping (Dwerryhouse et al., 1999). After 11 years, the corresponding figures were 29% in the ligation only group and 11% in the ligation and stripping group (Winterborn et al., 2004).

Despite these advantages, surgery was found wanting, especially with delayed clinical and quality of life improvements (Lurie et al., 2005; Rasmussen et al., 2013), return to activity (Lurie et al., 2003; Darwood et al., 2008; Subramonia and Lees, 2010) as well as extent of complications (Critchley et al., 1997; Defty et al., 2008) and cost (Rasmussen et al., 2011; Tassie et al., 2014; Marsden et al., 2015).

Complications often reported following surgical treatment of varicose vein include wound infections, haematoma formation, recurrence, numbness, paraesthesia, neuralgia, lymphatic damage, major vessel injury, residual veins and venous thromboembolism (deep vein thrombosis (DVT) and pulmonary embolus (PE)) (Critchley et al., 1997; Defty et al., 2008).

A variation of the conventional stripping technique was the introduction of cryostripping. This involves high ligation of the SFJ as in the conventional method and then insertion of a liquid nitrogen cryoprobe through the proximal GSV down to knee level (Disselhoff et al., 2008; Menyhei et al., 2008). Once the tip of the probe reaches the desired GSV level, freezing is initiated (to -80°C) and maintained for a

few seconds(Disselhoff et al., 2008). Immediately after, the GSV is invaginated by pulling the probe with a sudden upward movement.



Figure 7. The Erbokryo CA cryosurgical system

This method was compared to conventional stripping in a randomised controlled trial(Menyhei et al., 2008). In total, 146 patients with similar baseline characteristics were randomised. The Erbokryo CA cryosurgical system (Erbe GmbH, Germany) was used for the cryostripping part of the procedure. Six patients from the cryostripping group were excluded from final analysis because of incomplete GSV stripping. After a follow-up period of six months, no significant differences were noted in the quality of life between the two treatments. There was a low incidence of major haematoma and wound infection, again with no difference between the treatment methods used. The mean area covered with bruising was more extensive with conventional stripping (161cm^2) compared to 123cm^2 for cryostripping ($p=0.010$)(Menyhei et al., 2008). More patients receiving the conventional surgical method developed paraesthesia at 1 week (28 patients compared to 15 patients in the cryostripping group), but this difference was not significant. Pain scores for both methods were similar as well.

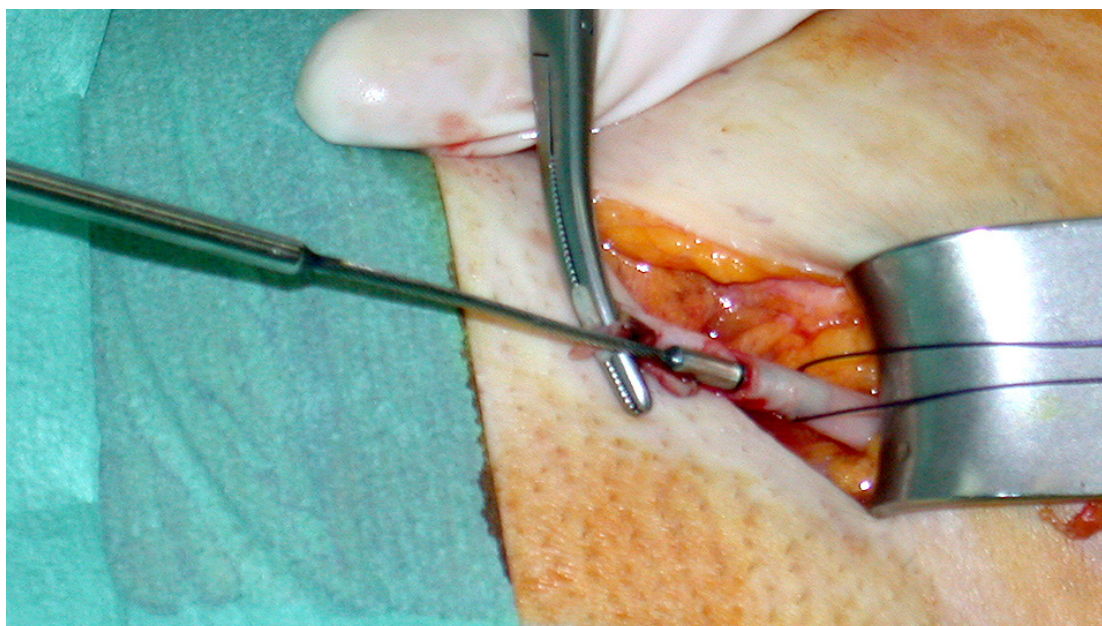


Figure 8. Insertion of the cryoprobe into the proximal great saphenous vein

Cryostripping was also compared to endovenous laser ablation (EVLA) in a randomised controlled trial. One hundred and twenty patients were randomised. The laser procedure was found to be quicker (mean duration: 17 minutes) compared to a mean duration of 24 minutes for cryostripping (Disselhoff et al., 2008). Over the first 10 days post-treatment, pain scores were also significantly better with EVLA (mean pain score: 2.9) compared to a mean pain score of 4.4 with cryostripping ($p=0.003$). There were similar rates of superficial thrombophlebitis, bruising and saphenous neuralgia between the two groups. However, there were more cases of groin infection with cryostripping (5% of patients versus 0 patient in EVLA; $p=0.244$) and induration (52% versus 15%; $p<0.001$). Patients receiving EVLA were significantly more likely to return to their normal activities within 10 days as well ($p=0.001$). After 2 years follow-up and using a life-table analysis, the overall freedom from duplex-defined recurrence was 77% in the EVLA group and 66% in the cryostripping group ($p=0.253$). At 5 years, 62% of patients from the EVLA group were free from duplex-defined recurrence compared to 51% from the cryostripping group ($p=0.246$) (Disselhoff et al., 2011). The clinical scores and quality of life scores in both groups improved over the 2-year and 5-year periods (Disselhoff et al., 2008; Disselhoff et al., 2011). No significant differences were noted between these two treatment methods. Comparison of the clinical and cost-effectiveness of both techniques over a 2-year period reveals that the cost per patient for EVLA was €2,783 compared to €2,651 for cryostripping (Disselhoff et al., 2009). Cryostripping

carried out in an outpatient setting seemed to be the more cost-effective strategy, although EVLA produced similar outcomes but at a marginally higher cost(Disselhoff et al., 2009).

2.1.2 Endovenous Ablation

In a bid to improve the outcomes following varicose veins treatment, more minimally invasive methods were introduced. These involve using a Seldinger technique to cannulate the vein at the lowest point of superficial venous reflux under ultrasound guidance, threading of a guidewire through the needle, removal of the cannulating needle, passage of the catheter sheath over the guidewire, removal of the guidewire and flushing of the catheter sheath to confirm position within the venous lumen. The endovenous catheter can then be inserted and positioned as necessary.

2.1.2.1 Endothermal ablation

Around the turn of the century, two new endovenous (within vein) thermal ablation technologies, namely, radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) were introduced. Both these techniques use heat to produce injury to the venous wall and are described below.

2.1.2.1.1 Endovenous Laser Ablation (EVLA)

In order to investigate the mechanism of action of EVLA, an experiment was designed whereby a silicone tube (6mm diameter) was joined to a transparent tube (2mm diameter) containing heparinised blood and different amounts of laser energy were applied via a fibre positioned in the middle of the silicone tube (Proebstle et al., 2002). As the laser power or pulse duration was being varied, the change in blood volume was recorded (through a change in blood level within the tube). Formation of a steam bubble was observed during laser energy delivery, the size of which was associated with the amount of energy delivered(Proebstle et al., 2002). Areas of the vein showed evidence of reddening, carbonization and perforation, especially at those sites nearest to the vein wall.

Navarro et al. (2001) described the first clinical trial of the use of laser for the treatment of varicose veins (Navarro et al., 2001). Thirty-three patients (44 GSV) with SFJ reflux and GSV incompetence were enrolled. The GSV was cannulated and a bare-tipped laser fibre was introduced. The tip was advanced and positioned 1-2cm distal to the SFJ. Following tumescent local anaesthetic (lidocaine 0.5% without adrenaline) infiltration, the patient was placed in the Trendelenburg position and manual finger pressure was used to further empty the vein. The ablative procedure consisted of laser energy delivered at a wavelength of 810nm along the GSV while the laser fibre was being slowly pulled back in 3-5mm increments. Compression stockings were applied post-operatively and patients were followed for up to 14 months (mean follow-up of 4.2 months). All treated GSV segments were found to be occluded (100%) (Navarro et al., 2001). The laser method was well-tolerated, appeared safe and seemed to be very effective in the short term.

A second study of EVLA confirmed the efficacy of the technique (Proebstle et al., 2002). Using a technique very similar to Navarro et al. (2001), but with a minor variation (utilising a 940nm laser instead), 26 patients (31 limbs) with GSV incompetence were treated. Most of the patients were females with a mean age of 57 years. The complete occlusion rate up to 28 days after treatment was 97% (one instance of incomplete occlusion) (Proebstle et al., 2002). Pain and ecchymosis were the most common complications, though they were deemed not as serious as the ones usually observed in those having surgical treatment.



Figure 9. Endovenous laser ablation catheter tip

In a prospective, non-randomised study evaluating EVLA in refluxing GSV, 490 patients (499 limbs) were recruited (Min et al., 2003). The mean age was found to be

42 years (ranging from 23 to 72 years) and most of the patients were females (83%). The follow-up period was 17 months (range: 1 to 39 months). The initial occlusion rate at 1 month was 98% (490 of 499 limbs treated), dropping to 97.5% (310 of 318 legs treated) by year 1 and 93.4% (113 of 121 legs treated) by year 2 (Min et al., 2003). Twenty-four percent of legs treated were noted to have bruising by the first weeks (all resolved by first month). Five percent of patients had evidence of thrombophlebitis.

2.1.2.1.2 Radiofrequency Ablation (RFA)

Radiofrequency ablation, similar to EVLA, involves insertion of a radiofrequency (RF) catheter into the vein to be treated and heating the tip of the catheter (electrode) using RF delivered at a frequency of 200-3000 kHz (Goldman, 2000). Energy is delivered in a continuous or sinusoidal wave mode and no neuromuscular cells are stimulated at the high frequency used. The electrode applies direct thermal damage to the tissue in contact with it (<1mm of tissue), while tissues further away from the heat source receive heat via conduction (Goldman, 2000). Vein wall fibrosis and/or thermocoagulation ensues.



Figure 10. A radiofrequency ablation generator and catheter

In one of the first clinical trial using this new technique, Goldman (2000) treated 10 patients (12 limbs) with great saphenous vein (GSV) incompetence using a Closure[®] catheter (VNUS Technologies, Sunnyvale, CA, USA). After injecting tumescent fluid around the vein and exteriorising it using a Muller phlebectomy hook, he inserted a 5 or 8 Fr RFA catheter device to within 1-2cm from the sapheno-femoral junction (SFJ). Manual pressure was then applied in the groin and the RFA generator was activated. When the catheter had reached 85°C for 30 seconds, it was pulled back at a rate of 3.5cm/min(Goldman, 2000). At 3 and 6 months, all those treated demonstrated ablated GSVs and resolution of all their pre-operative symptoms(Goldman, 2000).

The next stage in the evolution of the method was in the introduction of segmental ablation. Proebstle et al. (2008) reported the first clinical study using this novel device. The catheter (ClosureFast, VNUS Medical Technologies Inc., San Jose, California, USA) made it possible to treat truncal veins in segments at a temperature of 120°C during 20-second treatment cycles rather than the pullback method previously utilised by Goldman (2000)(Goldman, 2000; Proebstle et al., 2008). This initial study recruited 194 patients (252 limbs) with a mean age of 50.5 years(Proebstle et al., 2008). Once venous access was obtained, a 7-cm segmental heating catheter was inserted and positioned between 1-2cm below the SFJ. Tumescent fluid was then injected around the vein. Infiltration of this fluid causes a reduction in the diameter of the vein, better control of discomfort associated with the treatment and offers the surrounding structures protection from heat damage(Proebstle et al., 2008). The first segment (closest to SFJ) was double-treated with two 20-seconds cycles and, further distally, each subsequent segment was treated with only one cycle. Using a Kaplan-Meier method, the occlusion rate was found to be 99.6% at the 6 months follow-up (Proebstle et al., 2008).

The same research group conducted a multicentre trial using this segmental RFA device at 8 different sites in Germany and France(Proebstle et al., 2015a). Two hundred and twenty-five patients with refluxing GSVs (295 in total) were enrolled and followed up for 5 years, with 80.0 percent of them having a duplex ultrasound scan at final follow-up. Based on a Kaplan-Meier method, an occlusion rate of 91.9% and a rate of absence of reflux of 94.9% at 5 years was demonstrated(Proebstle et al., 2015a). The Venous Clinical Severity Score (VCSS) at 5 years showed a significant improvement from baseline (from 3.9 to 1.3; $p<0.001$).

When RFA was compared to high ligation and stripping, as in the prospective randomised trial of endovenous radiofrequency obliteration versus ligation and vein stripping (EVOLVeS), differences in occlusion and recurrence rates at 2 years was not significant (Lurie et al., 2005). This RCT, enrolling 85 well-matched patients, was probably not adequately powered to be able to demonstrate a difference though. The time to return to normal activities in the study was, nonetheless, significantly less in those receiving RFA compared to surgery (1.15 days v/s 3.89 days; $p=0.02$), as was the global quality of life (QoL) score ($p<0.005$) (Lurie et al., 2003; Lurie et al., 2005).



Figure 11. The Olympus-Celon RFITT generator has been introduced for the treatment of varicose veins. It is most often used for tumour ablation.

RFITT (radiofrequency induced thermotherapy) (Olympus Surgical Technologies Europe/Celon AG, Teltow, Germany) is another endovenous radiofrequency catheter available for the treatment of varicose veins (Braithwaite et al., 2013). It makes use of bipolar energy and is commonly utilised for tumour ablation. The catheter tip is not heated (unlike in segmental thermal ablation) and energy is delivered depending on the impedance from the surrounding tissues (van den Bos and Proebstle, 2013). The power output is usually set at 18-25W with the operator altering the power based on

the resistance obtained. The RFITT catheter is gently withdrawn, with the withdrawal speed being determined by the impedance of the venous wall and adjusted accordingly. The main effect produced is denaturation of the intima, mural cell death, and, coagulation of collagen and other proteins at a temperature of 70-100°C (Newman et al., 2014). In a multicentre non-randomised trial, 462 patients received treatment and attended follow up at 180 and 360 days (Braithwaite et al., 2013). Of those, 81.5% received their treatment under general anaesthesia and 73% had tumescent infiltration. The mean pullback rate was 1.8 ($\pm$ 1.3) cm/s and the mean power output was 23 ($\pm$ 3) W. Using a Kaplan-Meier method, the complete occlusion rate was found to be 98.5% at 180 days and 88.2% at 360 days. Higher occlusion rates were observed in those requiring a lower power output (18-20W) and slower pullback rate (less than 1.5cm/s). Sensory impairment was the most common complication of this procedure. The authors concluded that the RFITT procedure was an effective treatment method for varicose veins, but longer-term studies are warranted.

2.1.2.1.3 Steam Vein Sclerosis

Steam vein sclerosis (SVS) is one of the latest additions to the endothermal ablation of varicose veins. The intended purpose of this method is to reduce side-effects and to provide a safer and easier technique compared to the more traditional thermal methods.

Animal Studies

van den Bos et al. (2011) used an animal model in their proof-of-principle study of venous ablation using steam (van den Bos et al., 2011). Six sheep underwent steam ablation under general and tumescent anaesthesia. Sensors placed inside the sheep monitored for any temperature change. One of the veins treated was removed immediately post-intervention. For histological examination, all sheep were sacrificed, two of them at the 20 day point and the remaining four at 3 months. Another two sheep were treated with RFA and used as reference. Modest temperature rises were mostly noted, except for in one sheep where a temperature rise from 30° to 59°C was found in the subcutaneous layer. All treated veins were occluded, with a diameter

reduction from a mean pre-treatment value of 3.2mm to 1.4mm at 3 months (56% reduction)(van den Bos et al., 2011). Microscopic examination revealed the disappearance of the endothelial layer (immediately post-procedure) and fibrotic thrombosis with inflammation of the media, extending to the adventitia (at 20 days). At 3 months, major thickening of the vein wall with fibrosis and inflammation, altered elastic and collagen fibres, along with further significant luminal reduction was observed. The changes seen were very similar to those previously described with RFA(van den Bos et al., 2011).



Figure 12. The steam vein sclerosis generator, handpiece and catheter

Thomis et al. (2013) used goats to compare SVS to EVLA and RFA, and reported on further histological comparison. Four goats were treated with each modality, receiving endovenous ablation of the lateral vein of the hind leg. After one week, vein diameter had decreased by 26% in the SVS group, 6% in the EVLA group and 15% in the RFA group, respectively(Thomis et al., 2013). Luminal thrombosis was observed in most of the histological samples and all intervention groups showed evidence of vein wall destruction with extensive inflammation and haemorrhage (Thomis et al., 2013). There was no difference in the extent of vein wall damage and level of necrosis. None of the tissues studied showed damage to the fascial or

perifascial layer. This study, therefore, demonstrated that, *in vivo*, endothermal ablation with SVS was similar to RFA and EVLA.

Human Trials

A pilot study comprising 19 patients (20 limbs) with saphenous vein incompetence was also included in the original proof-of-principle article by van den Bos et al. (van den Bos et al., 2011). The mean age in the study was 53 years. All procedures were undertaken under local anaesthetic in an outpatient setting.

The technique consists of vein cannulation followed by insertion and placement of the steam catheter (1.2mm diameter) 3cm distal to the SFJ or SPJ(van den Bos et al., 2011). After tumescent infiltration, the veins were ablated using steam produced from a piston pushing water through a heated element situated just before the catheter. The exit holes on the catheter are kept very small and allow the creation of a pressure difference and reduction of energy loss. The steam transfers the energy to the vein wall, cools down and undergoes condensation to water. The amount of energy released at the tip of the catheter has been measured at 60J per pulse(van den Bos et al., 2011). Post-treatment, all patients were provided with compression stockings for 1 week. At 6 months, a small, short string was noted in 7 out of the 20 the treated veins (2 of those had minimal reflux). Complications were minor (phlebitis and ecchymosis), all noted at the one week follow-up. There were no further complications for the rest of the study period.

A further study, recruiting 20 patients with GSV incompetence, also investigated the effect of the SVS system(Mlosek et al., 2014). One steam pulse per centimetre was used for veins with diameter ≤ 5 mm, two pulses for veins between 5mm and 8mm, and three for veins >8 mm. Previous experiments had suggested that two steam pulses provide the required temperature necessary to ablate varicose veins(van Ruijven et al., 2011).

Initial scan showed that all veins were successfully ablated. Six months post-operatively, partial recanalisation was observed in one patient, giving an occlusion rate of 96%(Mlosek et al., 2014). The VCSS scores improved significantly at 6 months. Eighteen patients (90%) returned to their normal daily activity within 3 days.

2.1.2.1.4 Microwave Ablation

Microwave ablation is yet another addition to the armada of endothermal method of treating varicose veins, with a microwave generator producing radiofrequency in the microwave spectrum(Subwongcharoen et al., 2009). It is already in use for the ablation of hepatocellular carcinoma and kidney resection(Subwongcharoen et al., 2009). The initial impetus for using a microwave generator was the unaffordability of the traditional radiofrequency system for many hospitals(Subwongcharoen et al., 2009).

In vitro studies

Vein obtained from a patient with GSV incompetence was divided in 6 segments and implanted in the subcutaneous layer of pork meat(Subwongcharoen et al., 2009). The six slides were labelled C (control), S (sham), 40W, 50W, 60W and 70W, respectively. A microwave catheter was inserted in each of the veins and pulled back at a rate of 0.5cm/10s. Each slide was then sliced into 10 parts and histological examination was undertaken. Ablation was found in groups 40W, 50W, 60W and 70W.

Animal Studies

Another part of the same study included a swine model used to test the effect of microwave ablation. The swine was sacrificed 7 days after microwave treatment. Thermal injury was found in all layers of venous (and arterial) walls when using microwave energy set at 50W and 60W(Subwongcharoen et al., 2009).

Human Studies

Human trials included 20 patients with GSV reflux treated with endovenous microwave ablation set at 50W. Occlusion rates at 1 week, 6 months and 1 year were 100%, 65% and 65%(Subwongcharoen et al., 2009). No major complications were noted and no recurrences were found at 1 year follow-up.

Yang et al. (2013) conducted a randomised controlled trial looking at the efficacy of endovenous microwave ablation in the treatment of varicose veins (Yang et al., 2013). Two hundred patients were randomised to have conventional surgery (SFJ ligation and stripping) or microwave ablation with high-tie. The follow-up was for 24 months, with 171 patients available for analysis. The baseline characteristics of the two groups were similar. The mean operating time was significantly longer in those undergoing conventional surgery. The initial occlusion rate at 1 year was 97% in the microwave with high-tie group compared to no recurrent GSV or perforator veins detected in the high-tie and stripping group. There were more cases of ecchymosis in the surgery group (31.6%) compared to the microwave group (14.8%; $p=0.004$). There were more cases of skin burns noted in the microwave group though (10%) (Yang et al., 2013). Both groups showed similar improvements in the AVVQ and VCSS up to the 24 month follow-up. Recurrence rates at 2 years was 14% in the microwave with high-tie group compared to 28% in the surgical group ($p=0.02$). No clear advantage over traditional thermal methods was, however, demonstrated as, although a reduction in bruising complications in patients receiving microwave ablation was noted, the technique was also associated with a higher percentage of skin burns. There are no direct comparative studies between microwave ablation and either RFA or EVLA.

Despite these intriguing results, further studies are warranted to confirm the suitability and place of steam ablation and microwave ablation for varicose vein treatment.

2.1.2.1.5 Comparison of endothermal methods and their complications

Goode et al. (2010) compared EVLA (BioLITEC system, Biolitec AG, Germany) to RFA (Olympus Celon RFITT system, Teltow, Germany) in terms of pain sustained and followed up patients for 6 months in a randomised controlled study (Goode et al., 2010). A total of 66 patients (87 legs) were recruited. The pain score using a visual analogue scale (VAS) was significantly less with RFA than EVLA, especially on days 2-11 post-procedure. Bruising due to RFA was also found to be less than in EVLA. Both treatment groups showed similar improvement in patients' quality of life (QoL) and time to return to normal activity. The occlusion rate at 9 months was 78% in the EVLA group compared to 74% in the RFA group (Goode et al., 2010).

Shepherd et al. (2010) also found a lesser degree of discomfort with RFA (VNUS® ClosureFast™ system) compared to EVLA ((Shepherd et al., 2010a). They conducted a randomised clinical trial comparing these two treatment methods looking at the post-procedural level of pain (Shepherd et al., 2010a). They randomised 130 patients into each group. Less pain (as measured by using a 100mm-visual analogue scale, VAS) was noted in the RFA group compared to EVLT at day 3 (26.2mm v/s 36.8mm; $p=0.012$) and day 10 (22.0mm v/s 34.3mm; $p=0.001$) (Shepherd et al., 2010a). There were no significant differences in the time to resume normal activities and QoL.

Another prospective double-blind study was conducted to compare RFA (VNUS® ClosureFast™ system) to EVLA (EVLT, Pyramed, Vascular Solutions) in the treatment of the great saphenous vein (Nordon et al., 2011). One-hundred and fifty-nine patients were randomised (79 to RFA) and received their treatment under general anaesthesia. Both groups were well-matched with non-significant differences in age and gender as well as similar clinical CEAP class, baseline QoL, GSV diameter, length of vein treated, procedural time, tumescent volume and number of avulsions. The occlusion rates for both groups were 100% one week after surgery. After 3 months, the occlusion rate in the EVLA group was 96% compared to 97% in the RFA group ($p=0.67$) (Nordon et al., 2011). The median pain scores as assessed using a 0-100 visual analogue chart comparing RFA to EVLA on day 1 was 9.5 versus 28 ($p=0.001$), 6 versus 23.5 on day 3 ($p=0.001$) and 0 versus 13.5 on day 7 ($p=0.001$), respectively. Patients receiving EVLA also took significantly more analgesia ($p=0.02$) and had more bruising than the RFA group ($p=0.0001$). Both groups had similar improvement in their generic- and disease-specific QoL and took similar amount of time to return to work. There were no major complications reported. This study confirmed that RFA was less painful than EVLA and led to fewer bruising complications. However, there were no major differences in occlusion rates, QoL or time to return to work. This was a well-conducted study with appropriate power calculations and all assessors were blinded to treatment method used. The assessments were carried out at 3 months only though and a longer follow-up might have enabled a detection of a difference in occlusion rate or gain in QoL.

The reported early complications of the endothermal techniques are pain, bruising, phlebitis, nerve injury, arteriovenous-fistula formation, endovenous heat-induced thrombosis (EHIT), deep vein thrombosis (DVT), lignocaine toxicity (secondary to tumescent use) and wound problems and skin burns (Anwar et al., 2012b; Dexter et al., 2012). Later complications include skin pigmentation and nerve damage (Anwar et al., 2012b; Dexter et al., 2012).

2.1.2.2 Non-Thermal Non-Tumescent Ablative Methods

Endothermal technologies have the inherent disadvantage of using heat which can cause damage beyond the intended vein and require infiltration of tumescent anaesthesia. This, in turn, can give rise to lignocaine toxicity and the multiple needlesticks needed often cause procedural pain (Sadek and Kabnick, 2014). Hence, older (foam sclerotherapy) and newer methods have been introduced which do not require the use of any tumescence. These newer techniques include mechanochemical ablation (MOCA) and cyanoacrylate glue.

The MOCA method makes use of a rotating wire which scrape against the venous wall, injuring it and causing vasospasm, with the simultaneous injection of a sclerosant (Elias et al., 2013). Two methods currently utilise cyanoacrylate glue for venous sealing, namely the Sapheon™ VenaSeal™ Closure Device (formerly made by Sapheon Inc., Santa Rosa, California, USA, but lately acquired by Medtronic, Minneapolis, Minnesota, USA) and the VariClose® vein sealing system (Biolas®, Ankara, Turkey). Both methods involve placement of an endovenous catheter into the saphenous vein at some distance from the junction to the deep vein and injection of the cyanoacrylate adhesive. Both techniques are described below.

2.1.2.2.1 Foam Sclerotherapy

Foam sclerotherapy is the second line treatment of varicose veins recommended by the 2013 NICE guidelines (National Institute for Health and Care Excellence, 2013b). Sclerosing solutions react with endothelium damaging it (endosclerosis) and causing fibrosis (endofibrosis) of the vessel lumen (Goldman, 2002). Orbach (1944) initially described the combination of air and sclerosing drug to treat varicose veins: the so-called 'air block' technique (Frullini and Cavezzi, 2002). This technique, with a higher air to liquid ratio, was effective for the treatment of smaller veins, but was not suitable

for larger ones as the air would position itself on the upper side of the vein, thereby preventing contact of the sclerosing solution with endothelium. This led to high rates of treatment failure.



Figure 13. Foam sclerosant production using the Tessari method (two syringes and a three-way tap)

In the 1990s, modern foam sclerotherapy was created, when new methods of transforming liquid sclerosants into foam were described (Cavezzi et al., 2002). Sclerosing agents used as foam displace venous blood and increase endothelial contact, thereby, augmenting their sclerosing power (Tessari et al., 2001). One of the most widely used techniques to produce foam is the Tessari method, which requires two syringes and a three-way tap and enables the production of a stable and compact foam (Tessari et al., 2001). The optimal formulation was found to be one part liquid sclerosant to four parts air (Tessari et al., 2001). Evolution of the technique continued, with the introduction of ultrasound guidance (ultrasound guided foam sclerotherapy) or catheter directed foam sclerotherapy for the treatment of truncal veins (Bountouroglou et al., 2006; Smith, 2006; Kolbel et al., 2007). Two of the most common sclerosing solutions available are sodium tetradecyl sulphate (STS) and polidocanol (POL).

Yamaki et al. (2004) demonstrated the superiority of foam over liquid sclerosants in a comparative non-randomised study of ultrasound-guided sclerotherapy using either

foam or liquid(Yamaki et al., 2004). Sixty-two women, with mean age of 54.6 years, were recruited and received polidocanol either as foam or liquid to treat great saphenous vein (GSV) insufficiency. At 12 months follow-up, approximately 68% of patients receiving foam sclerotherapy had evidence of complete occlusion compared to 17.5% of those in the liquid therapy group ($p<0.0001$)(Yamaki et al., 2004). Despite both groups having similar characteristics, the study is limited by a lack of randomisation as well as unclear criteria used in recruitment. Myers and Clough (2014), however, found conflicting results in their prospective observational study evaluating the efficacy of liquid sclerosant with preliminary saline flush for ultrasound-guided sclerotherapy (UGS)(Myers and Clough, 2014). Their impetus for undertaking the trial was brought about by patients' resistance to the use of foam sclerotherapy, especially, with its possible neurological effects. Three-hundred and fifty-four patients (533 limbs) received treatment with liquid sclerosant if the truncal veins (GSV, SSV or anterior thigh vein) or tributaries had a diameter of less than 4mm. The sclerosing drug used was Polidocanol in various concentrations. After a follow-up period of 12 months, the occlusion rates, as calculated using an actuarial life-table analysis, was significantly better for tributaries (92%) compared to the truncal veins (65%) ($p<0.01$). Better occlusion rates were also obtained with dilute concentrations compared to more concentrated ones ($p<0.01$)(Myers and Clough, 2014). This study was limited by flaws, such as unclear volume and concentration of sclerosant used. Despite this, it presents some interesting findings, which will need to be confirmed in future trials.

In another study, consecutive patients attending for varicose vein treatment were offered ultrasound-guided foam sclerotherapy (UGFS) to refluxing truncal veins (saphenous and non-saphenous)(Darke and Baker, 2006). In total, 181 patients were enrolled and reviewed within 6 weeks of treatment. Approximately 60.0% were females with a median age of 52 years. The occlusion rate was 74% after the first intervention and a further 15% after two interventions(Darke and Baker, 2006). Common complications included phlebitis and pigmentation.

Coleridge-Smith (2006) evaluated his own series of 808 patients undergoing UGFS for incompetent truncal veins and, in the 459 patients attending follow-up at 6 months or greater, demonstrated an occlusion rate of 88% for the GSV and 82% for the short saphenous vein (SSV)(Coleridge-Smith, 2006). Three interventions (each separated

by 2 weeks) were required to achieve an occlusion rate of 99% of the unilateral varices.

When compared to other treatment modalities, foam sclerotherapy proved to be less effective. Rasmussen et al. (2011) conducted a randomised controlled trial to compare endovenous laser ablation (EVLA), radiofrequency ablation (RFA), UGFS and surgical stripping in patients with evidence of GSV incompetence (Rasmussen et al., 2011). Five hundred patients were recruited and the follow-up period was for 1 year. The primary outcome measure was treatment failure, which was defined as an open part of the treated vein segment measuring more than 10cm in length. The clinical, quality of life and radiological change after intervention was also recorded. Baseline characteristics for all four groups did not differ. At 1 year follow-up, there were significantly more cases of treatment failures in the UGFS group (16.3%) compared to the other three groups (less than 6%) ($p < 0.001$) (Rasmussen et al., 2011). Patients who were treated with either UGFS or RFA reported lower pain scores and returned to their normal activities earlier compared to those receiving EVLA or surgery ($p < 0.001$). All groups improved similarly in both clinical and quality of life scores. UGFS was also found to be the cheapest treatment method, especially when the cost of being off from work was taken into account.

Lower occlusions rates with foam sclerotherapy were again reported in the MAGNA trial (for 'vena saphena magna' which means 'great saphenous vein'). This was a randomised controlled trial comparing EVLA, UGFS and surgery in 223 patients (240 legs) (Biemans et al., 2013). The primary outcome measure was anatomic success on duplex ultrasound examination. At the 1-year follow-up, both EVLA and surgery had comparable occlusion rates (88.5% and 88.2%, respectively). The corresponding occlusion rate for UGFS was 72.7% ($p < 0.02$). All three groups also demonstrated similar improvement in the quality of life scores (CIVIQ and EQ-5D).

Tumescent anaesthesia was used in both the previous two studies in patients receiving endothermal methods. This anaesthetic solution acts as a heat sink for the transmitted heat energy and pushes surrounding tissues away, protecting them from burn injury (Gibson et al., 2007). It also helps push blood out of the vein and compresses the vein onto the probe, thereby enabling a more effective thermal injury

to the vein being treated (Gibson et al., 2007) and, hence, potentially explaining the high occlusion rates observed using this technique.

In order to investigate whether these effects are replicated in patients receiving catheter-directed foam sclerotherapy (CDFS), Devereux et al. (2014) conducted a prospective randomised clinical trial in which patients received CDFS with or without tumescence (Devereux et al., 2014). The tumescent fluid used was 0.9% saline only, as the addition of local anaesthesia and adrenaline would have been against the guidelines of the German Federal Institute for Drugs and Medical Devices, the organisation granting ethical approval for the study. Fifty patients were recruited, with 43 of them attending final follow-up at 12 months. At the end of the follow-up period, the complete occlusion rate was 74% in the CDFS with tumescent group compared to 75% in the CDFS group only (Devereux et al., 2014). The authors speculate that the lack of adrenaline in the tumescent might explain the similarities in the level of complete venous occlusion in the two arms of the study. Indeed, they suggest that the addition of adrenaline might have brought about a more potent reduction of the vein diameter and improve the occlusion rates of the CDFS/tumescent group.

The longest data to date following UGFS has been reported by Darvall et al. (2014) (Darvall et al., 2014). They described the patient-reported outcomes 5-8 years following treatment with UGFS. Out of the initial 351 patients (479 limbs) treated, 285 (81.2%) attended follow-up a minimum of 5 years later. Using a Kaplan-Meier plot, they estimated the proportion of their cohort requiring retreatment at 5 years to be 15.3%. There was also significant improvement noted in the Aberdeen Varicose Vein Symptom Severity score (AVSS), similar to that observed at earlier follow-ups. The physical component of the Short Form 12 (SF-12[®]) was also found to have improved compared to pre-treatment values. The mental component of SF-12[®] was, however, similar to baseline levels. Between 62.7% and 81.0% reported that their expectations with respect to social, work or leisure activities were either met or exceeded. Eighty-two percent of patients were highly satisfied (giving a score of 8 to 10) and more than 90% would recommend the treatment to their family and friends. The same group also demonstrated that, as well as improving the quality of life of patients, UGFS is less painful and leads to earlier return to work compared to surgery (Darvall et al., 2009a; Darvall et al., 2009b; Murad et al., 2011).

Unlike the clinician-prepared foam described above (physician-compound foam, PCF) which involve mixing a sclerosant solution with a gas in varying concentration, Varithena™ (BTG International Ltd.) is a polidocanol endovenous microfoam (PEM), a product which comes already prepared in a proprietary canister (Gibson and Kabnick, 2016; Vasquez and Gasparis, 2016). It is composed of oxygen and carbon dioxide (65:35 mixture) mixed with nitrogen at a concentration of less than 0.8% of nitrogen (Gibson and Kabnick, 2016; Vasquez and Gasparis, 2016). The microfoam produced has more stable bubbles with a diameter of 500µm (Todd et al., 2014). This product was used in the VANISH-2 study, a randomised, blinded multicentre trial treating GSV reflux (Todd et al., 2014). Better QoL improvement were noted in those receiving either 0.5% PEM or 1.0% PEM compared to the control group ($p < 0.0001$). At 8 weeks, the occlusion rate in the 0.5% PEM group was 83% compared to 86% in the 1.0% PEM group (Todd et al., 2014). A DVT rate of 5.7% was also noted, none of which were symptomatic (Todd et al., 2014).

Foam sclerotherapy has also been combined with other methods, notably, surgery and coil insertion, to improve the rate of occlusion of the GSV. One-shot scleroembolisation is one such method (Viani et al., 2014). In the first article describing its use, 9 patients with GSV reflux (6 patients with simple varicose veins and 3 with healed ulcers) were recruited and underwent day case treatment of the incompetent vein. The technique involves the introduction of an endovenous catheter in the GSV and, under ultrasound-guidance, placement of a standard platinum coil 1cm below the origin of the epigastric vein. The coil is 1mm wider than the calibre of the SFJ and causes the prompt occlusion of the terminal portion of the GSV. The final step is the injection of sclerofoam (2% Polidocanol), which causes fibrosis and occlusion of the vessel. Post-procedure, elastic bandage was applied to the treated limb. Patients were discharged the same day and advised to wear the compression for 15 days. All of them were followed for up to 3 months. After 1 week, one instance of recanalisation was detected which was successfully treated with foam sclerotherapy. At 3 months, therefore, all 9 patients were asymptomatic and had completely occluded GSV (Viani et al., 2014). In addition, no migration of the coil or compression of the CFV was noted and the coil was impalpable. There were no perioperative complications and no incidences of DVT. Advantages of the technique include the fact that it can be carried out under local anaesthetic as a day case procedure and does not require any tumescence. The average cost of the coil was

US \$120. This technique is promising, but the findings need to be confirmed with larger studies and longer term follow-up.

Ricci et al. (2014) described a technique called ultrasound assisted GSV ligation and division, which is another potential alternative to endothermal treatment(Ricci et al., 2014). Eighteen patients (20 GSVs) were enrolled. The procedure consists of prior vein marking, initial phlebectomies for varicosities followed by ultrasound-guided extraction and division of the GSV about 3cm below the SFJ as it courses over the adductor longus (an area relatively free from other structures). Foam sclerosant is then injected through the upper end until it comes out of the distal phlebectomy stab incisions. The proximal end is transfixed, leaving a short stump, while the distal end is ligated. Post-procedure, compression bandaging is applied for one week. At one month, the residual stump was patent in all cases with no evidence of reflux. At 6 months, one proximal GSV stump showed evidence of reflux originating from a pudental vein. This technique offers the advantage of sparing the junction tributaries and avoiding dissection, hence, possibly giving rise to less stimuli for neovascularisation. Potential problems are the likely difficulty in obese patients and large GSV diameter where the vein is extracted from. Moreover, it cannot be truly considered an NTNT as it still makes use of tumescent anaesthesia. Longer term follow-up as well as a larger cohort are required to confirm findings of this study.

Complications of Foam Sclerotherapy

In a multi-centre, prospective, controlled study looking at the side-effects and complications of foam sclerotherapy of the GSV and SSV, Gillet et al. (2009) recruited 1025 patients from 20 phlebology outpatient clinics(Gillet et al., 2009). Approximately 80% of the truncal veins treated were the GSV and the proportion of females was 76.2%. The average age was 54 ± 13.8 years. Foam was prepared using the Tessari method, with air being the gas used in 93% of cases. The median follow-up period was 20 days. There were 11 cases of venous thromboembolism recorded (1 PE and 10 DVT) ($11/1025 = 1.07\%$) as well as 8 cases of migraine (0.78%) and 7 (0.68%) reported an isolated visual disturbance. There was one episode of transient ischaemic attack (TIA) recorded, and the patient was found to have a patent foramen ovale (PFO) associated with an interatrial septal aneurysm (IASA). However, it is to be noted that PFO is quite common (20-30% of the

population) and the risk of stroke following foam sclerotherapy appeared to be extremely low. This rarity of neurological complications was also confirmed in a systematic review in 2012(Sarvananthan et al., 2012). The type of gas used has been implicated previously, but so far no concrete evidence has been obtained(Gillet et al., 2009; Parsi, 2011; Sarvananthan et al., 2012).

Other complications arising from foam injection include skin discolouration and pigmentation, but more serious adverse events such as anaphylactic reactions, venous thromboembolism (VTE) (DVT, pulmonary embolus (PE) or superficial venous thrombosis (SVT)), transient visual disturbance, migraines and strokes can occur, but these are rarer(Darke and Baker, 2006; Cavezzi and Parsi, 2012). Foam sclerotherapy can also results in extravasation of the foam into the tissues or inadvertent intra-arterial injections which can lead to skin necrosis(Cavezzi and Parsi, 2012).

Guidelines

In 2012, twenty-three European Phlebological Societies drafted the European guidelines for sclerotherapy in chronic venous disorders(Rabe et al., 2013). The guidelines reviewed the available evidence from the medical literature and gave recommendations regarding the indications, contra-indications, side-effects, concentrations, volumes, technique and efficacy of sclerotherapy (both liquid and foam) in the treatment of varicose veins and venous malformations. Sclerotherapy for the treatment of incompetent saphenous veins is also recommended and was given an evidence grading of 1A(Guyatt et al., 2006). The NICE Guidelines for Varicose Veins in the Legs (2013), for their part, recommend the use UGFS as second line treatment, if endothermal ablation is not suitable(Marsden et al., 2013).

Newer NTNT methods have recently appeared on the market and these are being promoted as offering the potential of higher occlusion rates, while maintaining improved quality of life and earlier return to activities, but without the side-effects of endothermal ablation.

2.1.2.2.2 Mechanochemical Ablation

A novel device, the ClariVein® mechanochemical ablation (MOCA) device (Vascular Insights, Madison, Connecticut, USA), has been introduced. NICE has recently fully approved the use of this technique in the treatment of varicose veins (interventional procedure guidance 557)(National Institute for Health and Care Excellence, 2016).

MOCA combines an endovenous mechanical method using a rotating wire with simultaneous injection of liquid sclerosant and avoids the use of heat and tumescent infiltration(Elias and Raines, 2012). The wire rotates at 3500 rotations per minute, injuring the venous intima while the sclerosant is infused through an opening close to the catheter tip(Elias and Raines, 2012).



Figure 14. The ClariVein® mechanochemical ablation catheter (Vascular Insights Inc.)

Animal Studies

Tal et al. (2014) tested the MOCA device on 11 male goats (12 veins included) and analysed the histological samples obtained from this caprine model(Tal et al., 2014). Four different treatments were examined: group 1 - the ClariVein® catheter and 1.5% sodium tetradecyl sulphate (STS) (MOCA procedure) (five veins); group 2 - ClariVein® and 0.9% saline (one vein); group 3 - 5mL injection of 1.5% STS (five veins); and, group 4 - 5mL injection of 0.9% saline (one vein). The lateral saphenous vein was selected and duplex ultrasound examinations were carried out pre-operatively and on days 14, 28, 56 and 84 to assess the degree of occlusion. At day 84, all animals were euthanised and underwent gross necropsy(Tal et al., 2014). All

the veins receiving the MOCA procedure (group 1) demonstrated complete or near complete occlusion on ultrasound assessments at 84 days, while the veins in the other treatment groups were still patent at the end of the study, thereby indicating the superiority of the ClariVein® catheter and sclerosant to produce vein occlusion and fibrosis rather than only using liquid sclerosant. Comparison of the saline groups (groups 2 and 4) showed more subintimal impingement and medial fibrosis in group 2 than in group 4. No adventitial fibrosis was demonstrated, however, and veins from both groups remained patent at the end of the study.

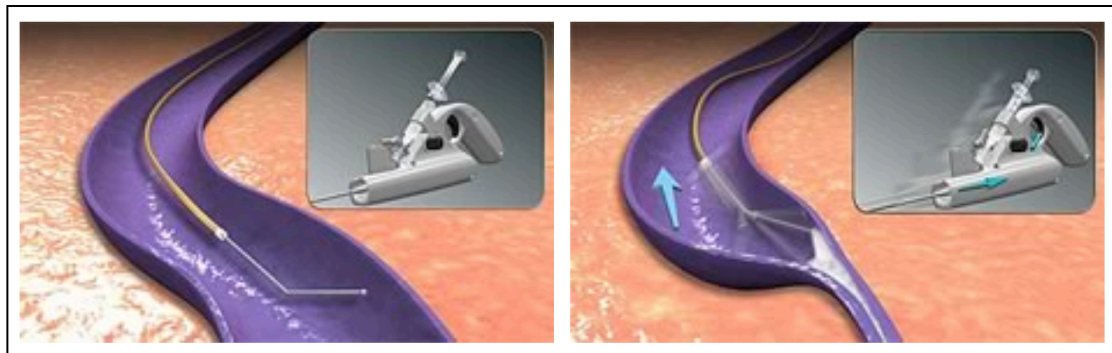


Figure 15. The process of mechanochemical ablation using the ClariVein® system (a) Rotating tip at the end of the catheter injures the venous intima (b) Liquid sclerosant injected from an opening close to the tip causes fibrosis

One limitation of the study is that the number of veins treated in each group is not equivalent and the question remains as to whether some of the changes noted could have been improved with inclusion of a larger number of veins. This study, in any case, illustrates the superiority of the MOCA procedure in achieving venous occlusion compared to using either the ClariVein® catheter alone or liquid sclerosant on its own.

Human Trials

In order to determine the safety and efficacy of the ClariVein® device, Elias and Raines (2012) recruited 29 patients with primary great saphenous vein (GSV) reflux and followed them at 4 different time points (Elias and Raines, 2012). Reflux of greater than 0.5 seconds or longer was determined at the SFJ while patients were in the standing position. A majority of the patients were females (60%) and the average age of the population was 54.3 years (range: 31 to 90 years). The baseline Venous Clinical Severity Score (VCSS) was 4.5 with the clinical CEAP (Clinical-Etiological-

Anatomical-Pathophysiological) between 2 and 4. The average treatment length was 37.5cm and the average diameter of the treated veins was 8.1mm. No patients complained of pain during the ablative procedure. There were no incidences of deep vein thrombosis (DVT), nerve or skin injury. The average follow-up period was 260 days. There was one case (1 out of 30) of recanalization giving a primary closure rate of 96.7% at 260 days(Elias and Raines, 2012). The authors, therefore, concluded that the new ClariVein® device was safe and appeared to be effective in the treatment of venous reflux(Elias and Raines, 2012). However, most of the patients recruited had CEAP stage 2 disease (77%) and there were three occurrences of ecchymoses. The authors postulate that this might be secondary to the rotating wire catching on a side branch or valve cusp.

About the same time, van Eekeren et al. conducted a similar study in the Netherlands to assess the applicability and safety of MOCA. Twenty-five patients with primary GSV reflux were recruited (30 limbs), undergoing mechanochemical ablation at two centres(van Eekeren et al., 2011). Most of the patients were women (72%) and the mean age of the population was 52 years. The CEAP classification ranged from C2 to C4 and the mean VCSS score was 3.3. The mean duration of the procedure was 20 minutes and the treated veins were on average 40cm in length and 6.1mm diameter at the sapheno-femoral junction. The median maximal pain score was 4 (interquartile range (IQR) 3-6) on a 10-point scale, while the mean maximum pain measured on day 1 post-procedure was 9mm on a 100mm visual analogue scale (VAS)(van Eekeren et al., 2011). There were no major adverse events and the minor complications included 9 cases of local ecchymosis at the puncture site and 4 of phlebitis. At the 6 weeks follow-up, the GSV was completely obliterated in 87% of cases (26 out of 30 legs treated) starting 2cm distal to the SFJ at the 6 weeks follow-up. Patient satisfaction was 8.5 (IQR 8-9) on a 10-point scale and the median VCSS decreased significantly from 3 to 1 ($P<0.001$)(van Eekeren et al., 2011).

The effect of MOCA on the small saphenous vein (SSV) has been studied by the same research team. The SSV accounts for approximately 15% of lower limb truncal venous incompetence(Boersma et al., 2013). Fifty patients with primary SSV incompetence were enrolled and received MOCA treatment to their incompetent SSV with 1.5% Polidocanol as sclerosant(Boersma et al., 2013). The primary outcome measures included anatomic success, which was defined as occlusion of the treated

vein and recanalised SSV or treatment failure defined as an open segment of >10cm. The median pain score using a VAS was 2cm (IQR 2-4 cm) and the median patient satisfaction was 8 (IQR 8-9). No major complications were recorded, including no evidence of nerve injury and no DVT. Minor complications were noted, mainly localised ecchymosis and induration and transient superficial thrombophlebitis in 14%. The occlusion rate was 100% (50 out of 50 limbs treated) and 94% (44 out of 47 legs treated) at the 6 weeks and 1 year follow-up, respectively. However, it is to be noted that different concentrations of the sclerosant were used to treat the proximal section, with 1.5% Polidocanol for the first 15 patients, but 2ml of 2% Polidocanol in the subsequent 35 patients (followed by 1.5% for the remainder of the vein). There were two occurrences of recanalisation in patients treated with the lower concentration, compared to 1 out of those who received 2% Polidocanol.

The same group again evaluated the 1-year results of MOCA in patients with GSV insufficiency (van Eekeren et al., 2014b). Consecutive patients with primary GSV insufficiency were included in the study. Ninety-two patients (106 limbs) were recruited. The mean age was 52 years with 67% of the cohort being females. Treatment failure was defined as a recanalised segment of >10cm of the treated GSV. MOCA was performed on 105 legs and the median post-procedural pain using a 0-100mm VAS during the first 14 days after treatment was 7.4mm. No major complications were observed, although there were incidences of thrombophlebitis, induration, localised haematoma and mild hyperpigmentation at the puncture site. The occlusion rate immediately post-procedure, at 6 months and at 1 year was 100%, 93.2% (96 of 103 limbs treated) and 88.2% (90 of 102), respectively (van Eekeren et al., 2014b). The mean VCSS score improved significantly at the 6-month and 1-year follow-up ($p<0.001$). Compared to baseline, the QoL improved significantly with a mean AVVQ score of 6.6 at 6 months ($p<0.001$) and 2.4 at year 1 ($p<0.001$).

There have been few studies comparing MOCA to endothermal ablation. One of these studies comprised of 68 consecutive patients treated for symptomatic unilateral GSV reflux and their post-operative pain score as well as early quality of life was assessed (van Eekeren et al., 2013). Thirty-four patients were assigned to either MOCA or radiofrequency ablation (RFA). There were 25 males and 43 females, with a mean age of 58 ± 17 years. There were no significant differences in the baseline

patient characteristics. The mean procedural pain during treatment was similar between the two groups ($p=0.16$). Patients receiving MOCA reported less pain compared to RFA over the first three days (6.2mm v/s 20.5mm; $p=0.004$) and during the first 14 days after treatment (4.8mm v/s 18.6mm; $p<0.001$)(van Eekeren et al., 2013). They also required less analgesia compared to the RFA group. Patients in both groups who developed post-operative thrombophlebitis and induration had higher pain scores. Treatment time was significantly shorter in the MOCA group ($p=0.02$). At 6 weeks, the median VCSS score improved significantly in both groups ($p<0.001$). Quality of life assessment showed that the AVVQ score improved in both the MOCA ($p=0.006$) and RFA ($p=0.002$)(van Eekeren et al., 2013). Time to return to normal activities and work was also found to be significantly shorter in the MOCA group. The authors, thus, concluded that post-operative pain is significantly lower after MOCA compared to RFA and the former was associated with a faster return to normal activities and work. This is the first study which has provided direct evidence of the lesser discomfort following varicose vein ablation and earlier return to activities in patients receiving MOCA. But, this was a non-randomised trial and the criteria used for patient selection is not clear. Moreover, the procedural pain score was no different in the two groups, but the authors allude to the fact that their sample size was too small to detect a difference and suggested carrying out a randomised trial.

The MARADONA trial (Mechanochemical endovenous Ablation versus RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence) has been designed to directly compare the anatomical and clinical success rate at one year compared to RFA and is hoping to recruit 230 patients in each group (460 patients in total)(van Eekeren et al., 2014a). Patients will then be followed up for 5 years, giving excellent long term data. The results of this are eagerly anticipated and expected in 2020.

Complications of Mechanochemical Ablation

Reported complications following MOCA include superficial thrombophlebitis, induration along the course of the treated vein, localised haematoma and mild hyperpigmentation at the puncture site(van Eekeren et al., 2014b). An increasingly recognised adverse event following MOCA is the rotating wire tip getting caught. This may give rise to ecchymoses, patient discomfort or resistance to pullback(Elias and

Raines, 2012; Mueller and Raines, 2013). However, as reported by Lane et al. (2015), rarely it can become stuck with no possibility of dislodgement, with dramatic consequences (the SSV was inverse stripped)(Lane et al., 2015a). There have been no reports of skin necrosis, deep vein thrombosis or nerve injury.

3.1.2.2.3 Cyanoacrylate Glue

Two methods of cyanoacrylate glue injection are currently in use to treat venous incompetence (VenaSeal™ Closure System and the VariClose® vein sealing system) and are discussed below.

What is glue?

The glue used in this tumescentless method is n-butyl cyanoacrylate (n-BCA), which was initially introduced in medical practice approximately 40 years ago(Idle et al., 2013). The first cyanoacrylate adhesive used at the time had low tensile strength and was associated with both acute and chronic inflammation(Idle et al., 2013).

N-butyl cyanoacrylate is an adhesive liquid monomeric agent which quickly polymerises and becomes solid when it comes into contact with a solution containing anions (e.g., with the hydroxyl groups in blood)(Linfante and Wakhloo, 2007). This subsequently leads to occlusion, marked inflammatory endothelial response, and, ultimately fibrosis(Linfante and Wakhloo, 2007). Further development of the material with the addition of plasticisers and stabilisers have improved its flexibility and reduced its toxicity(Idle et al., 2013).

This has resulted in cyanoacrylate glue being used more widely, for example, in ophthalmic surgery, cosmetic procedures, dental applications, tissue adhesion and haemostasis of acute bleeding such as endoscopic sclerotherapy of gastric variceal bleeding with high safety profiles reported in patients followed up for 10 years(Abbassi-Ghadi and Hafez, 2013). They have also been used intravascularly in treating type I and II endoleaks of abdominal aortic aneurysm repair procedure, varicocoeles, pelvic congestion syndrome and arterio-venous malformations (AVM)(Min et al., 2012).

Encouraged by the safety profile and efficacy demonstrated by the cyanoacrylates in endovascular procedures, Dr Raabe, an interventional radiologist from Washington (USA), looked into using a similar method for treating varicose veins (Morrison, 2015). The characteristics of the cyanoacrylate in use at the time were, however, unsuitable for the treatment of varicose veins and, therefore, the adhesive was modified and a new delivery system was devised allowing treatment of leg veins (Morrison, 2015).

Vein Sealing Devices and Technique Used

Two vein sealing devices are currently available. They are the VenaSeal™ Closure System (Medtronic, Minneapolis, Minnesota, USA) and the VariClose® vein sealing system (Biolas®, Ankara, Turkey). The technique of cyanoacrylate injection as well as the makeup and characteristics of the adhesives used differ.

VenaSeal™ Closure System

The VenaSeal™ Closure System was the first device to use cyanoacrylate to treat varicose veins and the technique of vein sealing involves injection of the adhesive followed by segmental pullback. Similar to contemporary endovenous techniques, a Seldinger method of cannulation is used to obtain access. Briefly, the truncal vein is cannulated, a 0.035-inch J-guidewire is threaded through, followed by insertion of a 7Fr introducer sheath (Almeida et al., 2013). Next, the delivery catheter is connected to a 3mL syringe containing the cyanoacrylate adhesive. This catheter system possesses hydrophobic properties which prevent it from adhering to the vessel wall as well as tiny air-filled microchannels which affords greater visibility under ultrasound guidance (Almeida et al., 2013). The catheter is then primed by firing the dispenser gun, with each trigger pull delivering 0.1mL of glue. To minimise the chances of premature contact between blood and the adhesive during catheter introduction into the venous lumen, the distal 3cm of the catheter tubing is kept empty. The catheter and introducer sheath are then connected and, under ultrasonic guidance, the catheter tip is advanced until it is 5cm from the sapheno-femoral junction (SFJ). Afterwards, 0.2mL of cyanoacrylate is delivered (two trigger pulls) while extrinsic pressure is exerted over the SFJ (above the tip of the catheter) using

the ultrasound probe, The delivery catheter is pulled back 3cm and pressure is applied to the treated segment for 3 minutes. Once more, the ultrasound transducer is placed above the tip of the catheter, 0.1mL of CAE (one trigger pull) is injected and 30 seconds of external pressure is applied. This process is repeated until the whole vein is treated. Once the whole vein has been treated, the catheter is removed and further pressure is applied onto the entry site. If no further treatment (e.g., tributary treatment) is necessary, a simple wound dressing is applied onto the entry site. There are no requirements to wear compression bandages or stockings.

Patients are then discharged, once they have spent a complication-free period in recovery.



Figure 16. The VenaSeal™ Closure System

VariClose® Vein Sealing System

The VariClose® system is similar to the VenaSeal™ system, but the cyanoacrylate used has a faster polymerisation rate. Venous access is obtained as for other conventional endovenous methods, while the delivery catheter has hydrophobic properties and is easily visualised under ultrasound. With a 3mL cyanoacrylate-containing syringe connected to a 4Fr delivery catheter, the latter is then primed by

gently pulling the trigger gun over 5 seconds (delivering 0.3mL of cyanoacrylate)(Bozkurt and Yilmaz, 2016). The catheter tip is advanced into the GSV and positioned 3cm distal from the SFJ. Extrinsic pressure is applied over the SFJ with the ultrasound transducer and the saphenous vein is treated by injecting 0.3mL for every 10cm of vein length. External compression is applied for 5 seconds following treatment of the first 10cm of vein. Thereafter, the catheter is retracted continuously at a rate of 2cm per second while constant pressure is applied by the ultrasound probe moving down the leg at the same rate. This procedure continues until the complete length of the vein is treated.

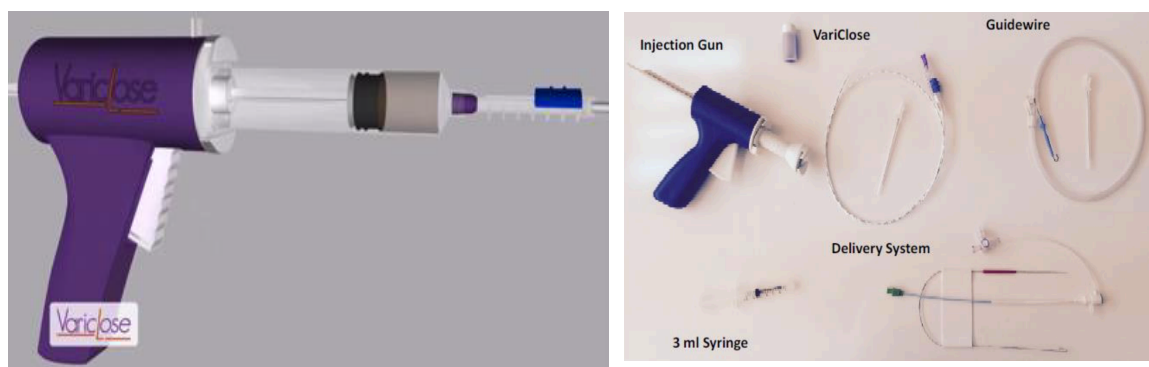


Figure 17. The VariClose® Vein Sealing System

A bandage is applied over the entry site only and, as for the VenaSeal™ system, no leg compression is necessary. Patients are discharged shortly afterwards with the advice to return to their normal activities as soon as they feel able to, but to not start exercising until the following day.

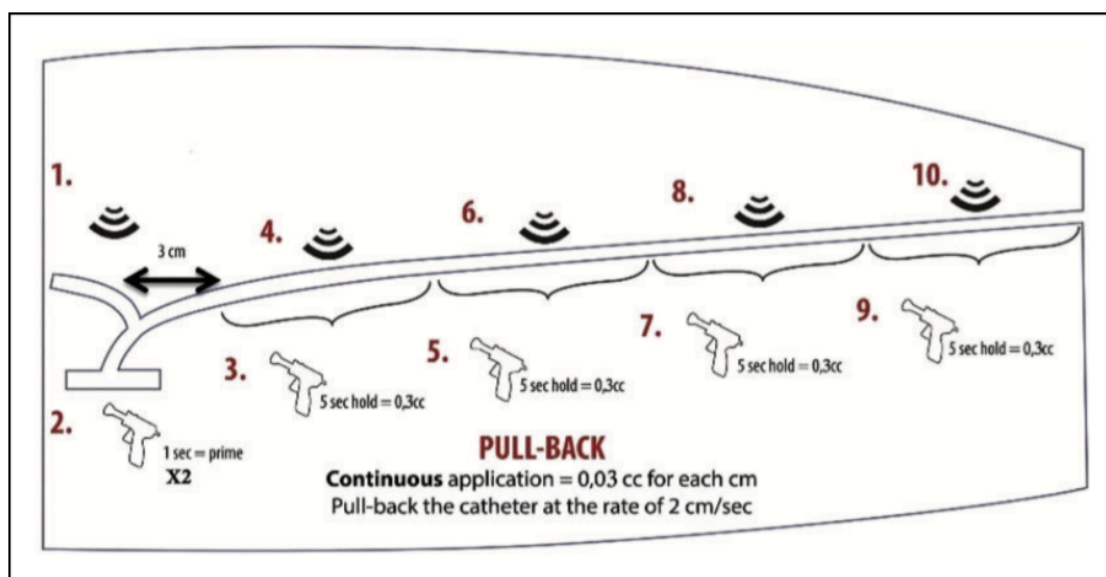


Figure 18. Vein sealing using the VariClose® Vein Sealing System. This involves positioning of the catheter 3cm distal from the sapheno-femoral junction, injection of 0.03mL/cm of cyanoacrylate and continuous pullback of the catheter at a rate of 2cm per second along with simultaneous application of pressure using the ultrasound probe.

	VenaSeal™	VariClose®
Country of origin	USA	Turkey
Venous access	Vein cannulation and sheath insertion	Vein cannulation and sheath insertion
Chemical used	Cyanoacrylate	Cyanoacrylate
Delivery catheter	Connected to delivery gun	Connected to delivery gun
Catheter pullback	Segmental	Continuous
External compression	Segmental	Continuous
Speed of polymerisation	Slow	Fast
Distance from SFJ	5cm	3cm
Post-intervention compression	None	None

Table 13. Comparison of the VenaSeal™ and VariClose® vein sealing systems

	VenaSeal™	VariClose®
Colour	Clear	Blue
Consistency	Viscous (like 'honey')	Runny (like 'water')
Polymerisation	Slow	Fast
Texture post-polymerisation	Soft	Hard

Table 14. Comparison of the cyanoacrylate characteristics of the two vein sealing systems

Animal Studies

Kailasnath and Chaloupka (2002) developed a bench top testing apparatus that permits direct measurement of evolving binding forces that develop during polymerization of CA(Kailasnath and Chaloupka, 2002). They compared the rate of polymerisation of CA using a plastic model vessel and a tissue model (common carotid artery of a swine). They found that there were three distinct stages of polymerization. The initial phase (phase I) demonstrated a linear rate of increasing tensile forces lasting less than 10 seconds followed by phase II which had a more constant tensile force (lasting up to 1 minute). Polymerisation was, however, not achieved in either phases. A final step (phase III) started at the end of the second phase and was characterised by an exponential rise in the tensile forces which lead to complete polymerisation(Kailasnath and Chaloupka, 2002). The rate of polymerisation and strength of the binding forces formed were variable and dependent on type and formulation of CA used(Kailasnath and Chaloupka, 2002; Min et al., 2012).

The first experiment looking at using CA adhesive as vein closure method in an animal model used the superficial epigastric veins (SEVs) of two swines(Almeida et al., 2011). The SEVs empty into the abdominal rectus vein (ARV) at the costal margin. The purpose of the experiment was to assess the feasibility of the proposed method as well as evaluating its safety and effect on the vein wall. With the swines under general anaesthetic, the right and left SEVs were cannulated followed by insertion of the CA adhesive delivery catheter (Sapheon, Santa Rosa, California). This venous closure system also incorporates a 3cc (cubic centimetre) syringe, a dispenser tip and a dispenser gun (Sapheon)(Almeida et al., 2011).

Four SEVs were treated in total and the two swines were sacrificed at day 60 post-treatment(Almeida et al., 2011). The SEVs were harvested and sections were studied macro- and microscopically. Explanted segments from the caudad, middle and cephalad areas were completely occluded with no patent segments. On histology, fibrous tissue and inflammatory cells were present, with 1 of the 3 examined sections exhibiting fibrotic projections which caused occlusion of nearly the entire lumen. The wall was segmentally thickened by fibrous tissue and the lumen was dilated by an abundant clear space containing moderate amounts of debris and coalescing, tree-

like bands of macrophages and spindle cells. The clear space appeared surrounded by multinucleated giant cells, which were presumed to be reacting toward foreign material. Spindle cells with dense eosinophilic matrix replaced the tunica intima and disrupted the tunica media. Additionally, the wall was disrupted by numerous aggregates of histiocytes and lymphocytes with lymphoid follicles. Also, a dark-coloured bulge (entrapped blood) in the vein was observed, though not visible on the skin.

These changes observed in the treated veins are consistent with chronic foreign-body-type inflammatory response. Unwanted migration of CA was not found, nor was recanalisation present in any of the treated veins. Evaluation of control segments lacked any significant histologic changes(Almeida et al., 2011).

Human Studies

VenaSeal™ Closure System

The first clinical trial of using cyanoacrylate adhesive for the treatment of varicose veins recruited 38 patients with great saphenous vein incompetence in a prospective non-randomised study(Almeida et al., 2013). Consecutive patients were enrolled and followed up at 48 hours and 1, 3, 6 and 12 months after their intervention with a clinical examination and a duplex ultrasound scan. Complete occlusion of the treated segment was considered as treatment success. A disposable Saphon Closure System (SCS) was used which included a delivery catheter with hydrophobic properties to prevent CA-mediated adhesion to the vein wall(Almeida et al., 2013). The catheter was removed after venous closure has been confirmed and a single adhesive bandage was applied. No additional procedures were carried out and no compression stockings or bandages were applied. Approximately three quarters of the patients were females with a median age of 51 years (range: 26-77 years)(Almeida et al., 2013). The mean GSV diameter at the SFJ was 8.0 ± 2.2 mm and the mean length of vein treated was 33.8 ± 9.1 cm. The mean volume of CA glue used was 1.3mL (range: 0.6-2.3mL). All the veins treated were completely occluded at the 48 hour follow-up. By the 12 months follow up, 3 patients had developed recanalisations of GSV, giving a complete occlusion rate of 92.1%(Almeida et al., 2013). Seven patients developed post-operative thrombophlebitis, 1 patient

developed cellulitis and one patient had hyperpigmentation at 12 month due to the treated vein being very close to the skin. In addition, 8 patients had evidence of thread-like thrombus extension across the SFJ into the common femoral vein (CFV) at the 48-hour follow-up (protruding a length of $12.6 \pm 9.9\text{mm}$). All thrombus extensions had resolved without any anticoagulation by the 6 months follow-up. The VCSS scores showed improvement from 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months ($p < 0.0001$). This study set out to determine the feasibility of using CA in the treatment of saphenous vein incompetence. It also demonstrated an occlusion rate comparable to those of endothermal ablation methods in use. Patients were seen again at the 12 and 24 months period (Almeida et al., 2015). Three patients presented with a GSV recanalisation of more than 5cm at 1, 3 and 6 months, respectively, with the occlusion rate at the 24 months mark using a life-table analysis being 92% (Almeida et al., 2015). The VCSS score at 24 months was lower than baseline, although it was still higher than the score at 6 months. These results demonstrate that CA is potentially an alternative to the endothermal methods, especially as no tumescent is needed. No compression therapy is prescribed since the technique does not cause perforation of the vein wall. Two of the authors had connections with the funding company, Sapheon Inc., and with consulting firms with an interest in the device.

Proebstle and colleagues (2013) undertook a prospective, multicentre clinical trial of endovenous CA embolisation of refluxing GSVs in seven centres across Europe (the eSCOPE study) (Proebstle et al., 2015b). Symptomatic patients with GSV incompetence confirmed on duplex ultrasound were recruited and treated with CA, starting at 5cm distal to the SFJ. This distance was selected as it would provide enough space for the ultrasound compression between the delivery catheter and SFJ as well as to enable glue propagation toward the SFJ following injections. No post-procedure compression was used. No adjunctive treatment or reintervention was undertaken for three months after the intervention. Clinical and quality of life assessments were carried out at baseline and patients were followed up at 48 hours and at 1, 3, 5 and 12 months initially. Seventy patients were enrolled in total with 79% of them being females. The mean age was 48.4 years (range: 22-72 years). The mean diameter of the GSV at the SFJ was 7.8mm and the mean length was 37.6cm. The mean treatment time was 18.6 minutes (range: 8-74 minutes). Using a life-table method, the complete occlusion (defined as no patent segment of more than 10cm)

rate was 92.9% at the 12 months follow-up point(Proebstle et al., 2015b). The patients' clinical and QoL scores were significantly improved. The most common adverse events were phlebitic reaction, occurring in 8 limbs. A single patient had a 6mm extension of thrombus into the common femoral vein. This was successfully treated with low molecular weight heparin. Thus, this study demonstrated that CA was safe and effective in the treatment of GSV reflux and an RCT comparing the technique to endothermal methods have been advocated.

Study	Occlusion Rate	
	CAE	RFA
Almeida et al. (2013 and 2015) <i>(Feasibility and first human study)</i>	12 months: 92% 24 months: 92%	-
Proebstle et al. (2015) <i>(eSCOPE study)</i>	6 months: 94.3% 12 months: 92.9%	-
Morrison et al. (2015) <i>(VeClose study)</i>	3 months: 99%	3 months: 96%

Table 15. Summary of occlusion rates from studies using cyanoacrylate ablation (*VenaSealTM Closure System*) (CAE: cyanoacrylate adhesive; RFA: radiofrequency ablation)

In the VeClose trial, a multicentre randomised controlled trial comparing cyanoacrylate embolisation and radiofrequency ablation for refluxing great saphenous veins, two hundred and twenty-two patients were recruited and randomised to receiving CA or RFA(Morrison et al., 2015). All patients were prescribed compression stockings to wear continuously for 3 days and only during waking hours for an additional 4 days. The primary study end-point was complete closure of the GSV defined as closure of the entire treated vein with no discrete patent segments of more than 5cm. All patients were followed up for 3 months. Prespecified models were used to impute missing data. Most patients were females (79%) and Caucasian (94%) with the most common CEAP clinical class being 2 and 3. The mean age was 49.0 years and 50.5 years for CA and RFA, respectively. The occlusion rate in both groups was 100% at day 3. At the 3 month point, the occlusion rates were 99% for CA and 96% for the RFA group. However, this was obtained using predictive statistical models to compensate for missing data (31/222). At 3 months, VCSS, AVVQ and generic quality of life all showed significant improvement compared to baseline (3.5, $p<0.01$; 8, $p<0.01$ and 0.03, $p=0.01$, respectively). There was a non-significant increased incidence of phlebitis in the CA group (20 vs 15 events, $p=0.36$). Most of these cases were mild and were successfully treated with

over-the-counter non-steroidal anti-inflammatory agents. There was, however, also less ecchymosis at day 3 in the CA group compared to the RFA group with 94.5% of patients from the CA group having bruising in less than 25% of the treated length (8.2cm) compared to 81.5% of the RFA group (8.8cm) ($p<0.01$). Mean intraprocedural pain scores for both methods were similar (CAE 2.2 versus RFA 2.4; $p=0.11$). Multiple imputation models showed non-inferiority with both optimistic and pessimistic models.

VariClose® Vein Sealing System

The VariClose® Vein Sealing System was investigated by Bozkurt and Yilmaz (2016) by comparing this cyanoacrylate device to endovenous laser ablation (EVLA) in patients having GSV incompetence (Bozkurt and Yilmaz, 2016). In this prospective, non-randomised study, 314 patients were recruited, alternatively allocated to one of the treatment options and followed up for 1 year. The mean age was 40.2 years for the EVLA group and 42.5 years for the CAE group. The mean length of GSV treated was 29.7 ± 8.1 cm for EVLA and 29.8 ± 5.4 cm for CAE. Pain scores using a numeric 0-10 visual analog scale were recorded as 6.5 ± 2.3 for EVLA, compared to 3.1 ± 1.6 for CAE ($p<0.001$). The time taken for the ablation procedure was significantly quicker with CAE (15 minutes for CAE v/s 33.2 minutes for EVLA; $p<0.001$). The occlusion rate at 12 months was found to be 95.8% for CAE and 92.2% for EVLA ($p=0.318$) (Bozkurt and Yilmaz, 2016). There was similar significant improvement noted in both the clinical scores (using the VCSS) and QoL scores (using the AVVQ) compared to baseline. The EVLA group had 7 cases of paraesthesia compared to none in the CAE group ($p=0.015$). This study, therefore, showed that CAE injection using the VariClose® device is a safe and effective method of varicose vein treatment with potential advantages in terms of patient comfort and procedural duration.

Complications of CA

The most commonly reported complications of CA use for the treatment of varicose vein disease, so far, include ecchymosis and phlebitis (Morrison et al., 2015). In the first trial of this technique, thread-like thrombus extensions were noted (Almeida et al., 2013). It was hypothesised that this was probably due to the catheter being positioned 3cm from the SFJ and not offering enough space for the glue to propagate

along the GSV(Almeida et al., 2013). Thus, this distance was increased with improvement noted in the rate of this complication. Nowadays, the acceptable distance in contemporary practice is 5cm(Morrison et al., 2015; Proebstle et al., 2015b). A distance of 3cm is, however, still used with the VariClose® Vein Sealing System and, so far, no incidences of extension of thrombus into the deep venous system has been recorded.

A concern with the method of cyanoacrylate delivery is the possibility of the adhesive getting stuck in the delivery sheath, thereby, making movement and retrieval of the catheter difficult. Fortunately, no such instances have been recorded for this theoretical risk.

Cyanoacrylate use in other conditions are associated with other potential problems. For example, when used in the treatment of gastric varices, CAE poses the risk of systemic embolisation, with reported cases of pulmonary embolism, stroke and multi-organ infarction in patients with a patent foramen ovale, or even recurrent sepsis caused by the embolised CAE glue acting as a septic focus(Bhat et al., 2013). These latter adverse events have not been reported thus far with cyanoacrylate use in varicose veins.

The non-thermal, non-tumescent methods of mechanochemical ablation and cyanoacrylate glue have been shown to be at least equivalent to endothermal techniques and probably superior to UGFS with respect to occlusion rates following varicose vein treatment. They also appear to offer better comfort and earlier return to normal activities. Despite their undeniable promise, further studies will hopefully be able to provide additional evidence of their respective merits.

Two studies were, therefore, conducted in our unit to evaluate both MOCA and CAE:

1. A randomised controlled trial comparing MOCA to RFA
2. A pilot study evaluating CAE

2.2 Randomised Controlled Trial comparing Mechanochemical Ablation to Radiofrequency Ablation

2.2.1 Introduction

A multicentre randomised controlled study was conducted to compare the intraprocedural pain score of MOCA to that of RFA. The clinical score, quality of life scores as well as the occlusion rate at 1 and 6 months were also recorded.

2.2.2 Methods

3.2.2.1 Recruitment

Patients referred for treatment of symptomatic varicose veins to the Vascular Department of Charing Cross NHS Hospital (Imperial College NHS Trust) and Northwick Park NHS Hospital (North West London Hospitals NHS Trust) in London were studied. Patients older than 18 years of age with primary great saphenous vein (GSV) or small saphenous vein (SSV) incompetence were identified at their outpatient visit by a member of the clinical team and were added to the waiting list for endovenous ablation and given information about the trial.

The inclusion criteria were being older than 18 years and reflux greater than 0.5 seconds in the saphenous veins. The exclusion criteria are tabulated below (Table 16).

Exclusion Criteria
Current deep vein thrombosis (DVT)
Recurrent varicose veins
Arterial disease (ABPI<0.8)
Veins less than 3mm in diameter
Hypercoagulability
Patients who are unwilling to participate
Inability or unwillingness to complete questionnaires

Table 16. Exclusion criteria

Consenting patients were then subsequently randomised to either MOCA (group A) or RFA (group B) truncal ablation using an online computerised service (Sealed

Envelope™, London, UK). In patients receiving treatment to both lower limbs, the more symptomatic side was included in the study.

No procedural blinding was possible due to the difference in techniques used, however, the investigator at follow-up was blinded as to treatment group.

2.2.2.2 Clinical Severity Scoring

At recruitment, all patients were evaluated by a vascular specialist. Their Venous Clinical Severity Score (VCSS), Venous Disability Score (VDS) and Clinical-Etiological-Anatomical and Pathophysiological (CEAP) classification was assessed. This was repeated at the 1 month and 6 months follow-up.

2.2.2.3 Quality of Life Scoring

Patients were also asked to complete the Aberdeen Varicose Vein Questionnaire (AVVQ), a validated disease-specific quality of life (QoL) questionnaire for varicose veins, and the EQ-5D-3L and EQ-VAS (EuroQol Group), a generic QoL questionnaire, prior to their procedure. They were asked to complete these questionnaires again when they attended follow-up at 1 month and 6 months.

2.2.2.4 Interventions

All varicose vein procedures were carried out under ultrasound guidance and local anaesthetic by vascular surgeons familiar with and approved in both ablative methods. For both techniques, the GSV or SSV was cannulated under ultrasound guidance after injection of local anaesthetic (1% Lidocaine). The catheter tip was positioned 2cm distal to the sapheno-femoral junction (SFJ) or sapheno-popliteal junction (SPJ). Cannulation was performed at the most distal point of reflux where cannulation was possible.

The method used for RFA has been described before (Shepherd et al., 2010a). MOCA was performed as previously described by van Eekeren et al. (2013) except that 2% sodium tetradecyl sulphate (STS) (Fibrovein™, STD Pharmaceutical Products Ltd., Hereford, United Kingdom) (made by mixing equal volumes of 1% STS

and 3% STS) was used instead of polidocanol. The total volume of liquid sclerosant used was calculated as per the manufacturer's guidance.

Infusion Rate/ Volume, STS																	
length, cm		15		20		25		30		35		40		45		50	
diameter, mm		Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml	Rate, ml/cm	Volume, ml
3		0.08	1	0.08	2	0.08	2	0.08	2	0.08	3	0.08	3	0.08	3	0.08	4
4		0.11	2	0.11	2	0.11	3	0.11	3	0.11	4	0.11	4	0.11	5	0.11	5
5		0.14	2	0.14	3	0.14	3	0.14	4	0.14	5	0.14	6	0.14	6	0.14	7
6		0.17	3	0.17	3	0.17	4	0.17	5	0.17	6	0.17	7	0.17	8	0.17	9
7		0.20	3	0.20	4	0.20	5	0.20	6	0.20	7	0.20	8	0.20	9	0.20	10
8		0.23	4	0.23	5	0.23	6	0.23	7	0.23	8	0.23	9	0.22	10	0.20	10
9		0.27	4	0.27	5	0.27	7	0.27	8	0.27	9	0.25	10	0.22	10	0.20	10
10		0.30	4	0.30	6	0.30	7	0.30	9	0.29	10	0.25	10	0.22	10	0.20	10
11		0.33	5	0.33	7	0.33	8	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
12		0.36	5	0.36	7	0.36	9	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
13		0.39	6	0.39	8	0.39	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
14		0.42	6	0.42	8	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
15		0.45	7	0.45	9	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
16		0.49	7	0.49	10	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
17		0.52	8	0.50	10	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
18		0.55	8	0.50	10	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
19		0.58	9	0.50	10	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10
20		0.61	9	0.50	10	0.40	10	0.33	10	0.29	10	0.25	10	0.22	10	0.20	10

Figure 19. Infusion rate and volume of sodium tetradecyl sulphate (STS) needed for use with the mechanochemical ablation device based on vein diameter and length of vein being treated. 1mL is added to the calculated value to compensate for the dead space within the catheter.

Stockings were worn for two weeks post-procedure, and patients were advised to mobilise for at least 1 hour every day and to return to their work and normal activities when they felt able to.

2.2.2.5 Pain Scoring

Immediately after patients have undergone their endovenous procedure, but before concurrent varicosity treatment with phlebectomy was performed (if indicated), patients were asked to record their maximum and average pain score during the procedure using a validated Visual Analogue Scale (VAS) by placing a mark on a 100-mm VAS (Shepherd et al., 2010a; van Eekeren et al., 2013). The pain score was also recorded as a number on a scale of 0 to 10 (Katz and Melzack, 1999).

2.2.2.6 Time to Return to Normal Activities

Before being discharged on the day of their procedure, patients were given a diary to record when they resumed normal activities and, if in employment, went back to work. These were returned at the 1 month appointment. No routine discharge medication was provided, but patients were allowed to take non-prescription analgesia as required.

2.2.2.7 Outcomes Measured

The primary outcome of the study is the degree of pain during endovenous ablation using a validated patient reported Visual Analogue Score (VAS). The secondary outcomes are improvement in the AVVQ scores, EQ-5D-3L, VCSS, VDS and CEAP at 1 month and 6 months, and time taken to return to normal activities and work. The occlusion rate at one month and 6 months was also determined by carrying out a venous Duplex scan. The four possible findings are complete occlusion of the saphenous vein, proximal vein occlusion, distal vein occlusion and open (see Table 17).

Occlusion Type	Definition
Complete occlusion	Whole treated vein segment is occluded
Proximal occlusion	>5cm proximal vein segment occluded, but >5cm open distally
Distal occlusion	>5cm distal vein segment occluded, but >5cm open proximally
Open	Whole treated vein segment is open

Table 17. Definition of vein occlusion

2.2.2.8 Power Calculations

Power calculations were based on the primary outcome of pain during the procedure. Detection of a 20mm difference in maximum pain score with a standard deviation of pain score of 20mm was considered a significant difference. The minimum target size was calculated to be 94 patients (47 per group) at 90% power and 5% significance. Allowing for loss to follow-up or protocol violations, an overall target recruitment of 170 legs (85 per group) was estimated.

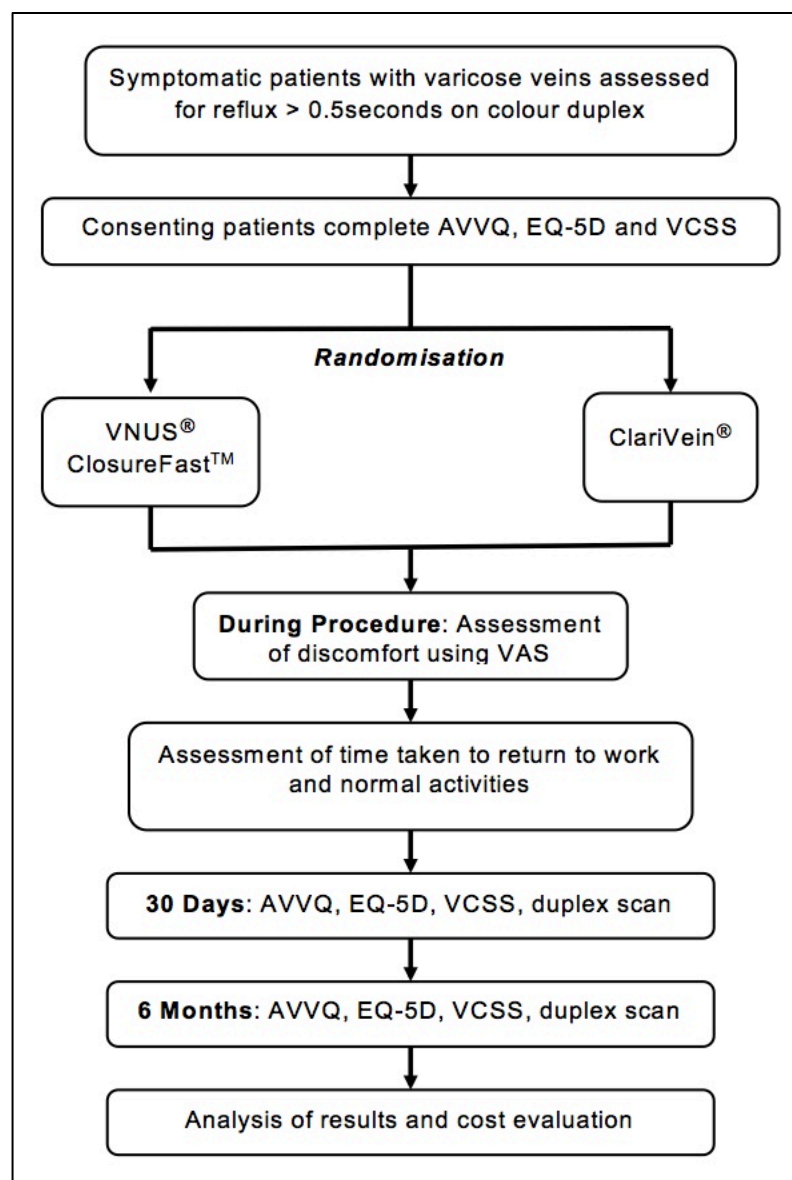


Figure 20. Flow diagram of the randomised controlled trial of radiofrequency ablation versus mechanochemical ablation

2.2.2.9 Study Registration and Ethical Arrangements

Ethical approval for the study was obtained from the National Research Ethics Service (NRES) Committee London – Chelsea (REC Ref.: **12/LO/0570**).

This study was registered on the Current Controlled Trials website (<http://www.controlled-trials.com>) (**ISRCTN06552809**).

2.2.2.10 Statistical Analysis

All statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, version 21, IBM, Armonk, USA). Significant differences between means were calculated using Student's T-test. A p-value of less than 0.05 was considered to be significant.

2.2.3 Results

One hundred and seventy patients were recruited between January 2013 and September 2014 and followed up for 6 months (Figure 21). Sixty-nine percent of patients were females with a mean age of 52.8 years. The proportion of GSVs treated was 86% and SSVs comprised 14%. Eighty-seven patients underwent MOCA and 83 patients RFA. Follow-up data was obtained in 76% of patients (n=129) at 1 month and 71% of patients (n=121) at 6 months.

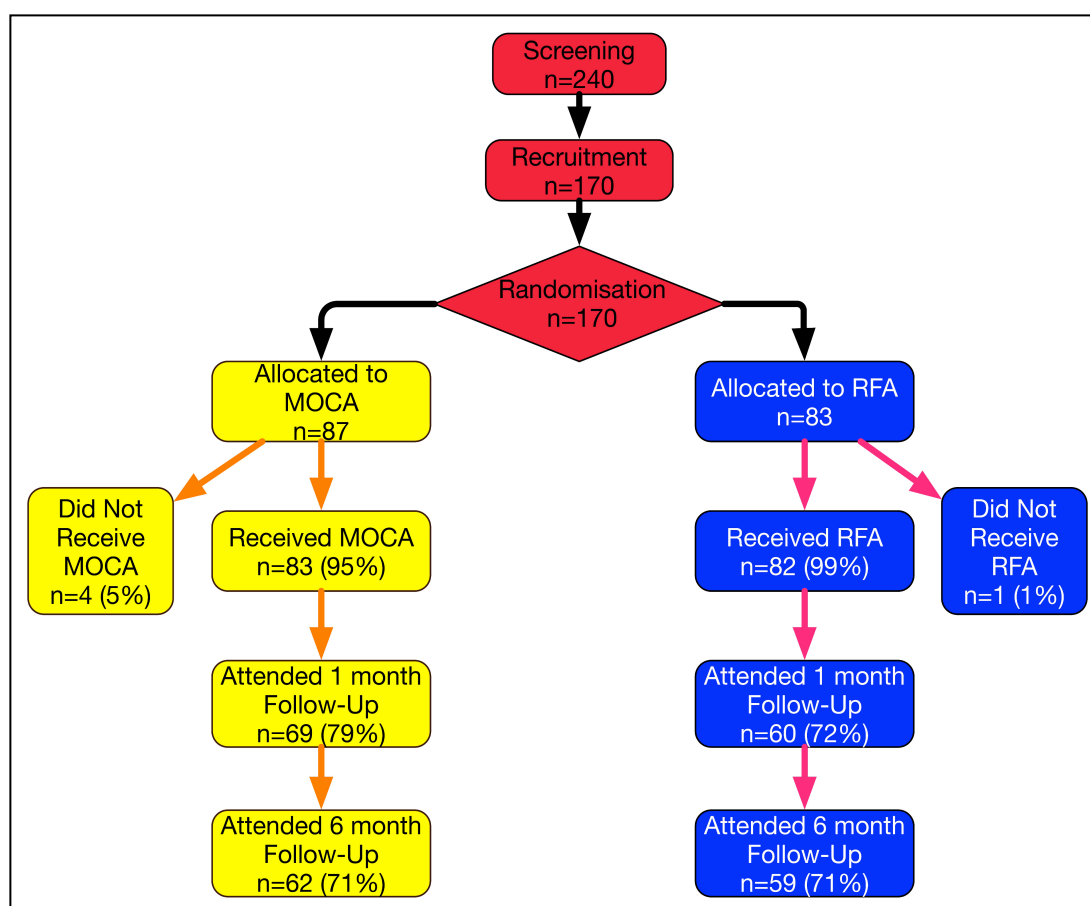


Figure 21. CONSORT diagram of the randomised controlled trial comparing MOCA to RFA

				MOCA	RFA	p-value
Females (%)				57	60	0.669
Age (years) [SD]				55.1 [18]	50.6 [17]	0.091
Left leg treated (%)				41	55	0.068
GSV (%)				88	84	0.429
Length of vein treated [Range]	GSV	vein (cm)	SSV	36.4 [16 to 65]	36.8 [12 to 56]	0.911
			SSV	23.3 [18 to 32]	19.3 [14 to 21]	0.318
Vein Diameter (mm) [SD]				7.0 [2]	7.4 [3]	0.325
Volume of sclerosant used (mL) [Range]				7.0 [2.0 to 11.0]	-	-
Avulsions carried out (%)				68	75	0.360

Table 18. Baseline characteristics and details of veins treated (MOCA: mechanochemical ablation; RFA: radiofrequency ablation; GSV: great saphenous vein; SD: standard deviation)

		MOCA (%)	RFA (%)	Total (%)
Baseline Clinical CEAP Classification	2	18.8	25.0	21.8
	3	27.5	22.4	25.0
	4	45.0	44.7	44.9
	5	6.3	6.6	6.4
	6	2.5	1.3	1.9

Table 19. The baseline CEAP classification (CEAP: clinical-etiological-anatomical-pathophysiological; MOCA: mechanochemical ablation; RFA: radiofrequency ablation)

The baseline scores for the Aberdeen Varicose Vein Questionnaire (AVVQ), Varicose Disability Score (VDS), Varicose Vein Clinical Score (VCSS) and Clinical Etiological Anatomical and Pathophysiological (CEAP) were collected. There were no significant differences in the baseline scores between the two treatment groups.

2.2.3.1 Intervention

The left leg was treated in 48% of cases and the great saphenous vein (GSV) ablated in 86.5% of procedures. Concurrent phlebectomies were carried out in 68% of patients in the MOCA group and 75% of those in the RFA group ($p=0.360$).

2.2.3.2 Primary Outcome Measure

The median maximum pain score using the visual analogue scale (VAS) was 15mm (interquartile range (IQR): 7-36mm) for the MOCA group compared to 33.5mm (IQR: 16-53mm; Mann Whitney, $p=0.003$) for the RFA group (Figure 22). Using the number scale of 0-10, the mean pain score was also found to be significantly less in the MOCA group (3.17 ± 2.4 v/s 4.58 ± 2.8 ; $p=0.001$).

The median average pain score during the procedure using the VAS was less in the MOCA group (10mm; IQR: 3-25mm) compared to 19.5mm (IQR: 9-38mm; Mann-Whitney, $p=0.003$) for endothermal ablation (Figure 23). The number scale also demonstrated a significantly lesser average pain when using MOCA than RFA (mean of 2.39 ± 2.3 v/s 3.24 ± 2.1 ; $p=0.021$).

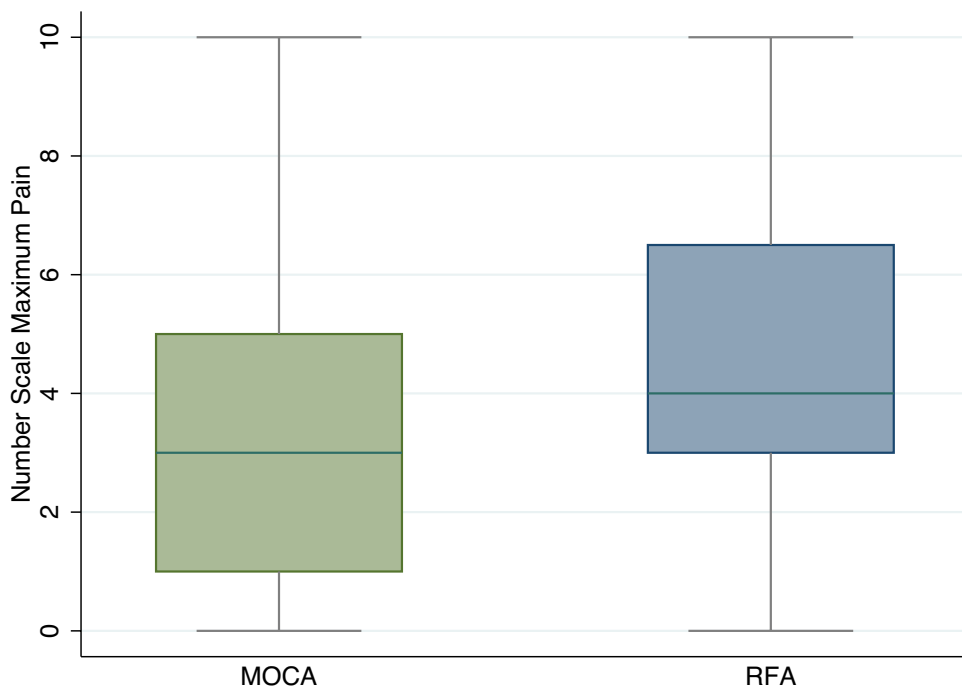
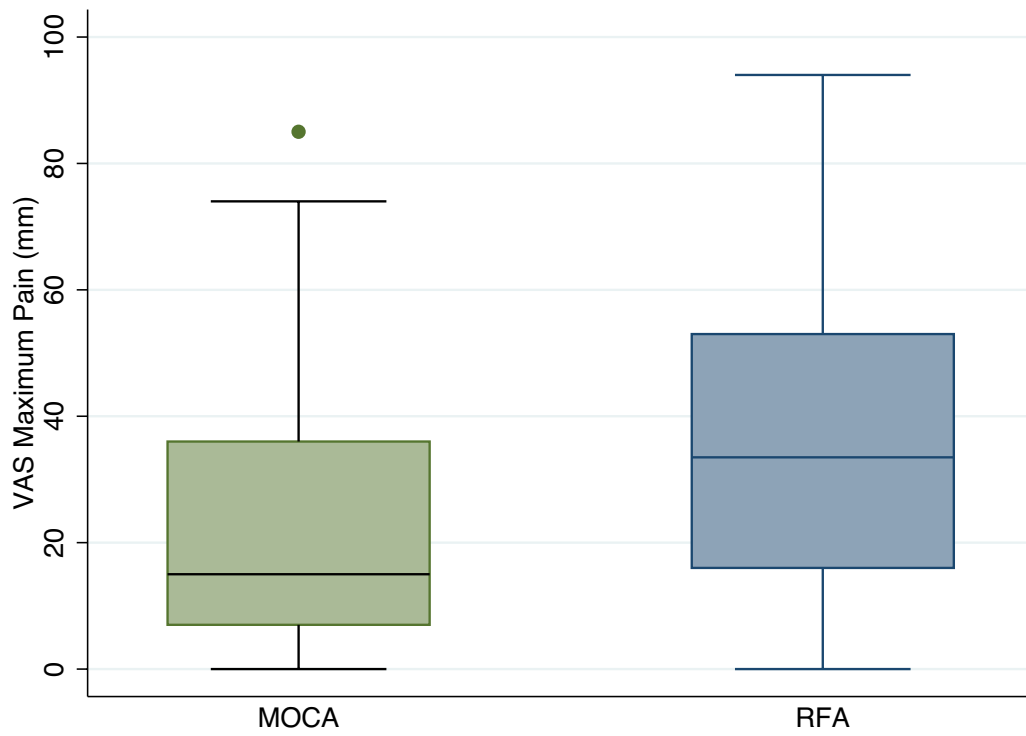


Figure 22. Maximum Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale ($p=0.003$) (Mann-Whitney), (b) – Number Scale ($p=0.002$) (Mann-Whitney).

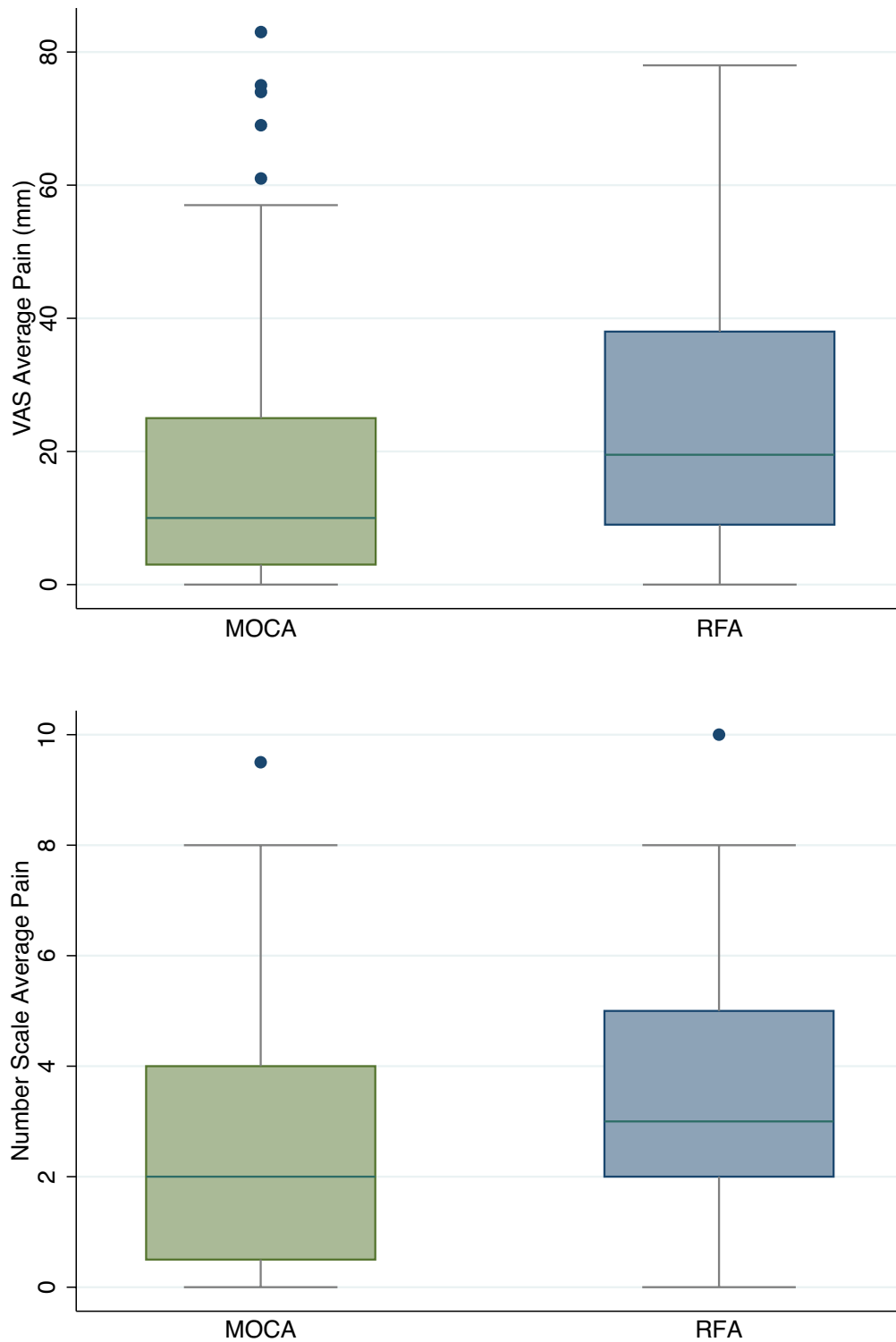


Figure 23. Average Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale ($p=0.003$) (Mann-Whitney), (b) – Number Scale ($p=0.004$) (Mann-Whitney).

The pain score in MOCA included the time from cannulation to vein ablation, while in RFA, it involved the time from cannulation, including infiltration of tumescence to completion of the ablation procedure.

2.2.3.3 Time to Return to Normal Activities

The mean time to return to normal activities was 3.4 (± 3.3) days for group MOCA compared to 3.6 (± 3.7) days for RFA ($p=0.700$).

The mean time to return to work was 3.7 (± 3.3) days for MOCA and 4.2 (± 3.5) days for the RFA group ($p=0.545$).

	Baseline		1 month Follow-up		6 months Follow-up		p-value
	MOCA	RFA	MOCA	RFA	MOCA	RFA	
Clinical Scores							
VCSS [SD]	6.4 [3]	5.6 [2]	2.7 [3]	3.3 [3]	2.5 [2]	2.7 [2]	0.746
VDS [SD]	1.4 [0.5]	1.3 [0.5]	0.51 [0.7]	0.65 [0.8]	0.27 [0.5]	0.5 [0.7]	0.124
QoL Scores							
AVVQ [SD]	23 [12]	22 [14]	14 [9]	16 [13]	13 [11]	16 [17]	0.605
EQVAS [SD]	80 [16]	80 [16]	84 [11]	77 [20]	81 [22]	77 [21]	0.458
EQ-5D-3L [SD]	0.70 [0.19]	0.75 [0.22]	0.79 [0.19]	0.77 [0.24]	0.81 [0.21]	0.69 [0.30]	0.011*

Table 20. Clinical and quality of life scores at baseline, 1 month and 6 months follow-up (AVVQ: Aberdeen Varicose Vein Questionnaire; EQ-5D-3L: EuroQol's EQ-5D instrument; EQ-VAS: EuroQol's Visual Analogue Scale; MOCA: Mechanochemical ablation; QoL: Quality of life; RFA: Radiofrequency ablation; VCSS: Venous Clinical Severity Score; VDS: Venous Disability Score). p-value: comparing scores at 6 months compared to baseline. * signifies significance. $p<0.05$ is considered to be statistically significant.

2.2.3.4 Clinical Scores at follow-up

Both groups showed significant improvement at both 1 and 6 months in all clinical measures, with no significant differences between the two groups (Figure 24 and Table 20).

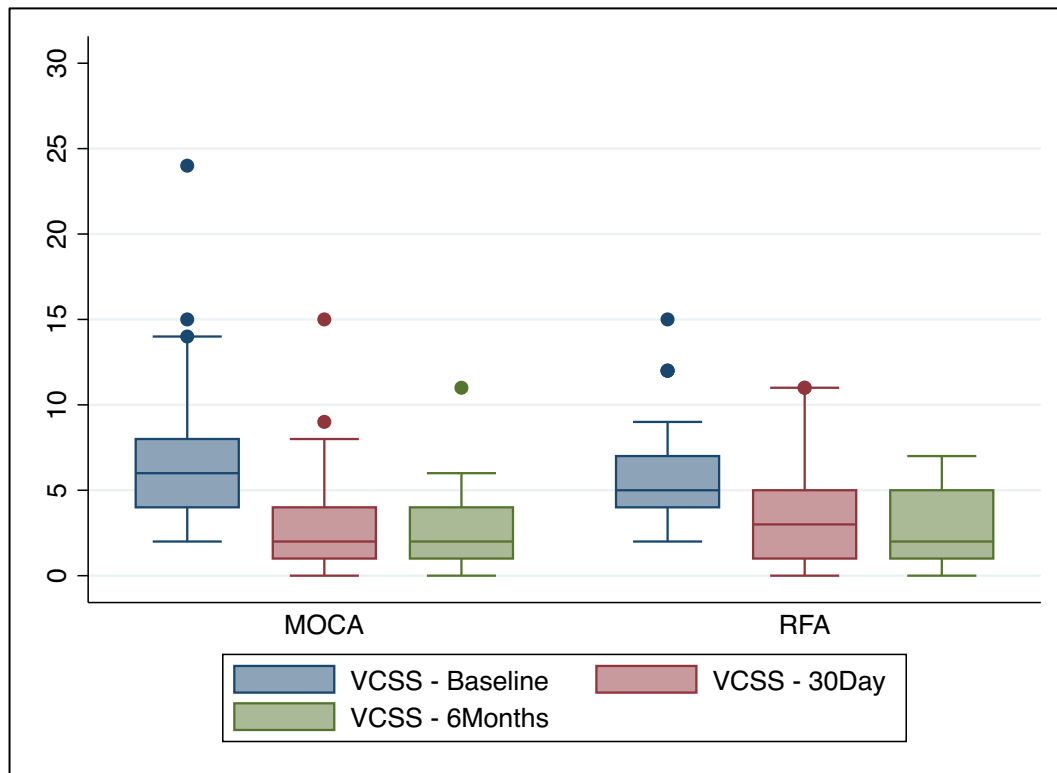


Figure 24. Venous Clinical Severity Score (VCSS) scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) ($p=0.746$).

2.2.3.5 Quality of Life Scores

The AVVQ, a measure of disease-specific quality of life, improved significantly in both groups by the one-month point and this remained similar at 6 months. AVVQ for MOCA at 6 months was 13 ± 11 compared to 14 ± 9 at 1 month, while for RFA, the corresponding figures were 16 ± 17 at 6 months and 16 ± 13 at 1 month. There was no difference between the two groups at 1 and 6 months (Figure 25 and Table 20).

EQ-VAS in both groups remained unchanged from baseline to 6 months. The EQ-5D for MOCA, however, improved to $0.81 (\pm 0.21)$ by the sixth month in MOCA, while EQ-5D worsened in RFA (0.69 ± 0.30 ; $p=0.011$) (Table 20).

2.2.3.6 Occlusion Rate

At 1 month, the complete or proximal occlusion rate was 92.7% in the MOCA group compared to 91.7% in the RFA group. At 6 months, the rates were 87.1% for MOCA

and 93.2% in the RFA group. There were no significant differences in the occlusion rates at 1 and 6 months ($p=0.40$ and $p=0.48$, respectively).

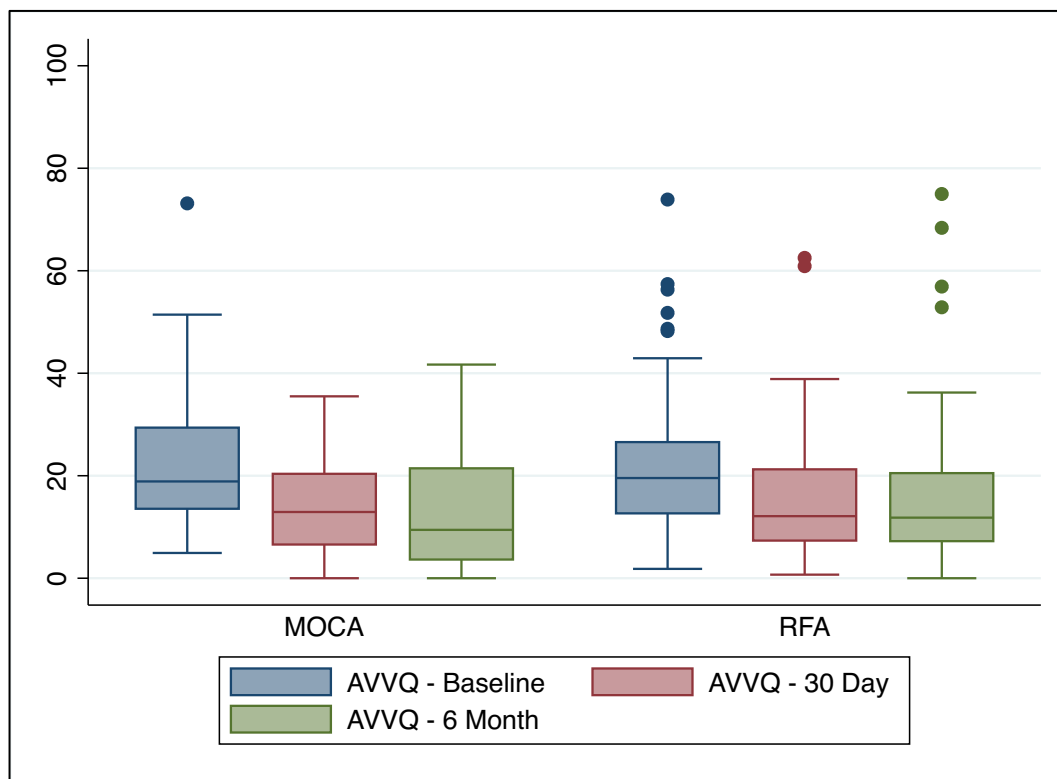


Figure 25. Aberdeen Varicose Vein Questionnaire scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) ($p=0.605$).

2.2.3.7 Complications

Two cases of deep vein thrombosis (DVT) were recorded (1 from each group). In the MOCA group, a tongue of thrombus protruded into the common femoral vein causing less than 50% reduction in diameter. This would have corresponded to an endovascular heat-induced thrombosis stage 2 (EHIT-2). A calf (popliteal vein) DVT occurred in the RFA group, which was an extension of a successfully treated SSV into the gastrocnemius vein, then to the popliteal vein. Neither patient with DVT had phlebectomies carried out.

Minor complications included 3 cases of thrombophlebitis in the MOCA group and 2 in the RFA group.

2.2.4 Discussion

With the efficiency of all the current endovenous techniques(Elias et al., 2013), intra-procedural issues with treatment such as pain and patient satisfaction have become more important. This was the first randomised controlled study comparing intra-procedural pain scores in patients receiving MOCA or RFA. The results from this study up to 6 months follow-up show that intra-procedural pain was significantly lower in patients undergoing MOCA compared to RFA. This difference may be explained by the additional injections required for tumescent infiltration. Patients from the MOCA group also showed a trend of earlier return to their normal activities, but this was not statistically significant. Importantly, early clinical, radiological and quality of life outcomes were equivalent between RFA and MOCA.

In a non randomised observational study of 68 patients, van Eekeren et al. found that post-procedural pain during the first 14 days was significantly lower in the MOCA group compared to patients having RFA (mean VAS over 14 days was 4.8 ± 9.7 mm in MOCA group versus 18.6 ± 17.0 mm; $p < 0.001$)(van Eekeren et al., 2013). The difference in pain scores is probably explained by the different methods used to ablate the incompetent veins. The RFA technique (thermal treatment) involves treatment by heat as well as tumescent anaesthesia infiltration to prevent thermal damage to surrounding tissues, both of which can be uncomfortable(van Eekeren et al., 2013). In that study, MOCA was also shown to be associated with an earlier return to normal activities(van Eekeren et al., 2013).

The overall occlusion rates in this cohort of patients was similar to that seen in other studies(Shepherd et al., 2010a; Gloviczki et al., 2011; Lattimer et al., 2012; Boersma et al., 2013; Elias et al., 2013; Marsden et al., 2013; van Eekeren et al., 2013) and longer term follow up is required before any definitive comments can be made on superiority of techniques with respect to patency.

These early results show a decreased pain profile for MOCA compared to RFA and flag up the potential benefits of the non-thermal, non-tumescent techniques compared to thermal treatment. Another NTNT, cyanoacrylate glue, nevertheless, had similar intraprocedural pain scores to RFA (CAE 2.2 versus RFA 2.4;

p=0.11)(Morrison et al., 2015), thereby questioning one of the presumed advantages of these newer endovenous methods.

2.2.5 Conflict of Interest

This study was funded by a commercial grant from ClariVein® manufacturer, Vascular Insights LLC. (Quincy, Massachusetts, USA), however, all study data collection, treatment and analysis was performed independently. Imperial College London was the research sponsor of the trial.

2.2.6 Funding

The research was funded by a research grant from ClariVein® manufacturer, Vascular Insights LLC. and a research grant from the Graham-Dixon Charitable Trust.

2.3 Pilot Study of Cyanoacrylate Adhesive use for the Treatment of Varicose Veins

2.3.1 Introduction

Cyanoacrylate adhesive is another technique available for varicose vein treatment. Similar to mechanochemical ablation, it is a non-thermal, non-tumescent (NTNT) method introduced to improve the patient experience during their varicose vein procedure.

A pilot study of the use of cyanoacrylate glue was, therefore, set-up. The device used was the Biolas VariClose® Vein Sealing System (FG Group, Ankara, Turkey). It has been reported that this method has had extensive evaluation in Turkey, with more than 8,000 patients treated in 200 centres over a 14-month period(2015). This vein sealing system has received its CE-marking, which indicates that the product meets all the legal requirements and product safety directives of the European Union (EU)(Hill et al., 2015).

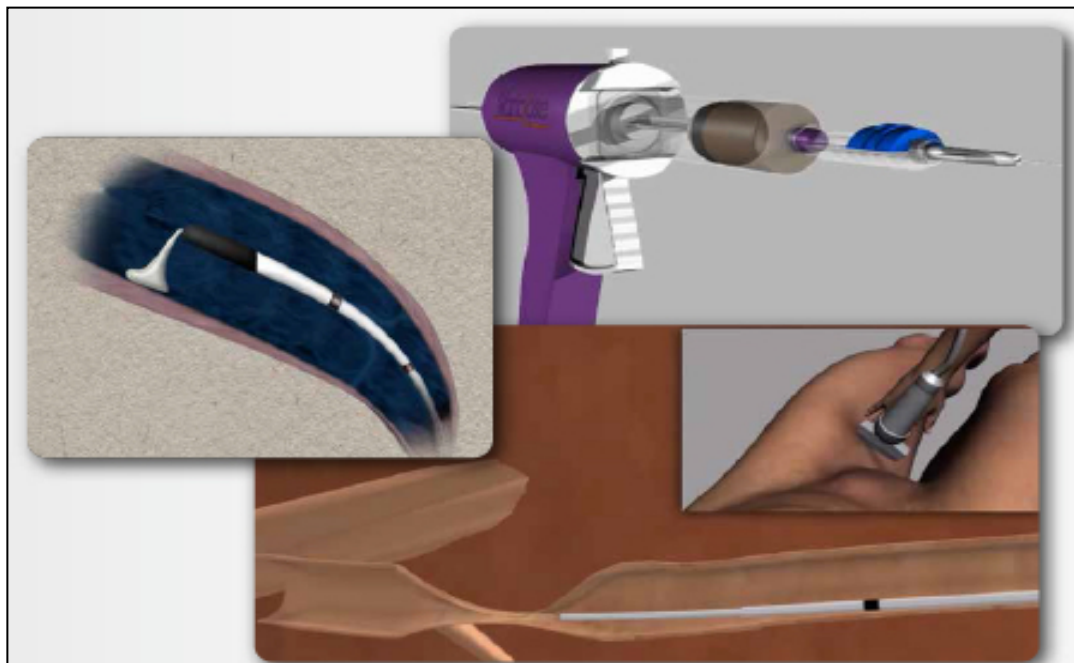


Figure 26. The Biolas VariClose® Vein Sealing System

2.3.2 Methods

2.3.2.1 Recruitment

Patients added to the waiting list for saphenous vein treatment at the Imperial College NHS Trust were approached and provided with information about this method. They were then invited to have their varicose vein procedure under local anaesthetic.

2.3.2.2 Inclusion and Exclusion Criteria

The inclusion criteria were:

1. Age > 18 years
2. GSV or SSV suitable for endovenous treatment

The exclusion criteria were:

1. Current DVT
2. ABPI < 0.8
3. Veins less than 3mm in diameter
4. Patients who are unwilling to participate
5. Inability or unwillingness to complete questionnaires

2.3.2.3 Clinical Scoring

At recruitment, all patients were evaluated by a vascular specialist. Their Venous Clinical Severity Score (VCSS), Venous Disability Score (VDS) and Clinical-Etiological-Anatomical and Pathophysiological (CEAP) classification was assessed. This was repeated at the 1 month and 6 months follow-up.

2.3.2.4 Quality of Life Scoring

Patients were also asked to complete validated disease-specific quality of life (QoL) questionnaire, namely the Aberdeen Varicose Vein Questionnaire (AVVQ) and the Chronic Venous Disease Quality of Life (CIVIQ-14) questionnaire. The CIVIQ-14 questionnaire was developed by Professor Launois with an educational grant from

Servier, a pharmaceutical company. Generic QoL questionnaires, the EQ-5D-3L and EQ-VAS (EuroQol Group), were also filled prior to their procedure. Patients were asked to complete these questionnaires again when they attended follow-up at 1 month and 6 months.

2.3.2.5 Interventions

All varicose vein procedures were carried out under ultrasound guidance and local anaesthetic. The GSV or SSV was cannulated under ultrasound guidance after injection of local anaesthetic (1% Lidocaine). The introducer sheath was positioned 6cm distal to the sapheno-femoral junction (SFJ) or sapheno-popliteal junction (SPJ). Cannulation was performed at the most distal point of reflux where cannulation was possible.

The adhesive was drawn up into a 5ml syringe, which was then connected to the cyanoacrylate catheter. The catheter was primed, advanced through the introducer sheath to a distance of 3cm distal to the SFJ or SPJ. With pressure applied onto the junction with the ultrasound probe, the adhesive was injected while simultaneously withdrawing the catheter at a rate of 2cm per second. The ultrasound was also advanced at the same rate down the leg. Additional pressure was applied to the saphenous vein afterwards for 30 seconds.

Following treatment of the saphenous segment, adjuvant phlebectomy or foam sclerotherapy was carried out to the tributaries, if clinically indicated. The entry point of the catheter was sutured with a synthetic, non-absorbable monofilament polypropylene suture. An injection of low molecular weight heparin (Enoxaparin 40mg) (not in patients on oral anticoagulants) and 625mg of oral Co-amoxiclav were administered perioperatively.

Compression stockings were not provided post-operatively. Those having adjuvant tributary treatment were provided with crepe bandage to wear for 24 hours.

2.3.2.6 Pain Scoring

Immediately after patients had undergone their endovenous procedure, but before concurrent varicosity treatment with phlebectomy or foam sclerotherapy was performed (if indicated), patients were asked to record their maximum and average pain score during the procedure using a validated Visual Analogue Scale (VAS) by placing a mark on a 100-mm VAS (Shepherd et al., 2010a; van Eekeren et al., 2013). The pain score was also recorded as a number on a scale of 0 to 10 (Katz and Melzack, 1999).

2.3.2.7 Time to Return to Normal Activities

Before being discharged on the day of their procedure, patients were given a diary to record when they resumed normal activities and, if in employment, went back to work. These were returned at the 1 month appointment. No routine discharge medication was provided, but patients were advised to take non-prescription analgesia as required.

2.3.2.8 Outcomes Measured

The primary outcome of the study is the degree of pain during endovenous ablation using a validated patient reported Visual Analogue Score (VAS).

The secondary outcomes are improvement in the AVVQ scores, CIVIQ-14 scores, EQ-5D-3L, VCSS, VDS and CEAP at 1 month, and time taken to return to normal activities and work. The occlusion rate at one month and 6 months was also determined by carrying out a venous Duplex scan. The four possible findings are complete occlusion of the saphenous vein, proximal vein occlusion, distal vein occlusion and open (see Table 17).

2.3.3 Results

Seventeen patients (20 limbs) were recruited and underwent treatment as above. In one patient, cannulation of the saphenous vein was not possible because of vein spasm. Eighty-five percent of limbs were reviewed at the 30-day follow-up.

The mean age was 54 (SD: ± 22) years. The mean baseline VCSS was 3.6 (± 2.5), which improved to 2.4 (± 3) at the 30-day point. Improvement was noted in the median EQ-VAS, AVVQ and CIVIQ-14 scores (see Table 21). Further analysis for statistical difference was not undertaken as this was a pilot study with a small number of patients.

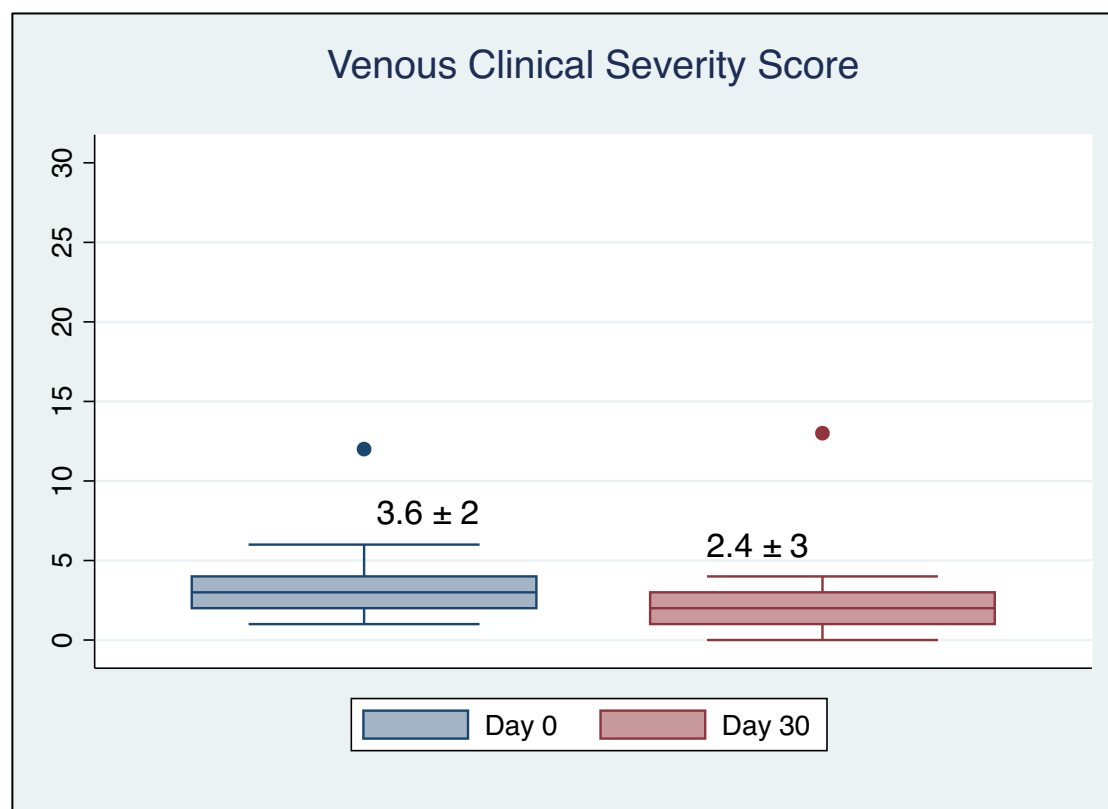


Figure 27. The Venous Clinical Severity Scores at baseline and after 30 days

	Generic		Disease-specific	
	EQ-VAS	EQ-5D	AVVQ	CIVIQ-14
Baseline [IQR]	80 [76-90]	0.714 [0.66-0.76]	15.1 [9.8-25.6]	27 [14-37]
30-day F/U [IQR]	85 [80-90]	0.704 [0.61-0.94]	10.0 [5.4-14.3]	12 [1.8-39]

Table 21. Improvement in the median generic and disease-specific quality of life (AVVQ: Aberdeen Varicose Vein Questionnaire; CIVIQ-14: Chronic Venous Insufficiency Questionnaire; EQ-5D-3L: EuroQol's EQ-5D instrument; EQ-VAS: EuroQol's Visual Analogue Scale; IQR: Inter-quartile range)

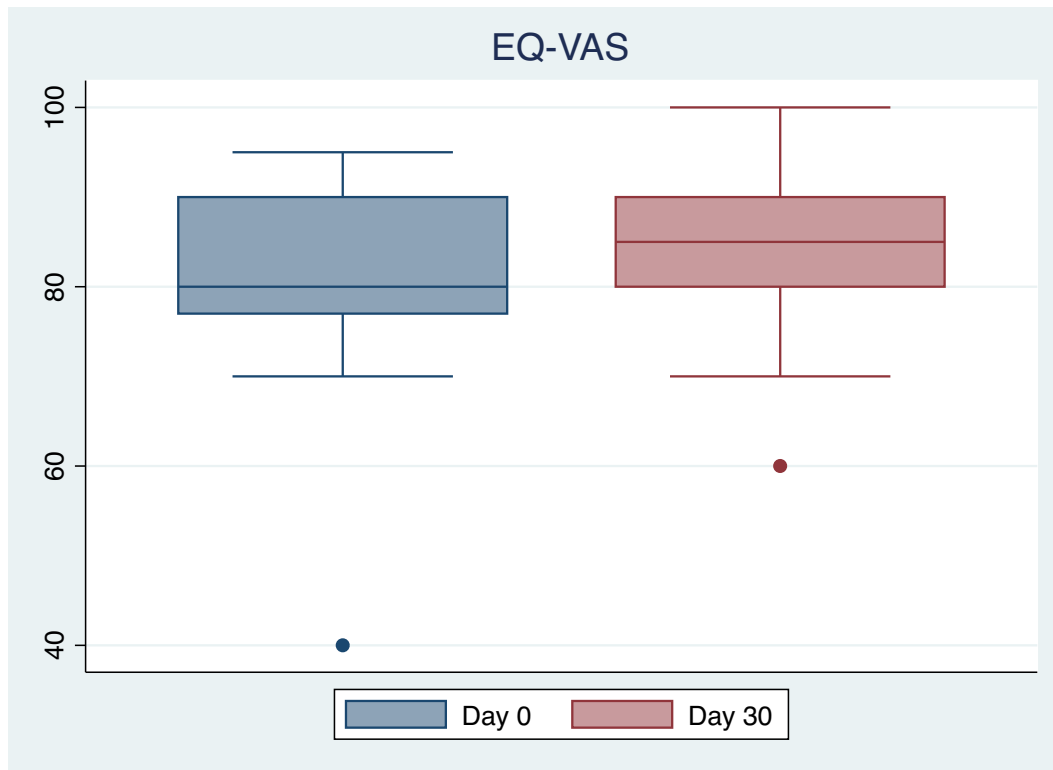


Figure 28. Comparison of the EQ-VAS scores at baseline and after 30 days

The median maximum pain score using a VAS was 34mm (interquartile range (IQR): 17-68mm) and 33mm (IQR: 7-58mm) for average pain. The corresponding figures for the numerical scale was 4 (IQR: 3-7) and 4 (IQR: 1-6), respectively. The complete/proximal occlusion rate at 30 days was 88%. One patient who was on an anti-Xa inhibitor (Rivaroxaban), had recanalization of her saphenous vein.

The median time to return to normal activities and work was 1 and 2 days, respectively.

One patient had phlebitis, for which she took a non-steroidal anti-inflammatory agent, with good effect.

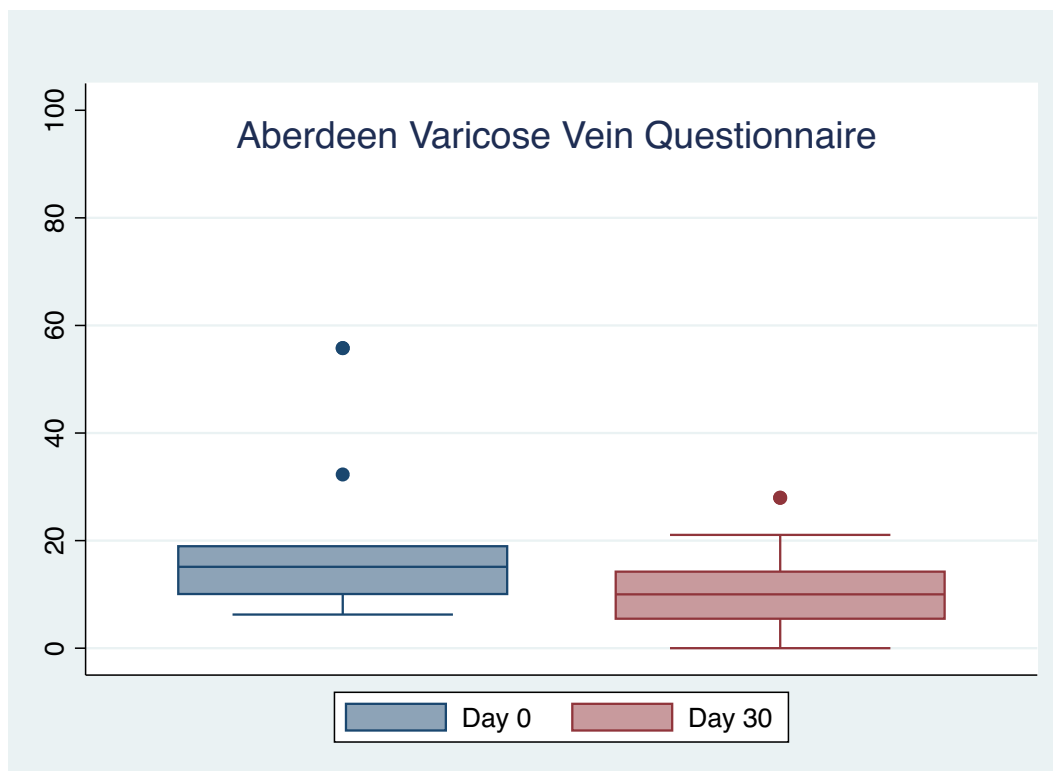


Figure 29. Comparison of the Aberdeen Varicose Vein Questionnaire (AVVQ) scores at baseline and after 30 days

2.3.4 Discussion

This pilot study demonstrates that this new cyanoacrylate adhesive is “safe” and associated with a low level of discomfort during its administration. It also leads to improvement in both the clinical scores and quality of life of patients. Further, adequately powered trials recruiting a sufficient number of patients would be able to clarify its safety and effectiveness.

CHAPTER 3

SYSTEMATIC REVIEW OF VARICOSE VEIN INTERVENTIONS

CHAPTER 3: SYSTEMATIC REVIEW OF VARICOSE VEIN INTERVENTIONS

3.1 Introduction

The 2013 NICE guidelines for the management of varicose vein disease offered new recommendations for referral and treatment of the condition (National Institute for Health and Care Excellence, 2013b). These new guidelines have been shown to bring about an increase in the number of patients being referred by up to 65% as well as a rise in the use of endovenous procedures carried out (Davies et al., 2015). Patients were also found to be referred at an earlier CEAP stage of their disease (Davies et al., 2015).

The NICE guidelines base their treatment recommendations mainly on the cost-effectiveness of the modality being used. In their analysis, they found that endothermal treatment was the most clinically effective treatment and produced the greatest gain in quality of life years (QALY) than other interventions (Marsden et al., 2015). Endothermal ablation had a 71% probability of being cost-effective at a threshold of £20,000 per QALY (Marsden et al., 2015).

Following their introduction and the potential they have shown to be of equivalent efficacy to the endothermal ablation methods, the newer NTNTs need to pass the test of both clinical and cost-effectiveness before they could be included in the armada to treat varicose veins by NICE.

Hence, a systematic review was undertaken with two main aims. These are:

- (a) To determine the relative efficacy of the different interventions by conducting a direct meta-analysis and network meta-analysis, and:
- (b) To determine the cost-effectiveness of the respective interventions.

3.2 Methods

A systematic review of randomised controlled trials comparing different treatment of varicose vein was undertaken. The search results were then reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009). In order to assess the methodological quality of included studies, the risk of bias assessment from the Cochrane Collaboration was used (Higgins et al., 2011).

Two investigators (RB and SO) independently conducted the literature search and assessed articles for inclusion. A third reviewer (AHD or DE) was available to resolve any disagreements between the two initial authors.

3.2.1 Re-intervention as an Outcome Measure

The process of finding an acceptable outcome measure to enable analysis of the effectiveness of each intervention proved arduous. This is mainly because there does not seem to be an agreement as to what measure to use when gauging if an intervention is effective. At present, there are a multitude of outcome measures in use, which complicates any attempt at comparing the results of different studies (Shepherd et al., 2011). These can mostly be classified as anatomical, haemodynamic, clinical or functional outcomes (see Figure 30).

A previous meta-analysis of endovenous therapies demonstrated a noticeable heterogeneity in terms of the criteria used for treatment success (van den Bos et al., 2009). Indeed, the criteria used included the occlusion rates, presence of reflux, presence of new varices, recanalisation and recurrences (van den Bos et al., 2009). Thakur et al. (2010) examined randomised clinical trials and found that 25 out of the 28 RCTs they selected measured recurrence as an end-point treatment (Thakur et al., 2010). Twenty-one of those used venous duplex ultrasonography, a diagnostic method, as the objective measure for recurrence (Thakur et al., 2010).

In their consensus document on recurrent varices after surgery (REVAS), Perrin et al. (2000) described REVAS as the presence of varicose veins in a lower limb previously operated on for varices (with or without adjuvant therapies) (Perrin et al., 2000).

However, they commented that this was a clinical definition that includes ‘true recurrences’, residual veins and varicose veins as a consequence of the disease, and described both clinical and diagnostic tests to enable a diagnosis of REVAS(Perrin et al., 2000). They highlighted a lack of agreement on the terminology used, which precluded the creation of a scientific base and the ability to adequately compare different studies. The consensus document identified two main groups of patients with REVAS, those with symptoms and those attending a routine outpatient follow-up(Perrin et al., 2000), thereby suggesting that not all patients with recurrent varicose veins necessarily develop symptoms or require additional treatment.

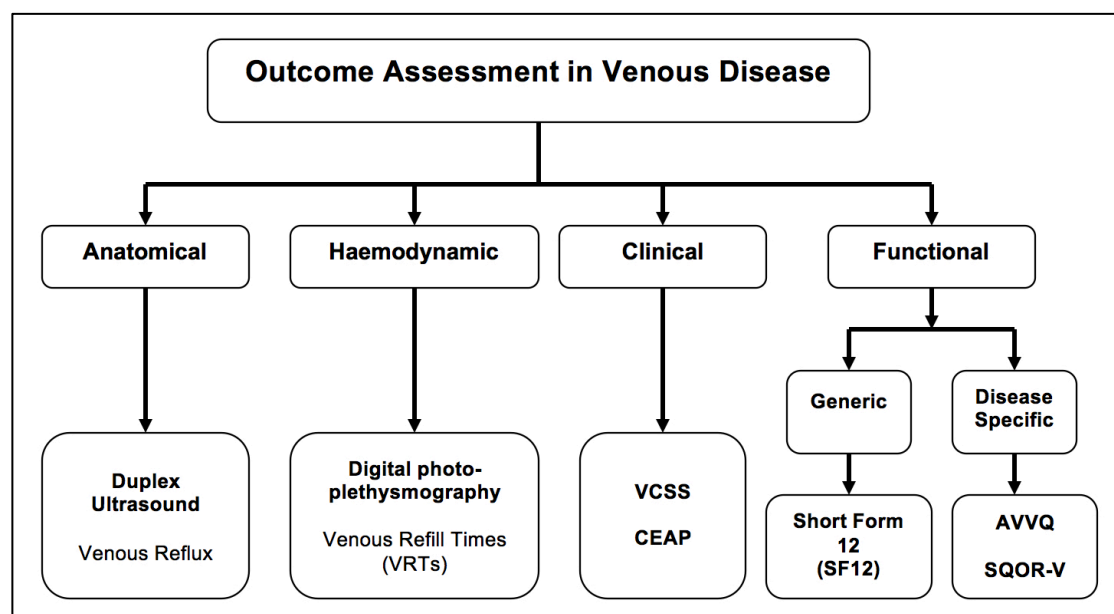


Figure 30. Outcome assessment in venous disease (AVVQ: Aberdeen Varicose Vein Questionnaire; CEAP: Clinical-Etiological-Anatomical-Pathophysiological; SQOR-V: Specific Quality of Life and Outcome Response-Venous; VCSS: Venous Clinical Severity Score) (from Shepherd et al., 2011)

As a result of all this uncertainty in terminology and definition, it was felt that one of the most consistent measure as to the effectiveness of a varicose vein intervention was the need for further treatment: any previously treated patient with a symptomatic recurrence will need to be considered for another intervention. This is the final step a formerly treated individual has to go through, regardless of the type of recurrence experienced, and is constant throughout most healthcare systems. Analysis of this outcome measure will not only allow a determination of the need for re-treatment with each method, but will also provide a reliable estimate of the longer-term cost and impact of each treatment modality.

Hence, the main outcome from this meta-analysis is to find out the re-intervention rate of GSV treatment as well as to determine the QoL improvement (if any) achieved. The time horizon used was 5 years.

3.2.2 Search Strategy

A systematic review was performed using the MEDLINE and Embase databases. The search strategy employed intended to include any RCT comparing the different treatment modalities for varicose veins. These were compression therapy (CONS), surgery (high ligation and stripping: HL/S), UGFS, EVLA, RFA, MOCA and CAE. The databases were searched from commencement to July 2015. Additional references were obtained by going through the list of references from the included RCTs and related articles.

As the main aim of the systematic review was to determine the clinical and cost-effectiveness of the newer NTNTs, non-randomised controlled trials of MOCA and CAE were also considered.

3.2.3 Inclusion Criteria

RCTs and non-RCTs of NTNTs were included if they reported on comparison of different interventions for treatment of the GSV. Only articles in English from 2000 to July 2015 were considered for inclusion. Once duplicates were excluded, full-text articles were reviewed and included in the systematic review if they met the inclusion criteria.

3.2.4 Data Extraction and Synthesis

Data was extracted for the populations included, treatment received, anaesthesia used, procedure times, quality of life improvements, clinical improvements, occlusion rates, recurrence rates and re-treatment rates. The purpose of the data extraction was to enable a meta-analysis to be performed (if suitable data was available) and to evaluate the cost-effectiveness of the different interventions.

3.2.5. Need for re-treatment

Re-intervention of the truncal vein indicates failure of the initial treatment or recurrence of symptoms. In patients receiving re-treatment, it is assumed that the health-related quality of life (HRQoL) is impaired from the time of their index procedure to the time of them requiring re-intervention. In practice, re-intervention can occur anytime between 6 months and 5 years following the initial treatment. Re-interventions have also previously been found to happen at approximately a constant rate up to 5 years(van den Bos et al., 2009).

For the purposes of this analysis, it is assumed that the minimum and maximum time for symptoms to recur is 6 months and 5 years, respectively, and that, on average, re-interventions are performed during the third year. Other assumptions made include the method of re-treatment, with 75% being treated with UGFS, 12.5% with endothermal ablation and 12.5% with surgery(van der Velden et al., 2015).

Varicose tributaries (varicosities) can either be treated simultaneously or at a different time as the truncal vein. Often, treatment of the GSV only is sufficient to improve the appearance and prominence of these varicosities. This has resulted in clinicians avoiding treating them at the initial procedure and adopting a 'wait-and-see' approach. However, the AVULS trial, comparing concurrent and delayed treatment of varicosities, found that simultaneous treatment was more effective, especially in terms of patients' gain in quality of life(Lane et al., 2015b). The model utilised assumes that concomitant phlebectomy will be used preferentially in all the treatment options under investigation, except for UGFS. Treatment of residual varicosities is predominantly via ambulatory phlebectomy (surgery) or UGFS.

3.2.6 Cost-Effectiveness Analysis

The cost-effectiveness analysis compared the various methods used with respect to QALYs (quality-adjusted life years) gained and cost of each modality to treat GSV incompetence. The cost perspective utilised was that of the National Health Service and social care system at 2015 prices. Both the costs and QALYs are discounted at 3.5% per year as per the NICE guidelines(National Institute for Health and Care Excellence, 2013a). A decision tree model was used, with re-intervention as the principal measure of treatment effectiveness. Re-intervention included re-treatment of

patients for symptomatic residual varicosities or, for recurrence or failed initial treatment of the truncal GSV incompetence. The assumption made was that the need for re-treatment of residual varicosities was independent from the need for re-interventions on truncal GSV incompetence. The time period considered for re-intervention was between 6 months and 5 years.

The overall cost of a given procedure is estimated as the sum of the cost of the procedure (staff time plus operating room overheads), equipment and consumables (amortised value of high-cost capital items such as generators, access catheters ablation fibres, sclerosing solutions and anaesthetic) as well as other related costs (preparation time, recovery time and other equipment cost). The probability that a given intervention was cost-effective was determined by utilising the commonly accepted NICE threshold of £20,000-£30,000 per QALY gained.

Probabilistic sensitivity analysis was carried out to determine the factors impacting on the total mean cost and QALYs. One thousand Monte-Carlo simulations of the model were performed to ascertain the probability that a chosen treatment has the highest net benefit at different cost threshold.

3.2.7 Assessment of Risk of Bias

The risk of bias for both RCTs and non-RCTs was conducted using the Cochrane collaboration criteria (Higgins et al., 2011) and the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) assessment tool (Sterne et al., 2016), respectively. This evaluation was carried out by DE and validated by another investigator (MOO).

The Cochrane collaboration's assessment of risk of bias includes seven items, namely, selection bias, allocation concealment, performance bias, detection bias, short-term attrition bias (missing data), long-term attrition bias and reporting bias. An attrition rate of less than 20% and an absolute difference in attrition rates between treatment groups (or to calculate using an acceptable method) less than 10% was considered as low risk of bias. In addition, a study was considered as having a low risk of bias if it reported on outcomes over at least 6 months.

The ROBINS-I assessment tool for non-RCTs similarly considers seven items. These are confounding, selection of patients into the study, classification of intervention, departures from intended interventions, missing data, measurement and reporting results. Studies were ascribed a low risk of bias if patients were recruited prospectively and consecutively, and that patient characteristics were similar between the groups under consideration.

3.2.8 Registration

The protocol for this systematic review was recorded on the PROSPERO (International Prospective Register of Systematic Reviews) register (registration number: **CRD42015029618**)(Epstein et al., 2015).

PROSPERO was launched by the Centre for Reviews and Dissemination at the University of York in February 2011(Palepu et al., 2011). It enables the prospective registration of systematic review protocols, with the aim of preventing the duplication of systematic reviews, reducing reporting biases and improving transparency(Palepu et al., 2011). Registration is free, but involves submitting the protocol to a panel of experts before publication onto the registry(Chien et al., 2012).

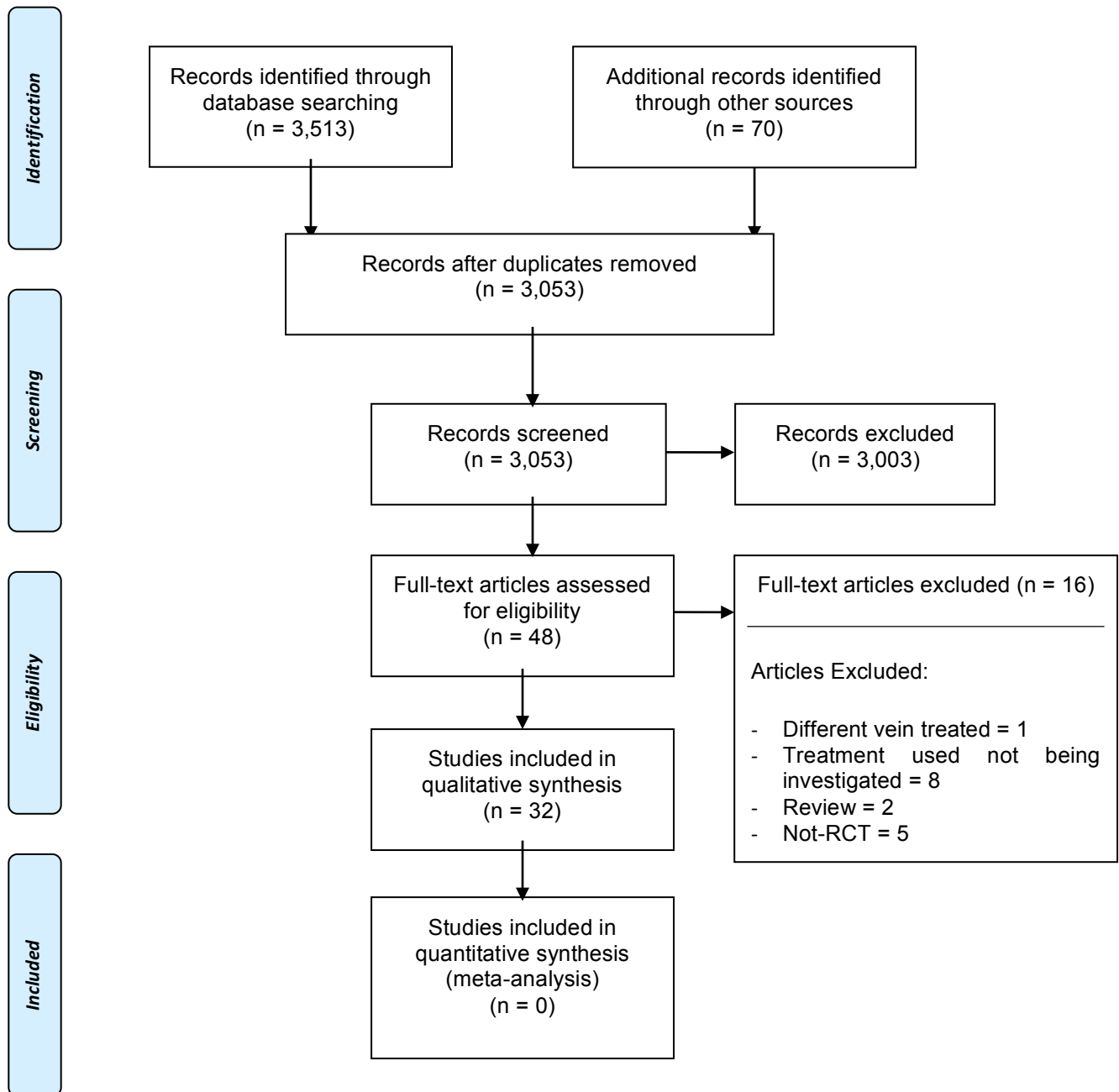
3.3 Results

3.3.1 Literature Search

Systematic review of the literature, review of references to identify additional articles and removal of duplicates resulted in 3,513 articles being considered (Figure 31). After title screening and review of abstracts, 48 eligible articles were identified. After review of full-text articles, 32 randomised controlled trials remained for qualitative analysis. One of the RCTs reported on two independent randomised studies and, so, was considered separately. A total of 33 RCTs was, thus, identified from that search. As there was insufficient randomised evidence of MOCA and CAE, a further search of the literature was undertaken which resulted in the identification of 10 articles reporting on comparative non-randomised studies involving one of the NTNTs. Therefore, a grand total of 43 studies were reviewed.

Information on truncal vein re-intervention was provided by 16 studies (13 RCTs and 3 non-RCTs). No studies (neither RCT nor non-RCT) reported on re-intervention data for CAE, while only data from non-RCT was available for MOCA.

Figure 31. PRISMA flowchart of randomised controlled trials (RCTs) comparing different interventions for treatment of varicose veins



3.3.2 Network of Treatment Comparisons

A network graph of evidence for truncal vein re-interventions from the thirteen RCTs shows that 8 randomised studies compared surgery (HL/S) to EVLA, 5 compared HL/S to UGFS and 1 compared HL/S to conservative treatment (CONS) (Figure 32). There were 4 trials comparing EVLA to UGFS and 1 comparing EVLA to RFA. Three RCTs reported on direct comparisons between HL/S, EVLA and UGFS. No studies compared RFA directly to HL/S, UGFS or CONS, and none provided a head-to-head comparison between CONS and EVLA or UGFS.

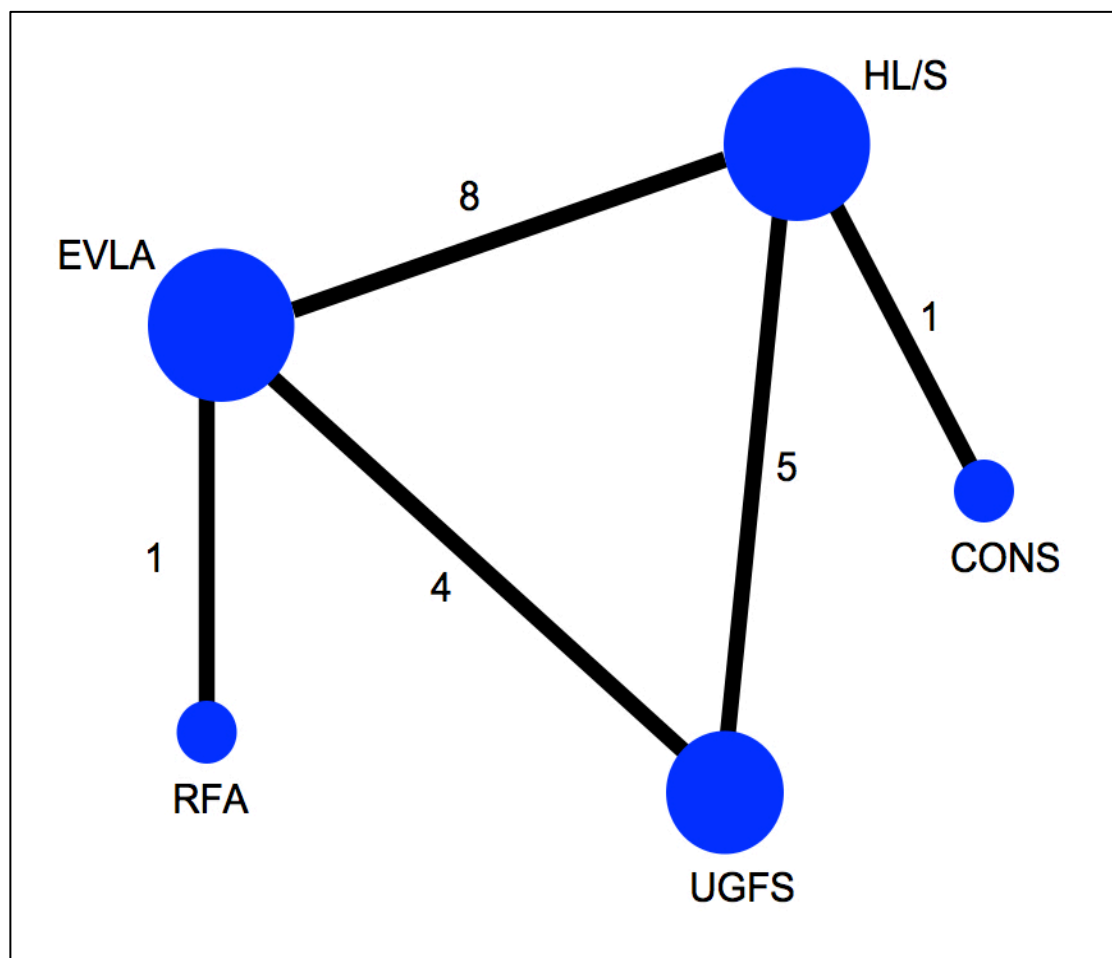


Figure 32. Network graph of the evidence for re-interventions on the truncal vein from 13 RCTs. Three studies were head-to-head comparison of EVLA-HL/S-UGFS. (CONS: conservative treatment; EVLA: endovenous laser ablation; HL/S: high ligation and stripping; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

3.3.3 Re-intervention of the Great Saphenous Vein

Re-intervention data of the truncal GSV obtained from the 13 RCTs was analysed using a random effects meta-analysis for each head-to-head comparison. A random effect meta-analysis model was utilised as this assumes that the treatment effect observed in each study varies because of real differences in the treatment effect along with sampling variability (chance)(Riley et al., 2011). Direct comparison of treatment effect demonstrates that HL/S and EVLA result in fewer re-interventions compared to either conservative care or UGFS. The rate of re-intervention was found to be similar between RFA and EVLA, and between EVLA and surgery (Figure 33).

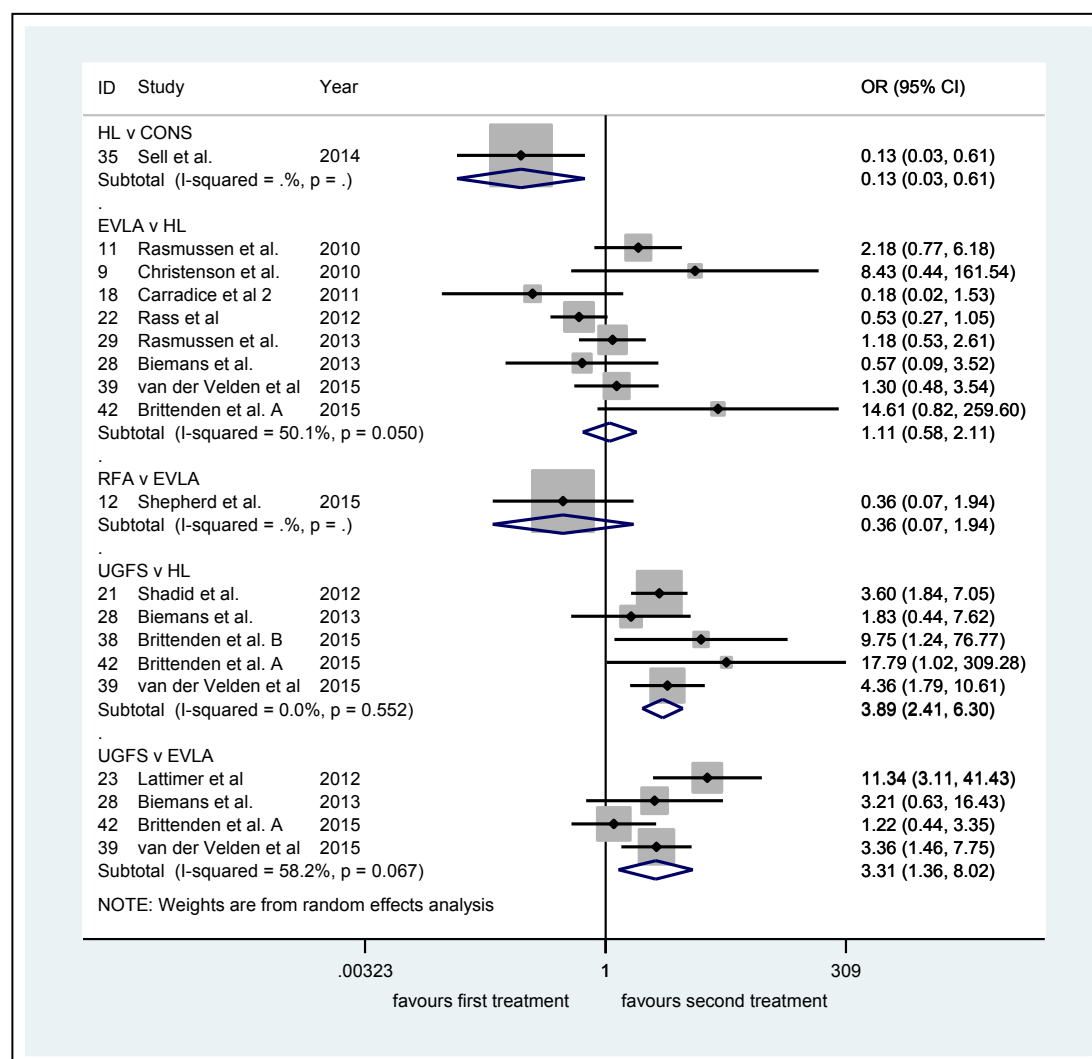


Figure 33. Forest plot of direct evidence for re-intervention on the truncal GSV using odds ratios (CONS: conservative treatment; EVLA: endovenous laser ablation; HL: high ligation and stripping; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

Since it was not possible to directly compare RFA with CONS, HL/S and UGFS, and CONS with EVLA and UGFS, a network meta-analysis (NMA)(Mills et al., 2013), allowing inferences to be made on interventions not compared directly, was performed. NMA confirms similar re-intervention rates of EVLA versus UGFS, surgery versus conservative care, and surgery versus UGFS as in the head-to-head comparisons.

To determine the consistency of the NMA, a direct estimate of the relative risk of each head-to-head pair can be compared with an indirect estimate of the relative risk using the NMA. Hence, the direct treatment effect of EVLA versus HL/S can be compared with the indirect treatment effect of EVLA versus HL/S via UGFS, a common comparator. The ratio between the direct and indirect treatment effect is 1.29, an acceptable degree of consistency in NMA as it is significantly less than 2 (one-tailed p-value=0.709). Despite not directly compared, NMA reveals that patients receiving EVLA are less likely to require re-intervention of their GSV compared to patients receiving conservative care (odds ratio (OR): 0.13; 0.02-0.82)(Figure 34 and Table 22). NMA also indicates that a higher probability of requiring re-intervention in patients undergoing UGFS compared to HL/S (OR: 3.44; 1.90-6.23), EVLA (OR: 3.56; 1.95-6.51) and RFA (OR: 9.80; 1.36-70.7) (Figure 34).

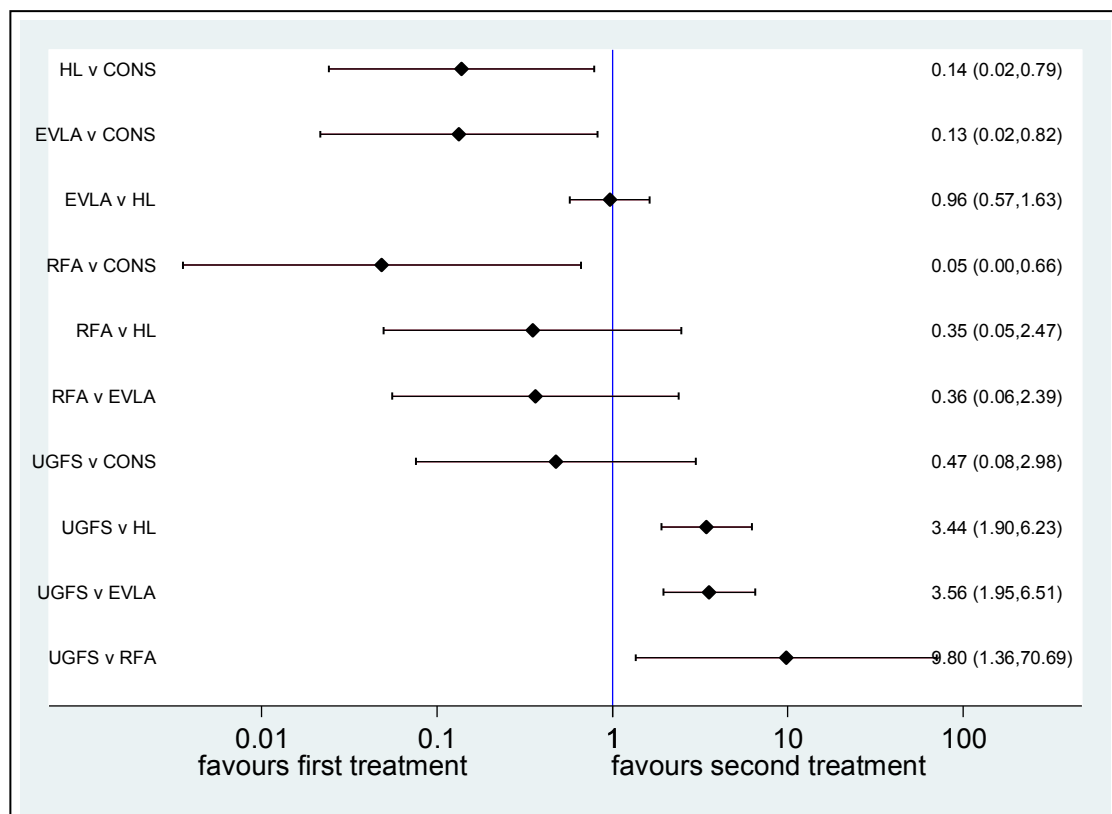


Figure 34. Forest plot of re-intervention of truncal veins using odds ratios estimated from a network meta-analysis (CONS: conservative care; EVLA: endovenous laser ablation; HL: high ligation and stripping; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

Intervention	Comparator	Mixed treatment comparisons from NMA			Direct treatment comparisons from RCTs			
		Odds ratio	95% CI		Odds ratio	95% CI		Number of RCTs
HL/S	CONS	0.138	0.024	0.786	0.13	0.03	0.61	1
EVLA	CONS	0.133	0.022	0.819				
EVLA	HL/S	0.965	0.571	1.629	1.11	0.58	2.11	8
RFA	CONS	0.063	0.003	1.458				
RFA	HL/S	0.454	0.033	6.259				
RFA	EVLA	0.471	0.036	6.155	0.47	0.04	5.31	1
UGFS	CONS	0.474	0.075	2.982				
UGFS	HL/S	3.436	1.896	6.228	3.89	2.41	6.30	5
UGFS	EVLA	3.563	1.951	6.506	3.31	1.36	8.02	4
UGFS	RFA	7.570	0.540	106.146				

Table 22. Odds ratio for re-intervention estimated from a network meta-analysis of different treatment (EVLA: endovenous laser ablation; HL/S: high ligation and stripping; NMA: network meta-analysis; RCT: randomised controlled trial; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

When ranking each treatment according to the highest probability of being the least likely to require re-intervention, RFA is ranked first, followed by EVLA, surgery, UGFS and, finally, conservative care (Table 23).

Rank	CONS	HL/S	EVLA	RFA	UGFS
Best	0.5	15.2	19.0	65.2	0.1
2nd	1.1	39.5	48.3	10.5	0.6
3rd	4.2	43.2	30.8	16.0	5.8
4th	18.9	2.0	1.9	6.8	70.4
Worst	75.3	0.1	1.5	1.5	23.1

Table 23. Probability of being the least likely treatment to require re-intervention (EVLA: endovenous laser ablation; HL/S: high ligation and stripping; NMA: network meta-analysis; RCT: randomised controlled trial; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

3.3.4 Analysis of Non-Randomised Trials

Three cohort studies reported on MOCA with a follow-up period of one to six months (van Eekeren et al., 2011; Elias and Raines, 2012; Bishawi et al., 2014). There was one re-intervention in 81 patient-years, suggesting a re-intervention rate of approximately 1.2 per 100-patient years, which is similar to EVLA, RFA and HL/S (Figure 35). However, there is insufficient data to derive any definitive conclusions. No data could be obtained as regards re-intervention following CAE and, therefore, no further analysis was possible.

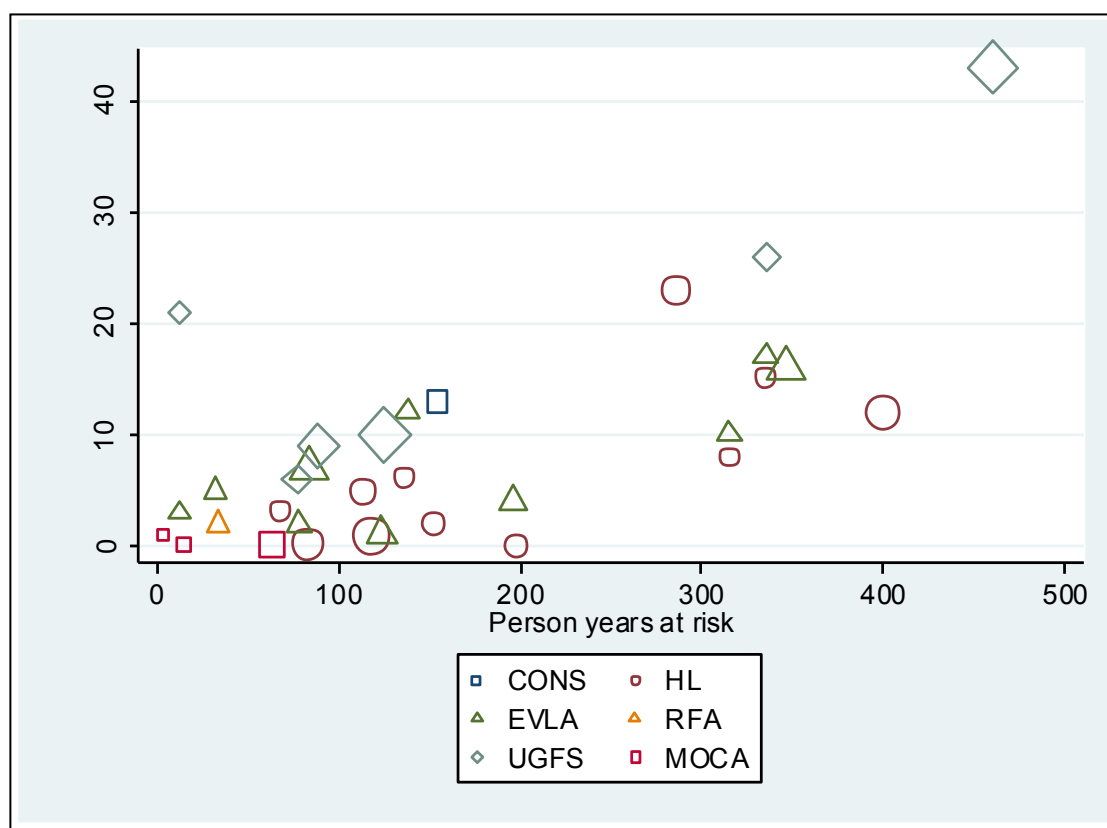


Figure 35. Number of re-interventions needed on the truncal vein estimated as per person years at risk using data from randomised controlled trials and non-randomised controlled trials (cohort studies). The area of each shape is proportional to the number of participants in the study. (CONS: conservative care; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

3.3.5 Analysis of Health-Related Quality of Life

The generic score using EuroQol's EQ-5D was reported in 5 RCTs for 1-13 weeks(Carradice et al., 2011b; Nordon et al., 2011; Brittenden et al., 2015; Morrison et al., 2015; Bootun et al., 2016a) and 5 RCTs reported for a period extending beyond 6 months(Michaels et al., 2006; Rasmussen et al., 2007; Carradice et al., 2011b; Brittenden et al., 2015; van der Velden et al., 2015). This shows that, between 1-13 weeks, the improvement in EQ-5D was similar for HL/S, EVLA, RFA, MOCA and CAE (Figure 36) and, ≥ 6 months, it was similar for HL/S and EVLA (Figure 37). However, at both time points, EVLA was shown to have a greater improvement than UGFS.

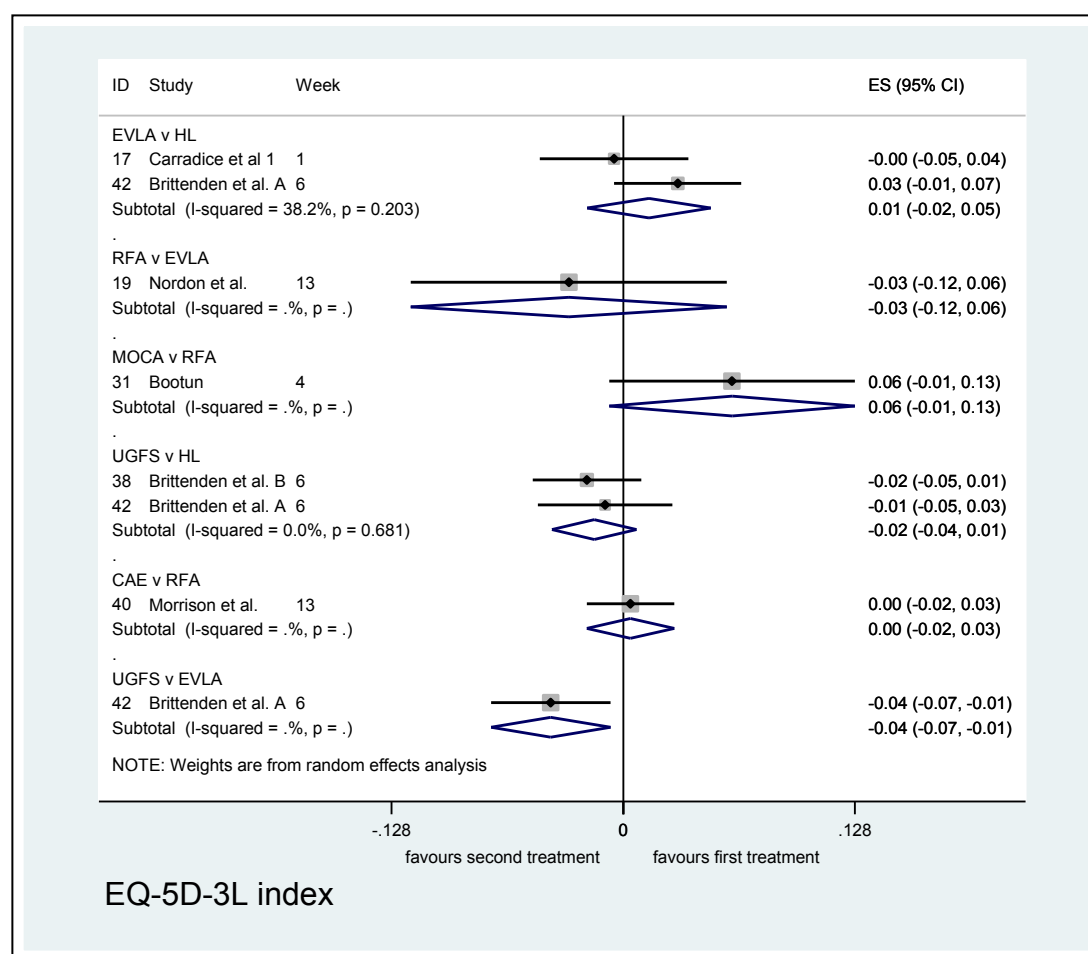


Figure 36. Forest plot of the mean differences in the EuroQoL's EQ-5D scores after a follow-up period of 1-13 weeks (CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

The disease-specific tool AVVQ was reported in 11 RCTs at 1-13 weeks (Subramonia and Lees, 2010; Carradice et al., 2011b; Nordon et al., 2011; Rasmussen et al., 2011; van Eekeren et al., 2011; Lattimer et al., 2012; Rasmussen et al., 2013; Mozafar et al., 2014; Brittenden et al., 2015; Morrison et al., 2015; Shepherd et al., 2015; Bootun et al., 2016a) and 13 RCTs at ≥ 6 months (Rasmussen et al., 2007; Darwood et al., 2008; Christenson et al., 2010; Goode et al., 2010; Rasmussen et al., 2010; Carradice et al., 2011b; Rasmussen et al., 2011; Rasmussen et al., 2013; van Eekeren et al., 2013; Mozafar et al., 2014; Brittenden et al., 2015; Shepherd et al., 2015; Lane et al., 2016). No significant differences were noted when comparing HL/S, EVLA, RFA, UGFS, MOCA and CAE at 1-13 weeks and ≥ 6 months (Figures 38 and 39).

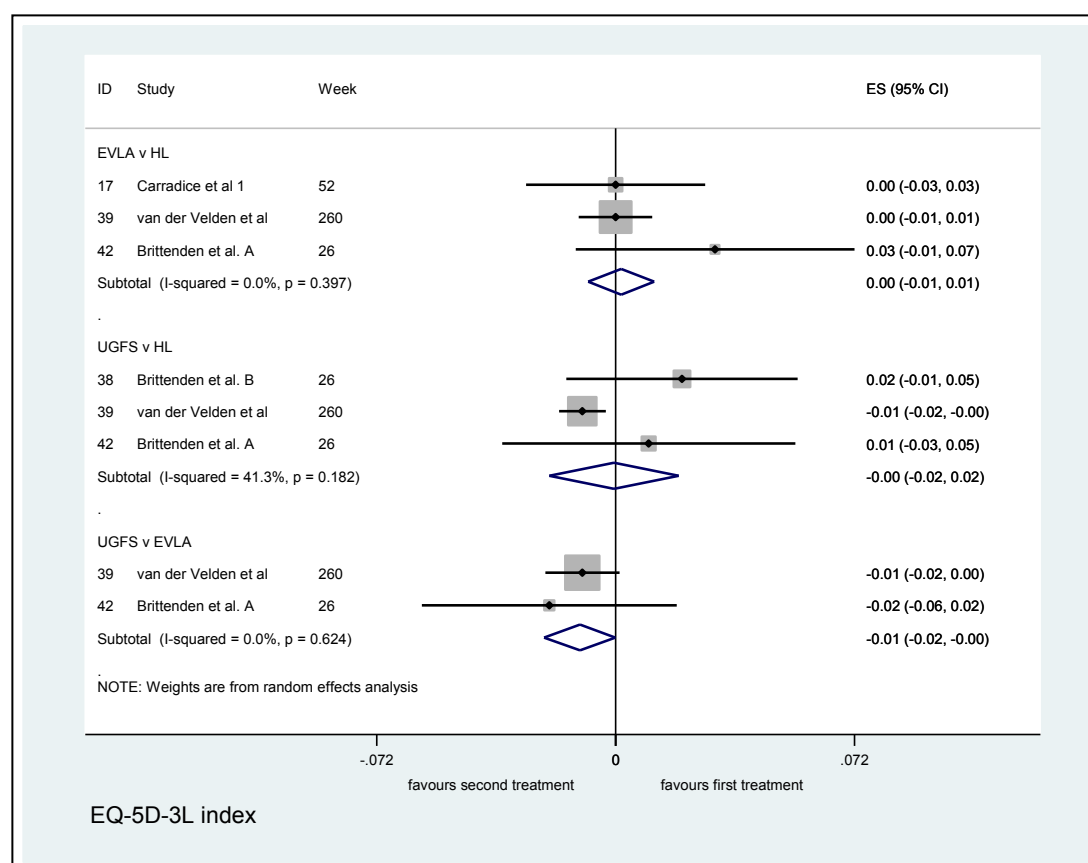
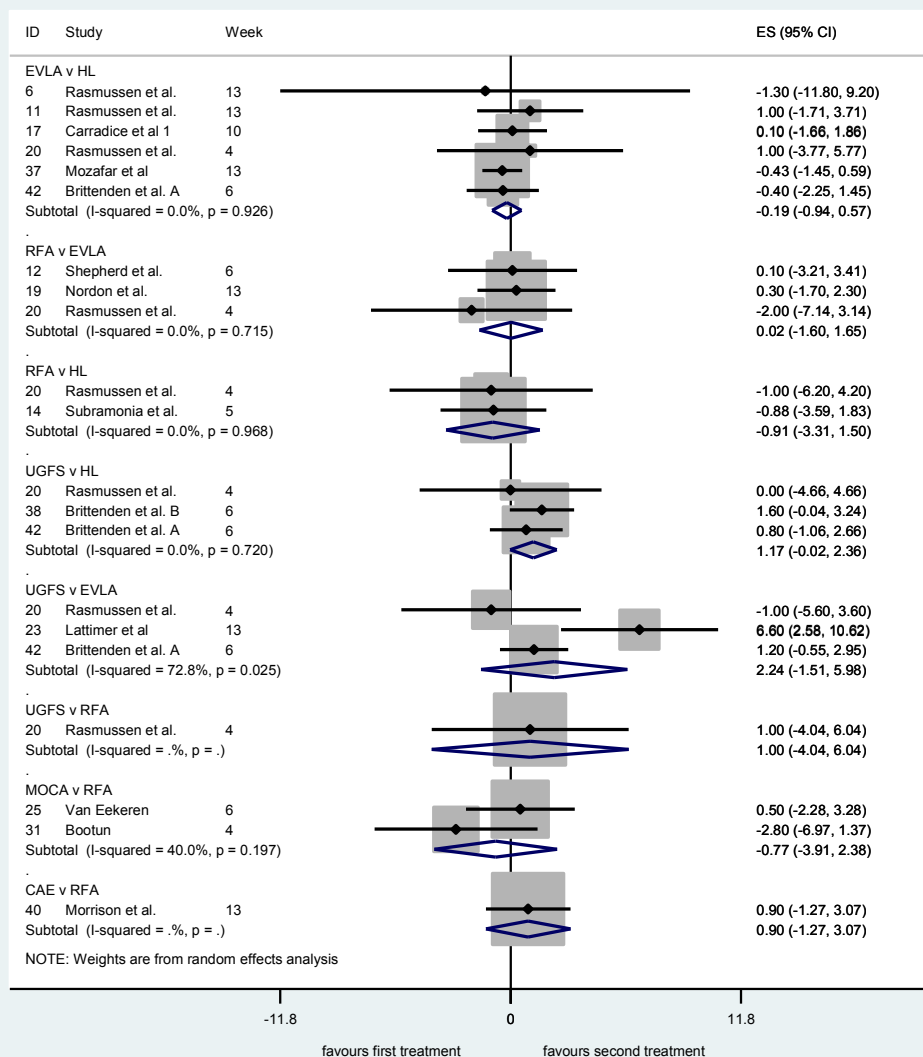


Figure 37. Forest plot of the mean differences in the EuroQoL's ED-5D scores after a follow-up period of 6 months to 5 years (EVLA: endovenous laser ablation; HL: high ligation and stripping; UGFS: ultrasound-guided foam sclerotherapy)



Aberdeen Venous Vein Score

Figure 38. Forest plot of the mean differences in AVVQ scores at 1-13 weeks (AVVQ: Aberdeen Varicose Vein Questionnaire; CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

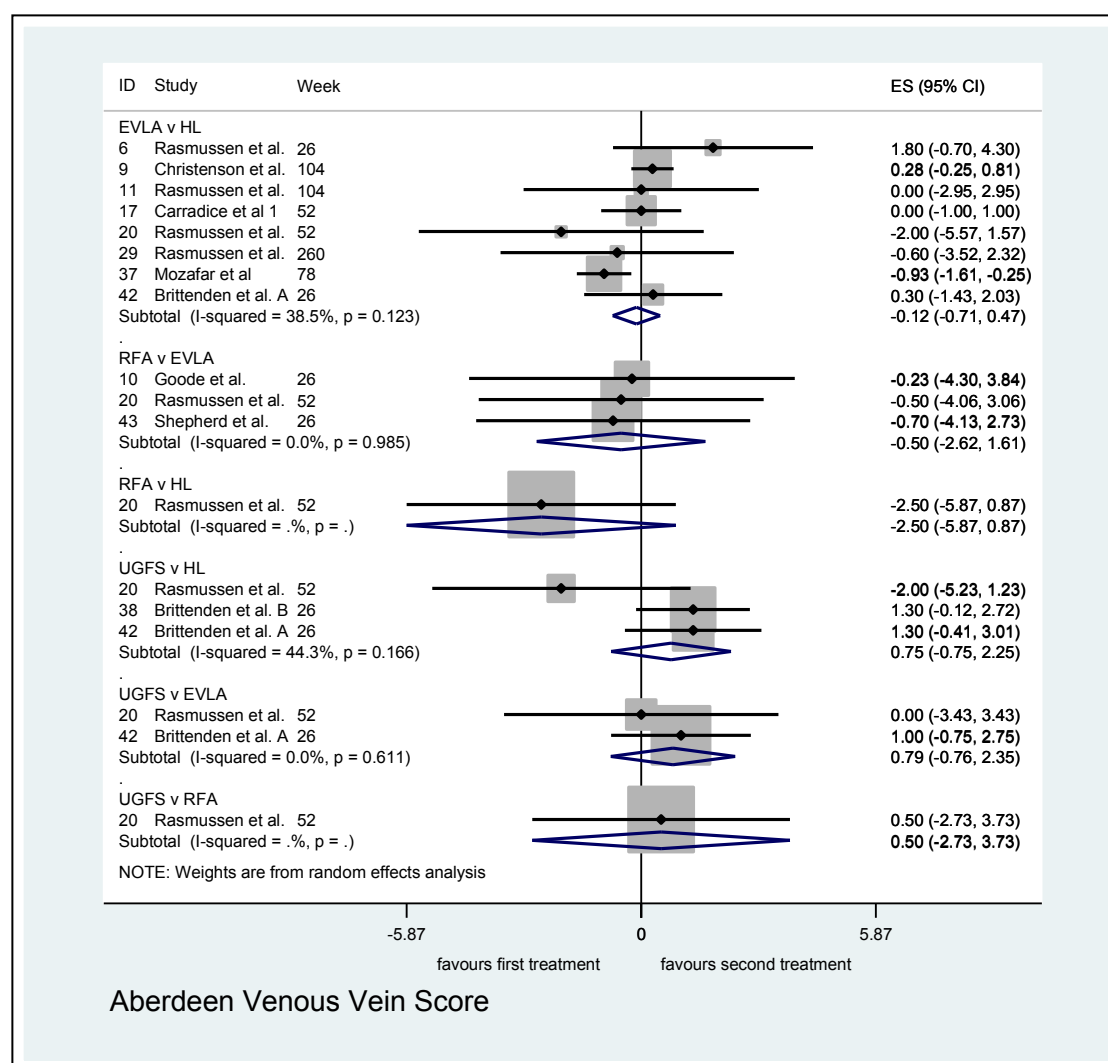


Figure 39. Forest plot of the mean differences in AVVQ scores at 6 months (AVVQ: Aberdeen Varicose Vein Questionnaire; EVLA: endovenous laser ablation; HL: high ligation and stripping; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

3.3.6 Risk of Bias

The surgical nature of the interventions used precludes blinding of both patients and personnel. Hence, this resulted in most studies being classified as high risk of bias for this category (Table 24). Only one study conducted a single-blinded study, blinding the patients to their treatment allocation, but, for practical reasons, the surgeons could not be blinded (Shepherd et al., 2010a). While blinding for outcome assessments is possible, only two studies ensured they had independent assessors at follow-up appointments (Shadid et al., 2012; Sell et al., 2014). Five studies failed to present studies on an intention-to-treat basis, had a high degree of missing data or did not use adequate statistical methods to compensate for the missing data (Rass et al., 2012; Shadid et al., 2012; Rasmussen et al., 2013; Sell et al., 2014; van der Velden et al., 2015). The relatively short-term follow-up of another study (3 months) also introduced a high risk of reporting bias (Lattimer et al., 2012).

All three non-RCTs reporting on re-intervention rates had a low risk of confounding as they all had similar inclusion/exclusion criteria and baseline patient characteristics (van Eekeren et al., 2011; Elias and Raines, 2012; Bishawi et al., 2014). However, the overall risk of bias was affected by a high percentage of missing data (>30%) (Bishawi et al., 2014) and less than 6 months duration of the study (van Eekeren et al., 2011) (Table 25).

Study	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
van der Velden	2015	LR	LR	HR	HR	Unclear	HR	LR
Shepherd	2015	LR	LR	LR	HR	Unclear	LR	LR
Brittenden A	2015	LR	LR	HR	HR	LR	LR	LR
Brittenden B	2015	LR	LR	HR	HR	LR	LR	LR
Sell	2014	LR	LR	HR	LR	Unclear	HR	LR
Rasmussen	2013	LR	LR	HR	HR	Unclear	HR	LR
Biemans	2013	LR	LR	HR	HR	Unclear	LR	LR
Lattimer	2012	LR	LR	Unclear	Unclear	LR	LR	HR
Rass	2012	LR	LR	HR	HR	Unclear	HR	LR
Shadid	2012	LR	LR	HR	LR	Unclear	HR	LR
Carradice	2011	LR	LR	HR	HR	LR	LR	LR
Rasmussen	2010	LR	LR	HR	HR	LR	LR	LR
Christenson	2010	LR	LR	HR	HR	LR	LR	LR

Table 24. Risk of bias in randomised controlled trials with re-intervention data. (HR: high risk of bias; LR: low risk of bias)

Study	Year	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in the measurement of outcomes	Bias in selection of the reported result
Elias	2012	LR	NI	LR	LR	LR	LR	LR
Bishawi	2013	LR	LR	LR	LR	SR	LR	LR
van Eekeren	2011	LR	LR	LR	LR	LR	LR	SR

Table 25. Risk of bias in non-randomised studies (cohort studies) of MOCA with re-intervention data (HR: high risk; LR: low risk; MOCA: mechanochemical ablation; NI: no information; SR: serious risk)

3.3.6 Cost-Effectiveness

Cost-effectiveness analysis is dependent on a number of factors. One of them is operative time, and for the purposes of the analysis, surgery is considered as the reference treatment. The differential time taken for the procedures as compared to surgery was estimated using a random effect network meta-analysis.

UGFS is shown to be a significantly faster procedure ($p=0.004$) (Table 26). There were no significant differences between the operative time taken with the other endovenous procedures (EVLA, RFA, MOCA and CAE) and surgery.

	Difference in operative time (minutes)	SE	z	P value	Confidence Interval	
EVLA	6.0	6.4	0.9	0.346	-6.5	18.6
RFA	5.2	6.5	0.8	0.428	-7.6	18.0
UGFS	-24.8	8.7	-2.9	0.004	-41.9	-7.7
MOCA	-5.5	11.3	-0.5	0.628	-27.6	16.6
CAE	10.2	16.2	0.6	0.531	-21.6	41.9

Table 26. Difference in operative time compared to surgery (HL/S) using a network meta-analysis (CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL/S: high ligation and stripping; MOCA: mechanochemical ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

	Source	HL	EVLA	RFA	UGFS	MOCA	CAE
Cost theatre (£)		529	338	333	143	270	362
Theatre time (min)	a	52	58	57	27	46	62
Cost per min, theatre (£)	b	10.27	5.87	5.87	5.35	5.87	5.87
Kit and equipment (£)		150	322	346	50	441	866
Kit (£)	c		256	280		375	800
Consumables & anaesthetic (£)	b	150	66	66	50	66	66
Other Costs (£)		257	72	72	42	72	72
Preparation (£)	b	29	29	29	28	29	29
Recovery (£)	b	74	32	32	4	32	32
Equipment (£)	b	4	11	11	10	11	11
Total Cost (£)		786	732	751	235	783	1300

Table 27. Breakdown of the cost of varicose vein procedures. Sources of cost are from: a. Network meta-analysis of randomised trials; b. From Brittenden et al. (2015); c. Manufacturers' list price and Rautio et al. (2002) (CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; QALY: quality-adjusted life years; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

The cost of each intervention was estimated which showed that the cheaper method was UGFS (£235 per treatment session) and the most expensive method was CAE (£1,300 per treatment session), mainly because of the large expenditure for the non-re-usable kit (Table 27).

Using a discounted rate of 3.5% to reflect the current value of the costs accruing over 5 years, the probability of patients having an initial treatment with one of the methods under investigation and then requiring either re-treatment for varicosities or truncal veins was calculated (Table 28). This demonstrates that patients receiving UGFS were more likely to require re-intervention for varicosities and truncal veins.

Strategy	Probability of re-treatment for varicosity (6 weeks)	Probability of truncal vein re-intervention during 5 years	Discounted QALY (5 years)	Discounted Total Mean Cost (5 years)
CONS	0.36	0.72	4.47	197
UGFS	0.36	0.56	4.48	394
RFA	0.04	0.26	4.50	745
MOCA	0.04	0.26	4.50	822
EVLA	0.04	0.26	4.50	824
HL	0.04	0.27	4.50	828
CAE	0.04	0.26	4.50	1392

Table 28. The probability of each intervention requiring re-treatment of varicosities at 6 weeks and re-treatment of their truncal veins at 5 years (CAE: cyanoacrylate injection; CONS: conservative care; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; QALY: quality-adjusted life years; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

The total cost and QALYs per person over 5 years was calculated (Figure 40) and this shows that CAE was associated with the highest overall expenditure per person while HL/S, EVLA, MOCA and RFA had similar costs and outcomes. An incremental cost per QALY of £16,320 was obtained when comparing EVLA to conservative care. The other treatment options were found to be more costly without any additional gain in effectiveness (dominated or extended dominated).

The probability of being cost-effective at a threshold of £20,000/QALY was 0.316 for EVLA, 0.265 for RFA, 0.170 for conservative care, 0.136 for UGFS, 0.111 for MOCA, 0.002 for HL/S and 0.000 for CAE (Figure 41).

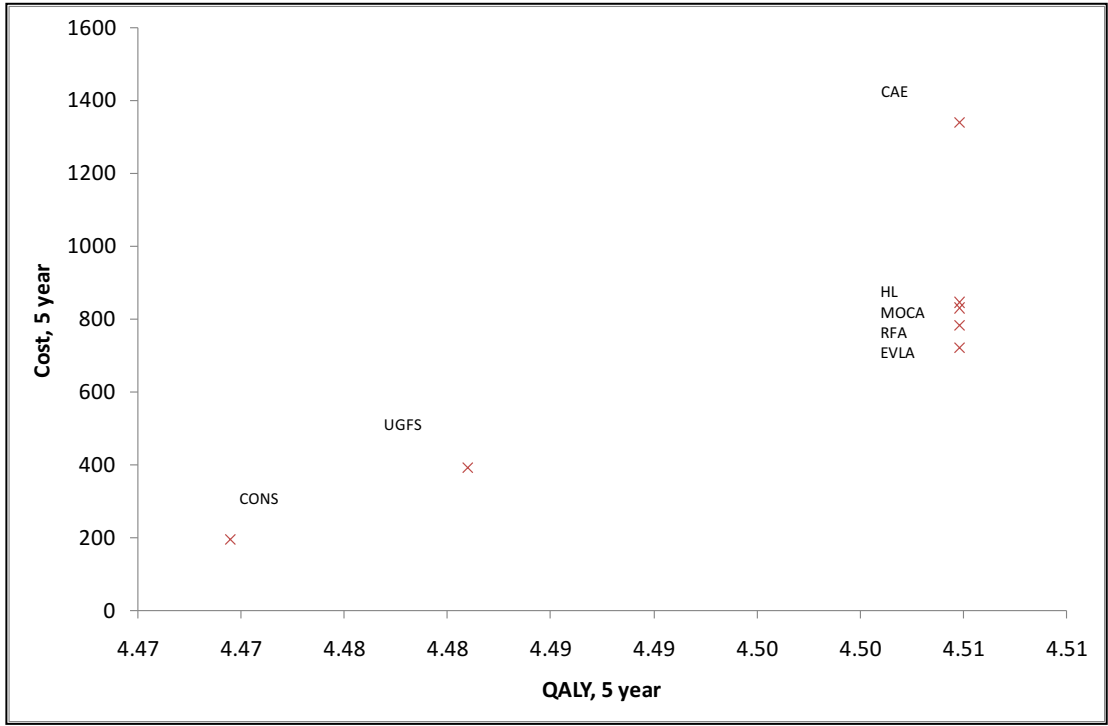


Figure 40. Total mean cost and QALY per person over 5 years for each treatment (CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; QALY: quality-adjusted life years; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

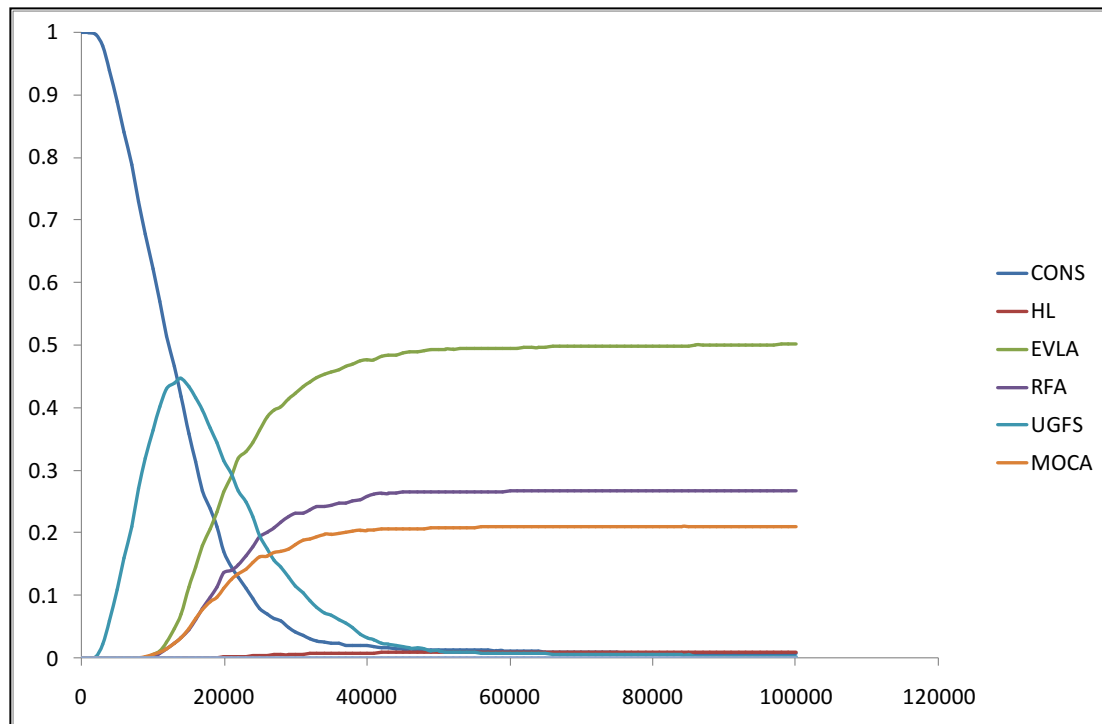


Figure 41. Cost-effectiveness acceptability curves for each treatment option. The curve shows the probability that a given treatment obtains the highest net benefit at different thresholds for cost-effectiveness. (CAE: cyanoacrylate injection; EVLA: endovenous laser ablation; HL: high ligation and stripping; MOCA: mechanochemical ablation; RFA: radiofrequency ablation; UGFS: ultrasound-guided foam sclerotherapy)

3.4 Discussion

This systematic review and analysis aimed to assess the comparative effectiveness and cost-effectiveness of current treatment methods for varicose veins.

The primary endpoint of re-intervention following treatment failure or recurrence was selected as it is often associated with worse quality of life (Beresford et al., 2003) and higher health care costs. Moreover, since it is easier to define, remains a consistent occurrence with any of the treatment options and simpler to record, it probably is a more suitable outcome measure compared to other more technical or clinical measures such as occlusion, revascularisation, treatment failure or recurrence. There is also a lack of agreed or consistent definition of the latter endpoints in the medical literature, which affects their value when making clinical decisions.

Analysis of re-intervention rates reveals that surgery, EVLA and RFA appear to have similar rates, with a lower likelihood of requiring re-treatment compared to UGFS and conservative care.

So far, no randomised studies have reported on re-intervention rates in patients undergoing MOCA or CAE. The three small cohort studies on MOCA seem to suggest that the re-treatment rate is similar to endothermal ablation and surgery, but the evidence is insufficient to deduce any firm conclusions. No information on re-intervention following CAE was available to carry out any meaningful analysis.

Over both short and longer-term follow-up, the disease-specific AVVQ scores appear to be similarly improved in HL/S, EVLA, RFA, MOCA and CAE. UGFS, on the other hand, seems to be associated with a lower quality of life as measured by EQ-5D over both short- and long-term period. This finding is at odds to the findings from a large prospective study which followed up patients receiving UGFS for at least 5 years (Darvall et al., 2014). It is also surprising considering that patients complain of less discomfort following this procedure and return to normal activities earlier than EVLA and surgery (Rasmussen et al., 2013).

The procedural time was fastest with UGFS, but there were no major differences between the other treatments. The total cost of each treatment modality demonstrates that CAE was, by far, the most expensive intervention and UGFS was the least expensive. All the other treatment methods, including MOCA, seem to have a relatively similar cost. This observation is again noted in the cost per QALY over 5 years. At a threshold of £20,000/QALY, the probability of being cost-effective appears to be highest for EVLA (0.316), followed by RFA (0.265), conservative care (0.170), UGFS (0.136), MOCA (0.111), surgery (0.002) and CAE (0.000), respectively. This confirms the findings from two recent cost-effectiveness analyses conducted by Gohel et al. (2010) and NICE, which showed that endothermal ablation was the most clinically- and cost-effective treatment (Gohel et al., 2010; Marsden et al., 2015). Comparison to non-thermal methods was not undertaken by NICE in their analysis though.

Several limitations are apparent when reviewing the results reported. Despite seemingly proper randomisation procedures, there was a lack of blinding, mostly explained by the difficulty encountered at initial assessment with interventional methods. Concealment of randomised status at follow-up was possible, but few studies ensured this was the case. Differences in the proportion of missing data between treatment groups without clear compensation by statistical methods led to several of the included randomised studies being at high risk of attrition bias. In spite of more than a decade of continuous and incremental usage, RFA was not commonly

compared in randomised controlled trials and was unable to provide meaningful data. Moreover, a number of what appeared to be non-randomised cohort studies with long trial duration were excluded. This would have added additional number of patients for statistical analysis.

A lack of studies, including randomised trials, evaluating MOCA and CAE also prevents any firm conclusions to be made regarding the merits of these two interventions. Though cohort studies were employed, a combination of small patient population, short follow-up, missing data and lack of comparator groups means that a degree of caution must be exerted when interpreting the results.

CHAPTER 4

PATHWAY IMPROVEMENT

CHAPTER 4: PATHWAY IMPROVEMENT

4.1 One Stop Clinic Review

4.1.1 Introduction

Honing the technique and making use of cost-effective methods of varicose vein treatment will allow some improvement in the outcomes of the condition. Although highly essential, this is only part of the solution and further progress could be made by refining the referral and treatment pathways.

Presently, over 35,000 varicose vein procedures are currently carried out in the UK(Marsden et al., 2013). It seems that the number of procedures is on the increase, especially since the release of the 2013 NICE guidelines on the management of varicose vein(Davies et al., 2015). The Department of Health has, thus, estimated that this is set to increase to 50,000 procedures per year. The National Health Constitution (NHS) Constitution, initially published in 2009, brings together the principles, values, rights and responsibilities of the NHS, one of which is for patients to start consultant-led non-emergency treatment within a maximum of 18 weeks of a GP referral(Department of Health, 2013). The NHS Operational Standards has set a minimum target of 90% of patients receiving consultant-led treatment within 18 weeks from referral to treatment (RTT) and managing the projected increase in varicose vein procedures in the NHS could prove rather problematic (2011; 2013).

Waiting for varicose vein interventions often results in worsening of the severity of the condition and the quality of life of patients(Sarin et al., 1993). Progression of varicose veins can also lead to complications such as leg ulcerations, whose management can be costly to the health service(Gohel et al., 2010).

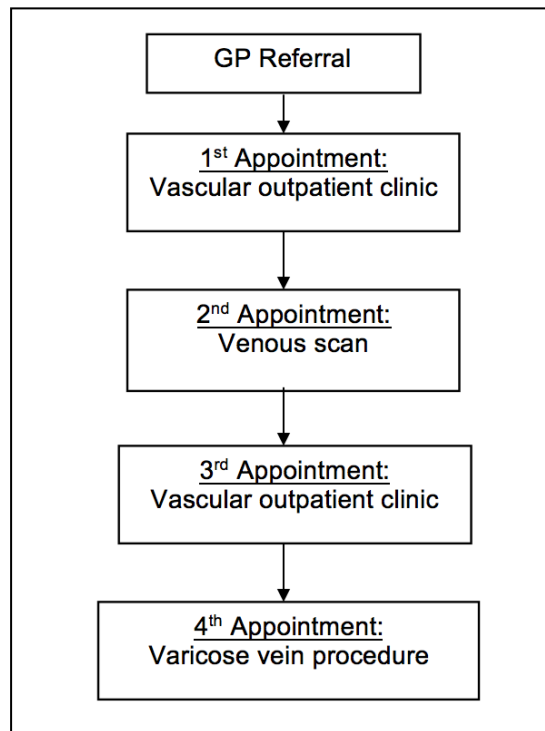


Figure 42. The normal care pathway for the management of varicose veins in the NHS

At present, patients referred to the Vascular Unit for consideration of varicose vein management have an initial appointment where the severity of the venous insufficiency is assessed clinically and, subsequently, have a venous Duplex scan to evaluate the extent and cause of any venous incompetence. If any treatable lesion is found, they are then added to the waiting list to come for the eventual varicose vein procedure. This means, they have to potentially attend at least two outpatient appointments as well as a separate appointment for their venous scans, before actually attending for their varicose vein procedure (Figure 42). Waiting for varicose vein interventions has been shown to lead to worsening of their conditions both clinically and radiologically (Sarin et al., 1993). Moreover, this wait can have a negative impact on the quality of life of patients waiting for elective surgery (Oudhoff et al., 2007).

A potential solution to this problem could be for patients to attend a special vein clinic, where they would be assessed, have their venous Duplex scans and, depending on the lesions shown, have their venous treatment on the same day.

Several hypothetical advantages of such a one-stop vein clinic are possible. This includes a faster enhancement of patient's quality of life, an improvement in patient

satisfaction, a reduction in the number of appointments, the abolition of any waiting times, societal benefits such as less time away from work and less expenditure on childcare as well as potential cost savings to the health service.

Possible disadvantages exist, however, including that patients may be inadequately prepared for their procedure or that they may not be suitable for same-day treatment. Moreover, especially in case of the latter situation and non-usage of the facilities, theatre time might be wasted.

<u>Advantages</u>	<u>Disadvantages</u>
• Faster referral to treatment time • Faster improvement in patient's clinical and quality of life • Faster improvement in patient's satisfaction • Reduction in number of appointments • No waiting time list • Less time away from work • Less need for childcare • Cost savings	• Patients inadequately prepared • Relatively short time to agree for procedure • Patients not suitable for same-day treatment • Theatre/procedure time unused as no patients suitable for treatment

Table 29. Potential advantages and disadvantages of a One-Stop Vein Clinic

4.1.2 Clinic and Referral Models

The existence of waiting times in a health service is often the result of a discrepancy between the demand for a particular intervention compared to the ability of the health service to supply it (Kreindler, 2010). This divergence in what is required and what is available may be due either to a deficiency of capacity or inefficiencies in the service despite adequate capacity (Kreindler, 2010). Common reasons for these shortcomings in health care provision are complicated booking systems, superfluous organisational steps and uneconomical usage of resources.

Several possible solutions have been proposed such as the pooling of patients awaiting similar interventions onto a single list, simplifying the clinical pathways or the establishment of 'one-stop shops' (offer different services on a single day) (Kreindler, 2010).

Monitor, an executive non-departmental entity of the Department of Health of England (part of NHS Improvement since 1st April 2016), researched ways to improve the productivity of elective care provision in the National Health Service (Monitor, 2015). It highlighted nine good practices when reviewing the provision of elective care in the field of ophthalmology and orthopaedics, five of which were deemed to be sufficient to enable most of the productivity gains in the NHS (Monitor, 2015).

First specialist input	Outpatient care	Inpatient pre-operative care	Surgery	Inpatient post-operative care	Follow-up post-discharge
1. Stratification of patients by risk and alignment of resources to risk	2. Streamlined diagnostics, outpatients and pre-assessment	3. Day of surgery admission	4. Specialisation and extended roles within team 5. Optimised scheduling 6. Surgical teams supported to use theatres efficiently	7. Standardisation of ward care and enhanced recovery 8. Proactive management of infections and readmissions	9. Nurse/allied health professional (AHP)-led follow-up for routine patients and level of follow-up aligned to patients risk profile

Table 30. Nine practice areas where operational improvements can be made in the National Health Service (Monitor, 2015)

1. Risk-stratification of patients and use of low-complexity pathways for patients at low-risk
2. Extension of clinical roles of lower grade staffs so they can take over tasks usually performed by consultants
3. Increase of theatre efficiency by rigorous measurement, communication and management of theatre procedures
4. Reduction of patient length of stay by improving recovery practices
5. Virtual follow-up arranged for uncomplicated patients

Table 31. Five of nine practices identified by Monitor which would allow the most productivity gains in the NHS (Monitor, 2015)

Patients can usually be stratified into the following categories (Monitor, 2015):

- Few medical problems requiring simple elective surgical procedures
- Multiple medical problems requiring simple elective procedures
- With or without multiple medical problems requiring complex elective procedures

One of the suggestions is to risk stratify patients into high- or low-risk and direct them to the most appropriate pathways accordingly (Monitor, 2015). This would then ensure that, once patient assessment is complete, less complex and resource-intensive services could be provided. Examples of such services include improving the process of preassessment, anaesthesia and post-operative support.

Usually, a number of outpatient visits is required before a final decision for treatment is made: the initial outpatient clinic, diagnostic tests and eventual discussion for treatment (Monitor, 2015). Attending outpatient clinics offering diagnostic services at a single outpatient visit would reduce the frequency of these appointments and is often referred to in the UK and internationally as a 'one-stop' assessment. The latter approach potentially improves the efficiency of a service, but it requires more intensive and judicious use of resources. Indeed, these 'one-stop' assessment clinics necessitate robust interactions between outpatient and diagnostic services, availability of same-day simple diagnostic tests (e.g., bloods, X-rays and ultrasound) as well as access to a consultant, even if only for advice.

4.1.3 Refining the One Stop Practice

The 'one-stop' assessment clinics have already proved to be invaluable, especially in the diagnosis of various malignancies. An improvement of this practice is possible by adding treatment to the assessment, i.e., providing an outpatient clinic, diagnosis and treatment on a single day. This alternative type of 'one-stop' shop (referred as 'one-stop' treatment clinic, to differentiate it from a 'one-stop' assessment clinic) appears to be an attractive option in health provision.

The often-cited benefits of this concept are the reduction in the number of hospital visits required and, hence, reducing/abolishing waiting times to eventual treatment. As a result, health service provision would become more economical.

As an example, Monitor described the experience of the Newcastle upon Tyne Hospitals NHS Foundation Trust (UK) in treating patients with wet age-related macular degeneration (AMD) (Monitor, 2015). This one-stop treatment clinic has been able to achieve an outpatient to injection rate of 55%. The management pathway is illustrated in Figure 43.

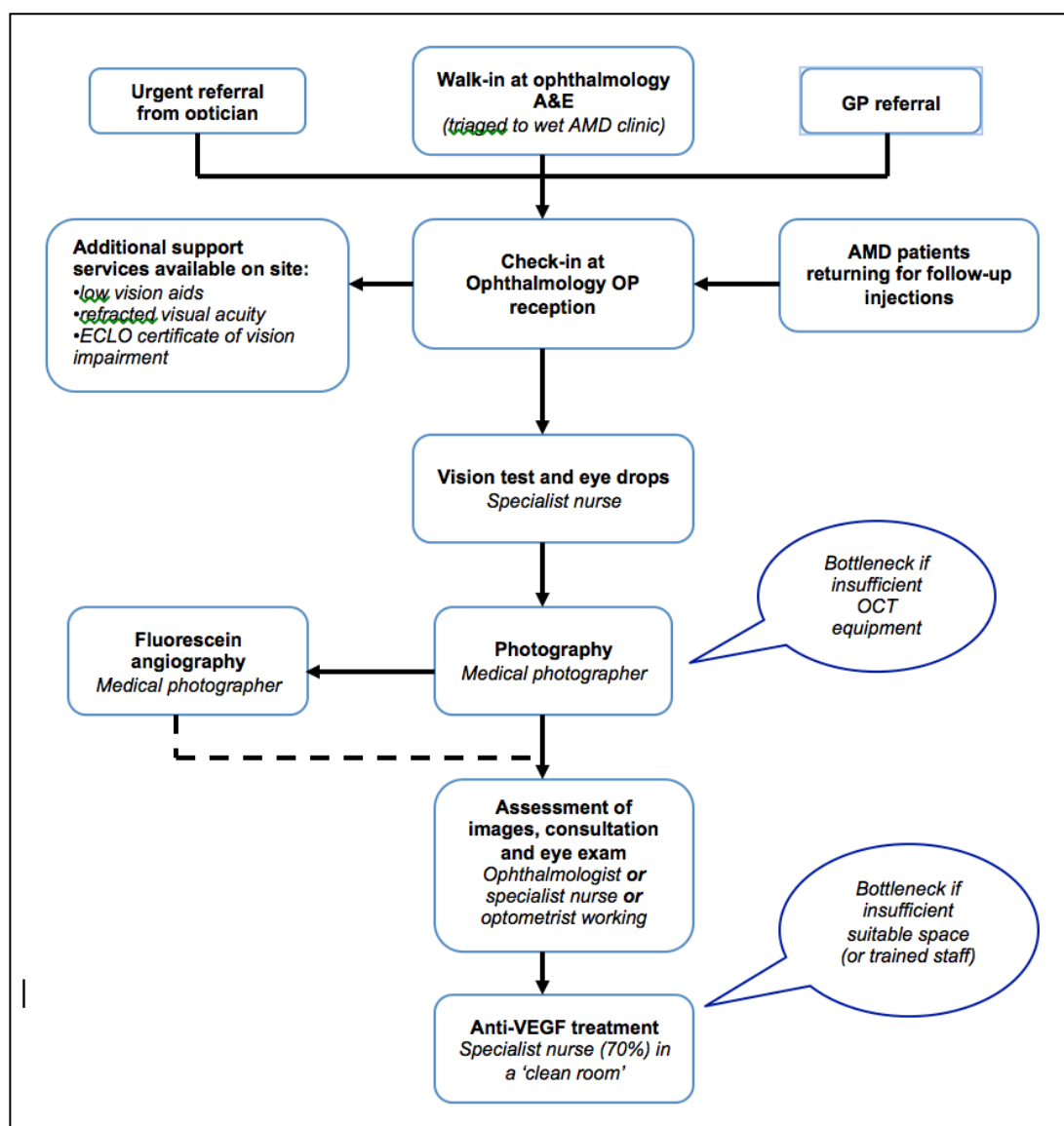


Figure 43. Modified diagram showing a one-stop clinic for the diagnosis, assessment and treatment of wet AMD at the Newcastle upon Tyne Hospitals NHS Foundation Trust (AMD, age-related macular degeneration; ECLO, eye clinic liaison office; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor)(Monitor, 2015)

4.1.4 One Stop Clinics in Surgical Specialties

As noted previously, this notion of carrying out a one-stop treatment clinic where patients are seen and treated on the same day is not new. These also already function very well in oncology, where a definitive diagnosis can be reached sooner. This concept has previously been reported in other surgical specialties and is as detailed below.

4.1.4.1 Ophthalmology: Cataract Surgery

Ophthalmology was one of the earliest specialties to embrace the concept of one stop clinics. An initial one-stop cataract service was set-up and operated between 1997 and 1999 at the Bristol Eye Hospital(Hughes et al., 2001). One hundred and ninety patients referred for consideration of cataract surgery over that period were selected from their referral letter. The main selection criteria were living a long distance away from the hospital and/or reasonable general health. Patients were invited to attend the service, with the invitation letter informing them that there was a possibility of them being operated on the same day. The morning was reserved for all necessary assessments while all procedures were carried out in the afternoon.

One hundred and fifty-six patients (82% of patients invited to the 'one-stop' clinic) underwent same day surgery(Hughes et al., 2001). There was a high satisfaction rate (94%), although this was not statistically significant when compared to patients attending a more conventional pathway. All patients were also satisfied with the amount of time they were given to decide on going ahead with the procedure or not. This is an indication that the need for a 'cooling off' period before patients decided about whether to have their procedure did not arise. This issue did not raise any concerns with the General Medical Council (GMC, UK) or the Medical Protection Society (MPS, UK) either(Hughes et al., 2001).

However, inefficient use of theatres were often noted (as low as 50% of the time) because not all patients attending the clinic were operated on. To improve on these figures, patients attending the conventional clinics were told that there was a chance they could be operated the same day and were added to the theatre list if space was available.

The authors suggested that this type of service could reduce the total number of hospital visits, thereby freeing up essential resources to be used elsewhere(Hughes et al., 2001). Moreover, there were no waiting lists as patients were seen and treated on a single day and seemed to be popular with patients. They pointed out though that the inefficient use of theatres observed could mean that all the potential advantages of this one stop treatment clinic would be nullified and may actually prove not to be superior to a one stop diagnosis clinic.

To this day, similar one stop service continues to be provided at the Bristol Eye Hospital for the management of ophthalmic conditions.

4.1.4.2 Orthopaedics: Carpal Tunnel Syndrome

Following the publication of the NHS plan (in 2000) and the NHS Improvement Plan (2005) which encourage adopting a different approach to delivering patient care, Reid et al. (2009) looked into improving the waiting times for patients with carpal tunnel syndrome (CTS)(Reid et al., 2009). They evaluated a one-stop CTS clinic for the diagnosis and treatment of the condition on the same day with the objective of reducing the waiting time for patients whilst, at the same time, maintaining clinical outcome and patient satisfaction(Reid et al., 2009).

GP referral letters were reviewed and selected patients were asked whether they would be willing to have the procedure carried out on the same day as their initial consultation. Patients who agreed to be treated on the same day were sent invitations to attend the one stop clinic. Patients were seen and examined on their appointment day, with patients sent to have carpal tunnel decompression or further investigations. All the procedures were undertaken under local anaesthesia and patients were discharged home on the same day.

Forty-nine patients, having a mean age of 52 years, were included. Surgical decompression was carried out in 94% of cases. The mean time patients waited to be seen following their referral was 9 weeks. No patients needed a day-case bed or overnight admission. Patients demonstrated higher functional scores as well as higher satisfaction post-procedure. Patients felt that they had sufficient amount of time to consider having their operations.

The one-stop carpal tunnel clinic was felt to be a more efficient and cost-effective way of treating this common condition(Reid et al., 2009).

4.1.4.3 General Surgery: Inguinal Hernia

Open Repair

A one-stop hernia repair was set up at a London hospital (UK) and GP referral letters were reviewed for selection (Putnis et al., 2004). Based on the referral letter, patients with primary unilateral inguinal hernia and no clear contra-indication to day surgery were contacted and informed about the proposed treatment plan. A health questionnaire was also sent for their GP to fill and, based on the responses obtained, patients deemed suitable for day-case surgery were asked to attend a special clinic for both assessment by the operating team and possible definitive surgery. Surgical repair was open, tension-free Lichtenstein mesh repair and patients received either a local or general anaesthetic.

Out of 110 referrals, 98 patients were considered suitable for day-case intervention and invited to attend. All patients were males and the mean age was 49.5 years. The American Society of Anesthesiologists (ASA) grade of those selected was I or II (normal healthy patient or mild systemic illness, respectively).

In the end, 92 patients (94% of total) underwent day-case procedure. Most of these were carried out under general anaesthesia (90 patients). Except for one patient who needed admission following development of urinary retention, all patients were discharged on the same day (Putnis et al., 2004).

The authors, therefore, concluded that patients with primary unilateral inguinal hernia could be treated efficiently in a one-stop clinic with low levels of cancellations and complications (Putnis et al., 2004).

Laparoscopic Repair

A Dutch hospital also looked at the safety and feasibility of setting up a one stop service for the treatment of inguinal herniae, but this time using laparoscopic total extraperitoneal (TEP) repair (Jutte et al., 2010).

Information about this one stop service along with the inclusion and exclusion criteria was sent to the local GP surgeries. Patients younger than 60 years with unilateral or bilateral inguinal hernia, but without a diagnosis of hypertension, insulin-dependent diabetes, or cardiac, pulmonary or anticoagulation medication were selected. Once assessed by their GPs, patients were asked to contact the hospital directly. Patients were provided with further information about inguinal hernia and its management on 3 separate occasions: by the GPs, by receipt of a leaflet about the procedure and by the general surgeons on the day of their appointment. With patients fully counselled, the TEP repair was undertaken as planned. Discharge was planned for the same day and patients were contacted again 2 weeks later, with an outpatient appointment offered, if clinically indicated.

In 12 months, 52 patients were recruited, 50 of them receiving a TEP repair(Jutte et al., 2010). Three patients required overnight stays and, at 2 weeks, 11 patients (22%) had symptoms of pain or swelling, 8 of whom, were eventually followed up in the outpatient clinic. Patients were overly satisfied with the service with 98% rating the one stop set-up as 'good' or 'excellent'.

Sixteen percent of all referrals received were direct referrals to the one stop service. Retrospective analysis and comparison with patients managed on the conventional pathway showed that a further 35% of all referrals (therefore, approximately half of all referrals) would have been suitable for the same day management.

The one stop concept, thus, appears to be safe, reduces the waiting time for intervention, is less costly and well accepted(Jutte et al., 2010). The authors do highlight potential issues with the service, such as patients with incorrect diagnoses presenting for treatment, patients not attending their appointment, those unfit for day-case procedures, inefficient use of theatre time, and unsatisfied patients(Jutte et al., 2010).

4.1.5 Application of the One Stop Pathway to Phlebology: the One Stop Vein Clinic

The one stop concepts have also been applied to vascular surgery with numerous centres already operating a one-stop diagnostic pathway. These allow patients to be seen, and receive a vascular scan, including a varicose vein scan, on a single day in the outpatient clinic(Sandison et al., 1997; Makris et al., 2006). Treatment is then usually provided on another day.

An enhancement of this model is feasible, namely, by the addition of a definitive therapeutic intervention to the one-stop diagnostic set-up. This seems to be a logical evolution in the treatment of varicose vein disease. Indeed, the introduction of endovenous ablation more than a decade ago makes this more than a possibility. These methods have caused a revolution in the management of varicose veins, enabling most procedures to be carried out under local anaesthetic and as day cases. Interventions carried out in such a manner in an outpatient or 'office-based' setting have also been shown to be cost-effective(van den Bos et al., 2009; Gohel et al., 2010).

Several factors determine the potential success of such a one-stop treatment pathway(Monitor, 2015).

Risk Stratification of Patients

Similar to Monitor's risk stratification(Monitor, 2015), three categories can be recognised when stratifying patients with varicose veins:

1. Patients with no or simple medical conditions requiring simple treatment
2. Patients with complex medical conditions requiring simple treatment
3. Patients with no, simple or complex medical conditions requiring complex treatment

The origin of varicose veins (whether primary, secondary (e.g., following deep vein thrombosis) or recurrent) determines the method of treatment needed. Secondary and recurrent varicose veins often exhibit a more complicated pattern and notoriously require more complex interventions. Primary varicose veins, on the other hand, are

generally considered simpler and easier to manage with more straightforward interventions. Day-case, local anaesthetic procedures are usually the preferred methods utilised. The use of local anaesthetic also allows patients with complex medical problems to be treated as day cases.

Patient Selection

Along with risk stratifying patients, other essential considerations exist to establish the suitability of patients. Patients living a relatively long distance from the hospital (Hughes et al., 2001), of a younger age group (Jutte et al., 2010) as well as being generally in good health without hypertension, diabetes, cardiac disease or on anticoagulation medications (Jutte et al., 2010) are important features taken into account. The inclusion of baseline observations (e.g., heart rate and blood pressure) and simple investigations can also be useful selection criteria (Putnis et al., 2004). One last issue is whether patients were actually willing to have all investigations and treatment on a single day.

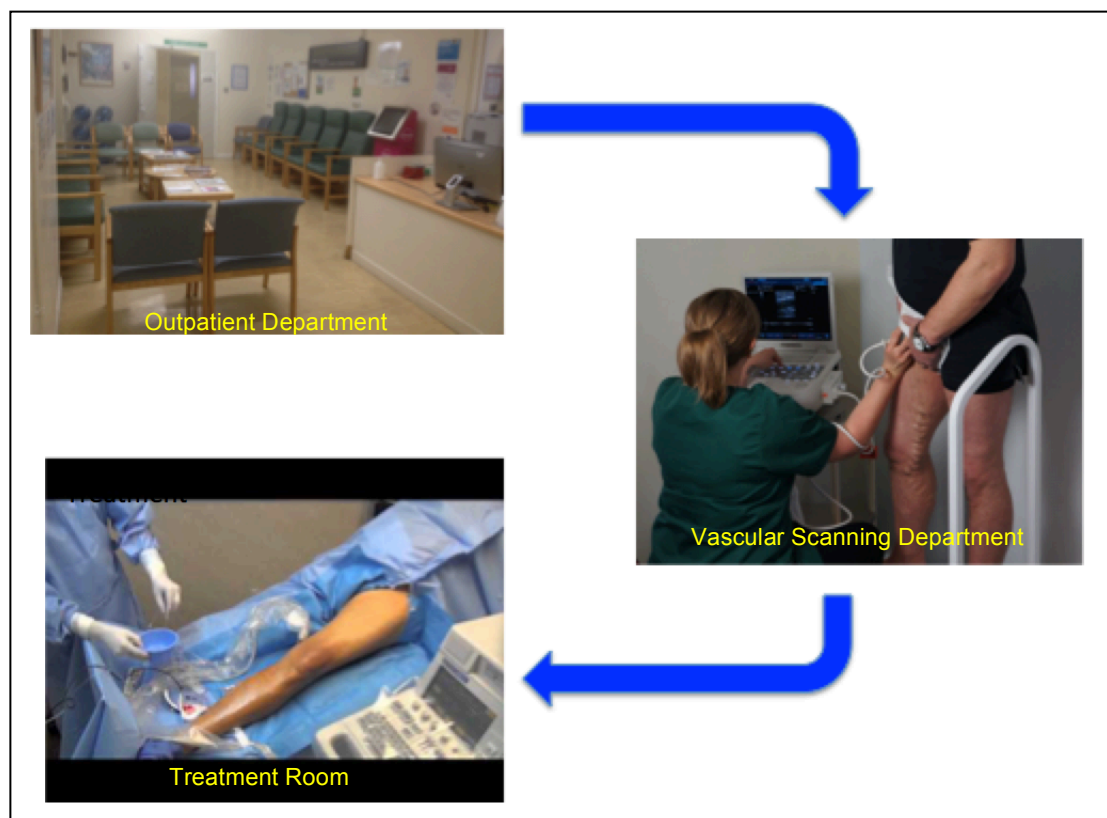


Figure 44. The stages in a one-stop vein clinic offering same day diagnosis and treatment

Streamlining Outpatients, Diagnostics and Treatment

The next step is ensuring that there is enough capacity for patients to be reviewed in the outpatient clinic, have a varicose vein scan and be treated. Thus, effective communication between all these departments is of utmost importance to enable the smooth and timely transfer of patients from one department to another.

Patients found to be suitable for same day treatment on their scans could receive further information regarding the proposed intervention, be allowed additional time to consider the options and be consented for the procedure.

Improving Theatre Efficiency

A 'one-stop' pathway is very reliant upon ensuring there are sufficient treatment slots to accommodate patients as well as allowing for quick patient turnaround. Patients could either be added to a routine elective list or to lists dedicated to those attending the 'one-stop' clinic.

Elective lists would enable patients to have their intended procedures and avoids the loss of theatre space as elective patients are already scheduled to be operated on it. However, depending on the number as well as the complexity of patients attending the 'one-stop' clinic, there is a possibility that theatres might overrun or even that some patients may get cancelled. A quick turnaround, which might help reduce the chances of this problem arising, could be facilitated by having staff familiar with the procedure scrub for the varicose vein interventions.

Dedicated one-stop lists, on the other hand, present the risk of theatre under usage of theatres, especially, if only a few or none of the 'one-stop' patients are found to be suitable for same day treatment.

Patient Recovery

Varicose vein interventions are increasingly being carried out under local anaesthetic, simplifying the recovery procedure. Patients attending a one-stop service would have a discharge procedure similar to elective patients after spending an appropriate amount of complication-free time in the recovery area.

Follow-up

Routine follow-up, especially after an uncomplicated varicose vein procedure, is probably unnecessary as most complications, if any, tend to occur within the first two weeks of treatment (Darvall et al., 2009a; Shepherd et al., 2010a; Rasmussen et al., 2011). The reported rate of any complication is approximately 5% immediately after a varicose vein intervention, increasing to almost 70% by 6 weeks (Brittenden et al., 2014). However, since most of these complications tend to be minor, it would be difficult to justify the associated additional expenditure for such outpatient appointments. It has been claimed that it is neither necessary nor cost-effective for patients to have a routine follow-up after uncomplicated interventions and that facilitating access to outpatient clinics might be more appropriate for those developing complications (Bailey et al., 1999). Unnecessary follow-ups could also be avoided by providing patients with information leaflets about the usual post-operative course, including likely complications and time to improvement (Bailey et al., 1999). In addition, a web-based follow-up service could be instituted instead (Marsh et al., 2014). Although shown to be effective and possibly also cost-effective, potential issues may arise, such as privacy issues when making use of telemedicine, a lack of internet access for some people or even the elimination of the doctor-patient interactions (Marsh et al., 2014).

Another option would be for patients' GPs to follow them up in the community. Lane et al. (2013) found that 45% of them would be happy to provide such a service, but 8% felt no follow-up was needed (Lane et al., 2013).

4.1.5.6 Benefits and Drawbacks of a One Stop Vein Clinic

A one stop vein clinic offers several potential benefits, including the possibility of eliminating waiting times and abolition of unnecessary outpatient appointments. This could, in turn, translate into cost savings to the health service. Attending a same day assessment and treatment service could also potentially lead to patients having a greater satisfaction and have an earlier improvement of their quality of life.

However, a few possible issues are also likely. For example, the main cause of patients' symptoms may not necessarily be varicose veins or they may have more complicated varicose veins disease than expected, precluding same day treatment. Moreover, the non-availability of a 'cooling off' period to consider the intervention options available could prove problematic, but this could be addressed, by judicious patient selection followed by thorough counselling about intervention and provision of information material prior to their scheduled appointments. Inefficient use of theatre facilities could also negate any potential benefits gained from operating a one stop vein clinic.

4.2 Survey to Assess Patient's Perspective of Varicose Vein Service

In order to investigate the current provision of varicose vein treatment in our unit, a patient survey was undertaken. Patients were also interrogated as to whether they might be attracted to alternative options to reduce the waiting time in the NHS.

4.2.1 Methods

As part of a service evaluation exercise, a questionnaire survey of patients attending the Vascular Outpatient Clinic with a venous complaint at Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, was carried out between March to June 2014. Patients were directly approached using a purposive sampling method and asked to fill an anonymous questionnaire about the service offered for varicose vein disease. Inclusion criteria were patients over the age of 18 years attending a new or a follow-up appointment prior to potential interventional treatment for their varicose veins.

Questionnaire Design

The non-validated questionnaire survey used (see Appendix 1) was made up of 32 questions subdivided into three sections:

1. Background: which contained questions about demographics, ethnic group, occupation, total family income, highest level of education attained, family history of varicose vein disease, medical history and previous varicose vein treatment.
2. Current attendance: which interrogated the reasons for the present attendance, effect on quality of life (using non-validated questions), time off requirements and acceptable times between outpatient appointments.
3. Proposed new clinic: which included questions about a proposed 'one stop' vein clinic offering same day diagnosis and treatment.

The questionnaire was piloted on a panel of vein specialists, composed of doctors and nurses, and underwent further changes to the current attendance and new clinic sections, prior to use on patients.

Statistical Analysis

Data is presented as mean with a standard deviation and range. All statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, version 21, IBM, Armonk, USA). A p-value <0.05 was considered significant.

4.2.2 Results

4.2.2.1 Demographics

One hundred and six non-consecutive patients completed the questionnaire over the 4 month period. Most patients were females (62.4%) and the mean age was 51 years (see Table 32 below).

Age (Mean $\pm$ SD) (range) (years)	51 $\pm$ 15 (22 – 87)
Females	62.4
Ethnic Origin	
Caucasian	84.7
Asian	9.2
Afro-Caribbean	3.0
Mixed	2.0
Other	1.0
Total Family Income	
Less than £20,000	36.1
£20,000 to £39,999	38.6
£40,000 to £59,000	15.7
£60,000 to £99,999	6.0
> £100,000	3.6
Level of Education Completed	
None	0.0
Primary education	2.7
Secondary education	32
Tertiary education (post-secondary)	32
Post-graduate	33.3

Table 32. Patient demographics. Values are in percentage, unless specified. (SD = standard deviation)

4.2.2.2 Ethnic Origin and Social Status

Approximately 85% were of Caucasian origin, with about 9% being Asians and 3% of Afro-Caribbean origin. Most patients (74.7%) had a total family income of less than £40,000, while less than 4% of our population earned more than £100,000. Around two-thirds of the patients have completed tertiary or post-graduate education.

4.2.2.3 Varicose vein symptoms and previous treatment

The commonest complaint was pain (73.4%), varicosities (62.2%), leg swelling (44.9%), heaviness (41.8%) and discolouration (36.7%). Both limbs were similarly affected. Three out of five patients admitted to having another family member affected with the condition. More than three quarters of patients reported that their venous disease affected their quality of life moderately or a lot.

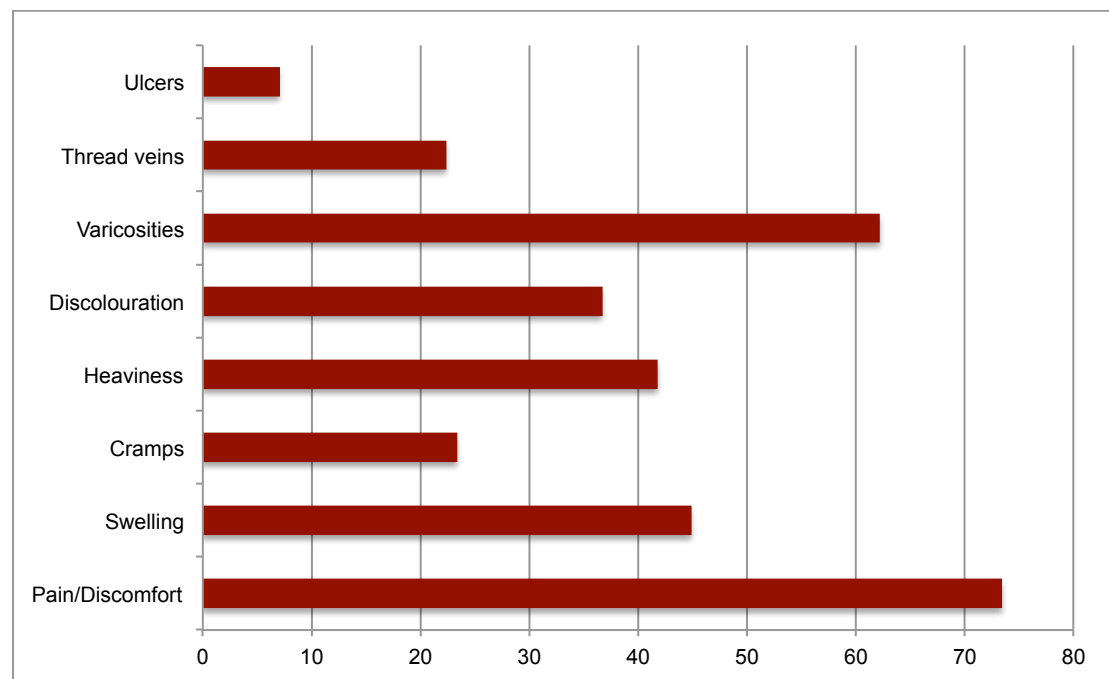


Figure 45. Most common venous symptoms prompting patients' attendance to the Vascular outpatient clinic

Approximately 35% of responders have had previous varicose vein treatment, with 71% stating that the information they were provided at the time was useful and 66% admitting it helped them understand the condition. Most patients had received treatment in the form of compression stockings previously (60%), while 37% have

had surgery and 31% have received one of the endovenous ablative procedures (foam/laser/radiofrequency).

Most patients (80%) were aware that surgery was a treatment option for varicose vein and 67% knew about endovenous ablation procedures.

4.2.2.4 Clinic Attendance

One in 5 patients needed to take time off to attend the clinic appointment. More than 90% of patients believed that the waiting time between their first Vascular appointment and a venous scan should be no more than 1 month. Interestingly, 29.5% had expectations for a same-day scan.

With regards to receiving treatment, 85% of patients believed varicose vein procedures should be received within 1 month of their Vascular clinic appointment (40% favoured it to be within 2 weeks) (Figure 46).

Statistical analysis was undertaken to assess if any association could be found between age, income or education and preferred choice of timings of venous scan or procedure. Arbitrary categories were established by dichotomizing age (less than 65 years and 65 years or above), income (less than £40,000 and greater than £40,000) and education (secondary education is highest level attained and tertiary education or higher). There was no correlation between preference of venous scan and procedural timings and dichotomized age (Pearson Chi-Square, $p = 0.154$ and $p = 0.507$, respectively), dichotomized income ($p = 0.579$ and $p = 0.872$, respectively) or education ($p = 0.099$ and $p = 0.578$, respectively).

4.2.2.5 Clinic Models

Patients were in favour of fewer outpatient appointments, with 53% of them favourable to having two appointments only (seeing doctor and having a Venous duplex at first appointment and treatment on second attendance). Forty-four percent found a 'one-stop' clinic (seen by Vascular specialist, followed by venous scan and procedure on same day) an attractive idea.

No correlation was found between choice of clinic models and dichotomized age, income or education ($p = 0.516$, $p = 0.438$ and $p = 0.685$, respectively).

Ninety percent of patients would consider attending such a 'one-stop' vein clinic offering same day diagnosis and treatment. Even in the eventuality of not receiving treatment on the day, nearly 90% of this group would still prefer to be invited for a 'one-stop' vein clinic. About one quarter of patients would find it difficult to take time off to attend another outpatient appointment.

Most patients would prefer to have prior written information or a website they could refer to prior to their appointment (53% and 46%, respectively). Sixty-five percent of patients would find a helpline number useful and 40% would also appreciate more time to mull over the available options prior to embarking on having a varicose vein procedure.

Patients were generally accepting of the fact that most procedures would be carried out under local anaesthetic (89%). Approximately 83% of patients wanted some form of follow-up, with two-thirds preferring to be seen by a Vascular specialist and 19% by a Vascular nurse. Fourteen percent wanted to be seen by their GP.

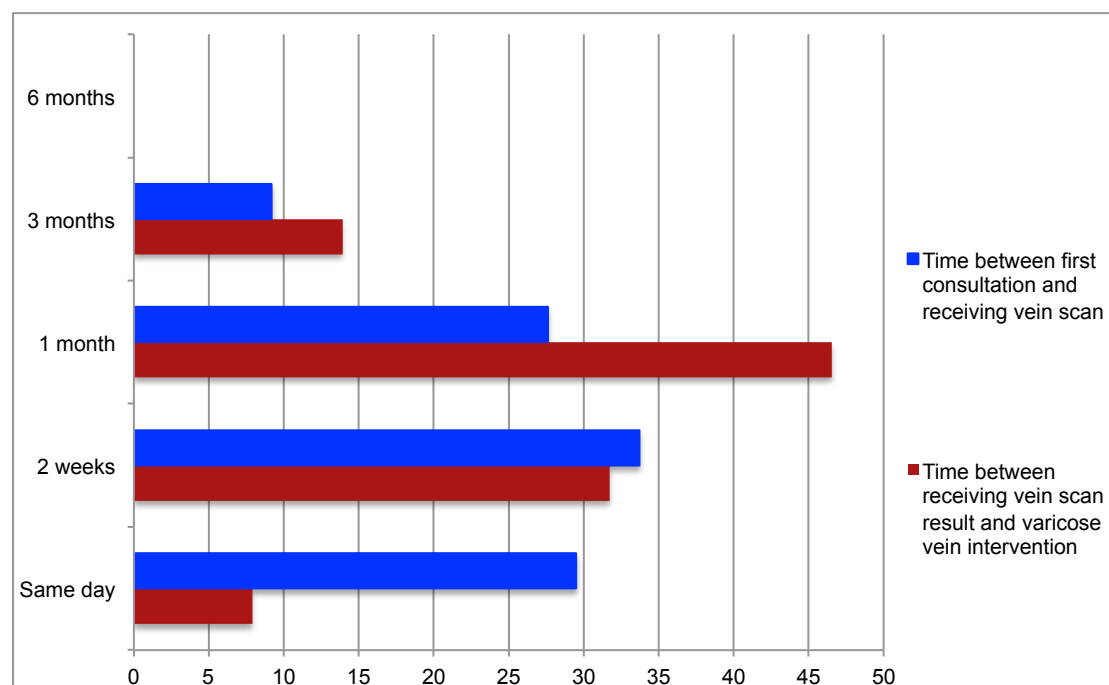


Figure 46. (a) Time interval patients believe is acceptable to wait between their first consultation and having a vein scan; (b) Time interval patients believe is acceptable to wait between being reviewed in clinic with their vein scan result and receiving varicose vein procedure

4.2.3 Discussion

The purpose of this questionnaire survey was to gauge patients' opinions about the varicose vein service currently being offered at our unit as well as assessing patients' views of a 'one-stop' vein clinic, which would offer same day diagnosis and treatment. More than 90% were decided that a waiting time of less than 1 month between a vascular appointment and venous scan and 85% believed varicose vein procedures should be performed within 1 month of their first appointment. Current guidelines from the NHS Operational Standards require more than 90% of patients to receive consultant-led treatment within 18 weeks from referral to treatment (RTT)(2011; 2013). These waiting times are regularly published, ensuring the NHS is aware and accountable to patients and the public(2010). In this present study, half of patients desired at most a two-attendance model whereby they are provided with a diagnosis at their first appointment and treated on the second attendance. Ninety percent of all patients were attracted to the idea of a 'one-stop' clinic offering same day diagnosis and treatment and around 46% expressed a firm preference to attend such a service. This model would theoretically help ease the pressure on outpatient clinics, freeing valuable outpatient clinic slots for more urgent cases. Offering treatment in such a manner could also ultimately lead to non-negligible cost savings to the health service.

A similar survey was conducted in our unit a few years ago(Shepherd et al., 2010b). Most patients were female (73%) and the most common symptom was pain/discomfort (75%). An increased level of awareness of endovenous methods was noted in this current study (67% compared to 40% in the Shepherd et al., 2010b). This better knowledge is likely secondary to increasing usage of these endovenous techniques and subsequent propagation through word-of-mouth or online sharing on social networking sites. Alternatively, it could be the result of increased access to a vast array of online information about varicose veins. As recently noted, an increase of nearly 30% has been found in people looking up 'varicose veins' on the internet(EI-Sheikha, 2015). Although this type of endeavour should be encouraged, the information found can be unreliable(Grewal et al., 2012).

In this present study, 89% of patients were happy to receive their procedure using local anaesthesia. This is marginally lower to the study by Shepherd et al. (2010)

who found that 63% of their population preferred local anaesthetic treatment or did not mind which method of anaesthesia was used (31%)(Shepherd et al., 2010b).

Another notable feature of this survey is that patients with symptomatic varicose veins were keen on reduced time from referral to treatment and having fewer vascular outpatient appointments prior to their treatment. More than 85% of patients believed that the maximum waiting time between vascular appointments should not exceed 4 weeks.

A large proportion of patients were keen on a post-intervention follow-up appointment with their Vascular specialist. Notably, most complications post-varicose vein surgery occur within the first two weeks (Bailey et al., 2001). Bailey et al. (2001) also looked at the need for any outpatient appointments and found that, if required, the appointment should be between 1-2 weeks so as to provide maximum benefit to patients(Bailey et al., 2001). Since then, newer, minimally invasive treatment methods have been introduced. Three studies similarly found that major complications using the newer endovenous treatments occurred within two weeks of treatment(Darvall et al., 2009a; Shepherd et al., 2010a; Rasmussen et al., 2011). Brittenden et al. (2014) found a rate of peri-procedural complications of 5.1% and recorded a rate of any complications of 69.1% at 6 weeks and 51.0% at 6 months(Brittenden et al., 2014). Most of these complications, which included numbness, persistent bruising, lumpiness, thread veins and skin staining, would usually be considered as minor. The extra costs for outpatient clinics for these minor complications would be difficult to justify in this era of tight spending in the National Health Service.

Routine follow-up outpatient clinics after uncomplicated surgery (trans-urethral resection of prostate, open/laparoscopic cholecystectomies, open/laparoscopic hernia repairs and varicose vein procedures) have also been shown to be neither necessary nor cost-effective and that easier access to outpatient clinics might be more appropriate for those developing complications(Bailey et al., 1999). It has also been suggested that provision of information leaflets describing likely complications and time to improvement following varicose vein interventions might be helpful in triaging patients and could potentially avoid unnecessary follow-up(Bailey et al., 1999).

Another argument against routinely following varicose vein patients is the evidence from randomised controlled trials, such as the on-going CLASS trial and recent AVULS (Ambulatory Varicosity avUlsion Later or Synchronized) trial, which demonstrate continuing improvement in both generic and disease-specific quality of life scores both at 6 months and 12 months post-intervention (Brittenden et al., 2014; Lane et al., 2015b). It could be hypothesised that routine early clinic visits may lead to unnecessary retreatment as well as additional costs, but may also actually hinder or delay access to those most at need.

Tennant and Ruckley (1996) indicated that approximately 34 medicolegal cases are brought against surgeons following their varicose vein interventions each year (Tennant and Ruckley, 1996), possibly representing the tip of an iceberg (Ray, 2005). The authors suggested that most of these medicolegal cases were the result of an inadequate consenting procedure and pre-operative assessment, with patients often having unrealistic expectations of the outcome of their interventions (Ray, 2005). A post-procedure assessment might, therefore, enable patients to discuss any possible complications, dissatisfaction or uncertainties and reduce the rate of litigation.

Generalisability of Study

This study has a number of potential limitations. The population studied consisted of patients already referred with venous complaints attending the Vascular outpatient clinics in a West London hospital; and it could be argued that it is not representative of the rest of the population of London or United Kingdom. However, 85% of patients were Caucasians in our survey, which is similar to the proportion in the UK population (87%) (Office for National Statistics, 2013). In addition, approximately 75% of our population earned less than £40,000, which is comparable to the banded gross household income in the United Kingdom (67%) (Office of National Statistics, 2014). Most of the patients in our study were females with a mean age of 51 years.

Another weakness of this study is the non-inclusion of the patients' baseline CEAP (clinical-etiological-anatomical-pathophysiological) classification. Even though CEAP classification can be useful to classify varicose vein disease severity, it is a relatively

poor predictor of change and there is uncertainty as to how the different stages relate to each other (National Institute for Health and Care Excellence, 2013b). This may also have enabled the identification of any patterns in the responses to the questions asked.

Knowledge of the period patients have waited from time of GP referral to clinic review or receiving treatment would again have strengthened the study by offering a direct comparison to the answers collected. This information was, however, not available. Furthermore, a larger sample size might have allowed determination of any association between patients' demographics and their views regarding their management. Outpatient clinics could then be tailor-made to suit the patients' expectations and improve their satisfaction with the service being offered.

4.2.4 Conclusion

The findings from this study indicate that patients are keen to be seen and investigated sooner than current practice allows. Patients favour treatment within one month in the majority of cases. The 'one-stop' vein clinic, one such alternative pathway, appears to be a potential option from a patient perspective and this is a concept that needs exploring further.

4.3 Evaluating the Feasibility and Acceptance of a One Stop Vein Clinic

The results of the patient survey we conducted showed that patients would prefer less time between being referred and having their definitive treatment. The one stop vein clinic model seemed an attractive option. Therefore, we looked at the setting up of a one stop vein clinic for the treatment of varicose veins and assessing the level of patient satisfaction as well as the cost benefits of such a service.

4.3.1 Objectives

The primary objective of the study was to determine the level of patient satisfaction with the service provided using a patient satisfaction questionnaire post-operatively.

The secondary objectives of the study were to measure the changes in quality of life (QoL) at baseline and at various time points. The cost of running such a one stop vein clinic compared to the normal clinic will also be compared.

4.3.2 Methods

GP referrals were screened and patients meeting the inclusion criteria were contacted to confirm their eligibility and asked whether they would be interested to attend the one stop vein clinic. Those agreeable were sent an information pack prior to their appointment.

The pack consisted of:

1. Information leaflet about the clinic
2. Information about varicose veins, their treatments and a telephone number as a helpline
3. The Aberdeen Varicose Vein Questionnaire (AVVQ), CIVIQ and quality of life questionnaire (EQ-5D)
4. Consent form to participate in the study

Patients declining to attend the one stop vein clinic and not wishing to participate in the research study were added to the normal care pathway.

Patients attending the clinic were reviewed by a Vascular Surgeon, who confirmed the patient's consent in the trial, then assessed the degree of venous disease and filled in the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification and Varicose Clinical Severity Score (VCSS). If the patient's symptoms were deemed secondary to venous disease, they were sent to have a Duplex scan to confirm the presence and extent of the venous disease. The results were reviewed by the Vascular Surgeons, and if the patients were suitable for endovenous ablation or UGFS, they were informed of the findings of the scan and proposed treatment. If, after consideration, they were happy to go ahead with the proposed intervention, they were consented and asked to wait for their intervention in the waiting area. If, however, they declined same day treatment, they were added to the conventional care pathway.

The varicose vein interventions were carried out in the Local Anaesthetic Varicose Vein Unit (LAVVU) (an 'office-based' procedure room) under local anaesthetic. Following treatment, the patients were asked to fill a patient experience questionnaire. They were subsequently discharged, similar to current practice. At 3 months, they were called or sent the AVVQ, CIVIQ and EQ-5D.

4.3.3 Inclusion & Exclusion Criteria

4.3.3.1 Inclusion Criteria

The inclusion criteria were:

1. Adults over the age of 18 years
2. Unilateral lower limb symptoms suggestive of venous disease on the GP referral letter

4.3.3.2 Exclusion Criteria

The exclusion criteria were:

1. Recurrent varicose veins
2. Known arterial disease or ABPI<0.8
3. Current deep vein thrombosis
4. Patients who withdraw their consents
5. Inability to complete the questionnaire

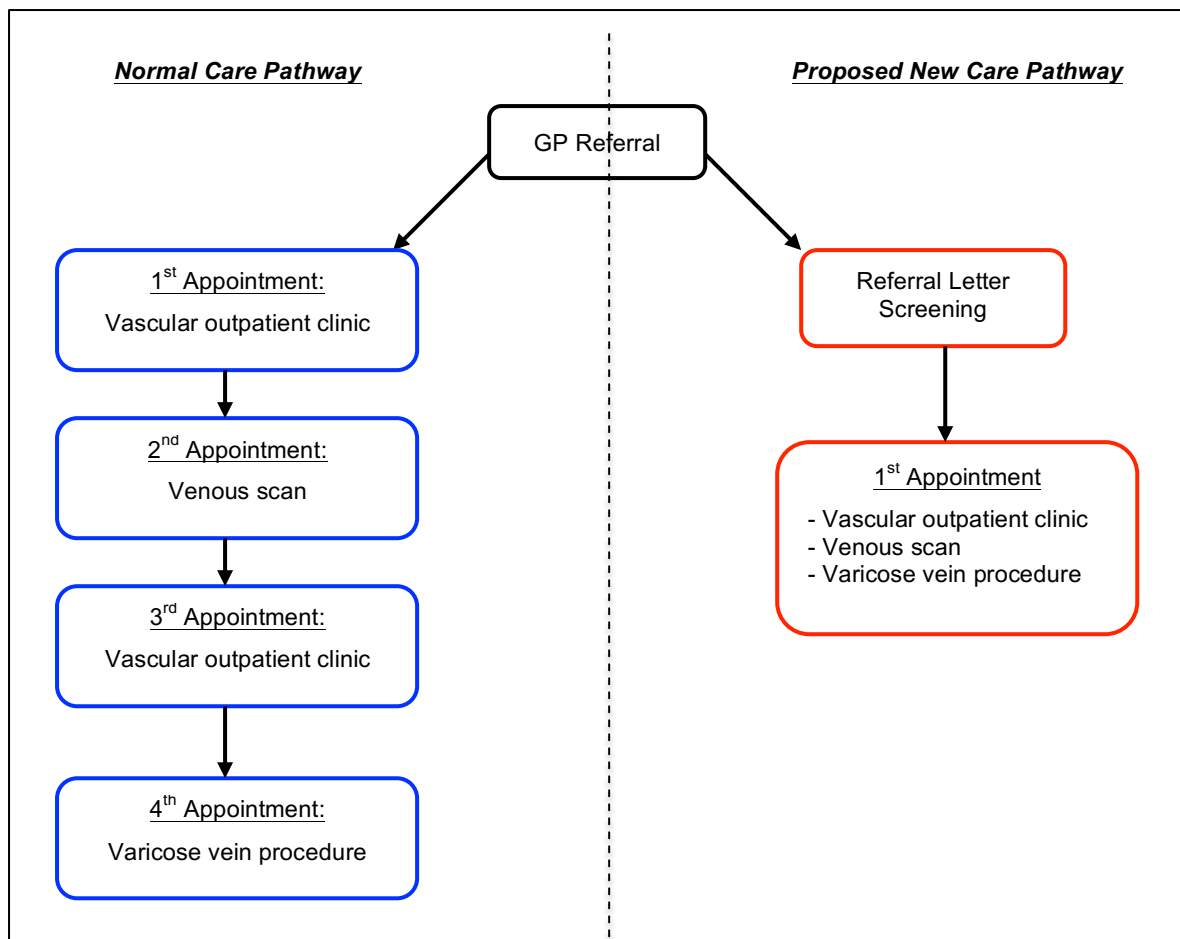


Figure 47. Comparison between the normal care pathway and the proposed new care pathway for patient with varicose veins

4.3.4 Patient Selection

This was a non-randomised study and patients were selected following screening of their GP referral letter. Patients were contacted and, if agreeable, were sent further information and a consent form and were invited to attend the one stop vein clinic.

4.3.5 Treatment Allocation

Treatment received was dependent on the findings on the venous Duplex scan. It was an endovenous procedure (either radio-frequency ablation or mechano-chemical ablation or ultrasound-guided foam sclerotherapy) with/without phlebectomies. All procedures were carried out under local anaesthetic and patients were discharged home later that day, similar to current standard of care.

4.3.6 Measurement of Outcomes

4.3.6.1 Primary Outcome

The patient satisfaction with the service provided was obtained using a patient satisfaction questionnaire administered post-operatively.

4.3.6.2 Secondary Outcomes

- Improvement in the generic quality of life scores measured using the EuroQoL's EQ-5D and EQ-VAS at 0 and 3 months
- Improvement in the Aberdeen Varicose Vein Disease (AVVQ) and Chronic Venous Disease Quality of Life (CIVIQ-14) scores at 0 and 3 month
- Comparison of the clinical outcome and cost of the One Stop Vein Clinic with the normal care pathway for patients with varicose veins

4.3.7 Ethical Arrangements

The National Research Ethics Service (NRES) Committee London – Fulham reviewed the application on the 11th August 2014 and gave a favourable ethical opinion for the study (**REC reference: 14/LO/1295**).

The National Health Service (NHS) Trust Research and Development approval have been sought prior to starting the trial.

4.3.8 Study Flow Diagram

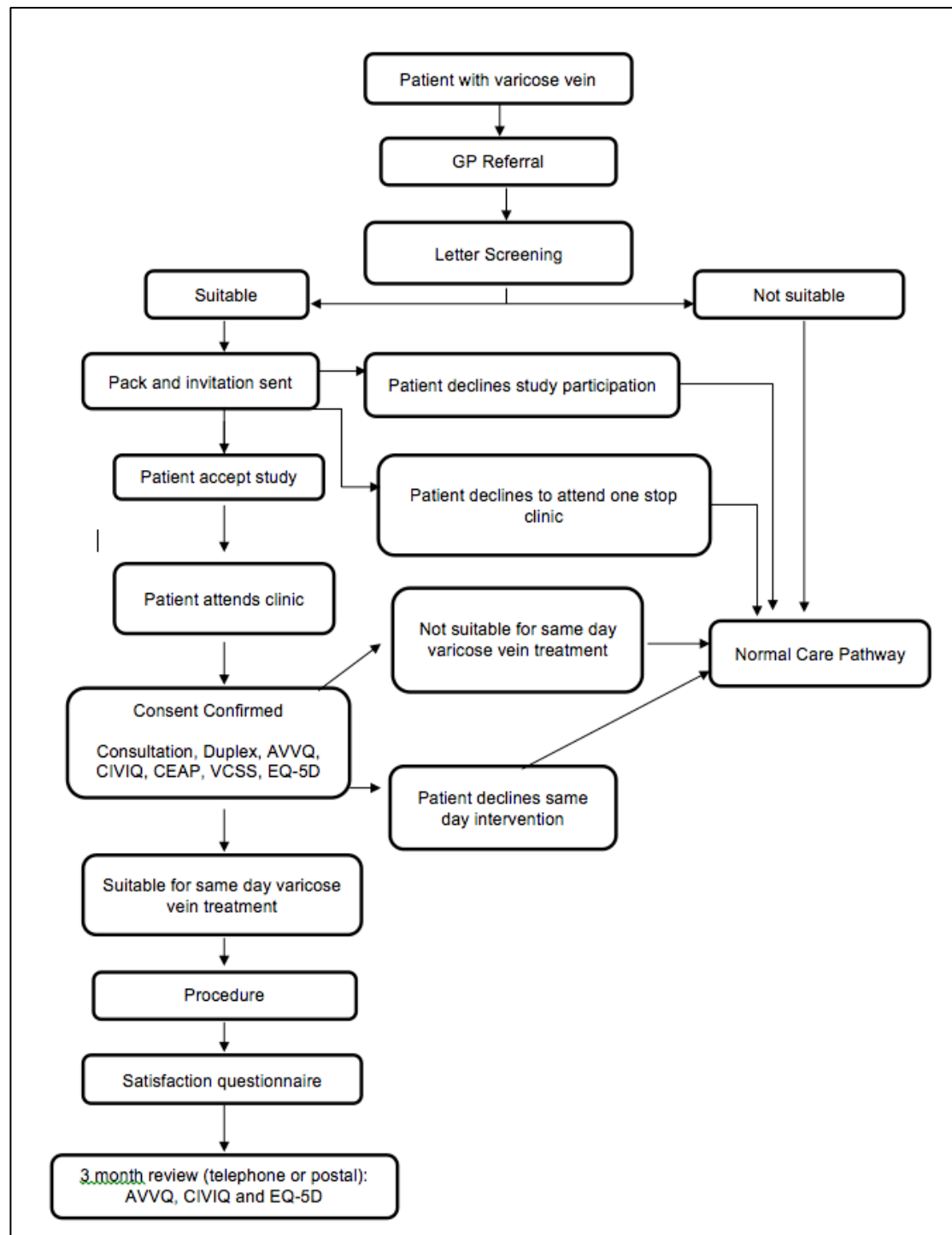


Figure 48. Study flow diagram [AVVQ: Aberdeen Varicose Vein Questionnaire; CEAP: Clinical-Etiological-Anatomical-Pathophysiological; CIVIQ: Chronic Venous Insufficiency Questionnaire; EQ-5D: EuroQoL's quality of life questionnaire; VCSS: Venous Clinical Severity Score]

4.3.9 Results

Despite ethical approval obtained since 2014, the study has been plagued by unforeseen complications. The Local Anaesthetic Varicose Vein Unit (LAVVU) in Charing Cross Hospital, where the procedures were meant to take place, was unavailable for nearly one year as it needed newer ventilation. Once it became operational again, there were insufficient veins lists to be able to accommodate the one stop vein clinic patients.

Nonetheless, five patients have been recruited to the study so far. Most of them were females (4 patients) and all were successfully treated on a single day. The mean age was 53 years (standard deviation, SD: ± 14 ; range: 37 to 76 years). The mean baseline clinical score was 4.75 (SD: ± 5). The mean ($\pm$ SD) baseline generic- (EQ-VAS and EQ-5D) and disease-specific (AVVQ and CIVIQ-14) quality of life was 85 (± 5), 0.730 (± 0.073), 18.8 (± 4.5) and 24.1 (± 5), respectively.

The median time taken to return to normal activities and work was 4.5 days and 1 day, respectively.

All patients waited approximately 4 weeks from being referred by their GP and being seen in the one stop vein clinic. They also felt that they had been given an adequate amount of time to decide as to whether they should go for the varicose vein procedure. The mean total time spent at the clinic was 4 hours and 40 minutes. Satisfaction was very high (mean of 9.6 over 10) and all would be willing to attend this type of clinic set-up again.

4.3.10 Discussion

The inconvenience of the unavailability of the LAVVU and veins list has seriously affected our recruitment to the study. However, patients are being added to the one stop clinic pathway whenever there is a possibility of their cases being done. Satisfaction is very high and it is reassuring that patients did not feel pressured to hasten their decision for treatment.

Thus far, patients have been selected according to very strict criteria, and this may explain why no issues have arisen on the day. Recruitment to this pilot study is ongoing and additional efforts are being made to improve the number of patients being selected, such as the addition of a research nurse to the research team. Data at the 3-month point is still being collected.

CHAPTER 5

POST-OPERATIVE IMPROVEMENT OF CARE: COMPRESSION THERAPY

CHAPTER 5. POST-OPERATIVE IMPROVEMENT OF CARE:

COMPRESSION THERAPY

5.1 Compression Following Endovenous Ablation Therapy

5.1.1 Introduction

Following improvement made in the pre-operative and operative pathways, the management of varicose vein disease could be further enhanced by alterations to the post-operative care offered to patients, more specifically, in terms of post-operative compression.

Currently, there is uncertainty about the use of compression stockings following varicose veins treatment. In their consensus statement in 2008, the International Union of Phlebology (UIP) stated that there is good evidence for using compression in certain clinical indications (Partsch and Baccaglini, 1995). These include the management of telangiectasia after sclerotherapy, varicose veins in pregnancy, prevention of thromboembolism and healing of ulcers. However, a few questions remain unanswered, such as the length of treatment and level of compression to be used (Partsch and Baccaglini, 1995). The International Compression Club (ICC) also noted the poor quality of studies looking at the use of compression devices in treated venous disease (Rabe et al., 2008). To remediate this situation, they devised a set of guidelines to address issues arising from such trials and offered recommendations to improve the validity of the final findings.

The American Venous Forum (AVF), the European Society for Vascular Surgery (ESVS) as well as NICE all recommend the use of compression stockings following varicose vein treatment (Gloviczki et al., 2011; National Institute for Health and Care Excellence, 2013b; Wittens et al., 2015). The 2013 NICE Guidelines on Varicose Veins in the Legs recommended the use of compression hosiery for no more than 7 days after intervention (Marsden et al., 2013). However, further research has also been advocated both by the NICE Guidelines and the European Society for Vascular Surgery (ESVS) into the clinical and cost effectiveness of compression bandaging or hosiery after interventional treatment (National Institute for Health and Care Excellence, 2013b; Wittens et al., 2015). In addition, the guidelines suggested

looking into the length of time compression bandaging should be worn, if shown to be beneficial(National Institute for Health and Care Excellence, 2013b).

Several researchers have looked into the practice of using compression after venous ablation. In a survey of the management of varicose veins by the members of the Vascular Society of Great Britain and Ireland, Edwards et al. found that the majority of surgeons used bandages post-operatively, with 49% using elastic bandages and 29% using non-elastic bandages(Edwards et al., 2009). Seventy seven percent then changed these to compression stockings. Bandages and stockings were both applied for a variable amount of time. In 2015, the members of the same society were again asked about their varicose vein practice and 87% of them stated that they used compression stockings following endothermal ablation and 60% used bandages(EI-Sheikha et al., 2015b). The corresponding figure for foam sclerotherapy was 83% using compression stockings and 64% using bandages. Once more, there was no consistency in the length of time patients were advised to wear them for.

The literature on the use of compression stockings following treatment of varicose vein is limited.

Between December 2006 and February 2008, Bakker and colleagues conducted a prospective randomised controlled trial on the use of compression stockings after endovenous laser ablation of the great saphenous vein(Bakker et al., 2013). One hundred and nine patients were approached with 93 finally randomised to use compression stockings for 2 days (Group A) and 7 days (Group B), respectively. All patients were followed up for 3 months post-treatment and the visual analogue scale (VAS) for pain was recorded at 48 hours, 1 week and 6 weeks. A physical examination and quality of life was assessed at 1 week and 6 weeks. Occlusion rate at the 3 month point was also evaluated. Physical function and vitality was shown to be significantly better in group B at 1 week follow-up, but there was no statistically significant difference at 6 weeks. At 1 week, it was also noted that the VAS score in group B (VAS score 2.0 ± 1.1) was significantly lower than in patients wearing compression stockings for 48 hours (VAS score 3.7 ± 2.1 ; $p \leq 0.001$)(Bakker et al., 2013). No significant difference was, however, observed at 6 weeks post-procedure. Limitations of the study include the high drop out of the trial (40 out of the initial 109 approached) and the absence of any phlebectomies or sclerotherapy in the patients.

Elderman et al. carried out a randomised trial to assess the effect of compression stockings after endovenous laser therapy (EVLT) for great saphenous vein incompetence (Elderman et al., 2014). Patients' reported pain scores and quality of life scores was evaluated on the day of the procedure 2-3 days afterwards and 2-6 weeks post-procedure. A total of 111 patients were initially randomised to stockings (n=55) and no stockings (n=56), but 29% of the patients were excluded after randomisation. The results from the remaining 79 patients were analysed. There was a statistically significant difference in the pain scores in favour of the stockings group up to day 7, but this difference was no longer present by week 6. There was also a greater use of analgesia in patients in the no stockings group compared to patients wearing stockings ($p < 0.05$). In addition, patients wearing stockings reported a statistically significantly higher score of satisfaction at 2 days (4.44 vs 4.15; $p = 0.04$) and at 6 weeks (4.59 vs 4.18; $p = 0.02$). The absolute difference between the two groups was, however, small. Two notable limitations of the study were the high level of exclusion post-randomisation (16 from each group) for a variety of reasons, which meant that the pre-study estimated required recruitment of 52 patients per group, was not met. The absence of any blinding of outcome measures at follow-up was also another weakness of the study.

These two studies seem to suggest that, in the short term at least, compression therapy was more advantageous in patients undergoing EVLA. Both studies were limited by the considerable drop-outs in both studies (40 patients of the original 109 approached in the Bakker et al. study and 32 patients from Elderman et al. trial) (Bakker et al., 2013; Elderman et al., 2014).

Hamel-Desnos et al. undertook a randomised controlled trial looking at the effect of compression in patients receiving foam sclerotherapy of the saphenous vein (Hamel-Desnos et al., 2010). No significant differences were found in the pain scores, inflammation, ecchymosis, induration, pigmentation or matting at 14 and 28 days. They concluded that additional use of compression had no impact on the effectiveness of obliteration of veins, satisfaction scores, symptoms and quality of life. Compliance was relatively low, with only 40% of patients wearing compression stockings everyday. The study was also limited by the small number of patients recruited (60 patients in total) and suggest that the study may not have been adequately powered to enable detection of a difference between the groups.

Another study investigating compression following UGFS utilised compression bandaging for 1 day and 5 days followed by TED stockings for 2 weeks(O'Hare et al., 2010). No significant differences were, however, noted in the pain scores, varicose vein severity score or rate of vein occlusion between the two groups at the 6 week follow-up. The use of some type of compression for the 2 weeks (whether bandaging or stockings) also makes it very challenging to determine whether the effects noted were due to the stockings or the bandages.

Compression use following non-thermal ablation is also a source of controversy. Following CAE, a simple bandage is applied at the puncture site, but no further compression is applied (Almeida et al., 2013; Almeida et al., 2015; Proebstle et al., 2015b). This is not felt to be necessary as the vein wall is not perforated during the ablative procedure(Almeida et al., 2013). MOCA, which also causes intimal injury without vein wall perforation, in turn, recommends the use of compression stockings(Elias and Raines, 2012; Boersma et al., 2013; Bootun et al., 2016a).

This demonstrates the inconsistency and variability witnessed in varicose vein practice with respect to the use of compression post-treatment. Mosti (2013) reported occlusion of the injured vein required a pressure of greater than 10-15mmHg needed to be applied at the thigh in the lying position and 40-50mmHg in the standing (Mosti, 2013). He also suggested that inelastic bandages exert a pressure greater than 50mmHg at the thigh level whereas elastic stockings apply a pressure of only a few mmHg at the same level(Mosti, 2013). Hence, use of class 2 compression stockings with pressures of 15-20mmHg would not be causing vein occlusion when the patient is in the standing position(Hamel-Desnos et al., 2010). Application of a novel cross-taped technique to exert eccentric compression onto the GSV following EVLA was shown, on computed tomography (CT) scanning, to be able to press the tissues deeper than compression stockings (Lugli et al., 2009). This also resulted in lower pain scores compared to the control group (Lugli et al., 2009).

In their meta-analysis, Huang et al. (2013) selected 4 RCTs looking at compression use following ligation and stripping with multiple phlebectomies published between 1991 and 2009, and having a sample size ranging from 104 to 220 patients(Huang et al., 2013). They found that there was no significant differences in pain, post-operative

complications, return to work or leg volume between wearing compression stockings for a short (3 to 10 days) or longer duration (3 to 6 weeks)(Huang et al., 2013). The authors point out though that their meta-analysis was based on a rather small group of studies with heterogeneous characteristics and methodologies, and recommended further well-conducted studies for an appropriate comparison.

A systematic review of the use of compression post-treatment also noted that studies, including RCTs, were mostly flawed with insufficient number of patients, different compression regimens and variable duration of compression application (0-7 days considered as 'short' duration and 5-42 days considered as 'long' duration)(El-Sheikha et al., 2015a). This heterogeneity and inconsistency in the results obtained from the various studies on compression post-treatment, thus, provides weaker evidence to produce management guidelines(El-Sheikha et al., 2015a). It has been advocated that this deficiency in evidence might be addressed by conducting properly planned and managed RCTs with adequate sample sizes(Bootun et al., 2016b)

The 2013 NICE Guidelines did not provide a firm guidance either, but has suggested a limit on the number of days compression bandaging, or hosiery, is prescribed for(National Institute for Health and Care Excellence, 2013b). The lack of evidence of compression use following endovenous is apparent and further research examining the clinical- and cost-effectiveness as well as the duration and optimal compression regimen of any compression has been recommended.

Knowledge and confirmation as to the exact role played by compression following varicose vein intervention would eventually allow us to improve our current management of the condition.

5.2 A multicentre randomised controlled trial of compression therapy following endothermal ablation of varicose veins (COMETA)

This lack of consensus as to the benefit of compression therapy post endovenous ablation and, NICE and ESVS guidelines recommending further research into its actual benefit prompted us to undertake a randomised controlled trial to evaluate these effects (National Institute for Health and Care Excellence, 2013b; Wittens et al., 2015). The study is assessing the impact of compression stockings following endothermal ablation.

5.2.1 Summary

This is a multicentre randomised controlled trial looking at the effect of compression therapy in patients having endovenous treatment for truncal incompetence of their varicose veins using either radiofrequency ablation (RFA) or endovenous laser therapy (EVLT). Patients will be randomised to either the compression group (group A) or the no compression group (group B).

The pain scores, compliance, quality of life scores, occlusion rate at 6 months as well as the cost effectiveness of each intervention will be assessed.

5.2.2 Objectives

The primary objective of the study is to determine patient's pain score for the first 10 days post-procedure using a validated 100mm visual analogue scale (VAS).

The secondary objectives are to compare the two treatment groups with respect to:

- The generic quality of life scores at baseline, 2 weeks and 6 months using the EuroQoL's EQ-5D
- The disease-specific quality of life scores at baseline, 2 weeks and 6 months using the EQ-5D, AVVQ and CIVIQ-14 scores
- The clinical change using the VCSS at baseline, 2 weeks and 6 months
- The degree of bruising and phlebitis at 2 weeks and 6 months
- The patient compliance with the intervention

- The time taken to return to work and normal activities
- Occlusion rates at 6 months
- Comparison of the cost effectiveness of the intervention

5.2.3 Description

This is an ongoing multicentre randomised clinical trial looking at the impact of wearing or not wearing compression stocking following endothermal ablation (either endovenous laser treatment (EVLT) or radiofrequency ablation (RFA)) of incompetent truncal veins. If clinically indicated, patients receive adjuvant treatment (e.g., concurrent phlebectomies or foam injection).

Patients are randomised to group A (compression) and group B (no compression). Only the use of compression is randomised while the decision as to which treatment to use is at the discretion of the clinical team.

5.2.4 Target Population

Patients referred for treatment of symptomatic varicose veins will be recruited if they are found to have primary great saphenous (GSV) or small saphenous vein (SSV) incompetence on colour duplex scan.

5.2.5 Inclusion Criteria

- Adults over 18 years of age
- Symptomatic GSV or SSV vein reflux > 0.5 seconds on colour Duplex
- Recurrent varicose veins, suitable for endothermal treatment

5.2.6 Exclusion Criteria

- Current DVT
- Recurrent varicose veins
- Arterial disease (ABPI<0.8)
- Vein diameter < 3mm
- Patient who are unwilling to participate
- Inability or unwillingness to complete questionnaires

5.2.7 Intervention

Patients are randomised to have compression (group A) or no compression (group B). The compression therapy used is Class II compression stockings (applying a pressure of 18-24mmHg at the ankle). The treatment offered is endothermal ablation (either endovenous laser treatment (EVLT) or radiofrequency ablation (RFA)) of incompetent saphenous veins. If indicated, adjuvant treatment to tributaries (e.g., concurrent phlebectomy or foam sclerotherapy) is permitted.

Patients randomised to group A are asked to wear a compression bandage for 24 hours, followed by compression stockings for 7 days.

Patients randomised to group B are provided with bandages to wear for 24 hours only, with no further compression afterwards.

At baseline, patients are asked to fill quality of life questionnaires (EQ-5D, AVVQ and CIVIQ-14) and are clinically assessed (CEAP and VCSS). On discharge after their varicose vein intervention, they are then provided with a diary to record their post-procedural pain score every day for 10 days using a validated visual analogue scale (VAS). They are also asked to record when they return to their normal activities and are back to work. An appointment is arranged 2 weeks and 6 months later.

Patients' GP are sent a letter to inform them of their patient's participation in the study.

5.2.8 Follow-up

Patients are followed up in the outpatient clinic at 2 weeks and 6 months.

Follow-up at 2 Weeks

At the 2 weeks' follow-up, the diary containing details of the pain scores and how soon patients were able to return to normal activities/work are collected. In addition, patients are asked about any bruising or phlebitis they have had in the two weeks after their procedure and how compliant they have been with the compression. They are examined and the Venous Clinical Severity Score (VCSS) is recorded. They are also asked to fill in the EQ-5D, AVVQ and CIVIQ scores.

Follow-up at 6 Months

At the 6 months follow-up, patients are examined and their VCSS is recorded. They are also asked to fill the EQ-5D, AVVQ and the CIVIQ scores. In addition, they receive a venous Duplex scan to determine occlusion of the treated vein.

5.2.9 Sample Size and Study Duration

The sample size needed to observe a difference of at least 10mm in the VAS score, with a standard deviation of 20mm was estimated. With power at 80% and 5% significance equivalence, we would need to recruit 126 patients (63 per group).

Previous studies looking at compression stockings have shown drop out rates close to 37% at 3 months(Bakker et al., 2013). Therefore, if we estimate a drop out rate of around 30% by 6 months, we would need to recruit approximately 164 patients. If we recruit at least 3 patients per week, this will be approximately a total of 156 patients that could potentially be randomised over the year. With 6 months follow-up, therefore, the study will be running for 18 months with a target recruitment of 150 patients.

5.2.10 Settings

The study is being carried out at the Charing Cross Hospital and the St Mary's Hospital (both part of the Imperial College Healthcare NHS Trust in London, United Kingdom).

5.2.11 Ethical Approval

Approval from the National Research Ethics Service (NRES) Committee - London (Fulham) was obtained and the Research and Ethics Committee (REC) reference is **15/LO/0181**.

The trial is also registered on the ClinicalTrials.gov website having a record number of **NCT02522845**.

5.2.12 Sponsor and Funding

Imperial College London is acting as the main sponsor for this study. Delegated responsibilities are assigned to the NHS trusts taking part in this study. The Graham-Dixon Charitable Trust has provided a grant for the conduct of this research study.

5.2.13 Results

One hundred and nine patients have been randomised so far, 49.5% to the compression group. Approximately 54% of the population were males and the mean age is 50 (± 15) years. The follow-up rate is currently 66% at 2 weeks. There were three incidences of protocol violation, with 2 patients randomised to the compression group not being provided with compression stockings and one patient from the no compression group receiving and using compression stockings post-operatively.

The baseline CEAP clinical class for the compression group was C2-3 52% and C4-C6 48%. The corresponding figures for the no compression group was C2-3 66% and C4-6 34%.

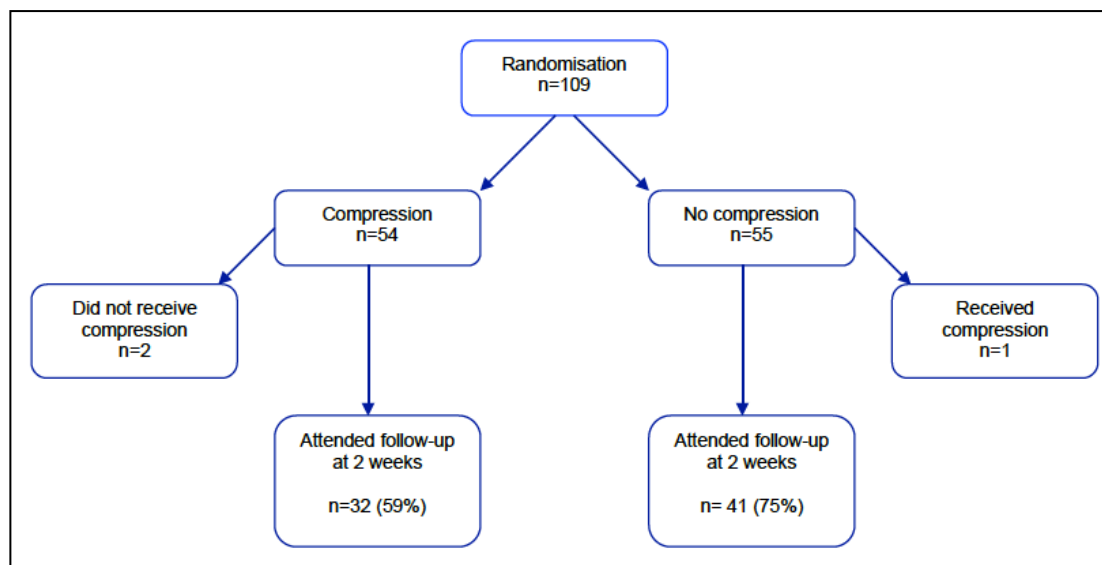


Figure 49. CONSORT diagram of the COMETA trial

Characteristic	Compression (n=54)	No Compression (n=55)	Total (n=109)	p-value
Age ($\pm$SD) (years)	49 ($\pm$ 16)	51 ($\pm$ 15)	50 ($\pm$ 15)	0.528
Sex (Male:Female)	65:35	44:56	54:46	0.027
BMI (kg/m²)	27	27	27	0.997
CEAP 2	22	38	30	
CEAP 3	30	28	29	
CEAP 4	32	32	32	
CEAP 5	14	2.1	8.2	
CEAP 6	2	0	1.0	

Table 33. Baseline patient characteristics. All units are in percentages unless specified. (BMI: body mass index; CEAP: clinical-etiological-anatomical-pathophysiological classification; SD: standard deviation)

The mean daily pain score in the compression group using a visual analogue scale (VAS) was 22.45 ($\pm$ 20) mm (mean numerical pain score: 2.7) and 32.93 ($\pm$ 25) mm (mean numerical pain score: 3.5) in the no compression group ($p=0.115$). Significantly better pain scores were noted in the compression group on days 2, 3, 4 and 5 compared to the no compression group (Figure 50). The pain scores on Day 2 was 24mm in the compression group versus 40mm in the no compression group

(p=0.21), 21mm versus 34mm on Day 3 (p=0.043), 21mm versus 36mm Day 4 (p=0.023) and, 18mm versus 35mm Day 5 (p=0.010), respectively.

Also, patient randomised to the no compression group seem to have a more gradual rate of improvement in their mean numerical pain scores than those provided with compression stockings (Figure 51). This difference was, however, only significant on days 2 (mean score in compression group 3.0 versus 4.5 in the no compression group; p=0.049), 4 (2.6 versus 4.2; p=0.020) and 5 (2.3 versus 4.2; p=0.011).

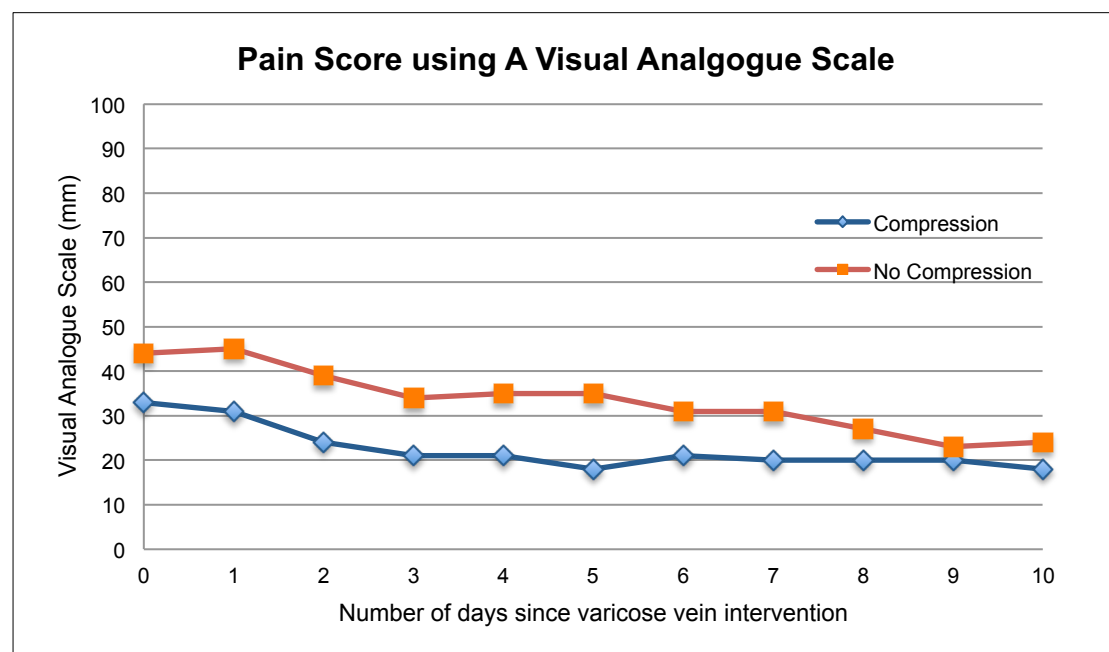


Figure 50. The mean recorded pain score using a 100mm visual analogue scale for each day following endothermal ablation. A significant difference was noted on days 2 to 5 between those randomised to compression stockings and those in the no compression group (see text).

The clinical scores and quality of life scores in both the compression and no compression groups show improvement from baseline (Table 34). The mean improvement in VCSS was -1.6 ± 2.5 in the compression group compared to -1.9 ± 2.2 in the no compression group (p=0.542). It, however, appears that, on these interim results, the extent of quality of life improvement observed in the no compression group is to a lesser degree compared to those receiving compression stockings. Indeed, the gain in QoL using the EQ-VAS, EQ-5D, AVVQ and CIVIQ-14 for the compression group was 10, 0.07, -3.3 and -6.6, respectively, compared to 5, -0.01, -0.7 and 4.7, respectively. Only the difference in CIVIQ-14 was statistically significant though (p=0.023).

Both groups returned to normal activities and work after a median of 2 days.

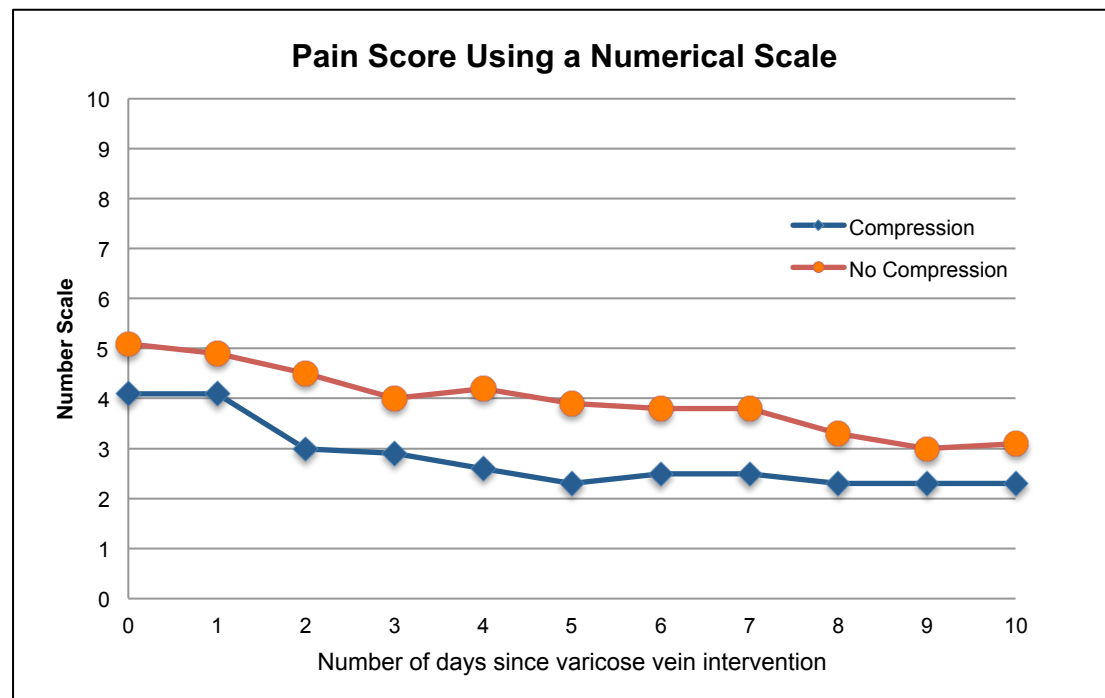


Figure 51. The mean recorded pain score using a 0-10 numerical scale for each day following endothermal ablation. A significant difference was noted on days 2, 4 and 5 between those randomised to compression stockings and those in the no compression group (see text).

	Baseline	2 Weeks Follow-up			p-value
	Compression	No compression	Compression	No compression	
<u>Clinical Scores</u>					
<i>VCSS [SD]</i>	5.1 [2.0]	4.2 [2.2]	3.6 [2.5]	2.5 [1.7]	0.542
<i>VDS [SD]</i>	1.1 [0.3]	1.1 [0.3]	0.59 [0.7]	0.31 [0.5]	0.041
<u>QoL Scores</u>					
<i>AVVQ [SD]</i>	19 [13]	19 [14]	17 [12]	17 [12]	0.194
<i>CIVIQ-14 [SD]</i>	31 [24]	27 [25]	23 [17]	29 [24]	0.023
<i>EQVAS [SD]</i>	73 [18]	80 [15]	84 [12]	83 [15]	0.137
<i>EQ-5D-3L [SD]</i>	0.72 [0.18]	0.75 [0.19]	0.78 [0.19]	0.75 [0.22]	0.194

Table 34. Clinical and quality of life scores at baseline and at the 2-week follow-up. Values are mean. (AVVQ: Aberdeen Varicose Vein Questionnaire; CIVIQ-14: Chronic venous insufficiency quality of life questionnaire; EQ-5D: EuroQol's EQ-5D; EQ-VAS: EuroQol's visual analogue scale; SD: standard deviation; VCSS: Venous clinical severity score; VDS: Venous disability score)

The degree of ecchymosis was assessed at the 2-week follow-up. This shows that 87.1% of patients from the compression group and 79.5% of the no compression

group had no evidence or less than 25% of the length treated affected by bruising ($p=0.112$).

There was one case of gastrocnemius deep vein thrombosis recorded in a 68 year old lady randomised to the no compression group. Another patient, randomised to the compression group and categorised as clinical class C4 at baseline, had developed a small ulcer at the ankle by the time of the first follow-up.

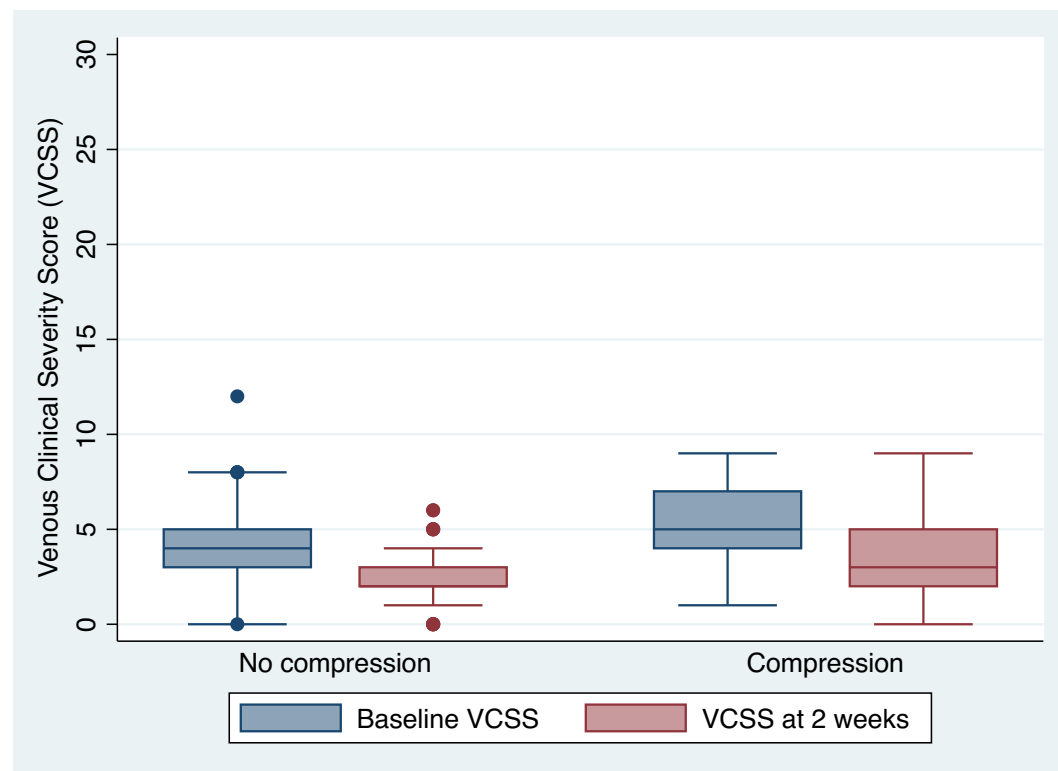


Figure 52. Comparison of Venous Clinical Severity Scores (VCSS) at baseline and at 2 weeks

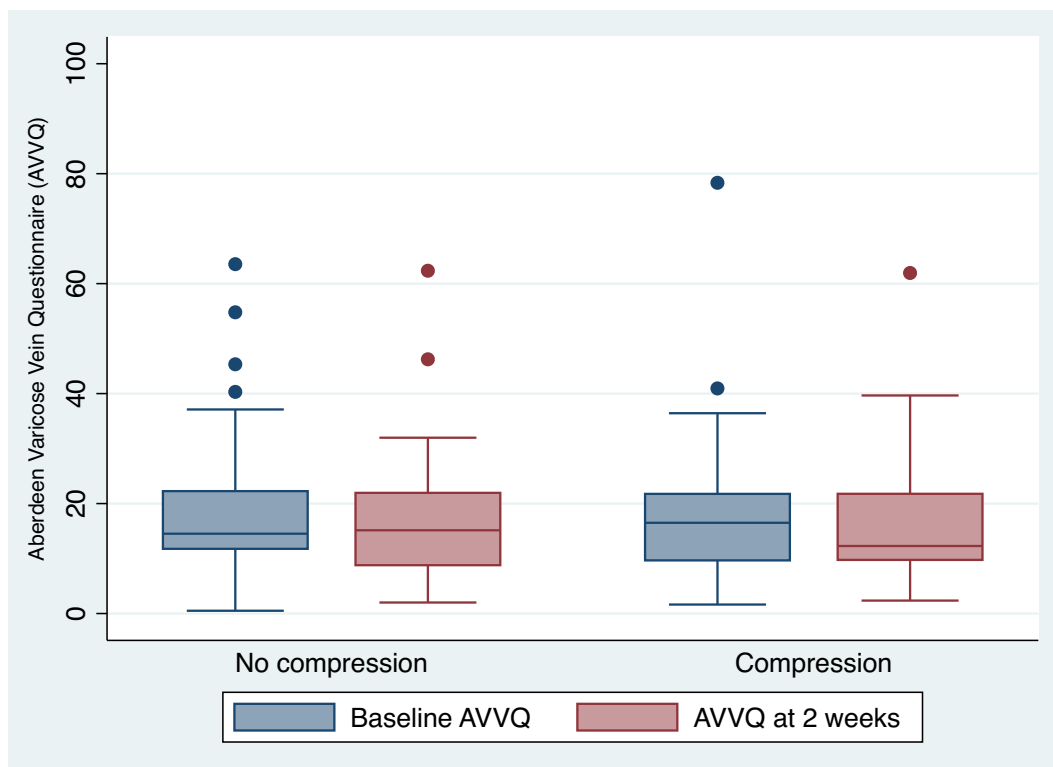


Figure 53. Comparison of the Aberdeen Varicose Vein Questionnaire (AVVQ) scores at baseline and 2 weeks

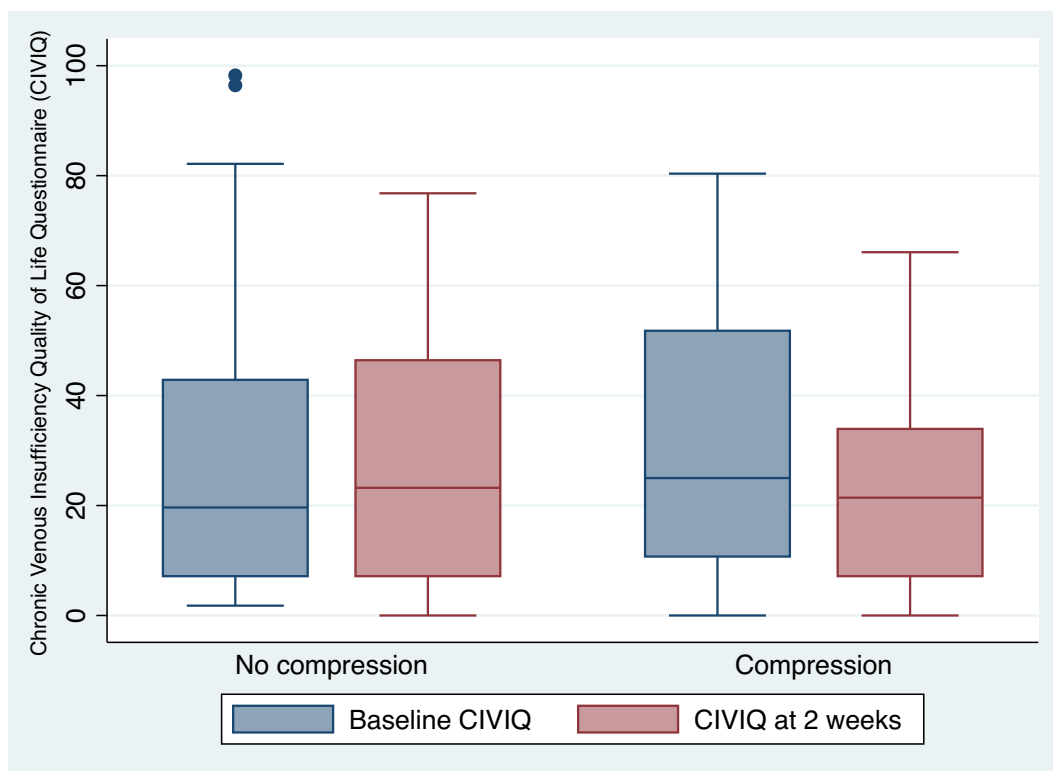


Figure 54. Comparison of the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) scores at baseline and at 2 weeks

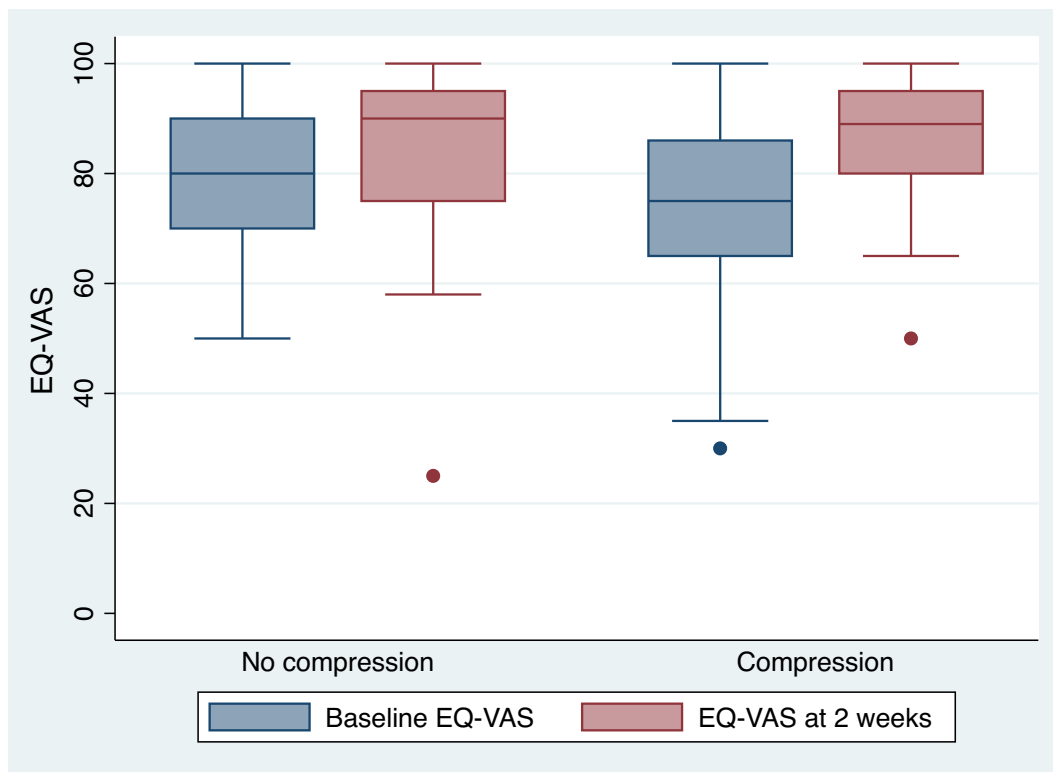


Figure 55. Comparison of EQ-VAS at baseline and 2 weeks

5.2.14 Discussion

These results indicate that wearing compression stockings following endothermal ablation is advantageous in the first few days following treatment. However, this benefit is no longer significant as from day 6. Formal collection of analgesia use was not undertaken, which would also have aided into determining the severity of the discomfort post-procedure. Moreover, this is not translated in notable differences in the clinical or quality of life scores. The time taken to resume activities or to return to work is similar in both groups as well. The degree of ecchymosis recorded was also similar between the two groups and the majority of the bruising observed occupied none or less than 25% of the area treated.

Two recent studies have also reported on the use of compression following endothermal ablation (Ayo et al., 2016; Ye et al., 2016). Ayo et al. (2016) recruited 70 patients to determine the efficacy and patient outcome of wearing or not wearing compression stockings following endovenous ablation (91% RFA and 9% EVLA) (Ayo

et al., 2016). There were no differences recorded in the pain score at 1 and 7 days and bruising was similar between the two groups. No significant differences were recorded in both the clinical scores (using VCSS) and QoL scores (using CIVIQ-2). All the GSV treated were successfully ablated and there were no major complications. This was a randomised study with similar baseline patient characteristics and valid endpoints. Unfortunately, there were no adequate power calculations for the study and the follow-up rate was rather poor (20% of patients at 90 days).

For their part, Ye et al. (2016) recruited 400 patients and assessed the outcomes in those randomised to compression stockings or not (Ye et al., 2016). They noted that patients in the compression group experienced significantly less pain and oedema compared to those in the no compression group. However, again, there were no major differences observed in quality of life measures and the time to return to normal activities.

The findings from this present trial are in line with the findings from Ayo et al. (2016) and Ye et al. (2016), mentioned above. Given the time constraints of this thesis, an earlier analysis of the results was undertaken. Hopefully, the final results will be able to shed further evidence as to the place of compression following varicose vein treatment.

CHAPTER 6

CONCLUSIONS

CHAPTER 6. CONCLUSIONS

Varicose veins affect a significant proportion of the population and have a negative impact on the general quality of life of patients. However, owing to disparities in the definitions utilised, populations studied, methods used and diagnostic tools employed, epidemiological studies have failed to provide a reliable estimate of the magnitude of this affliction.

There is also still ongoing uncertainty as to the exact pathogenesis of the disease, even though strides have been made in this field recently. A number of risk factors have been identified, but their precise role and mechanism of producing venous incompetence is unclear.

The disease is responsible for a number of physical and psychological effects. Attempts to classify the condition have resulted in an imperfect modality of classification to become widely used. Although contradictory at times, local and international guidelines are generally helpful, providing mostly a common direction for the management of varicose veins. Treating varicose veins has been demonstrated to lead to improved quality of life and assessment of outcomes, particularly in the form of PROMs, will likely determine the extent of future resource allocation, especially in the NHS in England. With funding in the NHS becoming increasingly stringent, justification of treatment modalities used based on their cost-effectiveness has become essential.

The main objectives of this work were to assess areas where major improvement can be made in the management of varicose veins.

Endovenous mechanochemical ablation and cyanoacrylate adhesive use are two of the newer treatment methods evaluated in a randomised controlled trial and a pilot study, respectively. In the RCT, 170 patients were recruited and randomised to either a thermal method, radiofrequency ablation, or a non-thermal, non-tumescent technique, MOCA. The baseline characteristics of both groups were similar. It was found that the median maximum pain score was significantly less with MOCA compared to RFA, both when using a visual analogue scale and a number scale. The clinical and quality of life scores improved similarly in both groups at 1 and 6 months,

and the time to return to work/normal activities was no different either. There were no significant differences between the occlusion rates at the end of the study period. This study demonstrated that MOCA is a potential alternative to endothermal treatment methods, but further long-term studies are needed to confirm its efficacy.

Twenty limbs were treated in the pilot study of cyanoacrylate embolisation with a low level of pain recorded during the procedure. Similar degrees of improvement were noted in the clinical and quality of life scores at the one-month follow-up. Patients returned to their normal activities a median of 1 day after their procedure and reported back to work a median of two days post-procedure. The occlusion rate was high, but additional studies, either longer-term cohort studies or comparative randomised controlled trials, might be able to shed more light on the effectiveness of this method.

A systematic review and cost-effectiveness analysis of all varicose vein interventions and re-interventions were also undertaken. Due to a lack of clarity as to the precise definition of recurrence in the literature, the outcome measure “re-intervention” was used as it is the definitive ensuing step once a previously treated patient develops a symptomatic recurrence. It was found that most of the RCTs included in the systematic review looked at conventional treatment methods, i.e., surgery, EVLA, RFA and foam sclerotherapy. Non-RCTs were included for the NTNT methods, but only one reported on re-intervention for MOCA. Direct comparison showed that surgery and EVLA had fewer re-intervention compared to conservative care and UGFS. Re-intervention data was similar between EVLA and surgery, and EVLA and RFA. A network meta-analysis was also carried out and this demonstrated that UGFS had a higher probability of re-intervention compared to surgery, EVLA and RFA. A similar re-intervention rate to surgery and the endothermal methods was obtained with MOCA (1.2 per 100-patient years). Generic quality of life measurement using the EQ-5D showed that similar improvement was achieved with surgery, EVLA, RFA, MOCA and CAE between 1-13 weeks. At more than 6 months, the improvement noted was no different between surgery and EVLA. EVLA was shown to lead to greater improvement compared to UGFS. None of the techniques investigated differed when the disease-specific quality of life was compared using the AVVQ. Procedures took less time and were cheaper with UGFS. CAE appeared to take longer and was the most expensive modality. At a threshold of £20,000 per

QALY, the probability of being cost-effective was 0.316 for EVLA, 0.265 for RFA, 0.136 for UGFS, 0.111 MOCA, 0.002 for surgery and 0.000 for CAE. However, the systematic review suffered from a number of biases (e.g., lack of blinding and concealment of randomisation status etc.). Moreover, the lack of RCTs looking at re-intervention for the non-thermal methods and the complete absence of any re-intervention data for CAE precludes any meaningful inferences to be drawn regarding their respective efficacy.

Another strategy explored was to change the management of varicose veins through looking at the perspective of patients first, then evaluating the process of providing same-day diagnosis and treatment. The patient survey found that patients were keen on a shorter delay between being seen in clinic and having their venous investigation as well as a shorter period of time between being seen in clinic and receiving their treatment. Ninety percent of patients were willing to attend a one-stop vein clinic offering diagnostic scans and treatment on a single day. The pilot study on this type of clinic showed that it is feasible to invite patients fulfilling strict criteria to attend such a one-stop clinic. All patients in the study attended the one stop clinic within 4 weeks of their referral and all felt they were provided with sufficient time to decide on their treatment. Satisfaction was also found to be high. The main issue has been the unavailability of the procedure room, but it is hoped that further patients would be recruited to this study.

Finally, the use of compression therapy following endothermal ablation was looked at in a randomised controlled trial. The preliminary results show that 109 patients have been enrolled and 66% of them had attended follow-up at 2 weeks. The mean daily pain score was lower in the compression group compared to the no compression group, but this was not significant. However, significantly less pain scores were recorded on days 2-5 in the compression group, indicating that compression stocking use in the first few days following treatment might be advantageous. No significant differences were noted between the two groups in terms of clinical and quality of life scores, except for a significantly worse score using the CIVIQ-14 in the no compression group. Both groups returned to their normal activities and work within 2 days. Hopefully, the final study results would be able to clarify the actual benefit of wearing compression stockings post-intervention.

This work illustrates that there is scope to improve patients' experience and outcomes in the current management of varicose veins by shortening the waiting time from referral to treatment, changing the treatment method used, and the care provided post-operatively. Further research into these strategies would be able to provide a clearer idea as to the benefit of the interventions evaluated.

CHAPTER 7

FUTURE PLANS

CHAPTER 7. FUTURE PLANS

The management of varicose vein disease remains an ever-evolving field and through this work, the areas which may be able to benefit the most from these developments have been investigated. This shows that improvement is possible in the way treatment is being delivered, the type of treatment offered as well as the care provided following venous intervention. This thesis included the outcomes from some of the current research being undertaken. However, further progress can still be achieved and possible future work to improve the outcome of varicose veins treatment include the following:

1. The introduction and evaluation of a One Stop Vein Clinic appears to be a natural continuation of the work carried out with success in other surgical specialties. The potential benefits of such a management strategy are the abolition of waiting times for patients with varicose veins as well as a reduction of unnecessary outpatient review. This could be associated with future reduced expenditure for treating this condition. Hence, the results of the Pilot Study on One Stop Vein Clinic could potentially be expanded to a full randomised study which would allow patients to be randomised either to the normal clinic pathway or to the one stop vein clinic pathway. This would permit a better examination of the pros and cons of such an intervention as well as elucidate its cost-effectiveness.
2. There is increasing evidence that non-thermal treatment method for varicose veins have a place in the armamentarium of the vascular surgeon. Both MOCA and CAE have been found to be efficacious, similar to current endothermal technologies. However, no direct comparison of these two modalities has yet been undertaken. As such, a direct comparative, and possibly, randomised study of these two techniques would be able clarify the similarities and differences between the outcomes using each method. Moreover, if sufficient data is obtained regarding re-intervention rates, this could be included in a systematic review and cost-effectiveness analysis later on.

3. Uncertainty exists as to the optimal treatment strategy for patients at each CEAP Clinical Stage. Despite the numerous trials undertaken, information as to the benefit of intervention at each CEAP clinical stage is lacking. The NICE guidelines have thus recommended conducting further research to determine the best treatment for varicose veins at each CEAP clinical stage(National Institute for Health and Care Excellence, 2013b). A potential answer could be provided by carrying out a randomised controlled trial of patients at different CEAP stages with linking of the clinical and quality of life outcomes to this baseline characteristic.
4. The recent AVULS trial suggested that concurrent varicosity treatment following endovenous ablation was beneficial(Lane et al., 2015b). However, there is no consensus as to whether phlebectomies or foam sclerotherapy is more beneficial and NICE has suggested looking at the clinical and cost-effectiveness of these two methods(National Institute for Health and Care Excellence, 2013b). Therefore, a comparative RCT of endothermal ablation with the treatment method of tributaries randomised would enable clinicians to ascertain the respective advantages of both.
5. The study of the effects of compression therapy following endothermal ablation is ongoing. A previous RCT looking at the use of compression following foam sclerotherapy recruited a relatively small number of patients(Hamel-Desnos et al., 2010). Conducting a similar RCT, but with more recruiting sites, might be able to provide a clearer answer as to the benefit of compression use following UGFS.
6. Following the experience from the studies conducted to produce this work, it has become obvious that reduced follow-up rates following varicose vein intervention is an issue which can be detrimental to the final results of the study. One way to address this problem would be to perform a systematic review of the drop-out rates from trial follow-ups in RCTs and determine whether there are ways to minimise its impact on study findings.

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APPENDICES

Appendix 1

Clarivein Patient Information Letter v3 & Consent Form v3
Charing Cross 04 May 2012



Vascular Department,
Charing Cross Hospital,
Fulham Palace Road
London, W6 8RF

Information Sheet for Research Participants

Randomised Clinical Trial comparing VNUS ClosureFAST™ with ClariVein for Varicose Veins

A single-centre, randomised clinical trial comparing endovenous thermal ablation with concomitant avulsions and delayed avulsions for the treatment of varicose vein disease

Dear Participant,

We would like to invite you to take part in the research study named above. Before you decide it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with friends, relatives or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part. Thank you.

What is the purpose of the study?

This study aims to compare radiofrequency thermal ablation of varicose veins with pharmacomechanical ablation of varicose veins (the difference between using heat to block off a vein and using chemicals and a mechanical device). We are comparing the procedural pain levels, technical success and the effect on how patients feel about their veins (quality of life).

Background Information

Varicose veins are a common problem and affect approximately 30-40% of the population at some point in their lives. The severity of varicose veins varies from purely cosmetic to severe leg ulceration and it has been shown that treating varicose veins results in significant improvements in quality of life.

Varicose veins are usually caused by abnormal blood flow - termed venous reflux in the long veins in the leg (termed great saphenous vein along the inside of the leg or the small saphenous vein at the back of the calf) which, although they cannot be seen, often cause symptoms such as aching and swelling. This also leads to the development of so called "varicose veins" close to the skin surface which are visible to the patient - the lumpy veins (termed varicosities).

New minimally invasive treatments have become available in the last decade - these are termed **endovenous ablation** treatments (inside-the-vein closure treatments). These techniques either use energy to heat the inside of the vein, causing it to stick together and

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block off (**ablation**). Alternatively, we can use chemicals (glues) to stick the vein together (**pharmacological occlusion**) or a combination of mechanical tip and chemicals to stick the vein together and block it off (**pharmaco-mechanical ablation**). All of these treatments seal off the problem vein.

In this trial we are using either radiofrequency heat ablation or pharmaco-mechanical ablation to seal off the vein.

Endovenous radiofrequency ablation treatment uses heat energy delivered via a probe inserted into the vein in order to treat the long veins in the leg, and has been shown to be safe and effective. The device is called VNUS ClosureFAST.

Pharmacomechanical ablation treatment uses a rotating metal tip to "scratch" the lining of the vein and inject a liquid chemical called sclerosant into the vein at the same time. The sclerosant causes the vein to stick together. This technique has also been shown to be safe and effective. The device is called Clarivein.

The varicosities (or lumpy veins) are removed via small cuts (<0.5cm long) in the skin termed "phlebectomies" or "avulsions", performed at the same time as the long veins are treated.

Foam sclerotherapy can be used as an alternative to "avulsions". This uses a special chemical made into foam, which is injected into the varicose veins using small needles. As with liquid sclerosant it causes the vein to stick together and block off (sclerose).

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not to take part. If you do decide to take part we will ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep. If you decide to take part you are still free to withdraw at any time. If you decide not to take part you do not have to give a reason, nobody will be upset and the standard of care you receive will not be affected.

What will I be asked to do if I take part?

We will ask you about your medical history and fill in a questionnaire with you. You will be assigned a trial number and your treatment plan will be allocated following randomisation. The randomisation will not affect the standard of your care. It will decide the treatment device used. Both are standard care treatment options.

You will then have endovenous treatment of your varicose veins with avulsions. The treatment will use either VNUS radiofrequency thermal ablation (heat treatment) or Clarivein pharmacomechanical ablation (mechanical and chemical treatment). This will be carried out under local anaesthetic. You will be asked to score the level of pain experienced during the procedure using a special scale (VAS - Visual Analogue Scale). You will then be asked to keep a patient diary for the 30 days after treatment. 30 days after your treatment you will be

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reviewed in clinic with a further questionnaire and a repeat venous duplex. Six months after your operation you will again be reviewed in clinic with a venous duplex ultrasound of your leg to assess technical success and another questionnaire.

We will record your name, date of birth, postcode, and NHS number. The information will be stored in a locked filing cabinet in a locked room and on a password protected research computer database, within the department of Vascular Surgery at Charing Cross Hospital, which is only accessible to the researchers. The information will be destroyed in 2020.

What other treatments are available?

Alternative treatments for varicose veins include open surgery, endovenous laser ablation and conservative treatment with compression therapy.

Endovenous laser ablation is a technique similar to endovenous radiofrequency ablation - i.e. it uses heat to stick the vein together and ablate it. It uses a special optical fibre to transmit a laser (focused light beam) into the vein. This laser generates heat and causes the same process of ablation to occur. It is very effective, but radiofrequency ablation has been shown to be better tolerated. It can be done under local or general anaesthetic, but requires all users (and the patient) to wear protective goggles.

Open surgery is the gold standard treatment but is far more invasive and has been shown to be associated with a slower recovery. This treatment involves a cut in the groin, and the vein is physically pulled out with a wire 'stripper'. The varicosities are then removed using avulsions as previously described. It can be done under local or general anaesthetic. It is associated with increased symptoms of pain and bruising after the operation. It has the same success rates as endovenous techniques.

Conservative treatment treats the symptoms but not the cause of the problem. It involves the wearing of compressive stockings all day, every day, for life. It does not involve an operation but does involve a lifestyle change.

Further information on these treatments is available on request.

What is the standard care provided in the department?

Current standard care in our department for Varicose Veins is very similar to the proposed trial plan. All patients receive an ultrasound scan of the veins in their leg to plan surgery. Varicose veins are all treated with endovenous radiofrequency ablation as standard, under local anaesthetic or general anaesthetic according to patient and surgeon preference. Avulsions are carried out simultaneously to the endovenous treatment. Immediately after the operation the treated leg is placed in a compression stocking. Procedures are all undertaken as a day case. The treatment is well tolerated by most. Patients are discharged to their GP's care post-operatively. All patients wear the provided compression stocking for 2 weeks post-operatively. You will be provided with a leaflet describing the procedure at your clinic appointment.

What is the difference for me if I take part?

If you enrol in the study, the only difference for you as the patient will be the treatment option (detailed above), and the follow-up appointments - in the study you will be seen twice

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post-operatively: at 30 days and 6 months; with a repeat vein scan at both appointments. We will also ask you to complete a pain score diary for the first 30 days, which will supply.

What are the possible side-effects, disadvantages or risks of taking part?

There are no specific side-effects, disadvantages or risks from taking part in this study as both treatments offered are standard practice. The differing techniques are utilised throughout the world.

The specific risks of varicose vein treatment are the same for all treatments - the most common are bleeding, bruising and infection. This is because cuts are made in the skin and the veins, which would be expected to lead to some bleeding, which is controlled at the operation. Cuts in the skin provide a possible route of entry for infection, which is controlled with antibiotics at the operation and further antibiotics if required.

The major complication associated with all varicose vein procedures is a deep vein thrombosis (DVT). This is a clot in the deep veins of the leg (famously called 'economy class syndrome'). This is reduced in the case of endovenous treatment due to reduced to pain post-operatively - patients are often back at work the day after the procedure.

Due to the minimally-invasive ("keyhole") technique the risk of serious bleeding is greatly reduced in endovenous treatment and we are able to give a special blood-thinning injection to help reduce the risk of clots in the leg veins.

What are the possible benefits in taking part?

You are not expected to gain any personal benefit from taking part in this study. However the information gained may help other people in the future. It is not possible to offer any financial incentive for taking part in the study.

What if something goes wrong?

Imperial College London has insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the research team (see below). The normal National Health Service complaints mechanisms are also available to you. If you are not satisfied with the response, you may contact the Imperial College Joint Research Office.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities to check that the study is being carried out in accordance with national guidelines. If an abnormality is found, which does not relate to

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Vascular Department,
Charing Cross Hospital,
Fulham Palace Road
London, W6 8RF

your veins, a referral to an appropriate specialist will be made, with your permission, and your General Practitioner will be informed.

What will happen to the results at the end of the research study?

We will publish the overall results of the study, whatever the findings, to allow doctors to learn from our findings. A one page plain English summary will be available from the email address below in around 2014. As a participant, you will not be personally identifiable in any publication.

Who is organising and funding the research?

The project is organised by Imperial College London. The investigators are employed by Imperial College Healthcare NHS Trust & Imperial College. The project is funded by Vascular Insights, the company who manufactures the Clarivein device. This study is being performed as part of a higher research degree (PhD) at Imperial College London.

Who has reviewed the study?

This research study is under review by the National Research Ethics Committee - NRES Committee London - Chelsea. The study reference number is 12/LO/0570.

Further Information:

Email: tristan.lane@imperial.ac.uk

Telephone: 0203 311 7335 and ask for Mr Tristan Lane (or any research team member)

Postal address: Tristan Lane, 4 North, Charing Cross Hospital, London, W6 8RF.

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Vascular Department,
Charing Cross Hospital,
Fulham Palace Road
London, W6 8RF

Participant Consent Form

Title of study:

Randomised Clinical Trial comparing VNUS ClosureFAST™ with ClariVein for Varicose Veins

Participant Number:

The participant should complete this whole sheet himself or herself.

(please initial each statement if it applies to you)

I have read and understood patient information sheet dated version ☐
I have received enough information to make up my mind ☐
I understand that I am free to withdraw from this study at any time ☐

I agree to

1. A medical history and clinical examination ☐
2. Ultrasound scans of my leg veins ☐
3. Complete a questionnaire regarding the state of my health ☐
4. Randomisation into one of two groups for treatment of my varicose veins ☐
5. Assessment at 30 days after treatment with a further questionnaire ☐
6. Assessment at 6 months after treatment with a further questionnaire and
an ultrasound scan of my leg veins ☐

I agree to be contacted by telephone/email to arrange the appointments and
questionnaires. ☐

I understand that my medical records and research data collected during the study
may be looked at by individuals from the research team, sponsor, from regulatory
authorities or from the NHS Trust, where it is relevant to my taking part in this
research. I give my permission for these individuals to have access to my records. ☐

I give permission to be contacted at the end of the study to enquire
about my health ☐

I give permission for my GP to be informed of my participation ☐

Patient Signature.....Date.....

(NAME IN CAPITALS).....

Person taking consent signature.....Date.....

(NAME IN CAPITALS).....

Patient ID:

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Appendix 2



Patient Information Sheet

Service Evaluation of the use of Cyanoacrylate Adhesive for the Treatment of Saphenous Vein Incompetence

What are varicose veins?

Varicose veins are usually caused by abnormal blood flow - termed venous reflux in the long veins in the leg (termed great saphenous vein along the inside of the leg or the small saphenous vein at the back of the calf) which, although they cannot be seen, often cause symptoms such as aching and swelling. This also leads to the development of so called "varicose veins" close to the skin surface which are visible to the patient - the lumpy veins (termed varicosities).

Varicose veins affect up to a third of the general population and it is known to affect the quality of life of patients. They cause a number of symptoms, including pain, achiness, leg swelling, itching. As they progress, they can lead to skin discoloration and skin ulceration.

Management of varicose veins

Treatment of varicose veins can prevent more severe complications as well improving the quality of life of patients. Over the past decade, new minimally invasive techniques have been introduced. These are becoming increasingly popular as they are associated with less complications and a more rapid return to normal activities.

Most of these techniques make use of thermal energy (heat) to treat the veins. To minimise any damage to surrounding structures (e.g., nerves, skin etc.), an infusion of local anaesthetic solution is required. This infusion requires several needle injections which can cause pain and discomfort.

Recently, newer methods have been introduced which do not use thermal energy and do not necessitate any fluid infusion. Cyanoacrylate adhesive injection is one such technique. It involves the injection of an adhesive (cyanoacrylate) into the vein. This causes a chemical reaction with the vein wall. As the reaction is taking place, pressure is applied onto the vein, ensuring that the vein wall sticks together.

Cyanoacrylate is a chemical which has been around for approximately 40 years and has been used medically for wound repair and the treatment of varices or vascular malformations (among others).

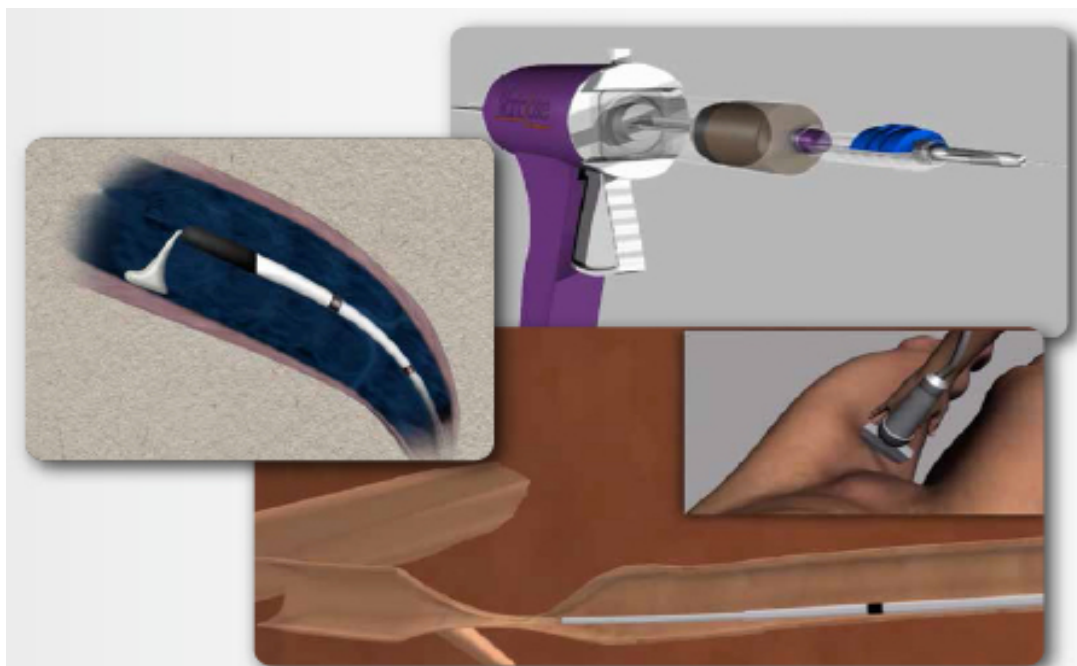
The treatment of varicose veins using glue has only been carried out over the past few years and, so far, the results are comparable to the thermal ablation (heat) techniques.

What is the VariClose® vein sealing procedure?

The Biolas VariClose® Vein Sealing System (FG Group, Ankara, Turkey) involves treating the vein by using a chemical called n-butyl cyanoacrylate. This chemical reacts with the vein wall and make it stick together.

For this endovenous ablation procedure (inside-the-vein closure treatment), access to the vein to be treated is obtained by injecting a small amount of local anaesthetic and cannulating (puncturing) the vein. The delivery catheter is then introduced, placed at the required position and the treatment is started. There is no need for tumescent infusion.

This product has been assessed by the European Union and it meets the directive enabling it to be used in surgical procedures and outside the body. This vein sealing system involves injection of cyanoacrylate and pressure onto the vein to close it off.



What are the advantages of this treatment?

The cyanoacrylate injection allows the procedure to be carried out without the need for tumescent infusion, which requires several needle injections. These can often cause discomfort/pain and bruising. Hence, it is expected to be less painful than the thermal (heat) methods of treatment. The procedure also only requires a small local anaesthetic injection and there is no need for general or spinal anaesthesia.

Also, as no heat is being applied, there is no danger of numbness, skin or nerve damage. The procedure is shorter compared to conventional heat treatments and patients are able to return to their normal activities and daily routines immediately afterwards.

What are the possible side-effects of this procedure?

The most commonly reported complications of this type of procedure are bleeding, infection, thrombophlebitis (inflammation of the vein), thrombo-embolism (DVT/PE: 'clot on lung or in leg'), pigmentation, recurrence and need for further procedures.

What happens after the procedure?

The procedures are all undertaken as a day case, using local anaesthetic and no further compression is required after the treatment. Patients are advised to return to their normal activities immediately after the procedure.

We will contact you to come back for a review at 1 month and 6 months, where you will undergo another assessment of the leg treated and be asked to fill quality of life questionnaires.

Where can I get more information about the procedure?

Further information is available from the **NICE (National Institute for Health and Care Excellence) Interventional Procedure Guidance 526 (Cyanoacrylate Glue Occlusion for Varicose Veins)**.

Further Information:

Email: r.bootun@imperial.ac.uk

Telephone: 0203 311 7335 and ask for Mr Roshan Bootun (or any research team members)

Postal address: Roshan Bootun, Clinical Research Fellow, Vascular Research Office, Room 4N13, Floor 4 North, Charing Cross Hospital, Fulham Palace Road, W6 8RF.

Appendix 3

Questionnaire About Service Provision at the Imperial College NHS Trust – Varicose Veins

Varicose veins affect up to 35% of the general population and it is known to affect the quality of life of patients. Treatment of varicose veins can prevent more severe complications as well improving the quality of life of patients.

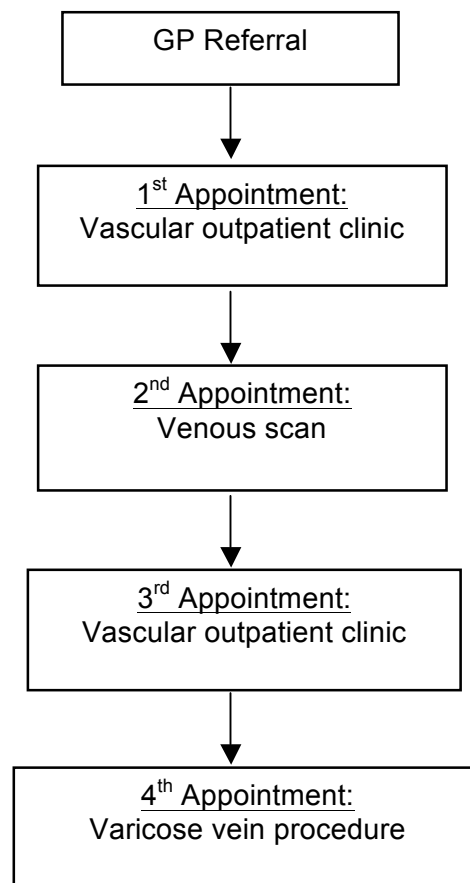
Nowadays, patients are referred by their General Practitioner and patients are seen routinely in the Vascular clinic. After having the consultation with one of the Vascular surgeons, patients with signs and symptoms suggestive of a venous cause are investigated with a venous scan. This scan usually takes place another day and patients are seen once again afterwards in the Vascular clinic. Based on the patient's signs and symptoms and findings from the venous scan, they are added to the waiting list to have a varicose vein procedure. Patients are then invited to attend the procedure on a different day. On the day of their procedure, they are scanned again and their vein is marked prior to having treatment to them. After the said procedure, they are discharged home, usually with no planned follow-up.

Thus, patients have at least three contacts with the hospital services from the time of being referred to the time of having their final treatment for their varicose veins. This process can take anything from a few weeks to months. During this time, the patients' symptoms and quality of life can worsen. In addition, the numerous appointments can be costly to the National Health Service.

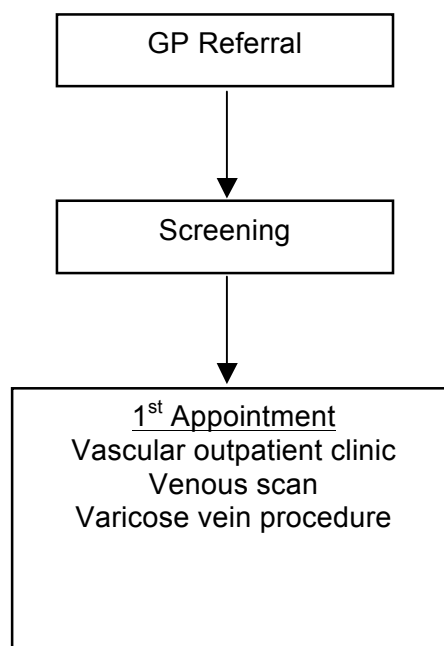
Hence, we feel that reducing the time between seeing a Vascular specialist, having a venous scan and then having a varicose vein procedure would be beneficial both to patients and to the NHS. As a result, we are planning to set up a special vein clinic where patients will be seen, have a venous scan and, then, depending on the findings of the scan, have treatment on the same day. Patients will be screened from their GP referral letter and those suitable will be invited to attend the clinic. This will reduce the number of times patients need to attend a clinic for consultation or scanning. The assumed benefit is a faster improvement in the leg symptoms and quality of life of patients as well as a reduction of the expenditure made on varicose vein treatment.

Currently, no such clinic exists in the UK and to know more about the expectations of patients attending the Vascular clinic for venous conditions, we are asking a few questions which will hopefully enable us to understand how to proceed with it. We would, therefore, be very grateful if you could answer the following few questions. These are divided into general background questions and those about the potential new service.

Standard Care Pathway



Proposed New Care Pathway



BACKGROUND

1. Age:.....years

2. Gender: Man ☐ Woman ☐

3. Occupation:.....

4. What is your ethnic group?

Choose one option that best describes your ethnic group or background:

White

- ☐ English/Welsh/Scottish/Northern Irish/British
- ☐ Irish
- ☐ Gypsy or Irish Traveller
- ☐ Any other White background (Please describe).....
.....

Black/African/Caribbean/Black British

- ☐ African
- ☐ Caribbean
- ☐ Any other Black/African/Caribbean background (Please describe).....
.....

Mixed/Multiple ethnic groups

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed/Multiple ethnic background (Please describe).....
.....

Asian/Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Chinese
- ☐ Any other Asian background (Please describe).....
.....

Other ethnic group

- ☐ Arab
- ☐ Any other ethnic group (please describe).....
.....

5. Education and Family Income:

What is your total family income?

- ☐ Less than £20,000
- ☐ £20,000 - £39,999
- ☐ £40,000 - £59,999
- ☐ £60,000 - £99,999
- ☐ £100,000 and over

What is your highest level of education attained?

- ☐ None
- ☐ Primary education
- ☐ Secondary education
- ☐ Tertiary education
- ☐ Post-graduate degree

6. Any family history of varicose disease? ☐ Yes ☐ No

7. Medical History:

Heart Disease	Y	N	Bleeding disorder	Y	N
Breathing Problems (COPD/Asthma)	Y	N	Smoker	Y	N
Diabetes	Y	N	Previous deep vein thrombosis/pulmonary embolism (clot in legs or on lungs)	Y	N

8. Have you had previous varicose vein treatment?

Yes (please go to Q9) ☐ No (please go to Q12) ☐

9. What information have you received in the past regarding varicose veins?

.....

.....

.....

.....

10. Did you find the information useful?

Yes ☐ No ☐

11. Has this helped with your understanding of the causes and management of venous diseases? ☐

Yes No

12. What treatment are you aware of? (Please tick all that apply)

- ☐ Endovenous procedures (laser/radiofrequency ablation/injection sclerotherapy)
- ☐ Compression stockings
- ☐ Surgery
- ☐ Other (please specify).....
-

13. What treatment have you received previously? (Please tick all that apply)

- ☐ Endovenous procedures (laser/radiofrequency ablation/injection sclerotherapy)
- ☐ Compression stockings
- ☐ Surgery

- ☐ Other (please specify).....
.....

Current Attendance

14. Reason for attending outpatient clinic today (please tick all that apply):

- | | |
|--|---|
| ☐ Leg pain/ache | ☐ Skin discoloration |
| ☐ Leg swelling | ☐ Bulging veins |
| ☐ Leg cramps | ☐ Thread veins |
| ☐ Legs feel heavy | ☐ Leg ulcers |

15. Which leg is most affected? Right ☐ Left ☐ Both ☐

16. How is your quality of life affected by your veins? (Tick one only)

- ☐ Not affected at all
☐ Affected a little
☐ Affected moderately
☐ Affected a lot

17. Have you needed to take time off work because of your varicose veins?

Yes ☐ No ☐

18. How long would you regard as acceptable to wait between a Vascular appointment and having a venous scan?

Same day ☐ 2 weeks ☐ 1 month ☐
3 months ☐ 6 months ☐

19. How long would you regard as acceptable between a consultation and attending for a varicose vein procedure?

Same day ☐ ☐ ☐
3 month ☐ 6 months ☐

20. Which of the following treatment model would you consider attending?

- ☐ Consultation with Vascular specialist on 1st appointment, venous scan on 2nd appointment and procedure on 3rd appointment
☐ Venous scan on 1st appointment, consultation with Vascular specialist on 2nd appointment and procedure on 3rd appointment
☐ Consultation and venous scan on 1st appointment and procedure on 2nd appointment
☐ Consultation, venous scan and procedure on 1st appointment
-

Proposed New Clinic

21. We are planning to organise a special clinic where patients with varicose veins would be seen by a Vascular specialist, have a venous scan and, depending on the findings of the scan, have treatment on the same day. Would this option appeal to you?

Yes ☐

No ☐

22. If yes, which of the following options about information received before the clinic would you find most useful?

- ☐ Information on the day about what the clinic is and what procedures are provided
- ☐ Prior written information about the clinic and procedures offered in the form of leaflets
- ☐ DVD with information about the clinic and procedures offered
- ☐ Website with information about the clinic and procedures offered

23. Do you think that having the possibility to have a phone conversation with one of the Vascular specialist or a Vascular nurse prior to the clinic appointment would be useful?

Yes ☐

No ☐

24. Everyone invited to the clinic will be having a venous scan. This may show that they are not suitable for intervention on the same day or may need more than one treatment. Others may need referral to a different specialty. Would this dissuade you from attending the clinic?

Yes ☐

No ☐

25. If after your venous scan it is found that you are unsuitable for treatment on the day, but rather you have to attend on a different day, how easy would it be to take time off for you?

- ☐ Very easy
- ☐ Easy
- ☐ Neither easy nor difficult
- ☐ Difficult
- ☐ Very difficult

26. Following the venous scan and the consultation with one of the Vascular specialist, would having more time to think about any possible procedures be your preferred option?

Yes ☐

No ☐

27. Would attending a clinic appointment for a different day so as to give you time to discuss with family/friends be useful? (Say how useful this would be on a scale of 0 to 10 (where 0 is not useful at all and 10 is very useful)).

0 1 2 3 4 5 6 7 8 9 10

28. Would attending a clinic appointment for a different day so as to discuss the procedure with a Vascular specialist be useful? (Say how useful this would be on a scale of 0 to 10 (where 0 is not useful at all and 10 is very useful)).

0 1 2 3 4 5 6 7 8 9 10

29. All the varicose vein procedures carried out in this special clinic will be under local anaesthetic. Would this be an issue for you?

Yes ☐ No ☐

30. Currently, most patients are discharged on the day of their varicose vein procedure. Would having a follow-up appointment be useful?

Yes ☐ No ☐

31. Who would be best to provide the follow-up appointment?

☐ Vascular specialist ☐ GP ☐

Other

☐ Vascular Nurse ☐ District Nurse

32. Is there anything else you would like to add?

Thank you very much for your help!

Appendix 4



Vascular Department,
Charing Cross Hospital,
Fulham Palace Road,
London,
W6 8RF.

Information Sheet for Research Participants

Pilot Randomised Controlled Trial Evaluating a One Stop Vein Clinic

A single-centre randomised controlled study looking at the setting up of a One Stop Vein Clinic whereby patients with varicose veins will be randomised to either having same day treatment or having treatment at different time points

Dear Sir/Madam,

We would like to invite you to take part in the above named research study. Before you decide, it is important for you to understand why this research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with friends, relatives or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part.

Thank you.

What is the purpose of the study?

The main aim of the study is to compare two different treatment options, the One Stop Vein Clinic (offering same day varicose vein diagnosis and treatment) and the normal care pathway (having management of varicose veins at different time points, same as current treatment pathway).

Background Information

Varicose veins affect up to 35% of the general population and it is known to affect the quality of life of patients. Treatment of varicose veins can prevent more severe complications as well as improving the quality of life of patients.

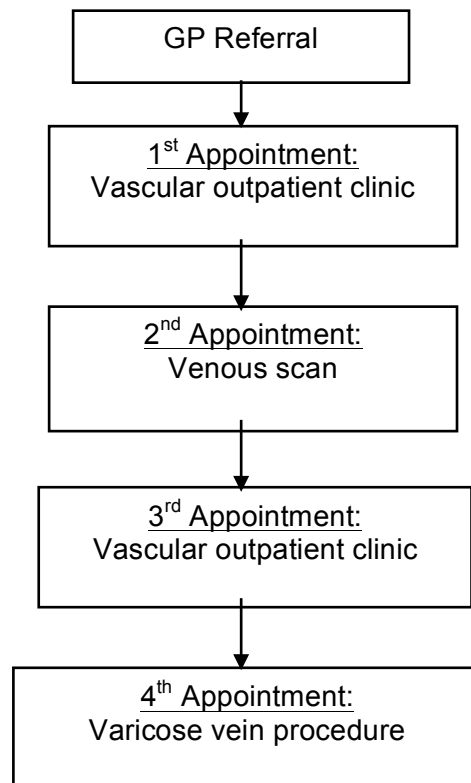
Nowadays, patients are referred by their General Practitioner and patients are seen routinely in the Vascular clinic. After having the consultation with one of the Vascular surgeons, patients with signs and symptoms suggestive of a venous cause are investigated with a venous scan. This scan usually takes place another day and patients are seen once again afterwards in the Vascular clinic. Based on the patient's signs and symptoms and findings from the venous scan, they are added to the waiting list to have a varicose vein procedure. Patients are then invited to attend the procedure on a different day. After the said procedure, they are discharged home, usually with no planned follow-up.

Thus, patients have at least three contacts with the hospital services from the time of being referred to the time of having their final treatment for their varicose veins. This process can take anything from a few weeks to months. During this time, the patients' symptoms and quality of life can worsen. In addition, the numerous appointments can be costly to the National Health Service.

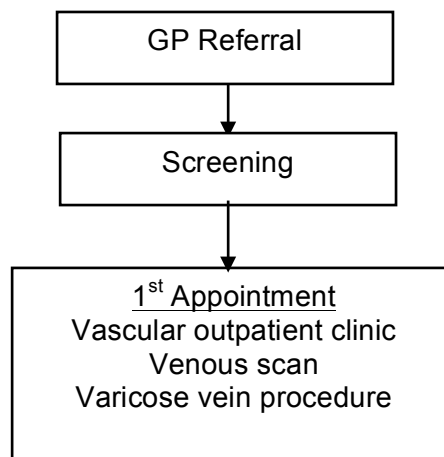
Hence, we feel that reducing the time between seeing a Vascular specialist, having a venous scan and then having a varicose vein procedure would be beneficial both to patients and to the NHS. As a result, we are planning to set up a special vein clinic where patients will be seen, have a venous scan and, then, depending on the findings of the scan, have treatment on the same day. Patients will be screened from their GP referral letter and those suitable will be invited to attend the clinic. This will reduce the number of times patients need to attend a clinic for consultation or scanning.

The assumed benefit is a faster improvement in the leg symptoms and quality of life of patients as well as a reduction of the expenditure made on varicose vein treatment.

Normal Care Pathway



Proposed New Care Pathway



What are varicose veins?

Varicose veins are usually caused by abnormal blood flow - termed venous reflux in the long veins in the leg (termed great saphenous vein along the inside of the leg or the small saphenous vein at the back of the calf) which, although they cannot be seen, often cause symptoms such as aching and swelling. This also leads to the development of so called "varicose veins" close to the skin surface which are visible to the patient - the lumpy veins (termed varicosities).

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not to take part.

If you do decide to take part we would be grateful if you could fill the attached reply slip, sign the consent form and questionnaire. If you decide to take part you are still free to withdraw at any time. Patients agreeing to attend the One Stop Vein Clinic will be randomised into two groups:

- (1) the One Stop Vein Clinic group – whereby patients will be having same day diagnosis and treatment
- (2) the normal care pathway group – where patients will be receiving management of varicose as per current treatment pathway in the NHS

Randomisation means that there is an equal chance of you being assigned to either group.

If you decide not to attend the one stop clinic and not to take part in any research, you do not have to give a reason. Nobody will be upset and the standard of care you receive will not be affected. We will be grateful if you could fill the attached reply slip and let us know of your decision. We will be sending you an appointment to attend the normal Vascular clinic instead and management of your varicose veins will be according to the current practice in the department.

If you decide not to attend the one stop clinic, but would still be happy to participate in the research by filling out questionnaires for us, we would be grateful if you could fill the attached reply slip, sign the consent form and questionnaire. We will confirm the consent again when you come to your clinic appointment. If you decide to take part you are still free to withdraw at any time.

What is the standard care provided in the department (Normal Care Pathway)?

Current standard care in our department for varicose veins differs in that patients are asked to attend a Vascular outpatient clinic, then offered a clinic appointment another day for a venous ultrasound scan. They are then seen again in the clinic after which they are added to the waiting list for a varicose vein procedure (see below).

What happens at the One Stop Vein Clinic?

We will be sending you an appointment to attend the new proposed clinic where we will confirm that you agree to be part of the study. We will ask you about your medical history and send you to have a venous scan. Based on the findings of your scan, we will inform you of the treatment available (see below) and obtain your

consent to perform the procedure on the same day. If after discussion, you decide not to have the same day varicose vein procedure proposed, we will add you to the routine waiting list for varicose vein procedures and you will be called in due course to have the procedure. After the procedure, we will be asking you to fill a patient satisfaction questionnaire.

We will contact you again after 3 months to find out how your symptoms are and to ask you questions about your quality of life.

What are the varicose veins procedures available?

The treatment provided will be dependent on the findings of your vein scan.

New minimally invasive treatments have become available in the last decade - these are termed endovenous ablation treatments (inside-the-vein closure treatments). These techniques either use energy to heat the inside of the vein, causing it to stick together and block off (ablation).

Varicose veins are all treated with endovenous radiofrequency ablation as standard, under local anaesthetic or general anaesthetic according to patient and surgeon preference.

The varicosities (or lumpy veins) are removed via small cuts (<0.5cm long) in the skin termed “phlebectomies” or “avulsions”, performed at the same time as the long veins are treated.

Foam sclerotherapy can be used as an alternative to “avulsions”. This uses a special chemical made into foam, which is injected into the varicose veins using small needles. As with liquid sclerosant it causes the vein to stick together and block off (scleroses).

Immediately after the operation the treated leg is placed in a compression stocking. Procedures are all undertaken as a day case. The treatment is well tolerated by most. Patients are discharged to their GP’s care post-operatively. All patients wear the provided compression stocking for 2 weeks postoperatively.

What other treatments are available?

Alternative treatments for varicose veins include open surgery, endovenous laser ablation and conservative treatment with compression therapy.

Endovenous laser ablation is a technique similar to endovenous radiofrequency ablation - i.e. it uses heat to stick the vein together and ablate it. It uses a special optical fibre to transmit a laser (focused light beam) into the vein. This laser generates heat and causes the same process of ablation to occur. It is very effective, but radiofrequency ablation has been shown to be better tolerated. It can be done under local or general anaesthetic, but requires all users (and the patient) to wear protective goggles.

Open surgery is the gold standard treatment but is far more invasive and has been

shown to be associated with a slower recovery. This treatment involves a cut in the groin, and the vein is physically pulled out with a wire 'stripper'. The varicosities are then removed using avulsions as previously described. It can be done under local or general anaesthetic. It is associated with increased symptoms of pain and bruising after the operation. It has the same success rates as endovenous techniques.

Conservative treatment treats the symptoms but not the cause of the problem. It involves the wearing of compressive stockings all day, every day, for life. It does not involve an operation but does involve a lifestyle change.

Further information on these treatments is available on request.

What are the possible benefits in taking part?

You are not expected to gain any personal benefit from taking part in this study. However the information gained may help other people in the future. It is not possible to offer any financial incentive for taking part in the study.

What if something goes wrong?

Imperial College London has insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the research team (see below). The normal National Health Service complaints mechanisms are also available to you. If you are not satisfied with the response, you may contact the Imperial College Joint Research Office.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities to check that the study is being carried out in accordance with national guidelines. If an abnormality is found, which does not relate to your veins, a referral to an appropriate specialist will be made, with your permission, and your General Practitioner will be informed.

What will happen to the results at the end of the research study?

We will publish the overall results of the study, whatever the findings, to allow doctors to learn from our findings. A one page plain English summary will be available from the email address below in around 2016. As a participant, you will not be personally identifiable in any publication.

Who is organising and funding the research?

The project is organised by Imperial College London. The investigators are employed

by Imperial College Healthcare NHS Trust & Imperial College. Partial funding for this study has been provided by the Graham-Dixon Charitable Trust.

This study is being performed as part of a higher research degree (PhD) at Imperial College London.

Who has reviewed the study?

This research study is under review by the National Research Ethics Committee – Fulham. The study reference number is: **14/LO/1295**.

Further Information:

Email: r.bootun@imperial.ac.uk

Telephone: 0203 311 7335 and ask for Mr Roshan Bootun (or any research team members)

Postal address: Roshan Bootun, Clinical Research Fellow in Vascular Surgery, Vascular Research Office, Room 4N13, Floor 4 North, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF.

Pilot Randomised Controlled Trial Evaluating a One Stop Vein Clinic

Patient ID:.....

Dear Sir/Madam,

We would be most grateful if you would be able to let us know whether you wish to attend the new proposed one stop vein clinic or would rather prefer to be seen in the normal vascular clinic. Three options are available and we would appreciate if you could fill in the reply slip attached.

We thank you for taking the time to go through the Information Leaflet.

Yours sincerely,

Mr Roshan Bootun,
Clinical Research Fellow in Vascular Surgery,
Room 4N13, Floor 4 North,
Charing Cross Hospital,
Fulham Palace Road,
London, W6 8RF.

Pilot Randomised Controlled Trial Evaluating a One Stop Vein Clinic

Reply Slip

Patient ID:.....

Please tick one of the boxes below, tear off the reply slip and post back in the self addressed envelope attached.

- ☐ I wish to participate in the research study and would be happy to be randomised to either the one stop vein clinic or the normal care pathway. (Please also sign the attached consent form and questionnaire and send all three in the enclosed self-addressed envelope).
- ☐ I DO NOT wish to participate in the research study and would prefer to attend a normal vascular clinic. I understand I will be sent an appointment to attend a routine vascular clinic. (Please tear off reply slip and send in the enclosed self addressed envelope)
- ☐ I DO NOT wish to attend the one stop vein clinic and would prefer to attend a normal vascular clinic. However, I am happy to participate in the research study as a patient who has declined randomisation to either the one stop clinic or normal care pathway (Please also sign the attached consent form and questionnaire and send all three in the enclosed self-addressed envelope)

Participant Consent Form
Pilot Randomised Controlled Trial Evaluating a One Stop Vein Clinic

Patient ID:.....

The participant should complete this whole sheet himself or herself.

(please initial each statement if it applies to you)

I have read and understood patient information sheet dated version ☐

I have received enough information to make up my mind ☐

I understand that I am free to withdraw from this study at any time ☐

I agree to: ☐

1. A medical history and clinical examination ☐

2. Ultrasound scans of my leg veins ☐

3. Complete a questionnaire regarding the state of my health ☐

4. Be contacted (by post or telephone) at 3 months after treatment with a further questionnaire ☐

5. Be randomised to either of two different treatment pathways ☐

I agree to be contacted by telephone/email to arrange the appointments and questionnaires. ☐

I understand that my medical records and research data collected during the study may be looked at by individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my records. ☐

I give permission to be contacted at the end of the study to enquire about my health ☐

I give permission for my GP to be informed of my participation ☐

Patient Signature.....Date.....

(NAME IN CAPITALS).....

Person taking consent signature.....Date.....

(NAME IN CAPITALS).....

Information Sheet for Research Participants

A multicentre randomised controlled trial of compression therapy following endovenous thermal ablation of varicose veins

A multi-centre study looking at the effect of compression therapy in patients having minimally invasive treatment for varicose veins after heat treatment of varicose veins.

Dear Sir/Madam,

We would like to invite you to take part in the above named research study. Before you decide, it is important for you to understand why this research is being done and what it will involve.

Please take the time to read the following information carefully and discuss it with friends, relatives or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part.

Thank you.

What is the purpose of the study?

The main aim of the study is to find out the effect of compression stockings following treatment of varicose veins.

Background Information

Varicose veins is a common condition which is known to affect the quality of life of patients. The treatment of varicose veins has been shown to reduce complications and also leads to improved quality of life.

Over the past decade, new minimally invasive techniques ('key-hole' procedures) have been introduced. These are becoming increasingly popular as they are associated with less complications and a more rapid return to normal activities. However, there is still uncertainty as to the role of compression therapy in the management of varicose veins, especially following treatment using these newer methods. The American Venous Forum (an American veins organisation) recommends the use of compression stockings to reduce the risk of clot (haematoma) formation, pain and swelling. The NICE Guidelines have recommended further research into the use of compression stockings as post-procedure intervention.

This study will be looking at the effect of compression in patients having minimally invasive treatment for varicose veins. Patients will be randomised to either the compression group (group A) or the no compression group (group B). The pain

scores, compliance, quality of life scores, occlusion rate at 6 months as well as the cost effectiveness of each intervention will be assessed.

What are varicose veins?

Varicose veins are usually caused by abnormal blood flow - termed venous reflux in the long veins in the leg (termed great saphenous vein along the inside of the leg or the small saphenous vein at the back of the calf) which, although they cannot be seen, often cause symptoms such as aching and swelling. This also leads to the development of so called "varicose veins" close to the skin surface which are visible to the patient - the lumpy veins (termed varicosities).

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not to take part. If you do decide to take part we will ask you to sign a consent form and give you a copy of this information sheet. If you decide to take part you are still free to withdraw at any time. If you decide not to take part you do not have to give a reason, nobody will be upset and the standard of care you receive will not be affected.

What will I be asked to do if I take part?

We will ask you about your medical history and fill in a questionnaire with you. You will be assigned a trial number and your treatment plan will be allocated following randomisation.

The randomisation will not affect the standard of your care. It will decide whether we are going to use any compression following treatment of your varicose veins.

You will then have endovenous (within the vein) treatment (using heat) of your varicose veins. The treatment will use either radiofrequency thermal ablation or laser treatment. This will be carried out under local anaesthetic.

Thereafter, if you have been assigned to the compression group, you will be provided with compression stockings to wear for one week. We usually advise wearing the stockings day and night for the whole week, and only taking them off if going for a shower (baths are not advised until wounds are healed). If putting the compression stockings on is an issue for you, we would try arrange for someone to provide help for you to put them on (e.g., district nurses).

If, on the other hand, you have been randomised to the no compression group, you will be discharged home without any compression.

You will be discharged home with a diary card to record your level of pain in the first 10 days following your varicose vein procedure as well as when you return to your normal activities and work. You will also be asked as to whether you have been using the compression stockings provided (if randomised to compression group). You will be reviewed in clinic 2 weeks post-procedure in clinic with a further questionnaire to fill. Six months after your operation you will again be reviewed in clinic with a venous duplex ultrasound of your leg to assess technical success and

another questionnaire to fill.

We will record your initials, study number and date of birth on the trial questionnaires. All data will be anonymised as each patient will be allocated a study number. The allocated study number key code will be kept on a password protected NHS computer at all the sites and data in paper form will be kept in a locked filing cabinet in a locked research office at each respective site. Both will only be accessible to researchers. The information will be kept for 10 years after the study ends and then destroyed.

What are the varicose veins procedures available?

New minimally invasive treatments have become available in the last decade - these are termed endovenous ablation treatments (inside-the-vein closure treatments). These techniques use energy to heat the inside of the vein, causing it to stick together and block off (ablation). The most common methods use radiofrequency ablation (similar to microwaves) and laser (focused light beam). It can be done under local or general anaesthetic.

The varicosities (or lumpy veins) are removed via small cuts (<0.5cm long) in the skin termed “phlebectomies” or “avulsions”, performed at the same time as the long veins are treated.

Foam sclerotherapy can be used as an alternative to “avulsions”. This uses a special chemical made into foam, which is injected into the varicose veins using small needles. As with liquid sclerosant it causes the vein to stick together and block off (sclerose).

Procedures are all undertaken as a day case. The treatment is well tolerated by most.

You will be randomised before your procedure to determine whether you will receive compression following the varicose vein procedure or not. The randomisation will be carried out using an online randomisation software. Randomisation means that you will have an equal chance of being assigned to the compression or no compression group. The varicose vein treatment to be provided will be decided by the clinical team and will not be subject to any randomisation. Post-intervention, those randomised to the compression group would be wearing the compression stockings for 1 week, while those from the no compression group will be discharged home without.

What are the possible benefits in taking part?

You are not expected to gain any personal benefit from taking part in this study. However the information gained may help other people in the future. It is not possible to offer any financial incentive for taking part in the study.

What if something goes wrong?

Imperial College London has insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part, you may be

eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the research team (see below). The normal National Health Service complaints mechanisms are also available to you. If you are not satisfied with the response, you may contact the Imperial College Joint Research Compliance Office.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team involved in this study. They may also be looked at by representatives of regulatory authorities to check that the study is being carried out in accordance with national guidelines. If an abnormality is found, which does not relate to your veins, a referral to an appropriate specialist will be made, with your permission, and your General Practitioner will be informed.

What will happen to the results at the end of the research study?

We will publish the overall results of the study, whatever the findings, to allow doctors to learn from our findings. A one page plain English summary will be available from the email address below in around 2016. As a participant, you will not be personally identifiable in any publication.

Who is organising and funding the research?

The project is organised by Imperial College London. The investigators are employed by XXX NHS Trust (depending on site where patient is being recruited).

At present, no external organisation is funding this study, even though we may still seek funding during the course of the study.

This study is being performed as part of a higher research degree (PhD) at Imperial College London.

Who has reviewed the study?

This research study is under review by the National Research Ethics Committee – XXX REC. The study reference number is XXX

Further Information:

Email: r.bootun@imperial.ac.uk

Telephone: 0203 311 7335 and ask for Mr Roshan Bootun (or any research team members)
Postal address: Roshan Bootun, Clinical Research Fellow in Vascular Surgery, Room 4N13, Floor 4 North, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF.

Participant Consent Form

A multicentre randomised controlled trial of compression therapy following endovenous thermal ablation of varicose veins

Participant Number:.....

The participant should complete this whole sheet himself or herself.

(please initial each statement if it applies to you)

I have read and understood patient information sheet dated version ☐

I have received enough information to make up my mind ☐

I understand that I am free to withdraw from this study at any time ☐

I agree to:

1. A medical history and clinical examination ☐

2. Ultrasound scans of my leg veins at 6 months ☐

3. Complete a questionnaire regarding the state of my health ☐

4. Randomisation into one of two groups for treatment of my varicose veins ☐

5. Assessment at 2 weeks and 6 months after treatment with a further questionnaire ☐

I agree to be contacted by telephone/email to arrange the appointments and questionnaires. ☐

I understand that my medical records and research data collected during the study may be looked at by individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my records. ☐

I give permission to be contacted at the end of the study to update me about the study findings ☐

I give permission for my GP to be informed of my participation ☐

Patient Signature.....Date.....

(NAME IN CAPITALS).....

Person taking consent signature.....Date.....

(NAME IN CAPITALS).....

Appendix 6: Clinical assessment of Varicose Veins

Hospital Number-----	MALE	FEMALE
Date of birth-----	Number of Pregnancies	
Age -----	Weight/ Kg	
Occupation-----	BMI>30	Yes No
Date-----	OCP or HRT	Yes No
	Smoker	Yes No
Past Medical History		
	Yes No	Yes No
Bleeding disorder	IHD	
DVT/PE		Leg ulcers
Diabetes	Hypertension	
Medications		

Previous treatment to Varicose Veins

Side	Site	Date	Treatment type

Appendix 7: Pre Operative Clinical Assessment

Score	Definition
0	Asymptomatic
1	Symptomatic, but able to carry out usual activities with out compressive therapy
2	Able to carry out usual activities only with compressive therapy and/or limb elevation
3	Unable to carry out usual activities even with compression and/or elevation
	Usual activities = patients activities before the onset of disability due to venous disease

Appendix 8: Venous Clinical Severity Score (VCSS)

Please indicate right or left leg or bilateral (R, L or B)

	Absent	Mild	Moderate	Severe
Pain	None	Occasional, non/no analgesia restricting	With moderate activity, occasional analgesia	Daily, severe limitations, regular analgesia
Varicose veins>4mm	None	Few	Multiple GSV	Extensive GSV and LSV
Venous oedema	None	Evening/ankle	Afternoon/above knee	Morning/requiring elevation
Skin pigmentation	None	Limited and old/brown	Diffuse lower third/ purple	Wide/ purple
Inflammation	None	Mild cellulitis in marginal area	Moderate involving most of gaiter area	Severe cellulitis or significant eczema
Induration	None	Focal <5cm	Medial or lateral less than lower 1/3	1/3 of lower leg or more
Number of active ulcers	0	1	2	3
Active ulcer duration	None	<3 months	>3 months <12 months	>12 months
Active ulcer diameter(cm)	None	<2	2-6	>6
Compression	Not used or non compliant	Intermittent use	Stockings worn most days	Stockings worn daily
Total				

Appendix 9: Clinical-Etiology-Anatomy-Pathophysiology (CEAP Classification)

Clinical	0	1A	1S	2A	2S	3A	3S	4aA	4aS	4bA	4bS	5A	5S	6
Etiology	Congenital			Primary			Secondary			No venous cause identified				
Anatomy	Superficial			Deep			Perforating			No venous location identified				
Pathology	Reflux			Obstruction			Both			No venous pathology identified				

Class 0 No visible or palpable veins

Class 1 Telangiectasia, reticular veins
ulceration

Class 2 Varicose Veins

Class 3 Oedema without skin changes

Class 4 Skin changes ascribed to venous disease

4a) Pigmentation or eczema

4b) Lipodermatosclerosis or atrophie blanche

Class 5 Skin changes and healed ulceration

Class 6 Active venous ulcers

A= Asymptomatic

S= Symptomatic

33. What is your ethnic group?

Choose one option that best describes your ethnic group or background:

White

- ☐ English/Welsh/Scottish/Northern Irish/British
- ☐ Irish
- ☐ Gypsy or Irish Traveller
- ☐ Any other White background (Please describe).....
.....

Black/African/Caribbean/Black British

- ☐ African
- ☐ Caribbean
- ☐ Any other Black/African/Caribbean background (Please describe).....
.....

Mixed/Multiple ethnic groups

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed/Multiple ethnic background (Please describe).....
.....

Asian/Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Chinese
- ☐ Any other Asian background (Please describe).....
.....

Other ethnic group

- ☐ Arab
- ☐ Any other ethnic group (please describe).....
.....

34. Any one else in your family with varicose vein disease?

.....

Appendix 10. Patient Diary

Please indicate at what stage you were able to return to work and your normal daily activities (the activities you were able to do prior to treatment).

Please also indicate the day when you stopped wearing the compression stockings (if provided).

(Please tick one box)

	Day I was able to resume my normal activities	Day I returned to work	Day I stopped wearing compression stockings (if provided)
Day of surgery			
Day after surgery			
2 days after surgery			
3 days after surgery			
4 days after surgery			
5 days after surgery			
6 days after surgery			
7 days after surgery			
8 days after surgery			
9 days after surgery			
10 days after surgery			
>10 days after surgery			

Please return to:

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Appendix 11. Patient Pain Diary (VAS)

Please put a mark on the line to indicate your maximum pain score on each day.

Please also write a score from 0 to 10 for your maximum pain on each day.

Example: If your pain score on day 4 is roughly about 5 over 10 (10 being the worst pain imaginable), you might want to indicate it as below:

Day 4	No pain 0 10 5 / Worst pain imaginable
--------------	--

Study Diary:

(0 = no pain and 10 = worst pain imaginable)

Day 0	No pain 0 10 Worst pain imaginable
Day 1	No pain 0 10 Worst pain imaginable
Day 2	No pain 0 10 Worst pain imaginable
Day 3	No pain 0 10 Worst pain imaginable
Day 4	No pain 0 10 Worst pain imaginable
Day 5	No pain 0 10 Worst pain imaginable
Day 6	No pain 0 10 Worst pain imaginable
Day 7	No pain 0 10 Worst pain imaginable
Day 8	No pain 0 10 Worst pain imaginable
Day 9	No pain 0 10 Worst pain imaginable
Day 10	No pain 0 10 Worst pain imaginable

APPENDIX 12: Quality of Life Questionnaire: EQ-5D

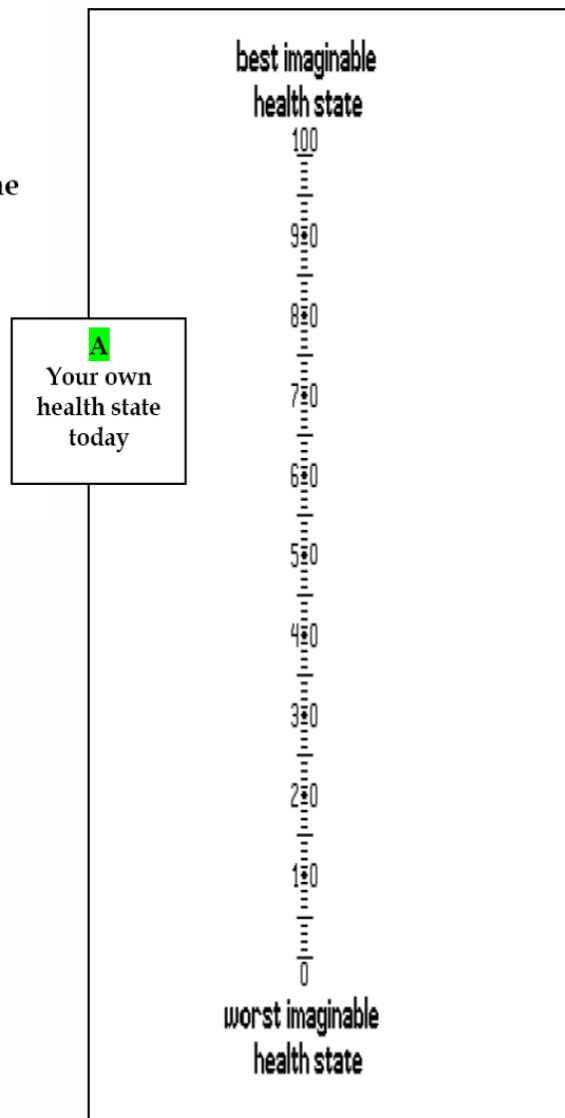
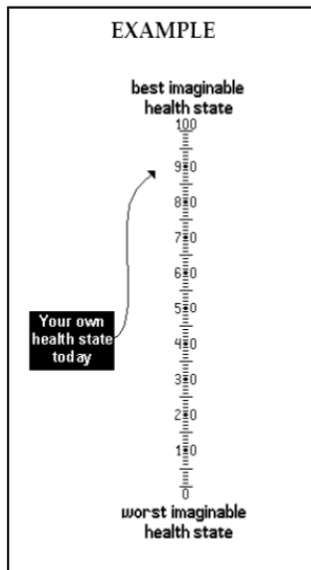
Pre-op questionnaire version 1- 6th August 2009

DESCRIBING YOUR OWN HEALTH TODAY

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

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

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



Your overall general health

Please indicate which statement best describes your own health state. (*Tick only one box in each group*)

Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐

Self-care	I have no problems with self-care	☐
	I have some problems washing and dressing myself	☐
	I am unable to wash myself	☐

Usual activities	<i>For example, housework, family or leisure activities</i>	
	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐

Pain/discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐

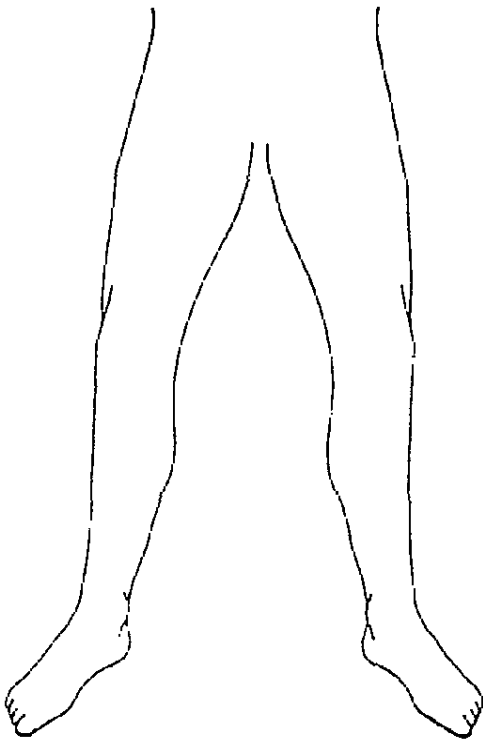
Anxiety/depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

Appendix 13: Aberdeen Varicose Vein Questionnaire

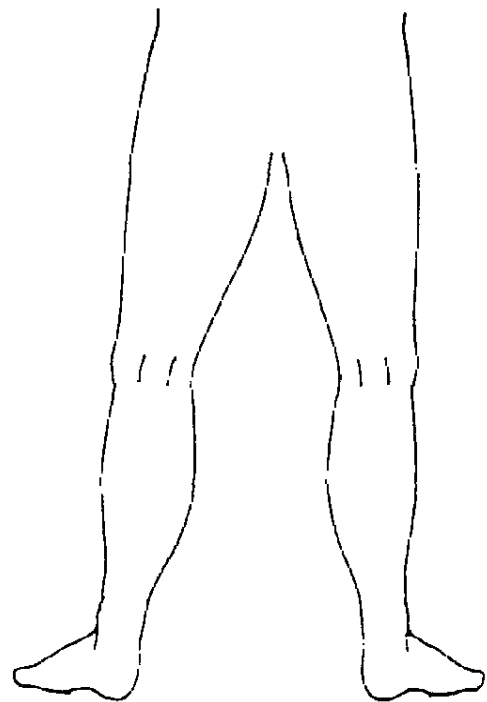
YOUR VARICOSE VEINS

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

Legs viewed
from front



Legs viewed
from back



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

(Please tick one box for each leg)

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

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

(Please tick one box for each leg)

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

4. **In the last two weeks, how much ankle swelling have you had?**
(Please tick one box)
- | | |
|---|--------------------------|
| None at all | ☐ |
| Slight ankle swelling | ☐ |
| Moderate ankle swelling (e.g. causing you to sit with your feet up whenever possible) | ☐ |
| Severe ankle swelling (e.g. causing you difficulty putting on your shoes) | ☐ |
5. **In the last two weeks, have you worn support stockings or tights?**
(Please tick one box for each leg)
- | | | |
|--|--------------------------|--------------------------|
| | R Leg | L Leg |
| No | ☐ | ☐ |
| Yes, those I bought myself without a doctor's prescription | ☐ | ☐ |
| Yes, those my doctor prescribed for me which I wear occasionally | ☐ | ☐ |
| Yes, those my doctor prescribed for me which I wear every day | ☐ | ☐ |
6. **In the last two weeks, have you had any itching in association with your varicose veins?**
(Please tick one box for each leg)
- | | | |
|-------------------------------|--------------------------|--------------------------|
| | R Leg | L Leg |
| No | ☐ | ☐ |
| Yes, but only above the knee | ☐ | ☐ |
| Yes, but only below the knee | ☐ | ☐ |
| Both above and below the knee | ☐ | ☐ |
7. **Do you have purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins?**
(Please tick one box for each leg)
- | | | |
|-----|--------------------------|--------------------------|
| | R Leg | L Leg |
| No | ☐ | ☐ |
| Yes | ☐ | ☐ |
8. **Do you have a rash or eczema in the area of your ankle?**
(Please tick one box for each leg)
- | | | |
|--|--------------------------|--------------------------|
| | R Leg | L Leg |
| No | ☐ | ☐ |
| Yes, but it does not require any treatment from a doctor or district nurse | ☐ | ☐ |
| Yes, and it requires treatment from my doctor or district nurse | ☐ | ☐ |

9. **Do you have a skin ulcer associated with your varicose veins?**
(Please tick one box for each leg)
- | | R Leg | L Leg |
|-----|--------------------------|--------------------------|
| No | ☐ | ☐ |
| Yes | ☐ | ☐ |
10. **Does the appearance of your varicose veins cause you concern?**
(Please tick one box)
- | | |
|---|--------------------------|
| No | ☐ |
| Yes, their appearance causes me slight concern | ☐ |
| Yes, their appearance causes me moderate concern | ☐ |
| Yes, their appearance causes me a great deal of concern | ☐ |
11. **Does the appearance of your varicose veins influence your choice of clothing including tights?**
(Please tick one box)
- | | |
|--------------|--------------------------|
| No | ☐ |
| Occasionally | ☐ |
| Often | ☐ |
| Always | ☐ |
12. **During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities?**
(Please tick one box)
- | | |
|--|--------------------------|
| No | ☐ |
| I have been able to work but my work has suffered to a slight extent | ☐ |
| I have been able to work but my work has suffered to a moderate extent | ☐ |
| My veins have prevented me from working one day or more | ☐ |
13. **During the last two weeks, have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)?**
(Please tick one box)
- | | |
|---|--------------------------|
| No | ☐ |
| Yes, my enjoyment has suffered to a slight extent | ☐ |
| Yes, my enjoyment has suffered to a moderate extent | ☐ |
| Yes, my veins have prevented me taking part in any leisure activities | ☐ |

Appendix 14

C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

Many people complain of leg pain. We would like to find out how often these leg problems occur and to what extent they affect the everyday lives of those who suffer from them.

Below you will find a list of symptoms, sensations or types of discomfort that you may be experiencing and which may make everyday life hard to bear to a greater or lesser extent. **For each symptom, sensation, or type of discomfort listed, we would like you to answer in the following way:**

Please indicate if you have experienced what is described in each sentence, and if the answer is 'yes', how **intense** it was. There are five possible answers, and we would like you to circle the one which best describes your situation.

Circle 1	if you feel the symptom, sensation of discomfort described does not apply to you
----------	--

Circle 2, 3, 4 or 5	if you have felt it to a greater or lesser extent
---------------------	---

QUALITY OF LIFE WITH VENOUS INSUFFICIENCY

- 1)** During the past four weeks, have you had any **pain** in your **ankles** or **legs**, and how severe has this pain been?
Circle the number that applies to you.

No pain	Slight pain	Moderate pain	Considerable pain	Severe pain
1	2	3	4	5

- 2)** During the past four weeks, how much trouble have you experienced at **work** or during your **usual daily activities because of your leg problems**?
Circle the number that applies to you.

No trouble	Slight trouble	Moderate trouble	Considerable trouble	Severe trouble
1	2	3	4	5

- 3)** During the past four weeks, have you **slept badly** because of your leg problems, and how often?
Circle the number that applies to you.

Never	Rarely	Fairly often	Very often	Every night
1	2	3	4	5

During the past four weeks, how much trouble have you experienced carrying out the actions and activities listed below because of your leg problems? <i>For each statement in the table below, indicate how much trouble you have experienced by circling the number chosen.</i>					
	No trouble	Slight trouble	Moderate trouble	Considerable trouble	Could not do it
4) Climbing several flights of stairs	1	2	3	4	5
5) Crouching, Kneeling down	1	2	3	4	5
6) Walking at a brisk pace	1	2	3	4	5
7) Going out for the evening, going to a wedding, a party, a cocktail party...	1	2	3	4	5
8) Playing a sport, exerting yourself physically	1	2	3	4	5

	Leg problems can also affect your mood. How closely do the following statements correspond to what you have felt during the past four weeks? <i>For each statement in the table below, circle the number that applies to you.</i>				
	Not at all	A little	Moderately	A lot	Completely
9) I have felt nervous/tense	1	2	3	4	5
10) I have felt I am a burden	1	2	3	4	5
11) I have felt embarrassed about showing my legs	1	2	3	4	5
12) I have become irritated easily	1	2	3	4	5
13) I have felt as if I am handicapped	1	2	3	4	5
14) I have not felt like going out	1	2	3	4	5

Appendix 15. Societal Questions

The following questions is to try assess the possible impact on society of patients having to take time off work or caring duties to attend a varicose vein appointment.

What is your total family income?

- ☐ Less than £20,000
- ☐ £20,000 - £39,999
- ☐ £40,000 - £59,999
- ☐ £60,000 - £99,999
- ☐ £100,000 and over

What is your highest level of education attained?

- ☐ None
- ☐ Primary education
- ☐ Secondary education
- ☐ Tertiary education
- ☐ Post-graduate degree

1. Did you need to take time off work to attend your varicose vein appointment?
☐ Yes ☐ No (Go to Question 3)
2. Did you have to take half a day or full day off?
☐ Half-day ☐ Full day
3. What is your hourly rate of pay at work?
.....
4. Do you have care commitments (e.g., children or relatives)?
☐ Yes ☐ No
5. Did you have to ask someone to look after your child/relative so you could attend your appointment?
☐ Yes ☐ No
6. Who did you ask?
.....
7. How much did you have to pay them?
.....

Appendix 16: Patient Satisfaction Questionnaire

Timing

1. How long did it take from you being referred to being seen in clinic today?
.....
2. Did you feel it was too long?
☐ Yes
☐ No
3. How easy was it for you to get the time off for your appointment today?
☐ Very easy
☐ Easy
☐ Neither easy nor difficult
☐ Difficult
☐ Very difficult

Comments:.....

Information Provided

1. You were sent information prior to your appointment today. How helpful was the information to improve your understanding of what was going to happen today?
☐ Very helpful
☐ Helpful
☐ Neither helpful nor unhelpful
☐ Unhelpful
2. Did you use the helpline number provided?
☐ Yes
☐ No

Clinic

1. At what time was your clinic time?
.....
2. At what time were you seen by the Vascular team?
.....
3. At what time did you have your venous scan?
.....
4. At what time were you seen by the Vascular team again?
.....
5. At what time did you have your varicose vein procedure?
.....
6. At what time were you discharged?
.....
7. How much time did you have to decide between being told by the Vascular specialist that you could have a varicose vein procedure today and agreeing to it?
.....

8. Did you feel that was enough time?

☐ Yes

☐ No

Satisfaction

On a scale of 0 to 10, where 0=very bad and 10=excellent:

1. How would you rate your experience of the service provided today?

0 1 2 3 4 5 6 7 8 9 10

2. How would you rate your experience from being referred by your GP to having a varicose vein procedure?

0 1 2 3 4 5 6 7 8 9 10

3. If given the choice, how likely are you to attend for a similar service again?

0 1 2 3 4 5 6 7 8 9 10

4. How likely are you to recommend the service you have received to your family or friends?

0 1 2 3 4 5 6 7 8 9 10

1. If you have the same choice again, would you have the same service as you had today (appointment, scan and procedure on same day)?

☐ Yes

☐ No

2. Any comments as to how this service could be improved?

.....
.....
.....
.....

3. Any other comments?

.....
.....
.....
.....

Appendix 17 - Prizes & Awards

1. The Graham-Dixon Charitable Trust Pump-Priming Grant (2014)
2. The Norman Tanner Medal (2014) – Royal Society of Medicine
3. The Franklin Travel Fellowship (2015) (to attend the American Venous Forum Meeting 2015 in Palm Springs, USA)
4. Certificate of Merit (2015) – Charing Cross Symposium 2015 (United Kingdom)
5. Travel Grant – Union Internationale de Phlébologie (UIP) Chapter Meeting 2015 (Seoul, South Korea)
6. 4th Union Internationale de Phlébologie (UIP)/Kreussler Young Sclerotherapy Scientists' Award 2015
7. International Travelling Scholarship (American College of Phlebology 2016)
8. The Franklin Travel Fellowship (2016) (to attend the American Venous Forum Meeting 2016 in Florida)
9. The Graham-Dixon Charitable Trust Pump-Priming Grant (2016)
10. Society of Academic and Surgical Research (SARS) Bursary (2017)

Appendix 18: Published Articles

1. **Bootun R**, Onida S, Lane TRA, Davies AH. To compress or not to compress: the eternal question of the place of compression after endovenous procedures. *Phlebology* 2016; 31 (8): 529-31.
2. Moon KH, Dharmarajah B, **Bootun R**, Lim CS, Lane TRA, Moore HM, Sritharan K, Davies AH. Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins. *Phlebology* 2016 Aug 10 [Epub ahead of print]
3. Lane TRA, **Bootun R**, Dharmarajah B, Lim CS, Najem M, Renton S, Sritharan K, Davies AH. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – Final results of the Venefit versus Clarivein for varicose veins trial. *Phlebology* 2016 May 24 [Epub ahead of print]
4. **Bootun R**, Onida S, Lane TRA, Davies AH. Varicose veins and their management. *Surgery* 2016; 34 (4): 165-71. (<http://dx.doi.org/10.1016/j.mpsur.2016.02.002>)
5. **Bootun R**, Davies AH. Long-term follow-up for different varicose vein therapies: is surgery still the best? *Phlebology* 2016; 31(1S): 125-129.
6. **Bootun R**, Lane TRA, Davies AH. A comparison of thermal and non-thermal ablation. *Reviews in Vascular Medicine* 2016; 4-5: 1-8.
7. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS, Najem M, Renton S, Sritharan K, Davies AH. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. *Phlebology* 2016; 31(1): 61-5.
8. **Bootun R**, Lane TRA, Davies AH. The advent of non-thermal, non-tumescent techniques for the treatment of varicose veins. *Phlebology* 2016; 31(1): 5-14.

To compress or not to compress: The eternal question of the place of compression after endovenous procedures

Roshan Bootun, Sarah Onida, Tristan RA Lane and
 Alun H Davies

The management of varicose vein disease has witnessed a dramatic transformation over the past decade. Surgery for this common condition, long considered the 'gold-standard' treatment, has gradually been replaced by endothermal ablation and ultrasound-guided foam sclerotherapy (UGFS). These minimally invasive techniques have allowed a more rapid improvement in patients' quality of life and return to normal activities. The focus on enhancing patients' experience even further has led to the introduction of newer, non-thermal, non-tumescent (NTNT) technologies. These completely obviate the need for uncomfortable thermal ablation and tumescent infiltration with possibly a similar level of efficacy as radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) in the short term.¹

The next potential area where a substantial difference in the management of varicose veins can be made is the use of compression therapy following endovenous ablation. It is widely believed that compression reduces post-operative swelling, haematoma formation and pain following surgery for varicose veins, but no irrefutable evidence exists.² Edwards et al.³ surveyed the members of the Vascular Society of Great Britain and Ireland and found that 75% used either elastic or non-elastic bandages post-operatively, with 77% changing to compression stockings afterwards. There was a high variability with respect to the length of time the bandages and stockings were worn for. Another questionnaire survey of the members of the same society demonstrated that following endothermal ablation, 87% of responders stated that they used compression stockings and 60% used bandages.⁴ Similar numbers used compression stockings and bandages after foam sclerotherapy. Once again, however, there was marked inconsistency in the length of time these were prescribed for.

Bakker et al.⁵ carried out a randomised controlled trial looking at the use of compression stockings for two days compared to seven days following EVLA of the great saphenous vein (GSV). At one week, the

physical function, vitality and pain score was significantly better in the seven-day compression group. By 6 weeks though, there were no major differences between the two groups.

Elderman et al.² also looked at the effect of compression stockings post-EVLA of the GSV. Patients were randomised to receiving either compression stockings or no stockings. Those in the no compression group had significantly worse pain scores up to seven days and used analgesia more frequently than the group randomised to compression.

These two studies appear to indicate a benefit in the short term of compression therapy in patients undergoing EVLA, but are limited by the considerable drop-outs in both studies (40 patients of the original 109 approached in the Bakker et al. study and 32 patients from Elderman et al. trial).^{2,5}

The role of compression therapy following UGFS has also been investigated. Hamel-Desnos et al.⁶ conducted a randomised study looking at the use of compression stockings post-foam sclerotherapy.⁶ Class 2 compression stockings (pressure exerted: 15–20 mmHg) were used. No significant differences were found in the pain scores, inflammation, ecchymosis, induration, pigmentation or matting at 14 and 28 days. Compliance was an issue with only 40% of patients wearing compression stockings everyday. Due to the relatively small sample size (60 patients in total), the study may not have been powered sufficiently to enable detection of a significant difference between the groups.

O'Hare et al.⁷ evaluated the use of compression bandaging for 1 and 5 days in patients having UGFS followed by TED stockings for two weeks. At the six-week point, no significant differences were noted in the

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pain scores, varicose vein severity score or rate of vein occlusion between the two groups.

The use of compression post-non-thermal ablation has recently joined this debate. Cyanoacrylate adhesive injection, one of the NTNTs, is routinely utilised with only a simple bandage applied to the puncture site.^{8–10} Almeida et al.,⁸ the original proponents of this deviation from usual varicose vein practice, suggested that compression was not required since the vein wall was not perforated during the ablative procedure.⁸ On the other hand, mechanochemical ablation, which causes only intimal injury and also does not puncture the vein, continues to be used with compression stockings.^{11–13} Studies investigating the role of compression following varicose vein treatment demonstrate a large amount of variability with respect to the type of compression used with some reporting both compression stockings and bandages usage.^{6,14,15} An applied pressure at the thigh of greater than 10–15 mmHg in the lying position and 40–50 mmHg in the standing position is said to be needed to occlude a traumatised vein.¹⁶ Compression with inelastic bandages exert a pressure greater than 50 mmHg at the thigh level, while elastic stockings apply a pressure of only a few mmHg at the thigh level.¹⁶ In their study, Hamel-Desnos et al.⁶ used class 2 compression stockings with pressures of 15–20 mmHg, which would have been inadequate to occlude the veins in the standing position.⁶ Lugli et al.¹⁵, for their part, used a novel cross-taped technique to exert eccentric compression onto the GSV following EVLA.¹⁵ This effect was confirmed on computed tomography (CT) scanning, showing that the eccentric compression pressed the thigh tissues deeper than with compression stockings. The results showed that the pain scores were significantly less in those receiving the cross-taped compression compared to the control group.¹⁵

Other inconsistencies often noted in trials have been with respect to the different methods of compression used and the variable duration that compression was applied for. O'Hare et al.⁷ looked at the use of compression bandages, but after day 1 and day 5, the compression was changed to TED stockings for two weeks. This makes it very difficult to determine whether the effects reported at the end of the study were due to the stockings or the bandages.

The above studies illustrate the problem faced when looking at compression in patients undergoing endovenous ablation. There is extensive heterogeneity with some trials demonstrating a clear benefit and others being inconclusive. This was again highlighted in a recent systematic review, which found that the evidence available is inadequate to produce guidelines.¹⁷ Indeed, the authors found that the articles were often let down by a number of flaws, most notably, by insufficient number of patients, different compression regimens

and variable duration of compression application (0–7 days considered as 'short' duration and 5–42 days considered as 'long' duration).¹⁷

The 2013 National Institute for Health and Clinical Excellence (NICE) Guidelines on varicose veins are unable to provide guidance either, other than to state a limit on the number of days compression bandaging, or hosiery, is prescribed for, when offered.¹⁸ NICE appears to be aware of the deficiencies in the available evidence, and has recommended further research into the clinical effects and cost-effectiveness of compression following varicose vein intervention as well as the duration of any therapy.

Ultimately, an answer addressing the role of compression after varicose vein intervention would allow us to improve the management we currently offer even further. This pursuit is, however, strongly hampered by an obvious lack of evidence. Well-conducted randomised controlled studies with, crucially, adequately powered sample sizes are urgently needed to try resolve this problem.^{19,20}

Declaration of Conflicting Interests

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Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins

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Abstract

Objective: Mechanochemical ablation is a novel technique for ablation of varicose veins utilising a rotating catheter and liquid sclerosant. Mechanochemical ablation and radiofrequency ablation have no reported neurological side-effect but the rotating mechanism of mechanochemical ablation may produce microbubbles. Air emboli have been implicated as a cause of cerebrovascular events during ultrasound-guided foam sclerotherapy and microbubbles in the heart during ultrasound-guided foam sclerotherapy have been demonstrated. This study investigated the presence of microbubbles in the right heart during varicose vein ablation by mechanochemical ablation and radiofrequency ablation.

Methods: Patients undergoing great saphenous vein ablation by mechanochemical ablation or radiofrequency ablation were recruited. During the ablative procedure, the presence of microbubbles was assessed using transthoracic echocardiogram. Offline blinded image quantification was performed using International Consensus Criteria grading guidelines.

Results: From 32 recruited patients, 28 data sets were analysed. Eleven underwent mechanochemical ablation and 17 underwent radiofrequency ablation. There were no neurological complications. In total, 39% (11/28) of patients had grade 1 or 2 microbubbles detected. Thirty-six percent (4/11) of mechanochemical ablation patients and 29% (5/17) of radiofrequency ablation patients had microbubbles with no significant difference between the groups ($p=0.8065$).

Conclusion: A comparable prevalence of microbubbles between mechanochemical ablation and radiofrequency ablation both of which are lower than that previously reported for ultrasound-guided foam sclerotherapy suggests that mechanochemical ablation may not confer the same risk of neurological events as ultrasound-guided foam sclerotherapy for treatment of varicose veins.

Keywords

Microbubbles, radiofrequency, mechanochemical, ablation, varicose veins

Introduction

Varicose veins are characterised by excessive dilatation and tortuosity of the superficial venous system and often present as visible bulging, surface veins, felt under the skin.^{1–3} The disease often affects the quality of life of patients through pain and ulcers with a significant burden to both health care systems and the wider socioeconomic climate.⁴ Over 40,000 operations are performed each year for varicose veins within the National Health Service in England and Wales⁵ consuming approximately £40 million in 2005–2006.⁶

As recommended by the National Institute for Health and Care Excellence (NICE) in the United

Kingdom, symptomatic varicose veins should be treated with minimally invasive techniques. These include endovenous laser ablation, radiofrequency ablation (RFA) and ultrasound guided foam sclerotherapy

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(UGFS).⁷ The recently introduced mechanochemical endovenous ablation (MOCA) (ClariVein®, Vascular Insights, Madison, USA) catheter is a new treatment that uses a stainless steel tip, which rotates at approximately 3500 r/min and simultaneously releases liquid sclerosant from its rotating tip causing fibrosis within the vein lumen. It has a potential advantage over RFA and laser ablation as tumescent anaesthesia is not required. Additionally, the occlusion rates of MOCA have been shown to be comparable with 90% occlusion at 2 years post-procedurally.^{8–10}

Some treatment modalities have had rare yet serious complications reported. Since 1997, there have been 13 cases of reported strokes following sclerotherapy.¹¹ Five of these patients were shown to have bubbles within the circulation with Bush et al.¹² demonstrating bubble presence in the vertebral artery using computed tomography (CT). Furthermore, the use of UGFS has been associated with transient events such as visual disturbance (1.4%)^{13–15} and stroke-like symptoms such as hemiparesis and dysarthria (0.01–2%).^{12,16–18}

Microbubbles have been shown to be present in the heart in 65–100% of patients undergoing UGFS.^{16,19,20} A microbubble is a minimal amount of gas contained within a stable membrane. It can give marked reflections of acoustic signals such as ultrasound. In particular, Ceulen et al.¹⁶ showed a large number of bubbles on echocardiogram of both right atria and ventricles of all 33 patients undergoing UGFS treatment. It is hypothesised that bubbles produced within the treated vein may detach and lead to paradoxical gas embolism possibly through common heart defects such as a patent foramen ovale (PFO), which has a prevalence of 26% in the general population, resulting in reduced cerebral arterial perfusion.¹⁹ Endovenous laser ablation, has been associated with one case of stroke in a patient shown to have a PFO.²¹ The authors of this case report believe that the stroke may have resulted from a paradoxical embolism of saphenic thrombus formed while withdrawing the endovenous catheter.

The concern regarding microbubbles and neurological symptoms has been minimal with endovenous RFA. Sounderajah et al.²² demonstrated that 5 out of 11 patients, undergoing RFA treatment of incompetent GSVs, had microbubbles in the right atrium and ventricle using transthoracic echocardiogram. Despite these findings, there have been no reported neurological complications.

To date, there have also been no known neurological complications reported from MOCA.^{23–26} However, there is a theoretical possibility that MOCA may produce bubbles. Microbubble generators used in chemical engineering utilise spinning discs within liquid surfactant at over 4000 r/min in order to manufacture stable bubbles.²⁷ This may be analogous to the rotational

mechanism of the ClariVein catheter in conjunction with liquid sclerosant, therefore, also creating stable bubbles during treatment. These bubbles have the potential to travel proximally in circulation and result in symptoms seen in UGFS.

Therefore, the aim of this pilot study was to perform imaging of the right atrium and right ventricle of patients to compare microbubble prevalence during RFA and MOCA procedures for varicose veins.

Methods

This was a prospective observational study with approval from the local research ethics committee (Research Ethics Committee reference number 11/LO/1358). Patients undergoing elective treatment of varicose veins at our institution were assessed for eligibility. Patients were included in the study upon agreement to the consent and qualifying to the following inclusion criteria:

- Patients over 18 years of age
- Presenting for treatment of primary refluxing great saphenous vein (GSV)
- Patients being treated by either RFA or MOCA
- Patients who consented to the written and oral information with the details of the study

Patients for treatment of the short saphenous vein (SSV) were excluded as they were required to be in a prone position for treatment thereby precluding transthoracic echocardiogram. Patients with ipsilateral recurrent varicose veins were also excluded as previous treatment may have occluded potential pathways of bubbles.

This study was performed as a prospective, non-randomised study with decisions regarding treatment modality made by the treating clinical team, Duplex ultrasound and patient preference. RFA was performed using the Covidien® Venefit™ (Covidien, San Jose, CA, USA) following infiltration of tumescent anaesthesia around the target vein (50 mL 1% lidocaine with 1:200,000 adrenaline in 1000 mL of 0.9% normal saline). MOCA procedures were carried out using the ClariVein® catheter (Vascular Insights, Madison, CT, USA)²⁶ with 2% sodium tetradecyl sulphate (STS) liquid sclerosant used with the device. RFA and MOCA were carried out as previously described in published literature.^{26,28} The dose of STS was calculated using the length and average diameter of the target vein as recommended by the manufacturer. During both MOCA and RFA procedures, the catheter tip was positioned at 2 cm distal to the sapheno-femoral junction. For both modalities, patients were supine initially and after a successful venous catheterisation,

patients were moved to the Trendelenberg position. Patients remained in this position for the remainder of the procedure. Procedures were performed by three different vascular surgeons all familiar with and approved in both ablative procedures.

During MOCA procedures, the speed of the catheter was determined by patient tolerance to three seconds of the device being operated without sclerosant. As per manufacturer guidance, the catheter was withdrawn within the vein 1 cm every 7 s whilst simultaneously injecting liquid sclerosant.

Transthoracic echocardiogram

Transthoracic echocardiogram was performed as previously described for bubble detection.²² A sonographer performed echocardiogram using a Philips iU22 ultrasound platform with an X3-1 curvilinear echo transducer (Philips, Bothell, WA, USA) to obtain a two-dimensional, apical four-chamber view of the heart. Negative control was initially established by 30 s acquisition of each patient's heart prior to the procedure to demonstrate that, in normal conditions, no bubbles were present. During RFA procedures, a 30 s footage loop was captured when the heating phase of RFA treatment commenced. This included 20 s of active thermal treatment with the device on and a 10-s interval after treatment to allow time for bubbles to travel to the heart. This was repeated until the end of the RFA treatment which was performed in 3 cm or 7 cm segments at the operator's discretion. The most proximal segment from the SFJ was double treated as previously described to ensure proximal closure.²⁹ As a result, the number of recordings was dependent upon the number of RFA heating cycles. For MOCA, an echocardiogram loop of footage was acquired on initial activation of the device without sclerosant. Subsequent loops of footage were then acquired for every syringe of sclerosant used during the treatment with a further 10-s interval acquired after the device was deactivated for each treatment cycle.

Neurological symptom questionnaire

Patients were examined by the operating vascular surgeons prior to consent. Post-operatively, patients were assessed for any symptoms using a questionnaire encompassing commonly reported neurological symptoms from varicose vein treatment.^{12,15,20,23,30,31} The questionnaire assessed for visual and speech disturbances, headache, motor symptoms, dizziness, nausea, vertigo and patients were also asked to report any other systemic symptoms that they experienced including pulmonary symptoms. Previously published literature has demonstrated the presence of

microemboli from UGFS in the right atrium and ventricles ranging from 45 s to 50 min after foam injection.^{16,17,19} Therefore, patients were assessed using the questionnaire immediately and 30 min after endovenous ablation.

Primary outcome

The Digital Imaging and Communications in Medicine (DICOM) echocardiogram loops were quantified offline by two independent blinded, trained observers; a radiology registrar (BD) and an ultrasound engineer (CK) both with over 2 years' experience of microbubble quantification enabling intra- and inter-reader reproducibility. They were visually scored according to the International Consensus Criteria grading guidelines^{32,33} used to assess the bubbles seen in a cardiac shunt test. Table 1 describes the echocardiogram for each grading and Figure 1 shows visual examples of the corresponding images.

Statistical analysis

The patient details were anonymised and procedural groups compared with the Mann-Whitney test using Prism version 6.01 (Graphpad Software, La Jolla, CA, USA). The inter- and intra-rater agreement of visual grading scales were analysed by Cohen's kappa coefficient score using MedCalc[®] version 13.2.0.0 (MedCalc Software bvba).

Results

Sixty-three consecutive patients were assessed for study eligibility between March and May 2014. After application of eligibility criteria and informed consent, 32 patients were recruited into the study. The study could not be completed in two patients due to failed venous cannulation from vasospasm of the GSV. Therefore, 30 patients were available for echocardiogram grading. Two scans were excluded during analysis due to poor scan quality from excessive out of plane imaging secondary to patient movement. The remaining 28 patient data collected were fully

Table 1. Grading system used in interpretation of the microbubbles from the echocardiogram.

Grading	Interpretation
0	No microbubble demonstrated
1	Presence of few microbubbles in inconsistent intervals
2	Stream of microbubbles
3	Opacification by a large area of microbubbles

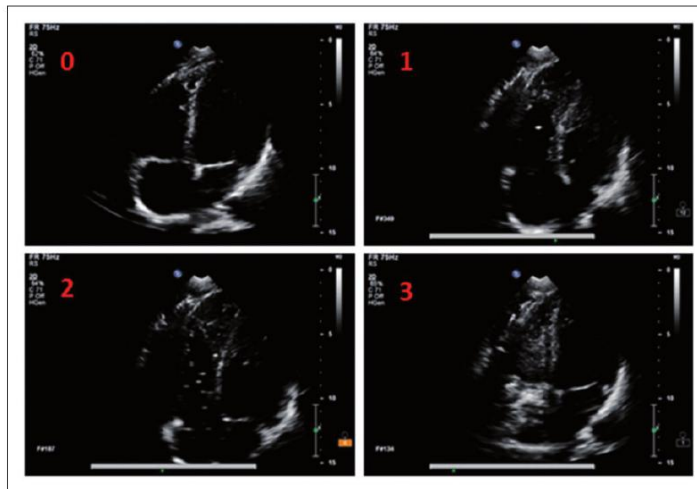


Figure 1. A visual depiction of the grading scale that was devised. The numbers indicate the grade assigned to amount of microbubbles presence.²² Grade 0 shown top left represents absence of any bubbles. Grade 1 on the top right is indicative of presence of few microbubbles in inconsistent intervals. Grade 2 shown on bottom left demonstrates stream of microbubbles. Grade 3 represents opacification by a large area of microbubbles.

interpreted and included for statistical analysis. Further details are shown in the STARD flow diagram in Figure 2.

Seventeen patients underwent RFA and 11 patients underwent MOCA treatments. Statistical analysis in all baseline demographic fields collected showed no significant differences between RFA and MOCA groups (Table 2).

Echocardiogram results

Four out of 11 patients (36%) in the MOCA group and 7 out of 17 patients (41%) in the RFA group had bubbles present in the right heart. The bubble gradings were all grade 1 (example shown in Figure 3) except one patient undergoing RFA which was reported as grade 2. The difference in the bubble grading between each group was not significant ($p=0.8065$). These findings are summarised in Figure 4.

The grading by the International Consensus guideline exhibited good reproducibility amongst observers indicated by Cohen's kappa value of 0.793 and 0.719 for intra- and inter-rater agreement, respectively.

No neurological complications were found in any of the 28 patients immediately or 30 min after the procedure.

Discussion

This study provides the first documented evidence of the presence of bubbles in the right heart following MOCA of varicose veins. Our results also add to previous work by Sounderajah et al.²² demonstrating the presence of bubbles in the right heart during RFA of varicose veins.

A statistically similar incidence and grading of bubbles produced between RFA and MOCA, infers that, if neurological complications are produced by bubbles, varicose vein treatment by MOCA appears to have a similar safety profile to RFA with regard to neurological complications. Previously, bubble grading has been largely grade 3 during UGFS;^{16,20} however, in this study both MOCA and RFA produced fewer bubbles with the majority being grade 1. Whilst the proposed theory that central neurological complications are caused by bubbles acting as air emboli in the cerebral circulation, findings suggest that a high intensity of bubble production is required for this to occur as demonstrated by the incidence of neurological symptoms after UGFS as compared to the reported safety profile of RFA.^{12,16,17,20} Additionally, the difference in bubble grading is unlikely to be a simple function of overall volume of sclerosant used in MOCA and UGFS

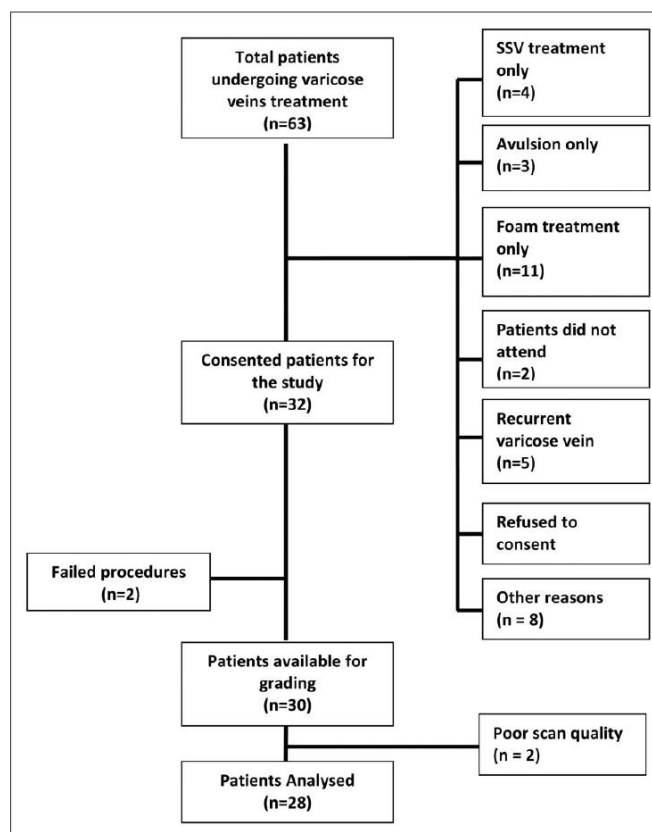


Figure 2. STARD flow diagram of the patient recruited in this study, 63 patients were assessed for eligibility. Thirty-two were consented after exclusion criteria were applied. Two procedures of consented patients failed and subsequently excluded from the study. Two poor scan quality participants were excluded. Twenty-eight participant data set were analysed.

with a range of 7–10 mL of 2% STS used in the current study when compared to 5 mL of 1% polidocanol foam and 2.5 mL of 3% STS used in the previous UGFS studies, respectively.^{16,19}

Nevertheless, Caggiati's report of stroke after the laser ablation treatment of varicose vein in 2010,²¹ brings the safety of RFA into question as they both utilise endothermal ablation to achieve closure of veins. Higher temperatures decrease the solubility of gases in liquid,³⁴ therefore, this could increase the number of bubbles produced, thereby increasing the grading intensity of bubbles produced during treatment. However, Caggiati suggested the cause of

stroke was likely to be saphenic thrombi emboli rather than gas emboli.

Our findings contribute to the current debate over causes of neurological symptoms reported from UGFS, where bubbles from foam sclerosant are believed to cause transient cerebral ischaemia by passing through a PFO in the heart and occluding the cerebral circulation.^{12,16,17,20} This study did not assess PFO in the subjects; however, PFO prevalence in the general population is reported to be 26% although the prevalence of right to left shunt may indeed be greater in patients with GSV incompetence.^{35,36} Despite this, our data showed a microbubble presence of 39% with

Table 2. Demographics of the patient population in each treatment modalities.

	RFA	MOCA	Unpaired <i>t</i> -test
Number of subjects	17	11	
Mean age	55	46	<i>p</i> = 0.1347
Mean weight	76.7 kg	72.7 kg	<i>p</i> = 0.6262
Mean VCSS	4.9	5.5	<i>p</i> = 0.4531
Leg treated	Left: 10 Right: 7	Left: 3 Right: 8	<i>p</i> = 0.1367
Mean length of vein treated	34.7 cm	39.1 cm	<i>p</i> = 0.3298
Gender	Male: 5 Female: 12	Male: 5 Female: 6	<i>p</i> = 0.444

MOCA: mechanochemical ablation; RFA: radiofrequency ablation; VCSS: venous clinical severity score.

no neurological symptoms in any of the subjects compared to the reported rates of neurological symptoms after foam sclerotherapy of 2%.^{13,30,37,38} This highlights that despite the presence of bubbles from vein treatment, neurological symptoms are much lower than the prevalence of PFO.

This pilot study was limited by a small sample size of non-randomised prospectively treated patients. At our institution, treatment modality decisions are made by the treating clinician in conjunction with patient preference, therefore, randomisation was not deemed appropriate for this pilot study. In accordance with NICE guidance, UGFS is not a first line treatment modality for GSV incompetence at our institution,⁷ therefore, the investigation of microbubble presence during UGFS was not undertaken in this study. However, using similar transthoracic echocardiogram

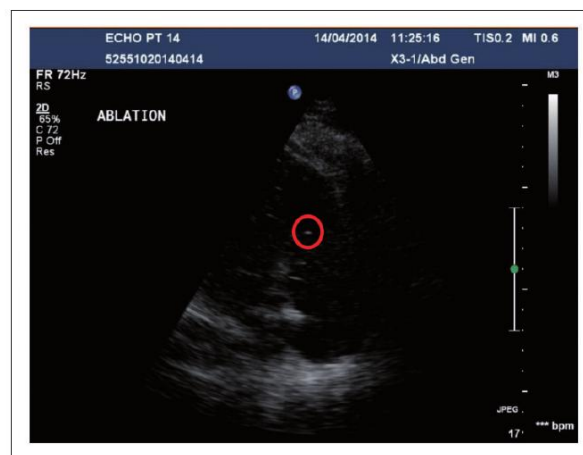
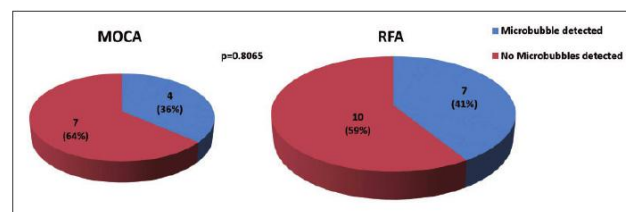
**Figure 3.** An example of a transthoracic echocardiogram scan from one of the participants showing grade 1 microbubbles.**Figure 4.** Number of subjects in each treatment modality. Each pie chart is showing the proportion of patients who had microbubbles detected in the echocardiogram and those who did not.

image acquisition and blinded quantification,²⁹ relative comparison of published literature demonstrating the presence of microbubbles during UGFS was possible.^{12,16,17,20} Only peri-procedural analysis of bubble detection and assessment of neurological symptoms was performed; however, based on previous literature this is when the majority of both of these events occur.^{16,17,19} Additionally, in this small patient cohort, neurological symptoms were very unlikely to occur; however, the primary outcome of this study was to assess and compare the presence of microbubbles in the right heart during venous ablation rather than their potential sequelae.

Conclusion

This study reports, for the first time, the detection of bubbles in the right heart during MOCA. We have also confirmed bubble presence in the right heart during RFA and shown no difference in prevalence or grade of bubbles between MOCA and RFA.

This similarity in bubble production between the two modalities, in conjunction with no previous reports of neurological complications from RFA, suggests that MOCA has similar safety profile to RFA. If neurological symptoms are caused by procedural bubbles, this study demonstrates that MOCA does not confer the same risk of neurological symptoms observed with UGFS.

Declaration of conflicting interests

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Ethical Approval

Ethics approval from the local research ethics committee (Research Ethics Committee reference number 11/LO/1358).

Guarantor

AHD.

Authors' Contributions

KHM, BD, TRAL, HMM and AHD designed the research; KHM and BD performed the search of the literature; KHM,

BD, BR, CSL and KS performed the data collection and analysis; KHM, BD and AHD wrote and revised the paper for submission, AHD retained overall responsibility over the research and paper. The authors acknowledge CK for image analysis.

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A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – Final results of the Venefit versus Clarivein for varicose veins trial

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Abstract

Background: Endovenous thermal ablation has revolutionised varicose vein treatment. New non-thermal techniques such as mechanical occlusion chemically assisted endovenous ablation (MOCA) allow treatment of entire trunks with single anaesthetic injections. Previous non-randomised work has shown reduced pain post-operatively with MOCA. This study presents a multi-centre randomised controlled trial assessing the difference in pain during truncal ablation using MOCA and radiofrequency endovenous ablation (RFA) with six months' follow-up.

Methods: Patients undergoing local anaesthetic endovenous ablation for primary varicose veins were randomised to either MOCA or RFA. Pain scores using Visual Analogue Scale and number scale (0–10) during truncal ablation were recorded. Adjunctive procedures were completed subsequently. Pain after phlebectomy was not assessed. Patients were reviewed at one and six months with clinical scores, quality of life scores and duplex ultrasound assessment of the treated leg.

Results: A total of 170 patients were recruited over a 21-month period from 240 screened. Patients in the MOCA group experienced significantly less maximum pain during the procedure by Visual Analogue Scale (MOCA median 15 mm (interquartile range 7–36 mm) versus RFA 34 mm (interquartile range 16–53 mm), $p=0.003$) and number scale (MOCA median 3 (interquartile range 1–5) versus RFA 4 mm (interquartile range 3–6.5), $p=0.002$). 'Average' pain scores were also significantly less in the MOCA group; 74% underwent simultaneous phlebectomy. Occlusion rates, clinical severity scores, disease specific and generic quality of life scores were similar between groups at one and six months. There were two deep vein thromboses, one in each group.

Conclusion: Pain secondary to truncal ablation is less painful with MOCA than RFA with similar short-term technical, quality of life and safety outcomes.

Keywords

Varicose veins, randomised controlled trial, endovenous ablation, mechanical occlusion chemically assisted ablation, radiofrequency ablation, pain

Previously Presented: Preliminary results have been presented at the Royal Society of Medicine Venous Forum, Charing Cross Symposium, Society for Academic and Research Surgery, the Controversies and Updates in Vascular Surgery Meeting and the American Venous Forum. A short report of early results has been published in *Phlebology*.

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Introduction

Varicose veins are a common condition worldwide and cause significant quality of life impairments with consequent healthcare costs.¹ Symptomatology is varied, as is progression to ulceration.^{2,3} Endovenous ablation with catheter-based technology, using radiofrequency energy or laser energy to cause thermal damage to the vein leading to fibrosis and occlusion, has revolutionised modern varicose vein treatment. Now any superficial vein navigable by a soft hydrophilic guidewire can be treated in this manner. These developments have led to endovenous thermal ablation being recommended as first line treatment by the National Institute for Health and Care Excellence.^{4,5} The aforementioned techniques, however, require the use of tumescent anaesthesia which involves multiple needle injections.⁶ In the past few years, new techniques have been developed and older techniques extended to alleviate the need for tumescent anaesthesia and improve the patient experience. One of the new techniques is mechanical occlusion chemically assisted endovenous ablation (MOCA), which uses a hybrid system of physical damage to the vein wall and liquid sclerotherapy to lead to scarring and fibrosis without the need for tumescent anaesthesia.^{7,8} The lack of requirement for multiple needle injections should in theory lead to reduced intra-operative and peri-operative pain. Recent work in a non-randomised study comparing RFA and MOCA has shown a reduced pain experience post-operatively for those patients undergoing MOCA.⁹ This study was designed to compare the pain levels encountered during the procedure between RFA (using the Medtronic Venefit RFA segmental catheter; Medtronic, Santa Rosa, CA, USA) and MOCA (using the Vascular Insights Clarivein catheter; Vascular Insights, Quincy, MA, USA), with MOCA hypothesised to be less painful. Initial results of this study have previously been published.¹⁰

Methods

The trial protocol and methodology have previously been reported¹⁰ and is described in full below. The trial was registered with Current Controlled Trials and the ISRCTN registry (<http://www.isrctn.com>) (ISRCTN06552809). The trial protocol, inclusion and exclusion criteria are freely available at <http://www.isrctn.com/ISRCTN06552809>. Ethical approval was obtained from the United Kingdom National Research Ethics Service, London – Chelsea Committee (Research Ethics Committee Reference: 12/LO/0570). Imperial College London were the trial sponsors (reference number JRCHH0431).

Patients

Patients with symptomatic primary varicose veins with either great saphenous vein (GSV) or small saphenous

vein (SSV) incompetence (>0.5 s reflux on colour duplex ultrasound), presenting to Charing Cross Hospital (Imperial College Healthcare NHS Trust) or Northwick Park Hospital (London North West Healthcare NHS Trust) in London, UK, were assessed clinically by independent clinicians and listed for treatment. Clinical stage and symptom scores were recorded. Once listed for treatment they were screened trial inclusion and invited to participate in the Venefit Versus Clarivein for Varicose Veins trial. Patients with recurrent varicose veins, current deep vein thrombosis, arterial disease (ankle brachial pressure index <0.8), veins <3 mm in diameter or hypercoagulability were excluded from participation. Additionally, patients unable or unwilling to complete questionnaires or to participate were also excluded. Consenting participants were then randomised on the day of treatment to either MOCA (group one) or RFA (group two), using an online computerised randomisation software (SealedEnvelope, London, UK). In patients with bilateral disease, the most symptomatic side was entered into the study. Patients completed generic and disease specific questionnaires prior to intervention.

Interventions

All procedures were carried out by trained vascular surgeons who were experienced in both techniques of endovenous ablation. No peri-operative analgesia or sedation was used. Standard distraction techniques were utilised with music and verbal distraction. Ultrasound guidance and local anaesthetic (and tumescent anaesthesia in the RFA group) were used in all procedures. Initial vein access (GSV or SSV) was performed under ultrasound guidance after injection of local anaesthetic (1% Lidocaine using a standard 3 cm length 23 Gauge needle), targeting the most distal point of venous reflux where cannulation was possible. A standard 7Fr vascular sheath was placed (Medtronic, USA). The treatment catheter tip was positioned 2 cm distal to the sapheno-femoral junction or sapheno-popliteal junction, assessed in both longitudinal and transverse views on ultrasound.

The standard method was used for RFA (Venefit, Medtronic, USA) as described before.¹¹ Concisely, cooled tumescent anaesthesia (either 360 ml Normal Saline with 40 ml 1% lignocaine with 1:200,000 adrenaline; or 500 ml normal saline with 20 ml 1% lignocaine and 5 ml 8.4% sodium bicarbonate, dependent on local protocol) was injected using a standard 4 cm length, 21 Gauge needle into the saphenous sheath using a Klein pump at 400 ml per minute to create a "1 cm halo" of tumescent along the vein to be treated (approximately 10 ml per cm). Then, RF segmental ablation was completed, with 20 s per treatment zone (7 cm or 3 cm dependent on catheter tip), and double treatment for the first segment.

MOCA (Clarivein, Vascular Insights, USA) was performed as previously described^{9,10} using 2% sodium tetradecyl sulphate (STS) (FibrovenTM, STD Pharmaceutical Products Ltd., Hereford, UK) (made by mixing equal volumes of 1% STS and 3% STS). Concisely, following cannulation and tip positioning under ultrasound guidance, the treatment tip was unsheathed and positioning rechecked. The sclerosant syringe was then attached. The device motor was engaged for 1–2 s to induce proximal vein spasm. Then, the activated catheter with rotating tip was steadily withdrawn by 1 cm every 7 s, whilst injecting sclerosant at a constant rate dependent on length of vein to be treated and volume of sclerosant. This sclerosant injection rates were calculated as per the manufacturer's guidance.

Immediately after completion of the endovenous ablation, patients were asked to report their pain experience on a 0–100 mm Visual Analogue Scale (VAS) and a 0–10 number scale.

If required (if symptomatic visible varicosities) and with patient consent, concomitant phlebectomies were then performed using standard Oesch hook technique with local tumescent anaesthesia.^{12,13}

All patients received a single prophylactic dose of low molecular weight heparin at the completion of the procedure. Use of prophylactic antibiotics was left to the discretion of the treating surgeon.

Stockings were worn for two weeks post-procedure, and patients were advised to return to their work and normal activities as soon as they felt able to.

Patients were reviewed at one month and six months post-procedure with clinical assessment, duplex ultrasound and asked to complete a questionnaire.

Outcome measures

The primary outcome of the study was the degree of pain experience during endovenous ablation using a validated patient reported VAS and 0–10 number scale, prior to completion of any phlebectomies. Patients were also asked to describe the duration of the pain as lasting seconds, minutes or several minutes. The secondary outcomes were improvement in patient-reported quality of life, both disease specific (Aberdeen Varicose Vein Questionnaire – AVVQ)¹⁴ and generic (Euroqol 5 Domain 3 Level – EQ-5D-3 L and EuroQol VAS)¹⁵, clinical scores (Venous Clinical Severity Score – VCSS, Venous Disability Score – VDS and Clinical Etiology Anatomy Pathology score)^{16,17} and time taken to return to normal activities and work. The primary outcome measure was assessed at the time of intervention. The secondary outcomes were assessed at one month and six months' post-operative follow-up. Technical success was also assessed at one month and six months with

validated, blinded venous duplex ultrasound scanning. There were four possible scan classifications: complete occlusion of the saphenous vein, proximal occlusion (>5 cm proximally occluded, with >5 cm open distally), distal occlusion (>5 cm distally occluded, with >5 cm open proximally) and open. Patency in the first 3 cm of the GSV was considered normal.¹⁸

Power calculations

Power calculations were based on the primary outcome of pain during the truncal ablation procedure as assessed by VAS. Detection of a 20-mm difference in maximum pain score with a standard deviation of pain score of 20 mm was considered a significant difference. The minimum target size was calculated to be 94 patients (47 per group) at 90% power and 5% significance. Allowing for loss to follow-up or protocol violations, an overall target recruitment of 170 legs (85 per group) was estimated.

Statistical analysis

Data were recorded prospectively on a bespoke database and analysed using SPSS version 23 (IBM, Armonk, USA), STATA version 14 SE (Statacorp, College Station, Texas, USA), Wizard Pro version 1.7.14 (Evan Miller, Chicago, IL, USA) and Prism version 6 (GraphPad, La Jolla, California, USA). Data were analysed using parametric and non-parametric statistical tests as dictated by the distribution of data. Normally distributed data are reported as mean and standard deviation, non-normal distributions are reported as median and interquartile range (IQR).

Results

A total of 170 patients were recruited between January 2013 and September 2014 from a potential 240 screened patients; 41% were male, 86% were GSV and 14% SSV. Baseline data are presented in Table 1, there were no significant differences between groups. A total of 87 were randomised to receive MOCA and 83 to RFA; 83 of the 87 MOCA cases underwent MOCA and 82 of the 83 RFA cases underwent RFA. There was one crossover in each group. Analysis was performed on an intention to treat basis. Treatment data are presented in Table 2, there were no significant differences between procedural details, including number of patients having concomitant phlebectomies and number of phlebectomies performed. See Figure 1 for the Trial Consort Diagram. Proportion of patients completing follow-up at one month was 76% (n = 129) and at six months was 71% (n = 121).

Table 1. Patient demographics – mechanochemical ablation group (MOCA) and radiofrequency ablation (RFA).

	Total	MOCA	RFA	Difference
n	170	87	83	ns
Male	70 (41.2%)	37 (42.5%)	33 (39.8)	ns (0.714)
Age ^a Median	50	54.5	48	ns (0.099)
GSV	147 (86.5%)	77 (88.5%)	70 (84.3%)	ns (0.427)
BMI >30	20 (13.4%)	13 (16.7%)	7 (9.9%)	ns (0.223)
CEAP ^b Median	4	4	4	ns (0.627)
VCSS ^c Median	5	6	5	ns (0.112)
VDS ^d Median	1	1	1	ns (0.135)
AVVQ	19.303	19.546	18.888	ns (0.592)
EQ5D QOL ^e Median	0.761	0.761	0.730	ns (0.989)
EQ5D VAS ^f Median	81.0	84.5	80.0	ns (0.050)

GSV: great saphenous vein; BMI: body mass index; CEAP: clinical etiology anatomy pathology; VCSS: venous clinical severity score; VDS: venous disability score; AVVQ: Aberdeen varicose vein questionnaire; VAS: visual analogue scale.

Table 2. Treatment characteristics.

	Total	MOCA	RFA	Difference
N	165	83	82	ns
Length of vein treated (GSV) (mm)	364	359	373	ns
Length of vein treated (SSV) (mm)	205	227	166	ns
Concomitant avulsions	74%	68%	76%	ns
Median number of avulsions	4	4	4	ns
Median vein diameter (mm)	7	7	7	ns

GSV: great saphenous vein; SSV: small saphenous vein; MOCA: mechanochemical ablation group; RFA: radiofrequency ablation.

Primary outcome

Maximum pain experienced during truncal ablation (Figure 2). Overall median maximum pain via VAS was 24 mm (IQR 10–45) and 4 mm (2–5) by 0–10 number scale. Maximum pain experienced during endovenous ablation as measured on VAS was significantly less in the MOCA group with a median of 15 mm (IQR 7–36 mm) versus 34 mm (16–53 mm), $p=0.003$ (Mann–Whitney). As measured on a number scale of 0–10, median maximum pain experienced was also significantly less in the MOCA group – 3 (1–5) versus 4 (3–6.5), $p=0.002$ (Mann–Whitney). Post hoc power analysis demonstrated 91% power at 0.05% significance for the VAS and 94% power at 0.05% significance for the number

scale. VAS and number scale showed a very strong correlation (Pearson's $r=0.96$, $p<0.001$).

Eighty-six percent of patients described the maximum pain as lasting seconds, and there was no difference in estimated duration of maximal pain duration between groups (90% seconds in MOCA group versus 82% seconds in RFA group, $p=0.169$).

'Average' pain experienced during truncal ablation (Figure 3). Overall median 'average' pain experienced was 15 mm (6–32) and 2.5 (1–4) by 0–10 number scale. 'Average' pain experienced during endovenous ablation was also significantly less in the MOCA group with both VAS – median of 10 mm (3–25 mm) versus 19.5 mm (9–38 mm), $p=0.003$ (Mann–Whitney); and number scale – median of 2 (0.5–4) versus 3 (2–5), $p=0.004$ (Mann–Whitney). Post hoc power analysis demonstrated 55% power at 0.05% significance for the VAS and 74% power at 0.05% significance for the number scale. VAS and number scale showed a very strong correlation (Pearson's $r=0.94$, $p<0.001$).

Sixty-eight percent of patients described the 'average' pain as lasting seconds, and there was a significant difference in estimated duration of "average" pain duration (76% seconds in MOCA versus 60% seconds in RFA group, $p=0.021$).

Secondary outcomes

Disease specific quality of life – AVVQ (Figure 4). Overall AVVQ significantly improved from baseline to one month post treatment (19.3 (13.2–28.7) to 12.8 (7.3–20.7), $p<0.001$), and this continued to be significant at six months (10.8 (4.3–20.5), $p<0.001$ (Friedman)). Between groups, there was no significant difference at baseline, one month or six month – 12.1 (7.3–21.2) for MOCA versus 12.9 (6.6–20.4) for RFA at one month ($p=0.799$); and 11.8 (7.2–20.5) for MOCA versus 9.4 (3.6–21.4) for RFA at six months ($p=0.511$), Figure 4.

General quality of life – EQ-5D QOL and EQ-5D VAS. Overall, EQ-5D QOL and EQ-5D VAS showed no significant change from baseline to six months (Median 0.761 (0.690–0.796) at baseline, 0.761 (0.690–1.000) at one month and 0.761 (0.659–1.000) at six months, $p=0.060$, Friedman). Between groups, there was no significant difference in EQ-5D QOL at one month (MOCA – 0.761 (0.659–1.000) versus RFA – 0.761 (0.690–1), $p=0.939$) or at six months (MOCA 0.761 (0.690–1.000) versus RFA 0.761 (0.486–1.000), $p=0.125$).

EQ-5D VAS was also not significantly different at either timepoint – at one month 85 (60–95) for MOCA versus 87 (80–90) for RFA ($p=0.227$) and at six months 85 (60–93) versus 89 (70–95) ($p=0.302$).

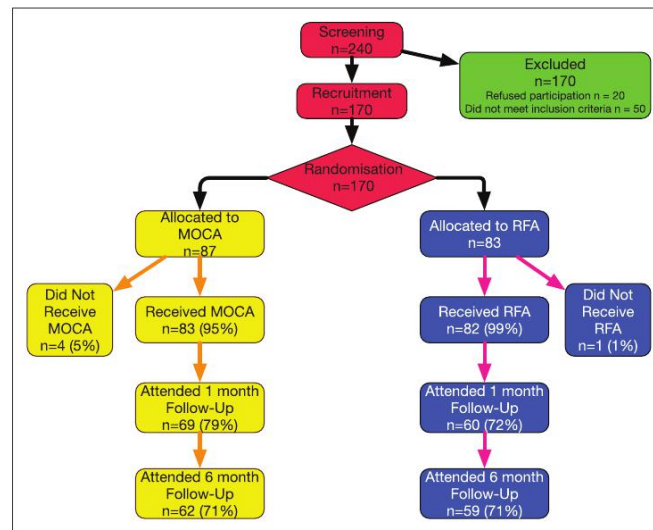


Figure 1. Venefit versus Clarivein for varicose veins consort diagram.

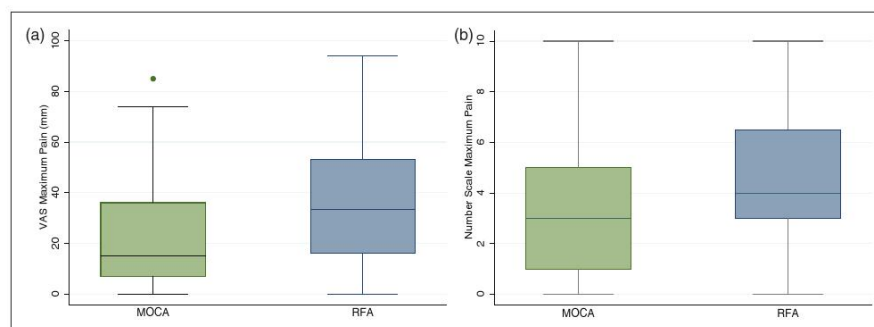


Figure 2. Maximum pain score during procedure for mechanochemical ablation group (MOCA) and radiofrequency ablation (RFA) (a) – visual analogue scale and (b) – number scale.

Clinical severity scoring – VCSS and VDS (Figure 5). Overall, VCSS significantly improved from baseline to one month (5 (4–7) versus 2 (1–5)) as did VDS (1 (1–2) versus 0 (0–1)), and both VCSS and VDS preserved this change at six months ($p < 0.001$, Friedman). Between groups, there was no significant difference for VCSS at either one month (MOCA 2 (1–4) versus

RFA 3 (1–5), $p = 0.096$) or six months (MOCA 2 (1–4) versus RFA 2 (1–5), $p = 0.536$) (Figure 5).

VDS also showed no significant difference between groups at one month or six months.

Return to work and return to normal activities. Overall, participants returned to work at a median of two days

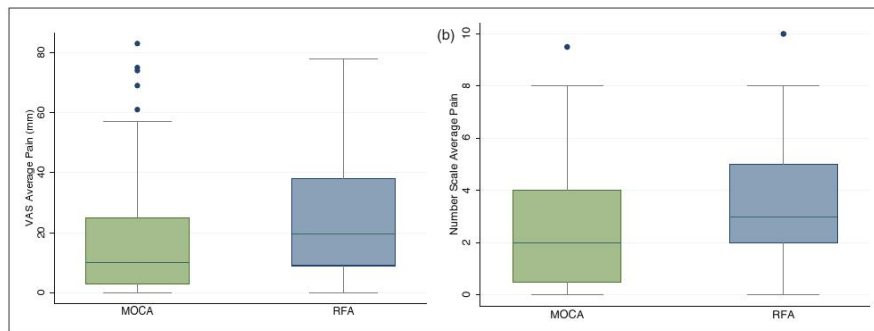


Figure 3. Average pain score during procedure for mechanochemical ablation group (MOCA) and radiofrequency ablation (RFA) (a) – visual analogue scale and (b) – number scale.

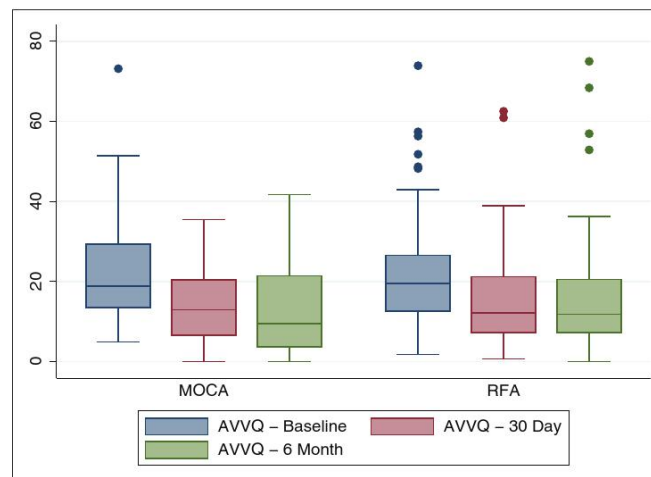


Figure 4. Aberdeen varicose vein questionnaire scores at baseline, one month and six months follow-up – by treatment group – mechanochemical ablation group (MOCA) and radiofrequency ablation (RFA).

(IQR 2–7) and to normal activities at a median of two days (IQR 1–6). There was no significant difference between groups for either return to work (MOCA Median 3, IQR 1–7 versus RFA Median 2, IQR 2–7, ns) or return to normal activities (MOCA Median 2, IQR 1–4 versus RFA Median 2, IQR 1–7, ns).

Technical success of truncal ablation. Overall complete or proximal occlusion rates were 92% at one month and 90% at six months. MOCA showed 93% complete or

proximal occlusion at one month, compared to 92% in RFA. At six months, the rates were 87% for MOCA versus 93% for RFA. There was no significant difference in occlusion rates at one month or six months ($p=0.403$ and $p=0.483$). Occlusion status had no significant effect on clinical or quality of life scores.

Complications. There were three cases of minor phlebitis along the treated vein in the MOCA group and two in the RFA group. Two deep vein thromboses (DVTs)

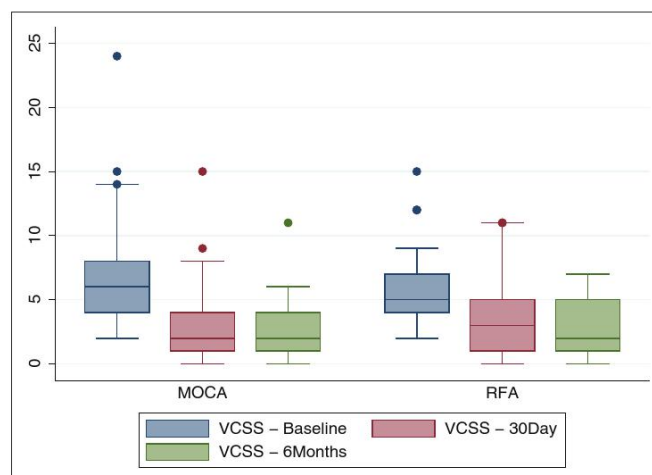


Figure 5. VCSS scores at baseline, one month and six months follow-up – by treatment group – mechanochemical ablation group (MOCA) and radiofrequency ablation (RFA).

occurred (1.2%) – one in each group. The MOCA DVT was a tongue of thrombus into the common femoral vein occluding <50% of the vein diameter (corresponding to Endovascular Treatment Induced Thrombosis stage 2¹⁹), and the RFA DVT was a calf vein thrombus. Neither DVT had had avulsions performed. There were no patient-reported cases of sensory disturbance at either clinical follow-up. No further procedures were required after initial treatment at six months of follow-up. No difference in cosmetic appearance or satisfaction was reported by patients at clinical follow-up. There were no significant differences in complications between groups.

Discussion

Varicose veins and chronic venous disease is a benign but progressive and pervasive disease. The treatment options have been transformed with endovenous ablation, allowing movement from the operating theatre to the outpatient suite. Recently, clinicians have begun searching for fine point percentage benefits in treatment.²⁰

This study shows that tumescentless treatment using MOCA for truncal veins has a reduced pain profile for truncal procedure, whilst retaining similar six-month occlusion rates, as compared to RFA. Patients improved similarly in both groups with respect to disease specific clinical scoring and disease specific quality of life values at all time points. The MOCA group did show a significantly larger improvement in AVVQ from

baseline to six months, despite no significant difference in baseline or six-month follow-up group values. This difference of 3.3 AVVQ points falls below the clinically significant threshold of five points used for previous studies.^{11,12} On simple group comparison, patients in the MOCA group also had an improved generic quality of life outcomes (EQ-5D QOL) at six months, despite similar post-operative complication rates. However, once corrected via linear regression for baseline differences there was no significant difference. No significant improvement was found from baseline to six months due to multiple testing correction (six month data were significantly improved from baseline when assessed directly) and loss to follow-up. This study was not prospectively powered to assess generic or disease QOL. It may also be possible that due to the severity of disease treated in this cohort, the reversibility of QOL detriment is limited.²¹

The occlusion rates at six months are equivalent for both modalities; however, both the RFA and MOCA groups had lower rates of occlusion than expected from the published literature. In the most recent study of long-term follow-up, a total or proximal occlusion rate of 92.7% at five years post RFA has been reported.¹⁸ However, a recent study comparing open surgery to endovenous laser ablation found a 41% recurrence rate at five years.²² The findings of this study may be secondary to detailed and independent post-operative duplex scanning or it may represent real world efficacy of these treatment types. The vascular scientists

performing the follow-up scans were experienced in the post-operative appearances of both techniques. It is unlikely that these rates are due to poor technique, due to extensive experience in all operators prior to commencement of the study (there was no "roll-in" period). Longer follow-up is needed to give detailed evidence of the robustness of the techniques. The total number of patients without successful occlusion at one month was 11 and at six months was 12, which limits the inferences that can be drawn from such occlusion rates.

Thus, this study supports the hypothesis that MOCA is an effective treatment for truncal vein incompetence and subjects the patient to a less painful ablative procedure. Additionally, this study provides evidence that MOCA with simultaneous phlebectomy is safe and effective in the short term.

The study was powered at 90% power and 5% significance to detect a 20 mm difference in mean pain scores on VAS, with the observed difference in medians found being 19 mm. This protocol power calculation required 47 patients per treatment group. However, target recruitment was inflated to 170 patients to compensate for expected 50% loss to follow-up; 121 patients (71%) attended six-month follow-up. The study treated 165 patients, and post hoc power calculations with these data show that for pain scores, the study had 91% power at 0.05% significance criterion.

The use of both VAS and number scale has provided evidence of their equivalence. The full study showed no significant reduction in pain scores from the initial report¹⁰ suggesting that there was no time dependent decrease in pain score to indicate a learning curve during the study.

This study was limited by lack of treatment blinding for the patients and interventional clinicians. This was due to the technical differences between devices, i.e. tumescent injections in the RFA group and device vibration in the MOCA group. Follow-up appointments and ultrasound scanning were treatment blind.

A further limitation of this study is the lack of long-term follow-up – only short-term occlusion rates are assessed in this study, with the primary outcome obtained at the time of procedure. Operating time was not recorded in this study; however, all cases were performed in standardised theatre sessions in single slots with one surgeon performing all tasks, and 74% of patients also underwent simultaneous phlebectomy.

A major limitation of all tumescentless techniques is how to treat varicosities left after truncal ablation, with level one evidence now supporting combined treatment with phlebectomies.^{12,13} This study was designed and commenced prior to the completion of latest trial, but took into consideration the fact that phlebectomies cause pain, and so pain scores taken after truncal ablation but before any phlebectomies were completed.

This, therefore, represents a significant limitation to the outcomes of this trial, as the pain scores reported above do not assess the complete treatment, except for those patients who did not undergo phlebectomy.

However, similar number of patients underwent phlebectomies in both treatment groups. In the context of tumescentless truncal ablation, the use of phlebectomies requires the use of additional local or tumescent anaesthesia, so further injections are not avoided. Indeed, the phlebectomies may be the over-riding cause of pain. However, tumescentless techniques still obviate the need for injections in the proximal thigh and groin, which may be more painful than distal injection in the leg. This would require further study to delineate. Additionally, volume of tumescent anaesthesia used was not formally documented.

This study did not assess pain scores after phlebectomy or after the periprocedural period.

Treatment of the varicosities with foam sclerotherapy in combination with truncal ablation is an alternative technique but has yet to be assessed formally in an appropriately powered randomised study; however, previous work has supported its use in principle.²³ MOCA presents a dilemma due to sclerosant dose limitations, with European consensus guidelines advocating a maximum dose of 10 ml of <3% concentration liquid STS sclerosant or 2 mg/kg polidocanol sclerosant and 10 ml of foam sclerosant.²⁴ Additionally, the treatment techniques leads to a variable dosage of sclerosant per centimetre treated, dependent on vein diameter, and governed by the Vascular Insights MOCA sclerosant guidance and instructions for use. Alternative tumescentless devices do not have such dose limitations, but published data are lacking. Studies examining volume limits would be beneficial to help guide both MOCA and pure sclerotherapy techniques.

Further studies examining pain experienced during combined phlebectomy and truncal ablation procedures would be of great benefit to ascertain the difference treatment devices make in simultaneous therapy – for the assessment of the whole treatment.

Conclusion

Mechanochemical truncal ablation offers patients reduced intra-procedural pain with equivalent technical success compared to radiofrequency truncal ablation at six months. Patients have equivalent disease specific quality of life and clinical outcomes, and returned to work and normal activities at similar times.

Further work with larger studies and extended follow-up is needed to assess long-term outcomes and recurrence rates.

Author contributions

TRAL and AHD conceived and setup the study. TRAL, RB, BD, CSL, MN, SR, KS and AHD performed the procedures and collated the data. TRAL and RB performed the data-analysis. TRAL wrote the first draft of the manuscript. TRAL, RB, BD, CSL, MN, SR, KS and AHD critically appraised, edited and approved the final manuscript. AHD is the guarantor.

Declaration of conflicting interests

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Varicose veins and their management

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Abstract

Varicose veins are a common condition, affecting up to a quarter of the UK population. They have been shown to negatively impact on patients' quality of life and are an important cause of morbidity. The treatment of varicose veins has, in turn, been shown to improve the quality of life of patients. Traditional techniques of saphenofemoral and saphenopopliteal junction ligation with or without vein stripping have been the mainstay of treatment for a long time. However, over the past 15 years, day-case minimally invasive endovascular interventions carried out under local anaesthetic have gradually replaced surgical methods. Nowadays, the majority of procedures are carried out using one of the endothermal ablation techniques (radiofrequency ablation [RFA] or endovenous laser ablation [EVLA]). However, these endothermal methods are often associated with discomfort as well as complications due to the use of heat energy. Recently, newer non-thermal, non-tumescent (NTNT) ablation techniques have been launched with the promise of similar effectiveness, but with less pain. This article discusses epidemiology, diagnosis and management of varicose veins, including the latest endovascular and targeted open surgical techniques.

Keywords: Ablation; cyanoacrylate; endovenous; haemodynamic; laser; mechano-chemical; radiofrequency; sclerotherapy; surgery; varicose veins

Definition

Varicose veins are common and affect 20–64% of the population.¹ They are a manifestation of chronic venous disease (CVD) and are characterized by tortuous, dilated superficial veins

>3 mm in diameter. The condition can occur anywhere in the body where there is poor venous return, but it is most often associated with the lower limb. Along with causing significant physical and physiological morbidity, varicose veins are known to have a negative impact on patients' quality of life.²

Epidemiology

Venous disease is extremely common, with similar incidences reported across the world. Spider veins (fine, dilated intradermal venules approximately 1 mm in diameter) affect up to 80% of the population¹ while the reported incidence of varicose veins is variable, ranging from 20% to 64%.

The main risk factors for the development of venous disease include family history, age, pregnancy, previous deep venous thrombosis (DVT) and congenital conditions such as Klippel–Trenaunay syndrome. Female gender is also considered to be a predisposing factor, although studies have shown similarly high prevalence in both males and females. There is currently insufficient evidence to implicate obesity, standing posture at work and physical activity in the aetiology of varicose veins.

Although highly prevalent, varicose veins are rarely life-threatening. However, despite their benign nature, they cause significant quality of life impairments.³ They are also expensive, their treatment accounting for approximately £40 million of NHS expenditure in 2005–6. Progression of venous disease to venous ulceration leads to vast costs – it is estimated that 2% of the NHS budget is spent on venous disease and venous leg ulcers.⁴

Varicose veins occur because of impairment of venous return secondary to reflux, obstruction or calf muscle-pump failure. The exact aetiology is unclear. What is known is that there is an increase in distal venous pressures, leading to the cutaneous changes typical of the disease.

Primary varicosities are due to incompetence in the superficial veins, often located at connections between the deep and superficial systems (saphenofemoral junction [SFJ], saphenopopliteal junction [SPJ] or perforating veins). This leads to enlarged, thin-walled veins with incompetent valves. It is still unclear whether the triggering event is valvular incompetence leading to vein wall stretching or a primary vein wall failure leading to valve leaflet separation and the resulting venous incompetence. Numerous research efforts are being concentrated to answer this question. Varicose veins most commonly occur in the great (GSV) and/or small saphenous vein (SSV) distribution (Figure 1). Surface examination can, however, be misleading.

Secondary varicosities arise as a result of pathology (often in the deep venous system) that has led to venous hypertension in the superficial system. Examples are DVT, deep venous incompetence or pressure on the pelvic veins from an intra-abdominal mass. The underlying pathology is best investigated by venous duplex and ultrasound abdomen/pelvis.

Diagnosis

Varicose veins are a significant cause of morbidity, affecting patients' quality of life.² Common symptoms include pain, achiness, heaviness, swelling, restless legs, cramps and itching. These correlate well with clinical disease severity.² On the other hand, there does not seem to be any correlation between varicose vein diameter and symptoms and quality of life.

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Figure 1 Varicose veins in the (a) long saphenous and (b) short saphenous vein distribution.

Symptoms are exacerbated by standing stationary or long sedentary periods and may be worse towards the end of the day. Leg elevation helps reduce the associated swelling, whilst walking significantly improves the symptoms, due to calf-pump action reducing the venous pressure.

When assessing these patients, it is important to rule out other diagnoses that may account for similar symptoms, including arterial, neurological and musculoskeletal disease. A history of DVT, previous leg trauma, venous surgery and a family history of DVT and hypercoagulable states are important.

Examination

When examining the patient with varicose veins, it is important to assess for significant complications of this disease process, such as progressive skin changes, superficial thrombophlebitis and bleeding varicosities.

Skin changes consist of venous eczema, lipodermatosclerosis, haemosiderin deposition, ulceration and atrophie blanche (scarring at sites of previous ulceration) (Figure 2). These are most commonly found around the malleolar, or gaiter, area.

Superficial thrombophlebitis is inflammation of the vein, which thromboses, becoming tender and erythematous. This is commonly treated with non-steroidal anti-inflammatory drugs and compression. Recently, however, anticoagulants (e.g. low molecular weight heparins) are commonly used to treat superficial thrombophlebitis close to the saphenofemoral and saphenopopliteal junctions.

Large, prominent varicosities may be prone to bleeding, either spontaneously or as a result of trauma. This is an indication for urgent treatment of varicose veins.

The patient should be assessed initially standing, allowing the veins to fill. A full neurovascular examination should be performed, paying particular attention to the assessment of the arterial vascular system. Hand-held Doppler (HHD) may be used as an adjunct in the clinical examination, to assess for the presence and level of

incompetence. However, it is not an accurate tool and cannot be depended upon—at the SFJ and SPJ the reported sensitivity has been as low as 56% and 23%, respectively.

Classification and outcome measurement

The CEAP (Clinical, Etiology, Anatomy, Pathophysiology) classification was developed in 1994 to describe the severity and aetiology of lower limb venous disease. The adoption of this system has allowed a standardized approach, enabling correlation between different studies and units (Box 1). This classification is, however, not useful as an outcome measure following treatment of varicose vein disease as the CEAP classification is rather static (e.g. a patient with skin changes will still be at CEAP clinical class 4 after treatment).



Figure 2 Venous ulceration over the medial malleolus (gaiter area).

CEAP classification of lower venous disease**Clinical Classification**

C0: no visible or palpable signs of venous disease

C1: telangiectasia or reticular veins

C2: varicose veins

C3: oedema

C4a: pigmentation or eczema

C4b: lipodermatosclerosis or atrophie blanche

C5: healed venous ulcer

C6: active venous ulcer

S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps

A: asymptomatic

Aetiological Classification

Ec: congenital

Ep: primary

Es: secondary (post thrombotic)

En: no venous cause identified

Anatomical Classification

As: superficial veins

Ap: perforator veins

Ad: deep veins

An: no venous location identified

Pathophysiological Classification

Pr: reflux

Po: obstruction

Pr,o: reflux and obstruction

Pn: no venous pathophysiology identifiable

Box 1

The venous clinical severity score (VCSS) is a better outcome measure and is recommended by the Society of Vascular Surgery/American Venous Forum. The VCSS is clinician-completed, scoring 9 hallmarks of venous disease in order of severity from 0 to 3.

Both disease-specific and generic tools are often used as assessment measures for patients with varicose veins. The Aberdeen varicose vein questionnaire (AVVQ) is a patient-completed quality-of-life (QoL) assessment tool comprising of 13-questions ranging from physical symptoms to social effect and cosmesis. Other assessment tools include the Chronic Venous Insufficiency Questionnaire (CIVIQ-14 and CIVIQ-20), the Venous Insufficiency Epidemiological and Economic Study (VEINES) Symptom and QoL assessments. Generic QoL questionnaires include the Short Form Health Survey (SF-36, SF-12, SF-8) and the EuroQoL-5 domain survey.

Good correlation has been shown between the AVVQ and CIVIQ-14 and the VCSS and generic QoL scoring systems.

Imaging

The gold-standard imaging technique is colour duplex ultrasound. This non-invasive dynamic imaging modality allows assessment of the deep and superficial venous systems, indicating the level of incompetence. Guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF), as well as the National Institute for Health and Care Excellence (NICE) recommend that patients with varicose veins should all

have preoperative duplex ultrasound scanning.^{5,6} Venography should be used only in cases with inconclusive duplex results.

Magnetic resonance venography (MRV) and computerized tomographic venography (CTV) are used to assess the abdominal and pelvic veins in complex cases where the site of venous incompetence is not in the lower limbs.

Referral and treatment

NICE issued new guidelines for the diagnosis and management of varicose veins in July 2013.⁶ This new set of guidelines offers greater clarity for the referral and treatment of varicose vein disease.

Referral of patients with symptomatic primary (or recurrent) varicose veins, skin changes, superficial venous thrombosis, venous leg ulcers or healed ulcers are now recommended. It appears that the introduction of the NICE guidelines has led to an increase in the number of referrals being received.⁷

Over the last decade, major advances have been made in the treatment of varicose veins, with a shift from the open techniques towards minimally invasive outpatient procedures. An ideal treatment for varicose veins should be effective, cheap, safe, performed in day surgery, with low recurrence rates and good clinical outcomes.

Open surgery

Open surgery has been the gold-standard treatment for varicose veins since the late 1800s, when Friedrich von Trendelenburg performed a mid-thigh open ligation of the great saphenous vein in a patient with an incompetent SFJ. With recent advances in minimally invasive surgery, endovenous ablation has become the treatment of choice, with the proportion of open surgery performed dropping from 83% in 2006–44% in 2012.⁸

Surgery for varicose veins can be performed under general, local or regional anaesthesia and is performed as a day-case procedure in all but special cases.

The basic principle is disconnection of the refluxing superficial venous system from the deep system.

Saphenofemoral junction ligation and saphenopopliteal junction ligation

Saphenofemoral junction ligation was described by John Homans in 1916. It consists of a groin incision and dissection down to the SFJ. Tributaries are identified, isolated and divided beyond secondary branch points. The GSV should be ligated flush with the common femoral vein via a transfixion suture or double tie. Despite addressing the main point of reflux in cases of SFJ incompetence, duplex studies have revealed ongoing reflux in the remaining segment of GSV. Winterborn et al. recommended stripping the GSV in combination with SFJ ligation, due to a 60% reduction in re-intervention after 11 years.⁹

Saphenopopliteal junction ligation involves making an incision in the popliteal fossa, dissection to the SPJ, which is ligated or transfixed. SPJ ligation is less successful than SFJ ligation, with high recurrence and complication rates, particularly regarding common peroneal nerve damage resulting in foot drop, which is a cause of litigation.

The risks of open ligation ± stripping include bleeding, infection, haematoma formation, nerve damage (e.g. saphenous

and peroneal), numbness, paraesthesia, recurrence and venous thromboembolism. The incidence of nerve lesions may be as high as 40% in full stripping; a significant reduction has been reported when partial stripping (to the knee) is performed. According to the Hospital Episode Statistics, the rate of DVT in SFJ ligation and stripping is 0.54%.

Ambulatory conservative haemodynamic management of varicose veins (CHIVA)

The French acronym CHIVA (*cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatoire*) is a minimally invasive, saphenous-sparing strategy for the treatment of varicose veins first described in 1988 by Franceschi and colleagues. Haemodynamic surgery is based on the premise that varicose veins arise secondary to a pathological venovenous shunt, which allows reflux between the superficial and deep systems. The aim of CHIVA is to disrupt this shunt by interrupting the refluxing venous outlets without compromising the saphenous vein. The technique relies on precise preoperative anatomical and haemodynamic duplex mapping of the areas of reflux, allowing the operator to identify specific areas to ligate that will enable disconnection of the venovenous shunt and fragmentation of the hydrostatic pressure column which forms in the incompetent superficial venous system upon standing. By ligating the origin of the incompetent venous segment, separating targeted areas and sparing perforators, the superficial system can still drain into the competent deep venous system. The procedure can be performed under local anaesthetic in day surgery.

In experienced hands CHIVA is more effective than saphenous stripping, with reduced long-term recurrence. Studies comparing CHIVA to EVLT reported significantly reduced pain scores, bruising and residual varicosities in the CHIVA group. There are currently no studies comparing CHIVA with RFA and it remains the preserve of specialist centres.

Ambulatory selective varices ablation under local anaesthesia (ASVAL)

ASVAL removes the venous reservoir by targeting superficial varicosities as opposed to the main refluxing saphenous vein. Via this technique, described by Pittaluga and colleagues, multiple phlebectomies are performed on varices without intervening on the refluxing saphenous veins.¹⁰ Their retrospective study revealed a postoperative reduction in saphenous vein reflux, improvement in symptoms and up to 88.5% of patients were free from variceal recurrence on 4-year follow up.¹⁰ Isolated phlebectomies appear to improve venous haemodynamics by reducing GSV reflux duration, peak velocity and diameter.

Compression hosiery

Compression hosiery has been reported in the literature since the 1950s although compression therapy has been used since biblical times. The technique works by applying graded external pressure to the skin (i.e. greatest at the ankle and reducing at the calf and thigh) and therefore to the superficial venous system, thereby reducing the venous reservoir in the dilated veins. Compression also increases venous flow in the lower limbs, reducing venous stasis and reflux. This reduction in venous pressure allows improved capillary pressure differentials and an improved arterial inflow. The combination of physiological effects translates in

reduced CVD symptoms and prevention of deterioration of skin changes associated with venous hypertension.

There is no formula for the amount of pressure needed for a specific symptom; however, generally the more severe the clinical picture the higher the Class of stockings used (Box 2). Class-II and -III compression have been shown to confer maximum benefit in patients with varicose veins and class-II below-knee stockings are the most commonly prescribed.

There is, however, a lack of high-quality evidence regarding the effect of compression hosiery on varicose veins. Studies are heterogenous, using different types of stockings in different patient groups with unclear methodology. A 2009 systematic review concluded that the evidence for the benefit of compression hosiery was equivocal.¹¹ There is some evidence that compression hosiery may reduce the rates of ulcer recurrence although again, comparison between studies is difficult.

Patients do report symptomatic relief after wearing compression hosiery. However, this is very subjective and the effect is limited to the period during which the stocking is worn. In addition, patients often find them uncomfortable, difficult to apply and remove, unsightly, and causing irritation.¹² Non-compliance rates as high as 33% have been reported.¹²

Importantly, good quality stockings are expensive (£50–100 per pair), and require the patient to wear them every day for life, with replacements at 3–6 monthly intervals. With the average patient attending in their 50s, this translates into a huge cost long-term.

The advantage of compression hosiery is that it has few side effects. Risks include skin necrosis in poorly fitted stockings, particularly in patients with diabetes or peripheral vascular disease. Compression hosiery should not be used in patients with an ankle brachial pressure index (ABPI) < 0.9.

This lack of evidence as to its benefits has prompted NICE to recommend against prescribing compression therapy unless no interventional treatment is suitable.⁶

Sclerotherapy

The practice of sclerotherapy involves inserting a small volume of sclerosant into a vein and applying compression, resulting in occlusive fibrosis without clot formation. There are three kinds of sclerosants:

- chemical irritants (chromated glycerine)
- osmotic (hypertonic saline)
- detergent (sodium tetradecyl sulphate [STS] and polidocanol [POL]).

European Classification of Compression Hosiery

Class I – 14–17 mmHg (light)

- Varicose veins; mild oedema

Class II – 18–24 mmHg (medium)

- Severe varicose veins; mild oedema; prevention of ulcer recurrence

Class III – 25–35 mmHg (strong)

- Severe varicose veins; post-phlebotic limb; prevention of ulcer recurrence; chronic venous insufficiency

Box 2

In the UK, STS and POL are more widely used, particularly for small reticular or spider veins.

Sclerotherapy was initially used in its liquid form (LS), via the 'air-block' technique. However, as sclerosant is deactivated by blood contact, liquid sclerotherapy suffered from poor occlusion rates due to rapid protein binding. The practice went out of fashion with the publication of randomized controlled studies showing poor long-term results compared to surgery.

The advent of foam sclerotherapy (FS) has reintroduced this practice. FS still utilizes STS or POL, but converts it from its liquid phase to foam by mixing it with air. Two syringes are connected by a three-way tap with liquid sclerosant and air (ratio 1:4). The mixture is oscillated between them until foam is produced (Tessari technique).¹³

The advantage of FS is increased potency of the sclerosant (allowing smaller volumes to be used), as the foam 'displaces' blood in the vein (increasing the contact area between foam and vein wall, increasing fibrosis and reducing thrombosis). This allows the treatment of truncal veins and large varicosities.

FS is more effective than LS with a similar side-effect profile and can be delivered accurately under ultrasound guidance. Reports comparing its effectiveness to open surgery are contradictory with some stating it is less effective and other RCTs suggesting it is just as effective as surgical stripping with high-ligation on 2-year follow up.¹⁴

Complications of foam sclerotherapy include anaphylaxis, DVT, skin pigmentation and tissue necrosis, particularly in cases of extravasation. Neurological complications are rare but when present can be serious, in the form of cerebrovascular accident (CVA), transient ischaemic attack (TIA), blurred vision or migraine. CVA and TIA have been reported in extremely low numbers. These are more likely to occur in patients with a right-to-left cardiac shunt, and may be due to small particles of sclerosant entering the cerebral circulation through said shunt or to air embolism.¹⁵ An alternative explanation is that the production of endothelin at the treatment point is the causative factor.¹⁵

The guidelines from the SVS and AVF recommend FS to treat tributaries and as an option for the treatment of the incompetent saphenous vein.³ Current NICE guidelines recommend using ultrasound-guided FS (UGFS) as second line treatment.⁶

Thermal ablation

Radiofrequency ablation (RFA)

RFA is a technique by which thermal energy (85°–120°C) is used to seal the incompetent vein via heat damage. RFA of the GSV was described by Goldman in 2000 using the VNUS Closure Plus™ catheter (San Jose, CA, USA).¹⁶ Since then the newer VNUS ClosureFast™ device has been developed, now known as the Venefit™ catheter since Covidien (Mansfield, MA, USA) acquired VNUS in 2009. The Olympus Celon RFITT™ is another kind of radiofrequency catheter.

The vein is cannulated under ultrasound guidance using the Seldinger technique and a bipolar catheter wire is inserted to approximately 2 cm from the junction between the superficial and deep systems (Figure 3a). Tumescence anaesthesia is instilled under ultrasound guidance (Figure 3b) with the aim of surrounding the vein, separating it from the surrounding structures in order to avoid thermal injury. Crucially it compresses the vein onto the catheter, increasing the energy transfer and reducing power requirements and also providing pain relief. Treatment without tumescence has shown poor technical outcomes.

Once adequate coverage is obtained and the temperature at the probe tip is reduced (approximately 25°C) the VNUS system can be activated and treatment started.

The patient should be placed in Trendelenburg position and extrinsic compression can be used to ensure vein wall/catheter apposition to maximize treatment efficacy.

The Venefit™ catheter's tip is active during treatment, heating a 7 cm or 3 cm segment of vein over 20-seconds at temperatures of 120°C depending on catheter. This allows a treatment rate of 0.35 cm/second, with visual and auditory feedback once the 20-seconds are complete. The catheter has an inbuilt feedback

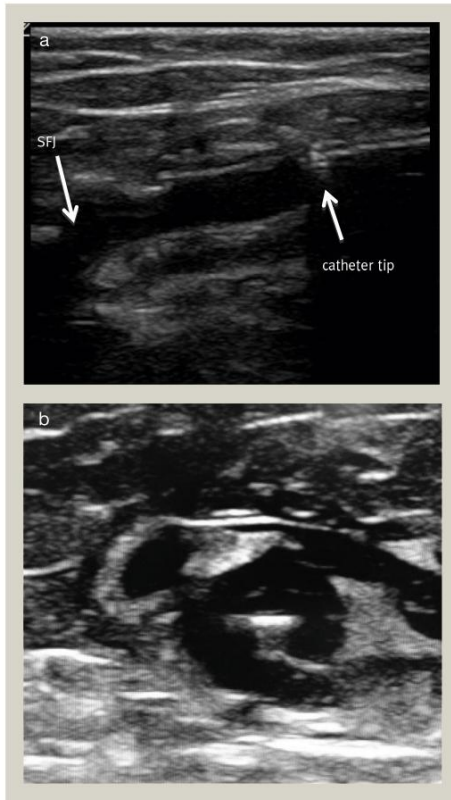


Figure 3 Ultrasound images of endovenous ablation. (a) Longitudinal view of saphenofemoral junction (GSV on the right of the screen joining the femoral vein on the left). Note the hyperechoic catheter tip at the far right of the screen positioned approximately 2 cm from the junction. (b) Tumescence anaesthesia. The catheter is hyperechoic; note the vein is collapsed onto the catheter and surrounded by hypoechoic of tumescent anaesthetic.

mechanism that enables delivery of consistently high temperatures and ongoing ablation by adjusting energy delivery. Usually two rounds of treatment are given in the segment closest to the junction to ensure adequate seal. Subsequently, the catheter is pulled back after each treatment.

The original ClosurePlus™ system required continuous pullback at a rate of 3 cm/minute resulting in a treatment rate of 0.05 cm/second, making it a longer procedure with potentially less consistent ablation as the rate of drawback may be difficult to gauge. The new generation ClosureFast™ catheters are superior to the ClosurePlus™ with respect to the rate of DVTs and obliteration of the GSV.

A meta-analysis comparing open and endovascular treatment of varicose veins found that at 3-months there was no significant difference in recurrence rates between open surgery, EVLT or VNUS, although endovenous ablation conferred a faster return to work.¹⁷ Prospective randomized studies also revealed that RFA has comparable results to high-tie and stripping with regard to recurrence both in the short, mid and long term.¹⁴ RFA was better tolerated by patients and associated with a quicker recovery period and improved quality of life scores.¹⁴ RFA has been shown to be a minimally invasive, safe and effective procedure for the treatment of varicosities; 3-year data confirms its durability.

When consenting patients for this procedure, they must be warned of the risk of bleeding, infection, nerve damage (due to direct thermal injury to the saphenous/sural nerve) and DVT. Risks specific to VNUS are difficulty with cannulation, guidewire passage and catheterization through tortuous segments, superficial burns, pigmentation and phlebitis.

Bipolar radiofrequency induced thermotherapy (Olympus Celon RFITT™) is an alternative to VNUS. The main differences are that it heats the vein to lower temperatures (85°C) and similarly to the ClosurePlus™ system it requires a continuous pullback technique. Its efficacy has been demonstrated in the incompetent saphenous veins, particularly when performed by a skilled operator. Studies comparing VNUS to RFITT are yet to be published.

Endovenous laser ablation (EVLA)

Introduced in 2001,⁹ EVLA uses laser (light amplification by stimulated emission of radiation) and fibre-optic catheter technology to generate thermal energy. It acts by heating the vein wall and blood, reaching temperatures of up to 800°C; this is not dependent on the laser wavelength itself but on the speed of pullback and on the power supplied. Unlike RFA, the catheter does not have a feedback mechanism to maintain a constant temperature. To prevent under or over-treatment it is important to maintain constant pullback at a rate of 1 cm every 5-seconds (0.2 cm/second); using 14W power the energy delivery is 70-J/cm. Newer wavelengths have shown comparable results with lower energy settings.^{18,19} The procedure for EVLA is the same as for RFA in terms of vein catheterization and use of tumescent anaesthesia.

EVLA has been shown to be effective for saphenous vein surgery, with impressive clinical outcomes that are at least comparable, if not better²⁰ than open surgery. As with RFA, patients tend to prefer the endovenous option, with better satisfaction, reduced postoperative pain and quicker return to work. Two-year follow up has revealed durable results. EVLA short-term outcomes are equivalent to high-tie and ligation, with reduced postoperative pain and bruising. RFA and EVLA have

similar outcomes, with >90% GSV occlusion rates.¹⁰ EVLA can be used in the GSV and SSV, as well as for branch varicose veins.

Complications of EVLA include bruising, induration, numbness, thermal burns and superficial thrombophlebitis. It is more expensive than conventional surgery, requiring additional equipment in the form of eye goggles, fibre-optic catheters, micropuncture kit and a protected room. The catheters are very small (0.5–2 mm diameter) and are relatively inflexible so can be difficult to navigate up a tortuous vein. The rate of post-operative DVT is 0.5%.

Overall, RFA and EVLA have been demonstrated to be probably superior to open surgical techniques for the treatment of varicose veins with similar improvement in quality of life. NICE, hence, recommend using them as first line treatment of truncal vein incompetence.⁶

Steam therapy (Steam Varicose System™)

In steam ablation a catheter delivering pulsated steam reaching temperatures of 120°C causes endothelial destruction and fibrosis. An original pilot study revealed satisfactory results with 65% occlusion rate at 6-months and the remaining 35% showing small-segment recanalization that was not clinically relevant. A subsequent study of 20 patients with GSV incompetence demonstrated an occlusion rate of 96% at 6 months follow-up and most patients returning to normal activity within 3 days.²¹

Larger comparative studies are awaited to determine the exact role of this new endothermal method in the management of varicose vein disease.

Non-thermal, non-tumescent ablation

Mechanochemical endovenous ablation

Mechanochemical ablation (MOCA) using the ClariVein® device (Vascular Insights, Madison, CT, USA) is a hybrid system composed of a rotating tip with simultaneous injection of liquid sclerosant. It does not use heat energy, thus obviating the need for tumescent anaesthesia.

The procedure is performed under local anaesthetic with percutaneous puncture under ultrasound guidance. The basic principles are as for endovenous ablation, with venous cannulation via Seldinger technique and catheter insertion up to 2 cm from the SFJ.

The ClariVein® device causes local mechanical damage via a wire placed at its tip, which rotates at 3500 rpm, abrading the intima of the vein, causing venospasm. Liquid sclerosant (STS or POL) is infused through an opening at the catheter tip, close to the rotating wire and the catheter is pulled back at a rate of 1–2 mm/second. Closure rates at 8-months have been reported as high as 96.7%.¹²

A randomized controlled trial comparing MOCA to RFA has shown the non-thermal, non-tumescent (NTNT) method to be less painful with similar occlusion rates and quality of life improvement noted at 1-month follow up.²² The 6-month follow-up data for this trial as well as results from the MARADONA (Mechanochemical endovenous Ablation versus RAdio-frequeNcy Ablation) and MESSI trials should provide a clearer indication as to the benefit of this NTNT.^{23,24}

The complication/side effect profile appears to be more favourable than standard endovenous ablation, this includes minor bruising at the puncture site and superficial phlebitis.

Sapheon™ venaseal closure system

The Sapheon™ Venaseal Closure System (Sapheon Inc, Santa Rosa, CA, USA) uses the same principle as endovenous ablation, with ultrasound-guided catheterization. A proprietary cyanoacrylate glue and ongoing manual compression are used to occlude the vein, which fibroses. The VeClose randomized controlled trial comparing RFA and cyanoacrylate randomized 222 patients with an occlusion rate of 96% observed in the thermal ablation group compared to 99% for the NTNT at 3 months.²⁵

Conclusion

Varicose veins are a common condition and their management has changed with the advent of thermal ablation, with equivalent quality of life improvement noted. Endovenous ablation also offers the possibility of day-case interventions and more rapid return to normal activities. The non-thermal methods, so far, are showing similar effectiveness and improvement in quality of life without the risks of thermal nerve damage. Longer term studies would provide us with a better indication as to their merits. ♦

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Long-term follow-up for different varicose vein therapies: is surgery still the best?

Roshan Bootun and Alun H Davies

Abstract

Management of varicose vein disease has changed drastically over the past decades. Since its introduction in vein practice, surgery has gone through several stages of evolution until the method of ligation with stripping eventually became and remained the standard for a long time. It was found to be effective at treating the condition and, indications of its beneficial impact on patients' quality of life soon also became evident. However, being associated with significant morbidity, surgery gradually fell out of favour, especially, once the newer endovenous techniques were launched around the turn of the century. These endothermal methods allowed procedures to be carried out under local anaesthetic as day case interventions, often with a similar or even better effect on occlusion rates and quality of life. In addition, there is mounting evidence that these newer techniques might be more cost-effective. This review evaluates surgical treatment of varicose veins compared to endovenous methods and also assesses its place in current phlebological practice.

Keywords

Varicose vein, surgery

Introduction

Varicose vein disease is a common condition affecting a significant proportion of the population and is known to lead to worse quality of life (QoL).^{1,2} Early monographs of venous disease and their surgical treatment date back to 1550 BC. Celsus, in first century Rome, proposed the concept of ligation and division of bleeding varicosities, while Galen, in the second century, introduced ligation and vein avulsion using specialised hooks.³ To a large extent, these early works inspired the current surgical techniques used to treat varicose veins.

Management of the condition has been transformed further over the past decade with surgical treatment of superficial venous incompetence no longer the mainstay of intervention. The introduction of endovenous thermal ablation, using either radiofrequency ablation (RFA) or endovenous laser ablation (EVLA), as well as improvement made in the use of foam sclerotherapy, however, gradually led to the desertion of surgery. The National Institute of Health and Clinical Excellence (NICE) guidelines (United Kingdom) on the management of varicose veins already recommend endothermal ablation as the first option to consider, relegating surgery only to a third-line alternative⁴ (Table 1).

Despite endothermal methods being accessible, uncertainty remains as to the ideal long-term treatment for varicose veins which would offer the best outcomes.

Anatomical success

Modern day surgical treatment of varicose vein disease typically involves ligation of the saphenofemoral junction (SFJ) (high ligation) or saphenopopliteal junction (SPJ) with or without stripping of the truncal vein. The technique allows the instant elimination of reflux in the offending vein and is often carried out under general or regional anaesthesia.

This type of surgical intervention has been found to be superior to ligation alone.

Dwerryhouse et al.⁵ looked at the reoperation rate for patients having surgery for GSV incompetence. This was a randomised study comparing ligation of sapheno-femoral (SFJ) only to SFJ ligation and stripping, and patients were initially followed up for 5 years. The rate of reoperation at 5 years was found to be 17% in those receiving ligation only compared to 4% in those also having stripping.⁵ After 11 years, the corresponding figures were 29% in the ligation only group and 11% in the ligation and stripping group.⁶

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Table 1. The 2013 National Institute of Health and Care Excellence (NICE) guidelines for the management of varicose veins in the National Health Service (NHS) recommend endovenous methods as first and second line treatment for varicose veins.

Interventional treatment

For people with confirmed varicose veins and truncal reflux:

- Offer endothermal ablation and endovenous laser treatment of the long saphenous vein
 - If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy.
 - If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery
- If incompetent varicose tributaries are to be treated, consider treating them at the same time.

Occlusion rate comparisons have revealed some conflicting results between surgical and endovenous management of varicose veins.

In the EVOLVEs randomised controlled trial comparing RFA to surgery, in the form of high ligation and stripping (HL/S), Lurie et al.⁷ recruited 85 patients and followed them for 2 years. Both treatment modalities were found to have comparable closure rates by the end of the study period.

However, later studies, such as another RCT comparing RFA and HL/S showed that endothermal ablation was superior. With 93 patients (98% CEAP class C2-3) randomised and treated as day-cases, all the patients receiving RFA had complete success of their treatment compared to 88% in those having surgery.⁸

Rasmussen et al.⁹ compared another endothermal ablation technique (EVLA) to surgery (HL/S) in patients with C2-4 disease and found that, after 6 months, the occlusion rate was 98% in the ligation and stripping group and 94.4% in the EVLA group. After 5 years, there were more cases of open, refluxing GSVs in the EVLA group compared to the surgery group (18% vs. 10%; $p = \text{NS}$), while there were slightly more recurrent varicose veins in the surgery group than the EVLA group (54.6% vs. 46.6%; $p = \text{NS}$).¹⁰ The rate of re-operations was, however, comparable (38.6% in EVLA and 37.7% in surgery; $p = \text{NS}$).

Another comparison of endovenous laser treatment and surgery (high ligation and stripping) showed that, at 3 months, the occlusion rate was 94% in the thermal ablation group compared to 87.5% in the surgical group.¹¹

In a prospective randomised controlled trial comparing EVLA to surgery (HL/S), Christenson et al.¹² randomised 204 patients, 97% of whom were in CEAP class C2-C4. They found that, at 1 year and 2 years, the GSV was absent in all patients who had surgery. There were seven cases of treatment failure in the EVLA group (five partial reopening and two complete reopening), but this did not reach significance ($p = 0.51$).¹²

A comparison of the endothermal methods (RFA and EVLA), high ligation and stripping and ultrasound-guided foam sclerotherapy (UGFS) by Rasmussen et al.¹³ recruited and randomised 500 patients. Most (95%) of patients were of CEAP class C2-3. It showed that the failure rates (defined as an open segment of more than 10 cm in length) at 1 year was 5.8% (RFA), 4.8% (EVLA), 4.8% (surgery) and 16.3% (UGFS).¹³

Long-term follow-up for RFA confirms the effectiveness of this endothermal method. Indeed, Proebstle et al.¹⁴ conducted an international, prospective, multicentre study to investigate the effects of RF segmental thermal ablation on the GSV in 225 patients (295 limbs). At 5 years, using a Kaplan-Meier method, the GSV occlusion rates was found to be 91.9%, while 94.9% of GSVs were found to be free from reflux.¹⁴

Biemans et al.¹⁵ conducted an RCT comparing EVLA, UGFS and surgery and reported after 1 year. More than 90% of the study population had a CEAP class C2-C4. The anatomic success rate at that point for EVLA and surgery were comparable (88.5% vs. 88.2%), while that of UGFS was lower (72.7%).¹⁵ After 5 years, the GSV was successfully treated/absent in 85% of legs in the surgery group, 77% in the EVLA group and 23% in the UGFS group ($p < 0.001$).¹⁶ At 5 years, patients receiving surgery or EVLA were also found to be four times more likely to have closure of the above-knee GSV than patients in the UGFS group.¹⁶

The CLASS trial is an ongoing multicentre study comparing foam sclerotherapy, surgery and EVLA. It has recruited 795 patients (96% of them in CEAP class C2-C4) and preliminary results at 6 months show significantly higher closure rates in patients undergoing surgery (84.4%) or EVLA (83.0%) than those receiving foam sclerotherapy (53.6%; $p < 0.001$) (no significant differences in closure rates between EVLA and surgery).¹⁷

The above studies demonstrate that surgery is a durable method and, at the very least, is comparable to endothermal methods, but superior to UGFS. However, anatomical success is considered more of a surrogate outcome measure, and the findings do not offer any indications as to the clinical or functional outcome following varicose vein intervention.

Clinical and QoL measures

The effect of surgery on QoL was investigated by Mackenzie and colleagues¹⁸ who recruited 203 patients undergoing surgery for varicose vein. Even though the Aberdeen Varicose Vein Symptom Severity Score (AVVSSS) was lower (improved) at the 4-week point, this was not significant (Wilcoxon signed rank test, $p = 0.44$) until 6 months and 2 years after intervention

($p=0.001$). The same research group also found that the proportion of GSV removed in the thigh correlated with gains in QoL at 6 months and 2 years after the procedure ($p=0.031$ and $p=0.14$, respectively).¹⁹ They concluded that there is an improvement in QoL seen as early as 4 weeks from the surgical procedure which continues for as long as 2 years.

In the EVOLVE study, the clinical score using the Venous Clinical Severity Score (VCSS) a few days after intervention (3 days and 1 week) showed that patients undergoing endothermal ablation (RFA) had a significantly more rapid clinical improvement than surgery, although that difference disappeared by the third week.⁷ The global QoL score (using CIVIQ2) also demonstrated a worsening of the QoL in surgery over the first few weeks and was still present by the end of the 2 years follow-up.

This early difference in clinical score was again shown in Rasmussen and colleagues¹⁰ study with worse VCSS in patients having surgery compared to those having EVLA, but this was no longer the case by the end of the first month. QoL, as measured using the AVVSS, improved significantly in both groups from the 3-month point onwards.¹⁰

Other studies, however, do not demonstrate such discrepancy in clinical or QoL scores. In their RCT, Christenson et al.¹² found comparable improvement in both the EVLA group and surgery group, despite the EVLA group having a higher incidence of recurrence with symptoms.

Shadid et al.²⁰ carried out a randomised controlled study comparing UGFS and surgery in the treatment of incompetent GSV. At the 2-year follow-up, no difference was apparent between the two groups with regard to VCSS or the EuroQoL's EQ-5D. A similar finding was observed in the MAGNA trial with the CIVIQ and EQ-5D scores improving in all groups (EVLA, UGFS and surgery) at 3 months and remaining stable.

In the CLASS trial, Brittenden et al.¹⁷ recruited 785 patients, randomising them to foam sclerotherapy, surgery or EVLA. At 6 weeks, a greater improvement in the VCSS score was found in those undergoing surgery (and EVLA) compared to those receiving foam sclerotherapy (1.8 vs 2.2; $p<0.001$). This difference was no longer present by 6 months though. The AVVQ also showed that patients having surgery achieved a better QoL at 6 months compared to foam sclerotherapy (7.8 vs. 9.1; $p<0.01$).

Return to activity and work

Post-surgical patients tend to take longer to go back to their normal activities or work. Lurie and his colleagues^{21,22} showed that patients from the surgery group were back to their normal activities a mean 3.89 days after

their procedure compared to a mean of 1.15 days for RFA ($p=0.2$). Patients were back at work a mean 4.7 days after their RFA and 12.4 days after having surgery.

When compared to EVLA, a similar picture becomes apparent. Similar differences in return to activities was also noted in Darwood¹¹ and Subramonia's studies.⁸

Rasmussen et al.¹³ also found that patients undergoing surgery took longer to return to their normal activities (median 4 days compared to less than 2 days for the endovenous methods). Such a difference was no longer apparent though when the time to return to work was looked at with patients returning to work a median 4.3 days following surgery compared to 3.6 days for EVLA.¹³

Complications

Commonly reported complications following varicose vein surgery are wound infections, haematoma formation, recurrence, numbness, paraesthesia, neuralgia, lymphatic damage, major vessel injury, residual veins and venous thromboembolism (deep vein thrombosis (DVT) and pulmonary embolus (PE)).^{23,24}

In their comparative RCT, Rasmussen et al.¹³ recorded one incidence of DVT, five cases of paraesthesia and six of hyperpigmentation in patients having surgery. The rate of these latter two complications was similar to those reported for the endovenous procedures, however. There was a significantly higher incidence of phlebitis in the endovenous ablation methods ($p=0.006$).¹³

Christenson et al.¹² noted significantly more cases of bruising in their surgical group compared to the EVLA group (15 vs. 2). No cases of wound infection or DVT were reported.

In the MAGNA study, a significantly higher number of patients undergoing surgery suffered from wound infection requiring systemic antibiotics ($p=0.03$).¹⁵ The overall rate of complications was also higher with surgery, but this was not significant ($p=0.64$).

In the CLASS trial, the surgery group had a comparable overall complication rate to UGFS and EVLA (3.5%, 3.8% and 3.3%, respectively) and similar serious adverse events related to treatment with the endovenous procedures (1.4%).¹⁷ A rather high incidence of numbness (15.6%) and persistent bruising (17.0%) was found to be still present at 6 months.

Cost-effectiveness

As the cost of healthcare is increasingly becoming a worldwide issue, there is a drive to use the most cost-effective interventions to achieve the best outcomes in varicose vein disease management.

Rasmussen et al.¹³ conducted a randomised trial comparing EVLA, RFA, UGFS and surgery and looked at

the cost of each procedure based on the reimbursement rates and productivity level in Denmark. Foam sclerotherapy was found to be the cheapest, while both surgery and EVLA were found to be the most expensive treatment options.

The National Institute of Health and Care Excellence (NICE, United Kingdom) uses a threshold of £20,000 to indicate the cost-effectiveness of treatments in the National Health Service (NHS). In their cost-effectiveness analysis, the CLASS trial investigators found that, at such a ceiling, EVLA had the highest probability of being the most cost-effective treatment for varicose vein disease compared to surgery.²⁵

Cost-effectiveness analysis conducted by NICE itself showed that surgery produced fewer gains in quality of life years (QALYs) at an increased cost compared to the endothermal methods.²⁶ Despite being more costly than foam sclerotherapy, endothermal ablation was also found to produce the greatest QALY gain and was the most clinically effective treatment. The incremental cost-effectiveness ratio (ICER, difference in cost between two possible interventions, divided by their effect) was in favour of endothermal ablation, making this method the most cost-effective strategy in treating varicose veins.²⁶

Conclusion

The case for the continuing use of surgical treatment options in contemporary practice soon becomes very apparent. It is a proven technique providing good anatomic success and instantaneous elimination of the cause of superficial incompetence. However, once clinical and QoL scores are taken into account, deficiencies start appearing with this intervention, with slower improvement noted. Moreover, it often results in a delay before patients can resume their normal activities and work, and can often lead to serious complications. The cost of surgical intervention is also quite prohibitive and it is proving to be a less cost-effective treatment option compared to the endovenous methods. The choice of varicose vein treatment to use in current practice is dictated by its cost-effectiveness, thereby, making surgery increasingly harder to justify.

Surgery, however, remains a very efficient method to treat venous incompetence and refinement of the technique could potentially enable it to improve some of the outcomes and hopefully make it a more cost-viable alternative. Hence, endovenous ablation, most specifically endothermal methods, will be around for the foreseeable future, unless the newer non-thermal, non-tumescent (NTNT) methods prove to be more advantageous.^{27–29}

Declaration of conflicting interests

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A comparison of thermal and non-thermal ablation



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ABSTRACT

Varicose vein disease is common and has an adverse effect on patients. Treatment of the condition has been demonstrated to improve patients' physical well-being and quality of life. Surgical treatment has for a long time been the 'gold standard' method until the launch of endovenous thermal ablation towards end of the twentieth century. Indeed, being less invasive and offering the possibility of day-case local anaesthetic procedures, they have gradually become the mainstay of contemporary varicose vein treatment. Vein ablation using steam and microwave are new additions to thermal methods, but there is currently insufficient evidence as to their effectiveness and place in the management of varicose veins. The superiority of thermal ablation is now being challenged by endovenous non-thermal methods. Foam sclerotherapy, until recently the only endovenous non-thermal technique available, has been joined by mechanochemical ablation and cyanoacrylate glue as viable alternatives to thermal ablation. It is believed that these new non-thermal methods will be able to offer additional benefits to patients. This review of thermal and non-thermal ablation techniques assesses their respective merit in the management of varicose veins.

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high-tie group compared to no recurrent GSV or perforator veins detected in the high-tie and stripping group. There were more cases of ecchymosis in the surgery group (31.6%) compared to the microwave group (14.8%; $p=0.004$). There were more cases of skin burns noted in the microwave group though (10%) [26]. Both groups showed similar improvements in the AVVQ and VCSS up to the 24 month follow-up. Recurrence rates at 2 years was 14% in the microwave with high-tie group compared to 28% in the surgical group ($p=0.02$). No clear advantage over traditional thermal methods was, however, demonstrated as, although a reduction in bruising complications in patients receiving microwave ablation was noted, the technique was also associated with a higher percentage of skin burns.

Despite these intriguing results, further studies are warranted to confirm the suitability and place of steam ablation and microwave ablation for varicose vein treatment.

2.5. Comparison of endothermal methods and their complications

Goode et al. compared EVLT to RFA in terms of pain sustained and followed up patients for 6 months in a randomised controlled study [27]. A total of 66 patients (87 legs) were recruited. The pain score using a visual analogue scale (VAS) was significantly less with RFA than EVLT, especially on days 2–11 post-procedure. Bruising due to RFA was also found to be less than in EVLT. Both treatment groups showed similar improvement in patients' quality of life (QoL) and time to return to normal activity. The occlusion rates at 9 months was 78% in the EVLT group compared to 74% in the RFA group [27].

Shepherd et al. also found a lesser degree of discomfort with RFA compared to EVLT [28]. They conducted a randomised clinical trial comparing these two treatment methods looking at the post-procedural level of pain [28]. They randomised 130 patients into each group. Less pain (as measured by using a 100 mm-visual analogue scale, VAS) was noted in the RFA group compared to EVLT at day 3 (26.2 mm versus 36.8 mm; $p=0.012$) and day 10 (22.0 mm versus 34.3; $p=0.001$) [28]. There were no significant differences in the time to resume normal activities and QoL.

Both endothermal methods are also associated with a number of complications such as pain, bruising, thrombophlebitis, skin burns, skin pigmentation, nerve damage, deep vein thrombosis and endothermal heat-induced thrombosis (EHIT) [29,30].

3. Non-thermal, non-tumescent (NTNT) methods

In an attempt to avoid these potential complications of endothermal ablation, non-thermal ablation technique were introduced, as detailed below.

3.1. Foam sclerotherapy

Foam sclerotherapy is the original NTNT, having gone through different stages to try perfect the technique. The combination of sclerosing drug and air used to treat varicose veins ('air block' technique) was initially described by Orbach in 1944 [31]. Sclerosing solutions have been shown to react with venous endothelium, causing damage (endosclerosis) and fibrosis (endofibrosis) of the vessel lumen [32]. With a higher air to liquid ratio, this technique was effective for the treatment of smaller veins, but was less successful with larger ones as the air bubble would lodge itself on the upper side of the vein and prevent contact with endothelium. This was associated with high rates of treatment failure. Modern sclerotherapy was devised in the 1990s, when new approaches to transform liquid sclerosants into foam were described [33]. Sclerosing foam displace venous blood and

increase contact with endothelium, thereby, increasing their sclerosing power [34]. The Tessari method of producing foam is probably one of the most common technique used in contemporary practice [34]. This involves connecting two syringes to a three-way tap and allows the production of a stable and compact foam [34]. Mixing one part of liquid sclerosant to four parts air has been found to be the optimal formulation [34]. Foam sclerotherapy evolved further with the introduction of ultrasound guidance (ultrasound guided foam sclerotherapy, UGFS) or catheter directed foam sclerotherapy (CDS) for the treatment of truncal veins [35–37]. Two of the most commonly used sclerosing solutions are polidocanol (POL) and sodium tetradecylsulphate (STS).

The superior efficacy of foam over liquid sclerosants was shown in a comparative (non-randomised) study of UGFS [38]. Sixty-two women, having a mean age of approximately 55 years, were recruited. They received the sclerosant polidocanol either as foam or liquid to treat GSV insufficiency. At the 12 months follow-up, 68% of those receiving foam sclerotherapy had occlusion of the GSV compared to 17.5% of those treated with liquid sclerosant ($p<0.0001$) [38]. Although both groups had comparable characteristics, a lack of randomisation and unclear criteria used in recruitment affects the validity of the results.

A larger cohort of consecutive patients were offered ultrasound-guided foam sclerotherapy (UGFS) to treat incompetent truncal veins (saphenous and non-saphenous) [39]. One hundred and eighty-one patients were enrolled and reviewed within 6 weeks of treatment. The median age was 52 years and most of the patients were females (60%). After the first intervention, an occlusion rate of 74% was achieved, with an additional 15% after two interventions [39]. Phlebitis and discoloration were the most common complications encountered.

Analysing his own series of 808 patients undergoing ultrasound-guided foam sclerotherapy for incompetent truncal veins, Coleridge-Smith achieved a occlusion rate of 88% for the great saphenous vein (GSV) and 82% for the short saphenous vein (SSV) [40]. Three interventions, each 2 weeks apart, were necessary to obtain an occlusion rate of 99%.

However, foam sclerotherapy was found to be less effective when compared to other modalities. In their randomised controlled trial, Rasmussen et al. compared UGFS, surgical stripping, endovenous laser therapy (EVLT) and radiofrequency ablation (RFA) in patients with evidence of GSV incompetence [41]. Five hundred patients were recruited in the study and they were follow-up for 1 year. Treatment failure, defined as an open segment of the treated vein measuring >10 cm in length, was recorded. Baseline characteristics for all four groups were comparable. The UGFS group had significantly more cases of treatment failures (16%) compared to the other three groups (less than 6%) ($p<0.001$) [41]. Patients undergoing UGFS or RFA reported less pain and resumed their normal daily activities earlier compared to those having surgery or EVLT ($p<0.001$). All the groups studied showed similar improvement in both quality of life and clinical scores. When the cost of being off from work was accounted for, UGFS was found to be the cheapest treatment method.

The MAGNA randomised controlled trial also reported lower occlusions rates in the UGFS group when surgery, UGFS and EVLT were compared in 223 patients (240 legs) [42]. The primary outcome measure of the trial was anatomic success on duplex ultrasound examination. At the 1-year follow-up, those treated with EVLT had an occlusion rate of 88.5%, those receiving surgical treatment had an occlusion rate of 88.2% while rate for UGFS was 72.7% ($p<0.02$). QoL scores (CIVIQ and EQ-5D) were similar in all three groups.

In the two preceding studies, those receiving endothermal methods had infiltration of tumescent anaesthesia. This anaesthetic solution presses the vein onto the probe and helps drive

1. Introduction

Approximately one third of the population is afflicted with varicose vein disease [1]. Along with affecting the quality of life of patients, it also causes physical symptoms such as achiness, swelling and itching, with further worsening of the condition leading to skin changes and ulcerations [2–7]. Treating varicose veins does, however, abolish these symptoms and improve the quality of life of patients [8–10]. Traditionally, this was accomplished surgically, by ligation of an incompetent saphenofemoral or saphenopopliteal junction (SFJ or SPJ) along with stripping of the refluxing truncal vein.

Minimally invasive methods to treat varicose veins were introduced towards the end of the twentieth century and these have dramatically changed how varicose veins are managed. Indeed, these thermal techniques (TT), radiofrequency ablation (RFA) and endovenous laser treatment (EVLT), have enabled procedures to be carried out as day-cases, often in an office-based setting. The past few years has seen the introduction of non-thermal, non-tumescent (NTNT) methods of vein ablation, which are aimed at avoiding the unpleasant effects of thermal treatments.

Both these thermal and non-thermal ablation techniques are looked at in this review.

2. Thermal technique (TT)

Present in the arsenal of the Vascular surgeon for more than a decade, endothermal techniques (radiofrequency ablation (RFA) and endovenous laser treatment (EVLT)) have transformed the way varicose veins are managed. They involve the transmission of heat energy, either from a laser diode or radiofrequency catheter, to the vein wall. Over time, they have transformed the contemporary management of varicose veins, so that both the American Venous Forum (AVF) (USA) and the National Institute of Clinical Excellence (NICE) (UK) have recommended endovenous thermal ablation as first line treatment of varicose veins [11,12].

2.1. Radiofrequency ablation

Radiofrequency ablation (RFA) involves transmitting heat energy directly from an active electrode to the vein wall endothelium at a frequency ranging from 200 to 3000 kHz [13]. The electrode heats a narrow rim of tissue (< 1 mm) in direct contact with it, while conduction ensures heat transfer to the deeper tissues. Collagen contraction of the vein wall or thermocoagulation of the vein wall ensues [13]. In one of the first clinical trial using this new technique, Goldman (2000) treated 10 patients (12 limbs) with great saphenous vein (GSV) incompetence using a Closure[®] catheter (VNUS Technologies, Sunnyvale, CA, USA). After infiltrating tumescent fluid around the vein and exteriorising it using a Muller phlebectomy hook, he inserted a 5 or 8 Fr RFA catheter device to within 1–2 cm from the sapheno-femoral junction (SFJ). He then applied pressure manually in the groin area and the RFA generator was activated. Once the catheter had reached 85 °C for 30 s, the catheter was pulled back at a rate of 3.5 cm/min [13]. At 3 and 6 months, all patients had ablated GSVs and resolution of all their pre-operative symptoms [13].

Segmental ablation using RF was the next stage in the evolution of the technique and Proebstle et al. [14] reported the first clinical study using this device. The catheter (ClosureFast, VNUS Medical Technologies Inc., San Jose, CA, USA) made it possible to treat truncal veins in segments at a temperature of 120 °C during 20-s treatment cycles rather than the pullback method utilised by Goldman (2000) [13,14]. The trial included 194 patients (252 limbs) and patients had a mean age of 50.5 years [14]. Once access

was achieved, a 7-cm segmental heating catheter was inserted and positioned between 1–2 cm below the SFJ. Tumescent fluid was then injected. The purpose of this fluid is to reduce the diameter of the vein being treated, control treatment-related pain and protect surrounding structures from heat damage [14]. Close to the SFJ, two 20-s cycles were applied, while further distally, each subsequent segments were treated with one cycle only. An occlusion rate of 99.6% at the 6 months follow-up was achieved, based on a Kaplan–Meier method [14].

The same group conducted a multicentre trial at 8 different sites in Germany and France [15]. Two hundred and twenty-five patients with refluxing GSVs (295 in total) were recruited and treated with RFA as above. They were followed up at different time points over 5 years, with 80.0 percent of them having a duplex ultrasound scan at final follow-up. Based on a Kaplan–Meier method once again, an occlusion rate of 91.9% and a rate of absence of reflux was 94.9% at 5 years was demonstrated [15]. The Venous Clinical Severity Score (VCSS), used to assess the clinical morbidity, at 5 years showed a significant improvement from baseline (from 3.9 to 1.3; $p < 0.001$).

When RFA was compared to high ligation and stripping, as in the prospective randomised trial of endovenous radiofrequency obliteration versus ligation and vein stripping (EVOLVES), non-significant differences in occlusion and recurrence rates were found at 2 years [16]. This study, which enrolled 85 well-matched patients, may not have been adequately powered to be able to show a difference though. However, the time to return to normal activities in the study was significantly less in those receiving RFA compared to surgery (1.15 days versus 3.89 days; $p = 0.02$) as was the global quality of life (QoL) score ($p < 0.005$) [16,17].

2.2. Endovenous laser treatment (EVLT)

Endovenous laser ablation was introduced towards the turn of the century with Navarro et al. describing the first clinical trial [18]. The study recruited 33 patients (44 GSV) having SFJ reflux with GSV incompetence. The pre-marked GSV was cannulated followed by insertion of a bare-tipped laser fibre. The laser fibre tip was positioned 1–2 cm below the SFJ and tumescent local anaesthetic (lidocaine 0.5% without adrenaline) was instilled. Trendelenburg positioning and manual finger pressure was used to empty the vein. The ablative procedure consisted of laser energy delivered at a wavelength of 810 nm along the GSV while the laser fibre was being slowly pulled back in 3–5mm increments. Post-intervention, compression stockings were applied and the patients were followed for up to 14 months (mean follow-up of 4.2 months). All treated GSV segments were found to be occluded (100%) [18]. The technique appeared safe, was well-tolerated and shown to be very effective in the short term.

The efficacy of EVLT was confirmed in a second study conducted by Proebstle et al. [19]. Using a similar technique as Navarro et al. [18], with a slight variation (a 940 nm laser was used instead), they treated 26 patients (31 limbs) with GSV incompetence. The mean age was 57 years and most of the patients were females. One patient had an incomplete occlusion giving a complete occlusion rate of 97% up to 28 days after treatment [19]. Common complications encountered were pain and ecchymosis, though these were not as serious as those usually seen in those having surgical treatment. One patient consented to have conventional surgery, with EVLT administered immediately following ligation of the SFJ, but before the stripping part of the procedure. Macroscopic examination of the wall of the treated demonstrated reddening, carbonisation and even perforation at the sites where the laser fibre tip was nearest to the wall during laser energy delivery. Gross vein wall destruction due to direct impact of the

laser beam or less pronounced heat-mediated vein wall injury was shown on microscopic assessment.

In a prospective, non-randomised study evaluating EVLT in incompetent GSV, 490 patients (499 limbs) were enrolled [20]. The mean age was 42 years (range: 23–72 years) and most of the patients were women (83%). Patients were followed up for 17 months (range: 1–39 months). The initial follow-up at 1 month showed an occlusion rate of 98% (490 of 499 limbs treated), dropping to 97.5% (310 of 318 legs treated) by year 1 and 93.4% (113 of 121 legs treated) by year 2 [20]. All bruising, observed in 24% of limbs treated at 1 week, were resolved by the first month. Phlebitis was noted in 5% of patients.

2.3. Steam vein sclerosis

Venous ablation using steam vein sclerosis (SVS) is one of the latest developments in the endothermal treatment of varicose veins. Its intended purpose is to reduce side-effects as well as providing a safer and easier technique compared to traditional thermal methods.

2.3.1. Animal studies

van den Bos et al. described a proof-of-principle study of steam ablation [21]. Six sheep were recruited and underwent steam ablation under general and tumescent anaesthesia. Sensors were placed inside the sheep to monitor any changes in temperature. Steam treated vein from one of the sheep was harvested immediately post-procedure. For histological examination, all of them were sacrificed, two at the 20 day point and four at 3 months. Two other sheep were treated with RFA and were used as reference. Most of the temperature rises were modest, except for in one sheep where a temperature rise from 30°C to 59 °C was noted in the subcutaneous layer. All treated veins were found to be occluded, with the diameter reduced from a mean pre-treatment value of 3.2 mm to 1.4 mm at 3 months (56% reduction) [21]. Microscopic examination revealed disappearance of the endothelial layer (immediately post-procedure), fibrotic thrombosis with inflammatory reaction of the media, extending to the adventitia (at 20 days) and major thickening of the vein wall with fibrosis and inflammation, alterations of elastic and collagen fibres, as well as further significant luminal reduction (at 3 months). These changes were similar to those previously reported for RFA [21].

Further histological comparison was provided by Thomis et al. [22]. They compared SVS to RFA and EVLA using goats. Four goats were assigned to each group and they all underwent endovenous ablation of the lateral vein of the hind leg. One week post-intervention, the vein diameter had decreased by 26% in the SVS group, 15% in the RFA group and 6% in the EVLA group, respectively [22]. Most of the histological samples demonstrated thrombosis within the lumen. All treatment groups displayed extensive vein wall inflammation and haemorrhage, indicative of destruction [22]. The extent of vein wall damage and level of necrosis was similar among all the groups. No fascial or perifascial damage was noted. SVS, hence, showed itself to be comparable to RFA and EVLA.

2.3.2. Human trials

The original proof-of-principle article by van den Bos et al. also included a pilot study conducted on 19 patients (20 limbs) with primary saphenous vein (GSV or SSV) incompetence [21]. The mean age was 53 years. All procedures were carried out under local anaesthetic in an outpatient setting.

The technique consists of vein cannulation followed by insertion and placement of the steam catheter (1.2 mm diameter) 3 cm distal to the SFJ or SPJ [21]. After tumescent infiltration, the veins were ablated using steam produced from a piston pushing water through a heated element situated just before the catheter. The

exit holes on the catheter are kept very small and allow the creation of a pressure difference and reduction of energy loss. The steam transfers the energy to the vein wall, cools down and undergoes condensation to water. The amount of energy released at the tip of the catheter has been measured at 60 J per pulse [21]. Post-treatment, all patients were provided with compression stockings for 1 week. At 6 months, a small, short string was noted in 7 out of the 20 the treated veins (2 of those had minimal reflux). Complications were minor (phlebitis and ecchymosis), all noted at the one week follow-up. There were no further complications for the rest of the study period.

A further study, recruiting 20 patients with GSV incompetence, investigated the effect of the SVS system [23]. One steam pulse per centimetre was used for veins with diameter ≤ 5 mm, two pulses for veins between 5 mm and 8 mm, and three for veins > 8 mm. Previous experiments had suggested that two steam pulses provide the required temperature necessary to ablate varicose veins [24].

Initial scan showed that all veins were successfully ablated. Six months post-operatively, partial recanalisation was observed in one patient, giving an occlusion rate of 96% [23]. The VCSS scores improved significantly at 6 months. Eighteen patients (90%) returned to their normal daily activity within 3 days.

2.4. Microwave ablation

Microwave ablation is another addition to the thermal treatment of varicose veins, with a microwave generator producing radiofrequency in the microwave spectrum [25]. It is already in use for the ablation of hepatocellular carcinoma and kidney resection [25]. The initial impetus for using a microwave generator was the unaffordability of the traditional radiofrequency system for many hospitals [25].

2.4.1. In vitro studies

Vein obtained from a patient with GSV incompetence was divided in 6 segments and implanted in the subcutaneous layer of pork meat [25]. The six slides were labelled C (control), S (sham), 40W, 50W, 60W and 70W, respectively. A microwave catheter was inserted in each of the veins and pulled back at a rate of 0.5 cm/10 s. Each slide was then sliced into 10 parts and histological examination was undertaken. Ablation was found in groups 40W, 50W, 60W and 70W.

2.4.2. Animal studies

Another part of the same study included a swine model used to test the effect of microwave ablation. It was sacrificed 7 days after microwave treatment. Thermal injury was found in all layers of venous (and arterial) walls when using microwave energy set at 50W and 60W [25].

2.4.3. Human studies

Human trials included 20 patients with GSV reflux treated with endovenous microwave ablation set at 50W. Occlusion rates at 1 week, 6 months and 1 year were 100%, 65% and 65% [25]. No major complications were noted and no recurrences were found at 1 year follow-up.

Yang et al. conducted a randomised controlled trial looking at the efficacy of endovenous microwave ablation in the treatment of varicose veins [26]. Two hundred patients were randomised to have conventional surgery (SFJ ligation and stripping) or microwave ablation with high-tie. The follow-up was for 24 months, with 171 patients available for analysis. The baseline characteristics of the two groups were similar. The mean operating time was significantly longer in those undergoing conventional surgery. The initial occlusion rate at 1 year was 97% in the microwave with

blood out of the vein [43]. This would allow a more effective thermal damage to the vein being treated and, hence, may explain the higher occlusion rates noted.

Devereux et al. investigated the effect of tumescent fluid in fifty patients receiving catheter-directed foam sclerotherapy (CDFS) [44]. The tumescent fluid used in this randomised controlled trial was made up of 0.9% saline only. The authors indicate that the guidelines from the organisation which granted ethical approval for the study, the German Federal Institute for Drugs and Medical Devices, would have prohibited the use of local anaesthesia with adrenaline. At the end of the follow-up period of 12 months, a complete occlusion rate of 74% was achieved in the CDFS group using tumescent compared to 75% in the CDFS group only [44]. The lack of adrenaline in the tumescent has been hypothesised to be the reason for the similar occlusion rates in the two study groups. Indeed, the authors speculate that adding adrenaline could have produced a more potent decrease of the vein diameter and, thus, increase the occlusion rates observed in the CDFS/tumescent group.

The longest follow-up data available for patients treated with UGFS has been reported by Darvall et al. [45]. They described the patient-reported outcomes 5–8 year following treatment with UGFS. Three hundred and fifty-one patients (479 limbs) were treated and 285 (81%) attended follow-up 5 years later. Using a Kaplan-Meier plot, they estimated that approximately 15% of their cohort would require retreatment at 5 years. Significant improvement was noted in the Aberdeen Varicose Vein Symptom Severity score (AVSS). The physical component of the Short Form-12 (SF-12[®]) was better compared to pre-treatment values (non-significant), but the mental component was no different to baseline. Between 62.7% and 81.0% of patients reported that their social, work or leisure activity expectations were met or exceeded. There was also high satisfaction rate (82%) of the procedure and 9 out of 10 patients would recommend it to their family and friends. This same research group had previously also described improvement in the quality of life of patients as well as an earlier return to work and less painful procedure compared to surgery [46–48].

Todd et al. conducted a randomised, blinded multicentre trial looking at polidocanol endovenous microfoam (PEM) injections to treat GSV incompetence (VANISH-2) [49]. PEM allows the delivery of a low-density sterile polidocanol injectable microfoam from a proprietary canister system [49]. The technique makes use of a gas mixture with a very precise ratio of oxygen and carbon dioxide (65:35) and low nitrogen content, allowing the formation of microfoam with stable bubbles measuring no greater than 500 μ m. Patients receiving either 0.5% PEM or 1.0% PEM had significantly better QoL scores than the control group ($p < 0.0001$). The occlusion rate at 8 weeks was 83% in the PEM 0.5% group compared to 86% in the 1.0% PEM group [49]. The incidence of deep vein thrombosis was 5.7%, but none of them were symptomatic [49].

Complications arising following treatment with UGFS include skin pigmentation, phlebitis, thromboembolism (pulmonary embolus or deep vein thrombosis) along with neurological symptoms, in particular, migraines, transient ischaemic attacks or visual disturbances [39, 50]. These neurological complications have been ascribed to the presence of a patent foramen ovale (PFO), which is a common finding in the population (20–30%) [50].

Newer non-thermal, non-tumescent methods have recently been introduced. These are being promoted as potentially having higher occlusion rates, improving the quality of life and leading to earlier return to activities, but without giving rise to the inconveniences of endothermal ablation [51].

3.2. Mechanochemical ablation

One such new device, the ClariVein[®] mechanochemical ablation (MOCA) catheter (Vascular Insights, Madison, CT, USA), has recently

been introduced which completely avoids the use of thermal and tumescent infiltration. The technique involves an endovenous mechanical method which uses a rotating wire (3500 rotations per minute) with simultaneous injection of liquid sclerosant (chemical component) [52]. The rotating wire causes mechanical damage to the lining of the vein wall while the sclerosant is infused through an opening close to the catheter tip to create fibrosis [52].

3.2.1. Animal studies

The device was tested on 11 males goats (12 veins) and the histological samples obtained were analysed [53]. The effect of four treatment groups were investigated. These consisted of: group 1–1.5% Sodium tetradecyl sulphate (STS) and the ClariVein[®] catheter (MOCA procedure) (five veins); group 2–0.9% saline and ClariVein[®] (one vein); group 3–5 mL injection of 1.5% STS (five veins); and, group 4–5 mL injection of 0.9% saline (one vein). The goat's lateral saphenous vein was selected and, in order to assess the degree of occlusion, duplex ultrasound examinations were conducted pre-operatively and on days 14, 28, 56 and 84. All animals were euthanised on day 84 and underwent gross necropsy [53]. Ultrasound evaluation at day 84 revealed that all the veins from group 1 were completely (or near completely) occluded. On the other hand, the veins from the other treatment groups were still open at the end of the study. This, therefore, suggests the superiority of the MOCA procedure (ClariVein[®] catheter and sclerosant) to produce vein occlusion and fibrosis.

One of the limitations of this study was the unequal number of veins treated in each group. This raises the question as to the validity of some of the effects noted. Indeed, it is possible the observation of the veins remaining open could have been different with inclusion of a similar number of veins in each group. However, this study does illustrate that the MOCA procedure was more effective at causing vein occlusion compared to using either the liquid sclerosant on its own or the ClariVein[®] catheter alone.

3.2.2. Human trials

Elias and Raines (2012) recruited 29 patients with GSV reflux to assess the safety and efficacy of the ClariVein[®] device [52]. The average follow-up period of the study was 260 days. Most of the patients agreeing to the study were females and the mean age of this cohort was 54 years. The baseline clinical CEAP (Clinical-Etiological-Anatomical-Pathophysiological) was between 2 and 4, while the baseline VCSS was 4.5. The ablative procedure was painfree and there were no major clinical complications. The primary occlusion rate was 96.7% at 260 days [52]. This study demonstrated that the new ClariVein[®] device was safe and seemed effective to treat incompetent truncal veins [52]. There were three occurrences of ecchymosis and the authors suggested that this could be secondary to the rotating wire getting caught onto one of the side branches or, even, onto a valve cusp.

Meanwhile in the Netherlands, van Eekeren et al. carried out a similar study to evaluate the safety and applicability of MOCA. They recruited 25 patients (30 limbs) with GSV reflux at two centres [54]. The mean age was 52 years and most of the patients were women (72%). Patients clinical CEAP was between C2 to C4, with a mean VCSS score 3.3. The mean maximum pain score one day post-procedure, as determined by using a 100mm visual analogue scale (VAS), was 9mm, while the median maximal pain score was 4 (interquartile range (IQR) 3–6) [54]. No major complications was recorded, but there were 9 cases of bruising at the puncture site and 4 patients developed thrombophlebitis. The GSV was completely occluded in 26 out of 30 legs treated (87% of cases) at the 6 weeks follow-up. Satisfaction was high (8.5 on a 10-point scale) and there was a significant decrease in the median VCSS from significantly from 3 to 1 ($P < 0.001$) [54].

The same research group looked at the result of mechanochemical ablation in patients with GSV reflux and followed them up for 1 year [55]. Ninety-two patients (106 limbs) with a mean age of 52 years were included in this study. One hundred and five patients finally underwent the MOCA procedure and the median pain score using a 0–100 mm VAS during the first 14 days after treatment was 7.5 mm. The common complications were thrombophlebitis, localised haematoma, induration and mild hyperpigmentation at the puncture site. The veins were scanned at several intervals and the occlusion rates immediately post-procedure, at 6 months and at 1 year were 100%, 93% and 88%, respectively [55]. Both the clinical score (VCSS) and QoL score (AVVQ) improved significantly by the 6 months and 1 year follow-up ($p < 0.001$).

Again, this same group investigated 50 patients to determine the effect of the use of MOCA in the treatment of the small saphenous vein (SSV) [56]. The sclerosant used in this study was 1.5% Polidocanol. The pain score using a visual analogue scale was 2 cm (IQR 2–4 cm) and patient satisfaction with the procedure was high (8; IQR 8–9). There were minor complications, mainly of localised ecchymosis and induration as well as transient superficial phlebitis (14% of patients). The occlusion rate at 1 year was found to be 94% (44 out of 47 legs treated). Dissimilar concentrations of the sclerosant were used to treat the proximal section, with a concentration of 1.5% Polidocanol used in the first 15 patients, and, for the remaining cohort, 2 ml of 2% Polidocanol was utilised for the proximal section, followed by 1.5% for the remainder of the vein. Two of those receiving the lower concentration had recanalised SSV, compared to 1 out of those who received the 2% Polidocanol.

In one of the studies comparing endothermal ablation to MOCA, 68 patients with symptomatic unilateral GSV reflux were selected to receive either MOCA or RFA [57]. The patients were equally distributed to the two treatment groups. Sixty-free percent were females and the mean age was 58 years. The baseline characteristics were comparable. The mean pain score during the ablative procedure was similar between the two groups ($p = 0.16$). Patients receiving the non-thermal technique had less pain compared to RFA over the first three days (6.2 mm versus 20.5 mm; $p = 0.004$) and during the first 14 days after treatment (4.8 mm versus 18.6 mm; $p < 0.001$) [57]. The MOCA group also required less analgesia compared to the RFA group. The treatment time using MOCA was found to be significantly shorter than using RFA ($p = 0.02$). In addition, patients in the MOCA group reported resuming their normal activities and work significantly sooner than those in the RFA group [57]. This was the first study which demonstrated a lesser degree of discomfort following truncal vein ablation as well as an earlier return to activities in patients treated with MOCA compared to an endothermal method. However, it is to be noted that this trial lacks formal randomisation and the criteria used for selecting patients is not very evident. In addition, there was no difference found in the procedural pain score between the two groups and the authors suggested carrying out a randomised clinical trial with a larger sample size.

Such an RCT comparing MOCA to RFA is currently under way in our unit and the early results, which included 119 patients, have been published [58]. The primary objective is to assess the intra-procedural pain scores as well as the improvement in clinical score and quality of life at 1 and 6 months. Sixty patients were randomised to the MOCA group. Patients in the MOCA group had significantly less maximum (19.3 mm versus 34.5 mm; $p < 0.001$) and average (13.4 mm versus 24.2 mm; $p = 0.001$) pain score compared to the RFA group [58]. Patients were followed-up for 1 month, and both the clinical and quality of life (QoL) scores showed improvement. Patients also returned to their normal activities/work at similar times and no differences in the complete/proximal occlusion rates was found between the two groups. The trial is in its final stages of data analysis.

The MARADONA (Mechanochemical endovenous Ablation versus RADIOfrequeNcy Ablation in the treatment of primary GSV incompetence) trial aims to directly compare the clinical and anatomical success rates of treatment with MOCA compared to RFA [59]. The intended total recruitment is 460 patients (230 patients per group). Patients will be followed up for 5 years, with the results of this study expected after 2020.

4. Cyanoacrylate glue

The VenaSeal® Sapheon Closure System (Sapheon Inc., Santa Rosa, Calif, USA) is another NTNT, using cyanoacrylate glue to treat venous reflux.

4.1. What is glue?

N-butyl cyanoacrylate (n-BCA), the glue used in this device, was initially introduced to medical practice approximately 40 years ago [60]. Initially, it was found to have low tensile strength and to give rise to both acute and chronic inflammation [60]. The n-BCA adhesive exists as a monomer in liquid state [61]. Once it meets an anionic solution (e.g., blood, which contains hydroxyl groups), it quickly polymerises and solidifies [61]. The end result is occlusion of the vessel being treated, pronounced inflammatory endothelial response and, ultimately, fibrosis [61]. With time, the material was made more flexible and less toxic by adding plasticisers and stabilisers [60].

Consequently, there was more widespread use of the adhesive including in ophthalmic surgery, tissue adhesion and haemostasis of acute bleeding (e.g., endoscopic injection of gastric variceal bleeding) [62]. Intravascularly, cyanoacrylate (CA) glue has been used to treat type I and II endoleaks following endovascular aortic aneurysms repairs, pelvic congestion syndrome, varicoceles and arterio-venous malformations (AVM) [62].

4.1.1. Animal studies

In 2002, Kailasnath and Chaloupka devised an apparatus to directly measure the binding forces created during the polymerisation process of CA [63]. They used a tissue model (the common carotid artery of a swine) and a plastic model to assess the rate of CA polymerisation. Three distinct stages were identified [63]. Phase I (the initial stage), lasting less than 10 s, showed the tensile strength of the polymer increasing at a steady rate. The material then maintains the same constant tensile strength for up to 1 min (Phase II). Polymerisation is, however, not achieved until the third phase. This final stage (Phase III) was typified by an exponential increase in the tensile forces leading to complete polymerisation [63]. They found that the type and formulation of CA used determine the rate of the polymerisation process and the strength of the binding forces [62, 63].

The effects of using CA adhesive as a vein closure method was first evaluated by treating the superficial epigastric veins (SEVs) of two swines using a CA delivery catheter (Sapheon, Santa Rosa, California) [64]. This closure system is composed of a 3cc syringe, a dispenser tip and a dispenser gun (Sapheon) [64]. The swines were euthanised sixty days post-intervention and the SEVs were removed for macro- and microscopic assessment. No patent segments were found. Histological examination showed the presence of fibrous tissue and inflammatory cells as well as fibrotic projections causing occlusion of the venous lumen. Further changes, consistent with a foreign-body-type inflammatory response, were noted.

4.1.2. Human trials

Almeida et al. [65] described the first clinical trial of the CA adhesive whereby 38 patients had treatment of their GSV reflux.

The CA catheter was positioned 4 cm distal to the SFJ. Post-operative review at 48 h gave an initial occlusion rate of 100%, dropping to 92% at the 24 months follow-up [65,66]. The most notable complication was the presence of thrombus extension across the SFJ into the femoral vein in 8 patients. No treatment was provided for these and they had all resolved by the 6 months follow-up. Other complications included thrombophlebitis, cellulitis and hyperpigmentation. The VCSS score improved significantly from 6.1 at baseline to 1.5 after 1 year ($p < 0.0001$).

Further work was done by Proebstle et al. [67] who carried out a multicentre trial looking at the use of CA to treat GSV reflux. Seventy patients with a mean age of 48.4 years were recruited. The catheter was positioned at 5 cm distal to the SFJ to allow for enough space for ultrasound compression between the delivery catheter and the SFJ. This also enables propagation of the adhesive toward the SFJ. The occlusion rate at 1 year, using a life-table method, was 92.9% [67]. Both clinical and QoL scores showed significant improvement. Eight patients developed a phlebotic reaction and one had thrombus extension into the femoral vein which was successfully treated with low molecular weight heparin. This study, therefore, confirmed that CA was effective in the treatment of GSV reflux. For both these studies, no compression therapy was utilised.

The VeClose trial was the first randomised clinical trial comparing an endothermal ablation method (namely, radiofrequency ablation) with cyanoacrylate [68]. Two hundred and twenty-two patients were randomised to receive either CA or RFA [68]. Again, the catheter was placed 5 cm distal to the SFJ. Compression stockings were provided for 7 days in both groups. The mean age for both groups was similar and most patients were females (79%). The initial occlusion rate after 3 days was 100%. The occlusion rate at 3 month point was 99% for CA compared to 96% for the RFA group. This rate of complete GSV closure was obtained using predictive statistical models to compensate for any missing data (31/222). The clinical and QoL scores all showed significant improvement compared to baseline. More patients developed phlebitis in the CA group, but this was not significant. The RFA group also had more ecchymosis (52%) compared to the CA group (32%; $p < 0.001$). Pain scores for both groups were comparable. The authors concluded that this demonstrates non-inferiority of the cyanoacrylate technique.

5. Conclusion

Studies conducted up to now appear to show similar occlusion rates as well as clinical and quality of life improvement of NNTs compared to the endothermal techniques. Although there is a suggestion of less pain during the ablative process, earlier return to normal activities and reduction in post-operative complications, this has not been irrevocably demonstrated. It is hoped that further randomised clinical trials comparing NNTs to TTs will be able to answer some of these questions.

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Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit™ versus ClariVein® for varicose veins trial

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Abstract

Objective: Endovenous techniques are, at present, the recommended choice for truncal vein treatment. However, the thermal techniques require tumescent anaesthesia, which can be uncomfortable during administration. Non-tumescent, non-thermal techniques would, therefore, have potential benefits. This randomised controlled trial is being carried out to compare the degree of pain that patients experience while receiving mechanochemical ablation or radiofrequency ablation. The early results of this randomised controlled trial are reported here.

Methods: Patients attending for the treatment of primary varicose veins were randomised to receive mechanochemical ablation (ClariVein®) or radiofrequency ablation (Covidien® Venefit™). The most symptomatic limb was randomised. The primary outcome measure was intra-procedural pain using a validated visual analogue scale. The secondary outcome measures were change in quality of life and clinical scores, time to return to normal activities and work as well as the occlusion rate.

Results: One-hundred and nineteen patients have been randomised (60 in the mechanochemical ablation group). Baseline characteristics were similar. Maximum pain score was significantly lower in the mechanochemical ablation group (19.3 mm, standard deviation ± 19 mm) compared to the radiofrequency ablation group (34.5 mm ± 23 mm; $p < 0.001$). Average pain score was also significantly lower in the mechanochemical ablation group (13.4 mm ± 16 mm) compared to the radiofrequency ablation group (24.4 mm ± 18 mm; $p = 0.001$). Sixty-six percent attended follow-up at one month, and the complete or proximal occlusion rates were 92% for both groups. At one month, the clinical and quality of life scores for both groups had similar improvements.

Conclusion: Early results show that the mechanochemical ablation is less painful than the radiofrequency ablation procedure. Clinical and quality of life scores were similarly improved at one month. The long-term data including occlusion rates at six months and quality of life scores are being collected.

Keywords

Varicose veins, endovenous treatment, mechanochemical ablation, radiofrequency ablation, pain score

Introduction

Varicose veins are a common problem, affecting approximately one-third of the United Kingdom population.¹ Both the National Institute of Health and Clinical Excellence and the Society for Vascular Surgery/American Venous Forum recommend endovenous thermal ablation as first-line treatment for truncal vein incompetence.^{1,2} However, thermal ablation

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requires the use of tumescent anaesthesia and is associated with intra-procedural pain and discomfort as well as carrying the risk of skin and nerve damage.^{3,4} This has, therefore, led to the development of non-thermal, non-tumescent ablative techniques such as mechanochemical ablation (MOCA) and cyanoacrylate glue.⁴

Recent studies have shown that Covidien® Venefit™ (Covidien, San Jose, CA, USA) radiofrequency ablation (RFA) and ClariVein® (Vascular Insights LLC., Quincy, MA, USA) MOCA have similar occlusion rates at one year.^{4,5} Less is known about the comparative intra-procedural patient experiences of pain and return to function.

The Venefit™ versus ClariVein® for Varicose Veins trial study aims to assess this question, and the early intra-operative results of this randomised controlled trial comparing thermal ablation (RFA) with non-thermal, non-tumescent ablation (MOCA) as well as the one-month follow-up data are reported here.

Methods

Recruitment

Patients referred for the treatment of symptomatic varicose veins to the Vascular Department of Charing Cross NHS Hospital (Imperial College NHS Trust) and Northwick Park NHS Hospital (North West London Hospitals NHS Trust) in London were studied. Patients older than 18 years with primary great saphenous vein (GSV) or small saphenous vein (SSV) incompetence were identified at their outpatient visit by a member of the clinical team and were added to the waiting list for endovenous ablation and given information about the trial.

The inclusion criteria are being older than 18 years and reflux greater than 0.5 s in the saphenous veins. The exclusion criteria are tabulated below (Table 1).

Table 1. Exclusion criteria.

Exclusion criteria
Current deep vein thrombosis (DVT)
Recurrent varicose veins
Arterial disease (ABPI < 0.8)
Veins less than 3 mm in diameter
Hypercoagulability
Patients who are unwilling to participate
Inability or unwillingness to complete questionnaires

ABPI: ankle brachial pressure index.

Consenting patients were then subsequently randomised to either MOCA (group A) or RFA (group B) truncal ablation using an online computerised service (Sealed Envelope, London, UK). In patients receiving treatment to both lower limbs, the more symptomatic side was included in the study.

No procedural blinding was possible due to the difference in techniques; however, the investigator at follow-up was blinded as to treatment group.

Clinical severity scoring

At recruitment, all the patients were evaluated by a vascular specialist. Their Venous Clinical Severity Score (VCSS), Venous Disability Score (VDS) and Clinical-Etiological-Anatomical and Pathophysiological (CEAP) classification were assessed. This was repeated at the one-month follow-up.

Quality of life scoring

Patients were also asked to complete the Aberdeen Varicose Vein Questionnaire (AVVQ), a validated disease-specific quality of life (QoL) questionnaire for varicose veins, and the EQ-5D-3L and EuroQol's visual analogue scale (EQ-VAS) (EuroQol Group), a generic QoL questionnaire, prior to their procedure. They were asked to complete these questionnaires again when they attended follow-up at one month.

Interventions

All varicose vein procedures were carried out under ultrasound guidance and local anaesthetic by vascular surgeons familiar with and approved in both ablative methods. For both techniques, the GSV or SSV was cannulated under ultrasound guidance after injection of local anaesthetic (1% Lidocaine). The catheter tip was positioned 2 cm distal to the sapheno-femoral junction or sapheno-popliteal junction. Cannulation was performed at the most distal point of reflux where cannulation was possible.

The method used for RFA has been described before.⁶ MOCA was performed as previously described by van Eekeren et al.³ except that 2% sodium tetradecyl sulphate (STS) (FibroVein™, STD Pharmaceutical Products Ltd., Hereford, UK) (made by mixing equal volumes of 1% STS and 3% STS) was used instead of polidocanol. The total volume of liquid sclerosant used was calculated as per the manufacturer's guidance.

Stockings were worn for two weeks post-procedure, and patients were advised to mobilise for at least 1 h every day and to return to their work and normal activities when they felt able to.

Pain scoring

Immediately after patients have undergone their endovenous procedure, but before concurrent varicosity treatment with phlebectomy was performed (if indicated), patients were asked to record their maximum and average pain score during the procedure using a validated Visual Analogue Scale (VAS) by placing a mark on a 100-mm VAS.^{3,6} The pain score was also recorded as a number on a scale of 0 to 10.⁷

Time to return to normal activities

Before being discharged on the day of their procedure, patients were given a diary to record when they resumed normal activities and, if in employment, went back to work. These were returned at the one-month appointment. No routine discharge medication was provided, but patients were allowed to take non-prescription analgesia as required.

Outcome measured

The primary outcome of the study is the degree of pain during endovenous ablation using a validated patient reported VAS. The secondary outcomes are improvement in the AVVQ scores, EQ-5D-3 L, VCSS, VDS and CEAP at one month and six months and time taken to return to normal activities and work. The occlusion rate at one month was also determined by carrying out a venous Duplex scan. The four possible findings are complete occlusion of the saphenous vein, proximal occlusion, distal occlusion and open.

Power calculations

Power calculations were based on the primary outcome of pain during the procedure. Detection of a 20-mm difference in maximum pain score with a standard

deviation (SD) of pain score of 20 mm was considered a significant difference. The minimum target size was calculated to be 94 patients (47 per group) at 90% power and 5% significance. Allowing for loss to follow-up or protocol violations, an overall target recruitment of 170 legs (85 per group) was estimated.

Study registration and ethical arrangements

This study was registered on the Current Controlled Trials website (<http://www.controlled-trials.com>) (ISRCTN06552809).

The ethical approval for the study was obtained from the National Research Ethics Service Committee London – Chelsea (REC Ref.: 12/LO/0570).

Statistical analysis

All statistical analysis was conducted using the Statistical Package for the Social Sciences (version 21, IBM, Armonk, USA). Significant differences between means were calculated using Student's *t* test. A *p* value of less than 0.05 was considered to be significant.

Results

Early results of this study show that 119 legs (117 patients) have been randomised, with 60 randomised to receive MOCA (group A) and 59 to RFA (group B).

Baseline characteristics

Fifty-nine percent of the population recruited were females (58% in group A). The mean age was 53.9 years (SD: 18 years) for the MOCA group and 48.9 years (SD: 17 years) for the RFA group (age range 18–90 years) (*p* = 0.120) (Table 2).

Table 2. Baseline characteristics and details of veins treated.

	MOCA	RFA	<i>p</i>
Females (%)	58	60	0.767
Age (years) (SD)	53.9 (18)	48.9 (17)	0.120
Left leg treated (%)	41.7	54.4	0.172
GSV (%)	90	83	0.254
Length of vein treated (cm)			
GSV (range)	36.4 (16–65)	36.8 (12–56)	0.911
SSV (range)	23.3 (18–32)	19.3 (14–21)	0.318
Vein diameter (mm) (SD)	7.0 (2.5)	7.4 (3.3)	0.595
Volume of sclerosant used (ml) (range)	7.0 (2.0–11.0)	—	—
Avulsions carried out (%) (SD)	68 (47)	77 (42)	0.300

MOCA: mechanochemical ablation; RFA: radiofrequency ablation; GSV: great saphenous vein; SSV: small saphenous vein; SD: standard deviation.

Table 3. Clinical and quality of life scores at baseline and at one-month follow-up.

	Baseline			One-month follow-up		
	MOCA	RFA	<i>p</i>	MOCA	RFA	<i>p</i>
Clinical scores						
VCSS (SD)	6.5 (2.9)	5.6 (2.4)	0.086	2.12 (1.8)	2.96 (2.9)	0.220
VDS (SD)	1.44 (0.5)	1.24 (0.5)	0.046*	0.53 (0.7)	0.69 (0.8)	0.451
QoL scores						
AVVQ (SD)	22.6 (9.9)	22.7 (12.8)	0.974	12.7 (10)	15.5 (13)	0.410
EQ-VAS (SD)	79.1 (17)	77.1 (16)	0.577	86.0 (9.3)	81.0 (14)	0.158
EQ-5D-3 L (SD)	0.692 (0.22)	0.744 (0.22)	0.259	0.842 (0.15)	0.782 (0.22)	0.279

MOCA: mechanochemical ablation; RFA: radiofrequency ablation; SD: standard deviation; VCSS: Venous Clinical Severity Score; VDS: Venous Disability Score; AVVQ: Aberdeen Varicose Vein Questionnaire; QoL: quality of life; EQ-VAS: EuroQol's visual analogue scale.

**P*-Value is significant.

The baseline scores for the AVVQ, VDS, VCSS and CEAP are tabulated in Table 3. All were similar except for the mean VDS score, which was greater for the MOCA group (1.44 (± 0.5)) compared to 1.24 (± 0.5) for the RFA group ($p < 0.05$).

Intervention

The left leg was treated in 48% of cases and the GSV ablated in 86% of procedures (Table 2). Concurrent phlebectomies were carried out in 68% of patients in the MOCA group and 77% of those in the RFA group ($p = 0.30$).

Pain score

The mean maximum pain score using the VAS during endovenous ablation was 19.3 mm (± 19) for the MOCA group compared to 34.5 mm (± 23) for the RFA group ($p < 0.001$). The corresponding mean maximum pain scores were 2.6 (± 2.2) for the MOCA compared to 4.4 (± 2.7) for the RFA group ($p = 0.001$).

The average pain distance was 13.4 mm (± 16) for the MOCA group and 24.4 mm (± 18) for the RFA group ($p = 0.001$), while the average pain score was 1.9 (± 2.0) and 3.2 (± 2.2) ($p = 0.002$).

The pain score in MOCA included the time from cannulation to vein ablation, while in RFA, it involved the time from cannulation, including infiltration of tumescence to completion of the ablation.

Time to return to normal activities

The mean time to return to normal activities was 3.5 (± 3.1) days for group MOCA compared to 4.8 (± 4.3) days for RFA ($p = 0.235$).

Table 4. Occlusion rates (%) at one-month follow-up.

	MOCA (%)	RFA (%)
1. Complete closure	83	92
2. Proximal occlusion	9	0
3. Distal occlusion	9	4
4. Open	0	4

MOCA: mechanochemical ablation; RFA: radiofrequency ablation.

The mean time to return to work was 5.3 (± 8.7) days for MOCA and 4.9 (± 3.6) days for the RFA group ($p = 0.887$).

Clinical and QoL scores at one month

Both groups showed improvement at one month in all clinical and QoL measures, with no significant differences between the two groups (Table 3).

Occlusion rate

Seventy-eight patients (66%) have attended follow-up at one month. Of those receiving MOCA, 92% either had complete (83%) or proximal occlusion (9%) (> 5 cm) compared to 92% (all complete) of those having RFA ($p = 0.790$). One patient from the RFA group had a completely patent saphenous vein at the one-month follow-up (Table 4).

Complications

In the MOCA group, there was no recorded incidence of deep (DVT) or superficial vein thrombosis (SVT) while, in the RFA group, two patients developed thrombophlebitis (3.4%) and one patient developed a non-occlusive popliteal vein DVT (1.7%). The DVT

occurred in a patient treated for GSV incompetence only (with no concurrent phlebectomy) and was an extension along the gastrocnemius vein to the popliteal vein.

Discussion

With the efficiency of all the current endovenous techniques,⁴ intra-procedural issues with treatment such as pain and patient satisfaction become more important. This is the first randomised controlled study comparing intra-procedural pain scores in patients receiving MOCA or RFA. The early results from this study with one-month follow-up show that intra-procedural pain was significantly lower in patients undergoing MOCA compared to RFA. This difference may be explained by the additional injections required for tumescent infiltration. Patients from the MOCA group also showed a trend of earlier return to their normal activities, but this was not statistically significant. Importantly, early clinical, radiological and QoL outcomes were equivalent between RFA and MOCA.

In a non-randomised observational study of 68 patients, van Eekeren et al.³ found that post-procedural pain during the first 14 days was significantly lower in the MOCA group compared to patients having RFA (mean VAS over 14 days was 4.8 ± 9.7 mm in MOCA group versus 18.6 ± 17.0 mm; $p < 0.001$). The difference in pain scores is probably explained by the different methods used to ablate the incompetent veins. The RFA technique (thermal treatment) involves treatment by heat as well as tumescent anaesthesia infiltration to prevent thermal damage to surrounding tissues, both of which can be uncomfortable.³ In that study, MOCA was also shown to be associated with an earlier return to normal activities.³

The overall occlusion rates in this small cohort of patients are similar to that seen in other studies,^{1-6,8} and longer term follow-up is required before any definitive comments can be made on superiority of techniques with respect to patency.

These early results show a decreased pain profile for MOCA compared to RFA and flag up the potential benefits of non-thermal, non-tumescent techniques compared to thermal treatment.

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Conflict of interest

All study data collection, treatment and analysis were performed independently.

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The advent of non-thermal, non-tumescent techniques for treatment of varicose veins

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Abstract

Varicose veins are common and their management has undergone a number of changes over the years. Surgery has been the traditional treatment option, but towards the 21st century, new endovenous thermal ablation techniques, namely, radiofrequency ablation and endovenous laser ablation, were introduced which have revolutionised the way varicose veins are treated. These minimally invasive techniques are associated with earlier return to normal activity and less pain, as well as enabling procedures to be carried out as day cases. They are, however, also known to cause a number of side-effects and involve infiltration of tumescent fluid which can cause discomfort. Non-thermal, non-tumescent methods are believed to be the answer to these unwelcome effects. Ultrasound-guided foam sclerotherapy is one such non-thermal, non-tumescent method and, despite a possible lower occlusion, has been shown to improve the quality of life of patients. The early results of two recently launched non-thermal, non-tumescent methods, mechanochemical ablation and cyanoacrylate glue, are promising and are discussed.

Keywords

Varicose veins, mechanochemical ablation, cyanoacrylate glue

The management of varicose veins has changed drastically over recent years, but the ideal treatment remains elusive. Traditionally, varicose veins have been treated with surgical ligation and stripping under general anaesthetic, but, over the past decade, minimally invasive techniques and local anaesthesia have become increasingly popular and indeed preferred.¹ These have also been shown to be associated with less peri-procedural pain and an earlier return to normal function.¹ These endovenous techniques are cost-effective, especially when performed in an outpatient or 'office-based' setting.²

The National Institute of Clinical Excellence (NICE) guidelines, published in July 2013, recommended the use of endovenous thermal ablation techniques, namely radiofrequency ablation (RFA) or endovenous laser ablation (EVLA), as first-line treatment for truncal vein reflux.^{3,4} Occlusion rates of greater than 90% have been demonstrated in studies looking at these two methods at up to 2 years of follow up.^{1,5–7}

However, because they make use of thermal energy to denature the venous wall, they have the potential of causing pain, skin burns, skin pigmentation, nerve damage and, even, arteriovenous fistula formation.^{8,9} To minimise these possible complications, tumescent

anaesthesia has to be infiltrated around the vein to be treated. This, in turn, can be a source of discomfort to patients.

Non-thermal, non-tumescent (NTNT) methods, hence, seem to be able to provide an alternative solution to the problems raised by these thermal techniques. In this review, we will be discussing the various NTNT techniques currently available.

Foam sclerotherapy: the original NTNT

Sclerosing solutions react with endothelium damaging it (endosclerosis) and causing fibrosis (endofibrosis) of the vessel lumen.¹⁰ In 1944, Orbach described the combination of air and sclerosing drug to treat varicose veins: the so-called 'air block' technique.¹¹ This technique, with a higher air to liquid ratio, was effective for

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the treatment of smaller veins, but was not suitable for larger ones as the air would position itself on the upper side of the vein, thereby preventing contact with endothelium. This led to high rates of treatment failure. In the 1990s modern foam sclerotherapy was created, when new methods of transforming liquid sclerosants into foam were described.¹² Sclerosing agents used as foam displace venous blood and increase endothelial contact, thereby augmenting their sclerosing power.¹³ One of the most widely used technique to produce foam is the Tessari method, which requires two syringes and a three-way tap and enables the production of a stable and compact foam.¹³ The optimal formulation was found to be one part liquid sclerosant to four parts air.¹³ Evolution of the technique has continued, with the introduction of ultrasound guidance (ultrasound-guided foam sclerotherapy) or catheter directed foam sclerotherapy for the treatment of truncal veins.^{14–16} Two of the most common sclerosing solutions available are sodium tetradecylsulphate (STS) and polidocanol (POL).

Yamaki et al.¹⁷ demonstrated the superiority of foam over liquid sclerosants in a comparative non-randomised study of ultrasound-guided sclerotherapy using either foam or liquid. Sixty-two women, with mean age of 54.6 years, were recruited and received polidocanol either as foam or liquid to treat great saphenous vein (GSV) insufficiency. At 12 months' follow-up, approximately 68% of patients receiving foam sclerotherapy had evidence of complete occlusion compared to 17.5% of those in the liquid therapy group ($p < 0.0001$).¹⁷ Despite both groups having similar characteristics, the study is limited by a lack of randomisation as well as unclear criteria used in recruitment. However, Myers and Clough (2014), using liquid Polidocanol in various concentrations found conflicting results with better occlusion rates when treating tributaries (92%) rather than truncal veins (65%) ($p < 0.01$).¹⁸

Consecutive patients attending for varicose vein treatment were offered ultrasound-guided foam sclerotherapy (UGFS) to refluxing truncal veins (saphenous and non-saphenous).¹⁹ In total, 181 patients were enrolled and reviewed within six weeks of treatment. Approximately 60.0% were females with a median age of 52 years. The occlusion rate was 74% after the first intervention and a further 15% after two interventions.¹⁹ Common complications included phlebitis and pigmentation.

Coleridge-Smith²⁰ evaluated his own series of 808 patients undergoing UGFS for incompetent truncal veins and, in the 459 patients attending follow-up at six months or greater, demonstrated an occlusion rate of 88% for the GSV and 82% for the short saphenous vein (SSV). Three interventions (each separated by two

weeks) were required to achieve an occlusion rate of 99% of the unilateral varices.

When compared to other treatment modalities, foam sclerotherapy proved to be less effective. Rasmussen et al.¹ conducted a randomised controlled trial to compare endovenous laser therapy (EVL), radiofrequency ablation (RFA), UGFS and surgical stripping in patients with evidence of GSV incompetence. Five-hundred patients were recruited and the follow-up period was for one year. The primary outcome measure was treatment failure, which was defined as an open part of the treated vein segment measuring more than 10 cm in length. The clinical quality of life and radiological change after intervention was also recorded. Baseline characteristics for all four groups did not differ. At one-year follow-up, there were significantly more cases of treatment failures in the UGFS group (16.3%) compared to the other three groups (less than 6%) ($p < 0.001$).¹ Patients who were treated with either UGFS or RFA reported lower pain scores and returned to their normal activities earlier compared to those receiving EVLT or surgery ($p < 0.001$). All groups improved similarly in both clinical and quality of life scores. UGFS was also found to be the cheapest treatment method, especially when the cost of being off from work was taken into account.

Lower occlusions rates were again reported in the MAGNA trial. This was a randomised controlled trial comparing EVLT, UGFS and surgery in 223 patients (240 legs).²¹ The primary outcome measure was anatomic success on duplex ultrasound examination. At the one-year follow-up, both EVLT and surgery had comparable occlusion rates (88.5% and 88.2%, respectively). The corresponding occlusion rate for UGFS was 72.7% ($p < 0.02$). All three groups also demonstrated similar improvement in the quality of life scores (CIVIQ and EQ-5D).

Tumescent anaesthesia was used in both the previous two studies in patients receiving endothermal methods. This anaesthetic solution acts as a heat sink for the transmitted heat energy and pushes surrounding tissues away, protecting them from burn injury.²² It also helps push blood out of the vein and compresses the vein onto the probe, thereby enabling a more effective thermal injury to the vein being treated²¹ and, hence, potentially explaining the high occlusion rates observed.

In order to investigate whether these effects are replicated in patients receiving catheter-directed foam sclerotherapy (CDFS), Devereux et al.²³ conducted a prospective randomised clinical trial in which patients received CDFS with or without tumescence. The tumescent fluid used was 0.9% saline only, as the addition of local anaesthesia and adrenaline would have been against the guidelines of the German Federal Institute

for Drugs and Medical Devices, the organisation which granted ethical approval for the study. Fifty patients were recruited, with 43 of them attending final follow-up at 12 months. At the end of the follow-up period, the complete occlusion rate was 74% in the CDFS with tumescent group compared to 75% in the CDFS group only.²³ The authors speculate that the lack of adrenaline in the tumescent might explain the similarities in the level of complete venous occlusion in the two arms of the study. Indeed, they suggest that the addition of adrenaline might have brought about a more potent reduction of the vein diameter and improved the occlusion rates of the CDFS/tumescent group.

The longest data to date following UGFS have been reported by Darvall et al.²⁴ They described the patient-reported outcomes 5–8 years following treatment with UGFS. Out of the initial 351 patients (479 limbs) treated, 285 (81.2%) attended follow-up a minimum of five years later. Using a Kaplan–Meier plot, they estimated the proportion of their cohort requiring retreatment at five years to be 15.3%. There was also significant improvement noted in the Aberdeen Varicose Vein Symptom Severity score (AVSS), similar to that observed at earlier follow ups. The physical component of the short form12 (SF-12®) was also found to have improved compared to pre-treatment values. The mental component of SF-12® was, however, similar to baseline levels. Between 62.7% and 81.0% reported exceeded or met expectations with respect to social, work or leisure activities. Eighty-two percent of patients were highly satisfied (giving a score of 8 to 10) and more than 90% would recommend the treatment to their family and friends. The same group also demonstrated that, as well as improving the quality of life of patients, UGFS is less painful and leads to earlier return to work compared to surgery.^{25–27}

Complications associated with UGFS include phlebitis, skin pigmentation, thromboembolism (pulmonary embolus or deep vein thrombosis) as well as neurological symptoms such as migraines, transient ischaemic attacks or visual disturbances.^{19,28} The occurrence of neurological symptoms has been attributed to the presence of a patent foramen ovale (PFO), a common finding in the population (20–30%).²⁸

Foam sclerotherapy has also been combined with other methods, notably, surgery and coil insertion, to improve the rate of occlusion of the GSV. One-shot scleroembolisation is one such method.²⁹ In the first article describing its use, nine patients with GSV reflux (six patients with simple varicose veins and three with healed ulcers) were recruited and underwent day case treatment of the incompetent vein. The technique involves the introduction of an endovenous catheter in the GSV and, under ultrasound-guidance, placement of a standard platinum coil 1 cm below the

origin of the epigastric vein. The coil is 1 mm wider than the calibre of the SFJ and causes the prompt occlusion of the terminal portion of the GSV. The final step is the injection of sclerofoam (2% Polidocanol), which causes fibrosis and occlusion of the vessel. Post-procedure, elastic bandage was applied to the treated limb. Patients were discharged the same day and advised to wear the compression for 15 days. All of them were followed for up to three months. After one week, one instance of recanalisation was detected, which was successfully treated with foam sclerotherapy. At three months, therefore, all nine patients were asymptomatic and had completely occluded GSV.²⁹ In addition, no migration of the coil or compression of the CFV was noted and the coil was palpable. There were no perioperative complications and no incidences of DVT. Advantages of the technique include the fact that it can be carried out under local anaesthetic as a day case procedure and does not require any tumescence. The average cost of the coil was US \$120. This technique is promising, but the findings need to be confirmed with larger studies and longer term follow-up.

Ricci et al.³⁰ described a technique called ultrasound-assisted GSV ligation and division, which is another potential alternative to endothermal treatment. Eighteen patients (20 GSVs) were enrolled. The procedure consists of prior vein marking, initial phlebectomies for varicosities followed by ultrasound-guided extraction and division of the GSV about 3 cm below the SFJ as it courses over the adductor longus (an area relatively free from other structures). Foam sclerosant is then injected through the distal end until it comes out of the distal phlebectomy stab incisions. The proximal end is transfixied, leaving a short stump, while the distal end is ligated. Post-procedure, compression bandaging is applied for one week. At one month, the residual stump was patent in all cases with no evidence of reflux. At six months, one proximal GSV stump showed evidence of reflux originating from a pudental vein. This technique offers the advantage of sparing the junction tributaries and avoiding dissection, hence, possibly giving rise to less stimuli for neovascularisation. Potential problems are the likely difficulty in obese patients and large GSV diameter where the vein is extracted from. Moreover, it cannot be truly considered an NTNT as it still makes use of tumescent anaesthesia. Longer term follow-up as well as a larger cohort is required to confirm findings of this study.

Newer NTNT methods have recently appeared on the market and these are being promoted as offering the potential of higher occlusion rates, while maintaining improved quality of life and earlier return to activities, but without the side-effects of endothermal ablation.

Mechanochemical ablation

A new device, the ClariVein[®] mechanochemical ablation (MOCA) device (Vascular Insights, Madison, CT, USA), has been introduced which avoids the use of heat and tumescent infiltration. It combines an endovenous mechanical method using a rotating wire with simultaneous injection of liquid sclerosant.³¹ The wire rotates at 3500 rotations per minute, injuring the venous intima while the sclerosant is infused through an opening close to the catheter tip.³¹

Animal studies

Tal et al.³² tested the MOCA device on 11 male goats (12 veins included) and analysed the histological samples obtained from this caprine model. Four different treatments were examined: group 1: the ClariVein[®] catheter and 1.5% sodium tetradecyl sulphate (STS) (MOCA procedure) (five veins); group 2: ClariVein[®] and 0.9% saline (one vein); group 3: 5 mL injection of 1.5% STS (five veins); and, group 4: 5 mL injection of 0.9% saline (one vein). The lateral saphenous vein was selected and duplex ultrasound examinations were carried out pre-operatively and on days 14, 28, 56 and 84 to assess the degree of occlusion. At day 84, all animals were euthanised and underwent gross necropsy.³² All the veins receiving the MOCA procedure (group 1) demonstrated complete or near complete occlusion on ultrasound assessments at 84 days, while the veins in the other treatment groups were still patent at the end of the study, thereby indicating the superiority of the ClariVein[®] catheter and sclerosant to produce vein occlusion and fibrosis rather than only using liquid sclerosant. Comparison of the saline groups (groups 2 and 4) showed more subintimal impingement and medial fibrosis in group 2 than in group 4. No adventitial fibrosis was demonstrated, however, and veins from both groups remained patent at the end of the study.

One limitation of the study is that the number of veins treated in each group is not equivalent and the question remains as to whether some of the changes noted could have been improved with inclusion of a larger number of veins. This study, in any case, illustrates the superiority of the MOCA procedure in achieving venous occlusion compared to using either the ClariVein[®] catheter alone or liquid sclerosant on its own.

Human trials

In order to determine the safety and efficacy of the ClariVein[®] device, Elias and Raines³¹ recruited 29 patients with primary great saphenous vein (GSV) reflux and followed them at four different time points.

Reflux of greater than 0.5 s or longer was determined at the SFJ while patients were in the standing position. A majority of the patients were females (60%) and the average age of the population was 54.3 years (range: 31 to 90 years). The baseline venous clinical severity score (VCSS) was 4.5 with the clinical CEAP (Clinical-Etiological-Anatomical-Pathophysiological) between 2 and 4. The average treatment length was 37.5 cm and the average diameter of the treated veins was 8.1 mm. No patients complained of pain during the ablative procedure. There were no incidences of deep vein thrombosis (DVT), nerve or skin injury. The average follow-up period was 260 days. There was one case (1 out of 30) of recanalization giving a primary closure rate of 96.7% at 260 days.³¹ The authors, therefore, concluded that the new ClariVein[®] device was safe and appeared to be effective in the treatment of venous reflux.³¹ However, most of the patients recruited had CEAP stage 2 disease (77%) and there were three occurrences of ecchymoses. The authors postulate that this might be secondary to the rotating wire catching on a side branch or valve cusp.

About the same time, van Eekeren et al.³³ conducted a similar study in the Netherlands to assess the applicability and safety of MOCA. Twenty-five patients with primary GSV reflux were recruited (30 limbs), undergoing mechanochemical ablation at two centres. Most of the patients were women (72%) and the mean age of the population was 52 years. The CEAP classification ranged from C2 to C4 and the mean VCSS score was 3.3. The mean duration of the procedure was 20 min and the treated veins were on average 40 cm in length and 6.1 mm diameter at the sapheno-femoral junction. The median maximal pain score was four (interquartile range (IQR) 3–6) on a 10-point scale, while the mean maximum pain measured on day one post-procedure was 9 mm on a 100 mm visual analogue scale (VAS).³³ There were no major adverse events and the minor complications included nine cases of local ecchymosis at the puncture site and four of phlebitis. At the six weeks' follow-up, the GSV was completely obliterated in 87% of cases (26 out of 30 legs treated) starting 2 cm distal to the SFJ at the six weeks' follow-up. Patient satisfaction was 8.5 (IQR 8–9) on a 10-point scale and the median VCSS decreased significantly from 3 to 1 ($p < 0.001$).³³

The effect of MOCA on the small saphenous vein (SSV) has been studied by the same research team. The SSV accounts for approximately 15% of lower limb truncal venous incompetence.³⁴ Fifty patients with primary SSV incompetence were enrolled and received MOCA treatment to their incompetent SSV with 1.5% Polidocanol as sclerosant.³⁴ The primary outcome measures included anatomic success, which was defined as occlusion of the treated vein and

recanalised SSV or treatment failure defined as an segment of > 10 cm. The median pain score using a VAS was 2 cm (IQR 2–4 cm) and the median patient satisfaction was 8 (IQR 8–9). No major complications were recorded, including no evidence of nerve injury and no DVT. Minor complications were noted, mainly localised ecchymosis and induration and transient superficial thrombophlebitis in 14%. The occlusion rate was 100% (50 out of 50 limbs treated) and 94% (44 out of 47 legs treated) at the six-week and one-year follow-up, respectively. However, it is to be noted that different concentrations of the sclerosant were used to treat the proximal section, with 1.5% Polidocanol for the first 15 patients, but 2 ml of 2% Polidocanol in the subsequent 35 patients (followed by 1.5% for the remainder of the vein). There were two occurrences of recanalisation in patients treated with the lower concentration, compared to one out of those who received 2% Polidocanol.

The same group again evaluated the one-year results of MOCA in patients with GSV insufficiency.³⁵ Consecutive patients with primary GSV insufficiency were included in the study. Ninety-two patients (106 limbs) were recruited. The mean age was 52 years with 67% of the cohort being females. Treatment failure was defined as a recanalised segment of > 10 cm of the treated GSV. MOCA was performed on 105 legs and the median post-procedural pain using a 0–100 mm VAS during the first 14 days after treatment was 7.4 mm. No major complications were observed, although there were incidences of thrombophlebitis, induration, localised haematoma and mild hyperpigmentation at the puncture site. The occlusion rate immediately post-procedure, at six months and at one year was 100%, 93.2% (96 of 103 limbs treated) and 88.2% (90 of 102), respectively.³⁵ The mean VCSS score improved significantly at the six month and one-year follow-up ($p < 0.001$). Compared to baseline, the QoL improved significantly with a mean AVVQ score of 6.6 at six months ($p < 0.001$) and 2.4 at year one ($p < 0.001$).

There have been few studies comparing MOCA to endothermal ablation. One of these studies comprised of 68 consecutive patients treated for symptomatic unilateral GSV reflux and their post-operative pain score, as well as early quality of life was assessed.³⁶ Thirty-four patients were assigned to either MOCA or radio-frequency ablation (RFA). There were 25 males and 43 females, with a mean age of 58 ± 17 years. There were no significant differences in the baseline patient characteristics. The mean procedural pain during treatment was similar between the two groups ($p = 0.16$). Patients receiving MOCA reported less pain compared to RFA over the first three days (6.2 mm vs. 20.5 mm; $p = 0.004$) and during the first 14 days after treatment (4.8 mm vs. 18.6 mm; $p < 0.001$).³⁶ They also required

less analgesia compared to the RFA group. Patients in both groups who developed post-operative thrombophlebitis and induration had higher pain scores. Treatment time was significantly shorter in the MOCA group ($p = 0.02$). At six weeks, the median VCSS score improved significantly in both groups ($p < 0.001$). Quality of life assessment showed that the AVVQ score improved in both the MOCA ($p = 0.006$) and RFA ($p = 0.002$).³⁶ Time to return to normal activities and work was also found to be significantly shorter in the MOCA group. The authors, thus, concluded that post-operative pain is significantly lower after MOCA compared to RFA and the former was associated with a faster return to normal activities and work. This is the first study which has provided direct evidence of the lesser discomfort following varicose vein ablation and earlier return to activities in patients receiving MOCA. But, this was a non-randomised trial and the criteria used for patient selection is not clear. Moreover, the procedural pain score was no different in the two groups, but the authors allude to the fact that their sample size was too small to detect a difference and suggested carrying out a randomised trial.

A multicentre randomised clinical trial (RCT) comparing MOCA to RFA in the treatment of GSV or SSV and looking at the intra-procedural pain scores and improvement in quality of life at one and six months is currently ongoing in our unit.³⁷ The early results have already been published and 119 patients, having similar baseline characteristics, have been randomised (60 of them to the MOCA group). These results demonstrate significantly lower maximum (19.3 mm versus 34.5 mm) and average VAS pain score (13.4 mm versus 24.2 mm) in the MOCA group compared to the RFA group ($p < 0.001$ and $p = 0.001$, respectively). Seventy-eight patients (66%) attended their one-month follow-up appointment. Both clinical and quality of life (QoL) scores had improved by then. However, there was no significant difference in the time taken to return to normal activities and work. The complete/proximal occlusion (occlusion of the whole treated segment or more than 5 cm of the proximal segment) rates at one month was found to be 92% in both groups ($p = 0.89$). The trial has completed its recruitment phase and is in the final stages of follow-up and analysis.

The MARADONA trial (Mechanochemical endovenous Ablation versus RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence) has been designed to directly compare the anatomical and clinical success rate at one year compared to RFA and is hoping to recruit 230 patients in each group (460 patients in total).³⁸ Patients will then be followed up for five years, giving excellent long term data. The results of this are eagerly anticipated and expected in 2020.

Complications of mechanochemical ablation

Reported complications following MOCA include superficial thrombophlebitis, induration along the course of the treated vein, localised haematoma and mild hyperpigmentation at the puncture site.³⁵ An increasingly recognised adverse event following MOCA is the rotating wire tip getting caught. This may give rise to ecchymoses, patient discomfort or resistance to pullback.^{31,39} However, as reported by Lane et al.,⁴⁰ rarely it can become stuck with no possibility of dislodgement, with dramatic consequences (the SSV was inverse stripped). There have been no reports of skin necrosis, deep vein thrombosis or nerve injury.

Cyanoacrylate glue

Another tumescentless method recently introduced is the sapheon venaseal closure system (Sapheon Inc., Santa Rosa, Calif, USA), which makes use of cyanoacrylate glue to treat venous incompetence.

What is glue?

The glue used in this tumescentless method is n-butyl cyanoacrylate (n-BCA), which was initially introduced in medical practice approximately 40 years ago.⁴¹ The first cyanoacrylate adhesive used at the time had low tensile strength and was associated with both acute and chronic inflammation.⁴¹

N-butyl cyanoacrylate is an adhesive liquid monomeric agent, which quickly polymerises and becomes solid when it comes into contact with a solution containing anions (e.g. with the hydroxyl groups in blood).⁴² This subsequently leads to occlusion, marked inflammatory endothelial response, and, ultimately fibrosis.⁴² Further development of the material with the addition of plasticisers and stabilisers has improved its flexibility and reduced its toxicity.⁴¹

This has resulted in cyanoacrylate glue being used more widely, for example, in ophthalmic surgery, cosmetic procedures, dental applications, tissue adhesion and haemostasis of acute bleeding such as endoscopic sclerotherapy of gastric variceal bleeding with high safety profiles reported in patients followed up for 10 years.⁴³ They have also been used intravascularly in treating type I and II endoleaks of abdominal aortic aneurysm repair procedure, varicoceles, pelvic congestion syndrome and arterio-venous malformations (AVM).⁴³

Animal studies

Kailasnath and Chaloupka⁴⁴ developed a bench top testing apparatus that permits direct measurement of evolving binding forces that develop during

polymerisation of CA. They compared the rate of polymerisation of CA using a plastic model vessel and a tissue model (common carotid artery of a swine). They found that there were three distinct stages of polymerization. The initial phase (phase I) demonstrated a linear rate of increasing tensile forces lasting less than 10 s followed by phase II, which had a more constant tensile force (lasting up to 1 min). Polymerisation was, however, not achieved in either phases. A final step (phase III) started at the end of the second phase and was characterised by an exponential rise in the tensile forces which leads to complete polymerization.⁴⁴ The rate of polymerisation and strength of the binding forces formed were variable and dependent on type and formulation of CA used.^{43,44}

The first experiment looking at using CA adhesive as vein closure method in an animal model used the superficial epigastric veins (SEVs) of two swines.⁴⁵ The SEVs empty into the abdominal rectus vein (ARV) at the costal margin. The purpose of the experiment was to assess the feasibility of the proposed method as well as evaluating its safety and effect on the vein wall. With the swines under general anaesthetic, the right and left SEVs were cannulated followed by insertion of the CA adhesive delivery catheter (Sapheon, Santa Rosa, California). This venous closure system also incorporates a 3 cc (cubic centimetre) syringe, a dispenser tip and a dispenser gun (Sapheon).⁴⁵

The method of treatment used was as follows. The catheter tip was positioned 2 cm distal to the SEV-ARV junction. Pressure was then applied with the ultrasound transducer just cephalad to the catheter tip. Using a slow deliberate trigger pull of 3-s duration, 0.16 mL of CA was delivered to the target vein. The delivery system (sheath plus catheter) was immediately pulled back 3 cm after this initial injection and transverse compression applied for 30 s to allow interaction between CA and the vein wall. This process was repeated every 3 cm until the vein was treated.

Four SEVs were treated in total and the two swines were sacrificed at day 60 post-treatment.⁴⁵ The SEVs were harvested and sections were studied macro- and microscopically. Explanted segments from the caudad, middle and cephalad areas were completely occluded with no patent segments. On histology, fibrous tissue and inflammatory cells were present, with one of the three examined sections exhibiting fibrotic projections which caused occlusion of nearly the entire lumen. The wall was segmentally thickened by fibrous tissue and the lumen was dilated by an abundant clear space containing moderate amounts of debris and coalescing, tree-like bands of macrophages and spindle cells. The clear space appeared surrounded by multinucleated giant cells, which were presumed to be reacting toward foreign material. Spindle cells with

dense eosinophilic matrix replaced the tunica intima and disrupted the tunica media. Additionally, the wall was disrupted by numerous aggregates of histiocytes and lymphocytes with lymphoid follicles. Also, a dark-coloured bulge (entrapped blood) in the vein was observed, though not visible on the skin. The changes observed in the treated veins are consistent with chronic foreign-body-type inflammatory response. Unwanted migration of CA was not found, nor was recanalisation present in any of the treated veins. Evaluation of control segments lacked any significant histologic changes.⁴⁵

Human trials

The first clinical trial of using cyanoacrylate adhesive for the treatment of varicose veins recruited 38 patients with great saphenous vein incompetence in a prospective non-randomised study.⁴⁶ Consecutive patients were enrolled and followed up at 48 h and 1, 3, 6 and 12 months after their intervention with a clinical examination and a duplex ultrasound scan. Complete occlusion of the treated segment was considered as treatment success. A disposable Sapheon Closure System (SCS) was used, which included a delivery catheter with hydrophobic properties to prevent CA-mediated adhesion to the vein wall.⁴⁶ The catheter was removed after venous closure has been confirmed and a single adhesive bandage was applied. No additional procedures were carried out and no compression stockings or bandages were applied. Approximately three quarters of the patients were females with a median age of 51 years (range: 26–77 years).⁴⁶ The mean GSV diameter at the SFJ was 8.0 ± 2.2 mm and the mean length of vein treated was 33.8 ± 9.1 cm. The mean volume of CA glue used was 1.3 mL (range: 0.6–2.3 mL). All the veins treated were completely occluded at the 48-h follow-up. By the 12 months' follow-up, three patients had developed recanalisations of GSV, giving a complete occlusion rate of 92.1%.⁴⁶ Seven patients developed post-operative thrombophlebitis, one patient developed cellulitis and one patient had hyperpigmentation at 12 month due to the treated vein being very close to the skin. In addition, eight patients had evidence of thread-like thrombus extension across the SFJ into the common femoral vein (CFV) at the 48-h follow-up (protruding a length of 12.6 ± 9.9 mm). All thrombus extensions had resolved without any anticoagulation by the six months' follow-up. The VCSS scores showed improvement from 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months ($p < 0.0001$). This study set out to determine the feasibility of using CA in the treatment of saphenous vein incompetence. It also demonstrated an occlusion rate comparable to those of endothermal ablation methods in use. Patients were

seen again at the 12 and 24 months' period.⁴⁶ Three patients presented with a GSV recanalisation of more than 5 cm at one, three and six months, respectively, with the occlusion rate at the 24 months' mark using a life-table analysis being 92%.⁴⁷ The VCSS score at 24 months was lower than baseline, although it was still higher than the score at six months. These results demonstrate that CA is potentially an alternative to the endothermal methods, especially as no tumescent is needed. No compression therapy is prescribed since the technique does not cause perforation of the vein wall. Two of the authors had connections with the funding company, Sapheon Inc., and with consulting firms with an interest in the device.

Proebstle et al.⁴⁸ undertook a prospective, multicentre clinical trial of endovenous CA embolisation of refluxing GSVs in seven centres across Europe.⁴⁷ Symptomatic patients with GSV incompetence confirmed on duplex ultrasound were recruited and treated with CA, starting at 5 cm distal to the SFJ. This distance was selected as it would provide enough space for the ultrasound compression between the delivery catheter and SFJ, as well as to enable glue propagation toward the SFJ following injections. No post-procedure compression was used. No adjunctive treatment or reintervention was undertaken for three months after the intervention. Clinical and quality of life assessments were carried out at baseline, and patients were followed up at 48 h and at 1, 3, 5 and 12 months initially. Seventy patients were enrolled in total with 79% of them being females. The mean age was 48.4 years (range: 22–72 years). The mean diameter of the GSV at the SFJ was 7.8 mm and the mean length was 37.6 cm. The mean treatment time was 18.6 min (range: 8–74 min). Using a life-table method, the complete occlusion (defined as no patent segment of more than 10 cm) rate was 92.9% at the 12 months' follow-up point.⁴⁸ The patients' clinical and QoL scores were significantly improved. The most common adverse events were phlebitic reaction, occurring in eight limbs. A single patient had a 6 mm extension of thrombus into the common femoral vein. This was successfully treated with low molecular weight heparin. Thus, this study demonstrated that CA was safe and effective in the treatment of GSV reflux and an RCT comparing the technique to endothermal methods have been advocated.

In the VeClose trial, a multicentre randomised controlled trial comparing cyanoacrylate embolisation and radiofrequency ablation for refluxing great saphenous veins, two hundred and twenty-two patients were recruited and randomised to receiving CA or RFA.⁴⁹ All patients were prescribed compression stockings to wear continuously for three days and only during waking hours for an additional four days. The primary study end-point was complete closure of the GSV

defined as closure of the entire treated vein with no discrete patent segments of more than 5 cm. All patients were followed up for three months. Prespecified models were used to impute missing data. Most patients were females (79%) and Caucasian (94%) with the most common CEAP clinical class being 2 and 3. The mean age was 49.0 years and 50.5 years for CA and RFA, respectively. The occlusion rate in both groups was 100% at day 3. At the three-month point, the occlusion rates were 99% for CA and 96% for the RFA group. However, this was obtained using predictive statistical models to compensate for missing data (31/222). At three months, VCSS, AVVQ and generic quality of life all showed significant improvement compared to baseline (3.5, $p < 0.01$; 8, $p < 0.01$ and 0.03, $p = 0.01$, respectively). There was a non-significant increased incidence of phlebitis in the CA group (20 vs. 15 events, $p = 0.36$). Most of these cases were mild and were successfully treated with over-the-counter non-steroidal anti-inflammatory agents. There was, however, also less ecchymosis at day 3 in the CA group compared to the RFA group with 94.5% of patients from the CA group having bruising in less than 25% of the treated length (8.2 cm) compared to 81.5% of the RFA group (8.8 cm) ($p < 0.01$). Venous access and mean intraprocedural pain scores for both methods were similar. Multiple imputation models showed non-inferiority with both optimistic and pessimistic models.

Complications of CA

The most commonly reported complications of CA use for the treatment of varicose vein disease, so far, include ecchymosis and phlebitis.⁴⁹ In the first trial of this technique, thread-like thrombus extensions were noted.⁴⁵ It was hypothesised that this was probably due to the catheter being positioned 3 cm from the SFJ and not offering enough space for the glue to propagate along the GSV.⁴⁶ In subsequent trials, this distance was increased with resultant improvement in the rate of this complication and the acceptable distance in contemporary practice is now 5 cm.^{48,49} CA injection, when used in the treatment of gastric varices, poses the risk of systemic embolisation, with reported cases of pulmonary embolism, stroke and multi-organ infarction via a patent foramen ovale, or even recurrent sepsis caused by the embolised CA glue acting as a septic focus.⁵⁰ These latter adverse events have not been reported thus far with CA use in varicose veins.

Conclusion

So far, mechanochemical ablation and cyanoacrylate glue have been shown to be at least equivalent to

endothermal techniques and probably superior to UGFS with respect to occlusion rates. They also appear to offer better comfort and earlier return to normal activities. Despite their undeniable promise, further randomised controlled trials with longer follow-up will hopefully be able to provide more robust evidence of their respective merits.

Conflict of interest

None declared.

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APPENDIX 18 - PUBLISHED ABSTRACTS

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12. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. *British Journal of Surgery* 2015; 102 (S5): 4. (SARS 2015 Abstract)
13. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. *British Journal of Surgery* 2015; 102 (S2): 2. (VSGBI 2014 Abstract)
14. Moon KH, Dharmarajah B, **Bootun R**, Lim CS, Lane TRA, Moore HM, Sritharan K, Davies AH. Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation for varicose veins. *British Journal of Surgery* 2015; 102 (S2): 18. (VSGBI 2014 Abstract)

APPENDIX 19 - NATIONAL & INTERNATIONAL ORAL PRESENTATIONS

1. **Bootun R**, Taha M, Busuttil A, Davies AH. The use of deep venous stenting for acute venous thrombosis of the lower limb. January 2017. *(Presented in the Abstract Session at the Annual meeting of Society of Academic and Surgical Research)*
2. **Bootun R**, Epstein D, Onida S, Ortega-Ortega M, Davies AH. Effectiveness of treatments of varicose veins: systematic review and evidence synthesis. January 2017. *(Presented in the Abstract Session at the Annual meeting of Society of Academic and Surgical Research)*
3. **Bootun R**, Onida S, Lane TRA, Davies AH. Pilot study of the use of cyanoacrylate in the treatment of varicose veins. January 2017. *(Presented in the Abstract Session at the Annual meeting of Society of Academic and Surgical Research)*
4. Taha MAH, Busuttil A, **Bootun R**, Davies AH. A systematic review of stenting in the management of acute deep venous thrombosis. September 2016. *(Presented by MAHT in the Abstract Session at the 30th Annual Meeting of European Society of Vascular Surgery)*
5. **Bootun R**, Onida S, Karia M, Grant Y, Najem M, Shalhoub J and Davies AH. Venous thromboembolism assessment scoring in patients undergoing superficial venous intervention: US and UK perspective on risk stratification. July 2016. *(Presented at the joint meeting of 17th Annual Meeting of the European Venous Forum and Venous Forum of the Royal Society of Medicine)*
6. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Six month clinical outcomes of a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. July 2016. *(Presented at the joint meeting of 17th Annual Meeting of the European Venous Forum and Venous Forum of the Royal Society of Medicine)*
7. Bootun R and Davies AH. Treatment of acute venous femoro-iliac thrombosis: change the paradigm? June 2016. *(Invited Presentation at Multidisciplinary European Endovascular Therapy Meeting (iMEET) 2016)*
8. Bootun R and Davies AH. Post-operative compression after varicose vein treatments: yes or no? June 2016. *(Invited Presentation at Multidisciplinary European Endovascular Therapy Meeting (iMEET) 2016)*
9. Onida S, **Bootun R**, Grant Y, Najem M, Shalhoub J, Davies AH. Venous thromboembolism risk assessment – what's the score? February 2016. *(Presented at the 28th Annual Meeting of the American Venous Forum (AVF) 2015)* (also presented as poster)

10. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. February 2016. *(Presented at the 28th Annual Meeting of the American Venous Forum (AVF) 2015)* (also presented as poster)

11. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. February 2016. *(Invited lecture presented at the 9th Annual Conference of the Venous Association of India 2016 [VAICON 2016], Jaipur, India)*

12. Onida S, **Bootun R**, Grant Y, Najem M, Shalhoub J, Davies AH. Venous thromboembolism risk assessment – what's the score? January 2016. *(Presented by SO at the Norman Tanner Best Abstract Prize Session at the Royal Society of Medicine 2016)*

13. Onida S, **Bootun R**, Grant Y, Najem M, Shalhoub J, Davies AH. Venous thromboembolism risk assessment prior to superficial venous disease intervention – what's the score? January 2016. *(Presented by SO at the Abstract Session of the Annual Meeting of the Society for Academic and Research Surgery (SARS))*

14. **Bootun R** and Davies AH. Vascular Trauma. Oct 2015. *(Presented at the 17th Congress of the Turkish Society of Vascular and Endovascular Surgery and 8th Congress of the Turkish Society for Phlebology)*

15. **Bootun R**, Lane TRA, Davies AH. Kreussler Young Scientists' Sclerotherapy Award 2015: Randomised Controlled Trial of Compression Therapy following Foam Sclerotherapy of Varicose Veins. August 2015. *(Presented in the Prize Session of the Union Internationale de Phlebologie (UIP) Chapter Meeting 2015)*

16. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Six-month clinical outcomes of a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. August 2015. *(Presented in the Abstract Session of the Union Internationale de Phlebologie (UIP) Chapter Meeting 2015)*

17. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Six-month clinical outcomes of a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins (VVCVV) trial. July 2015. *(Presented in the Abstract Session of the 16th Annual Meeting of the European Venous Forum 2015)*

18. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. April 2015. (*Presented in the Abstract Session of the Charing Cross International Symposium and was awarded a Certificate of Merit for best presentation*)

19. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. February 2015. (*Presented at the 27th Annual Meeting of the American Venous Forum (AVF) 2015*) (also presented as poster)

20. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. January 2015. (*Presented by AHD at the Controversies and Updates in Vascular Surgery (CACVS) 2015*)

21. Dharmarajah B, Hoon K-H, **Bootun R**, Lim CS, Lane TRA, Moore HM, Sritharan K, Davies AH. Assessment of acoustic reflectors in the right heart during mechanochemical and radiofrequency ablation of the great saphenous vein. (*Presented at the Annual Meeting of the Society for Academic and Research Surgery (SARS) 2015*)

22. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. January 2015. (*Presented in the Patey Prize Session at the Annual Meeting of the Society for Academic and Research Surgery (SARS) 2015*)

23. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. November 2014. (*Presented in the Venous Prize Session at the Annual Vascular Society of Great Britain and Ireland (VSGBI) Meeting 2014*)

24. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. October 2014. (*Presented at the President's Day of the Royal Society of Medicine (Section of Surgery and Venous Forum) and awarded the Norman Tanner Prize for best presentation*)

25. Lane TRA, **Bootun R**, Dharmarajah B et al. VNUS versus Clarivein for Varicose Vein (VVCVV) Trial. April 2014. (*Presented by TRAL at the Venous Forum of the Royal Society of Medicine and Awarded 2nd Place in the Abstract Competition*)

APPENDIX 20 - NATIONAL & INTERNATIONAL POSTER PRESENTATIONS

1. **Bootun R**, Onida S, Lane TRA and Davies AH. Pilot Study of the use of cyanoacrylate adhesive in the treatment of varicose veins. Nov 2016. *(Presented at the 30th Annual Congress of the American College of Phlebology, Anaheim, CA, USA)*
2. **Bootun R**, Epstein D, Onida S, Ortega-Ortega M and Davies AH. Effectiveness of treatments of varicose veins: systematic review and evidence synthesis. Nov 2016. *(Presented at the 30th Annual Congress of the American College of Phlebology, Anaheim, CA, USA)*
3. **Bootun R**, Onida S, Lane TRA and Davies AH. Pilot Study of the use of cyanoacrylate adhesive in the treatment of varicose veins. July 2016. *(Presented at the joint 17th Annual Meeting of the European Venous Forum and Venous Forum Meeting of the Royal Society of Medicine)*
4. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. February 2016. *(Presented at the 28th Annual Meeting of the American Venous Forum 2016)* (also presented as an oral presentation)
5. Onida S, Grant Y, **Bootun R**, Najem M, Shalhoub J, Davies AH. Comparison of the UK Department of Health and US Caprini venous thromboembolism risk assessment scores in individuals undergoing varicose vein surgery. February 2016. *(Presented by SO at the 28th Annual Meeting of the American Venous Forum 2015)* (also presented as an oral presentation)
6. Onida S, **Bootun R**, Grant Y, Najem M, Shalhoub J, Davies AH. Comparison of the UK Department of Health and US Caprini venous thromboembolism risk assessment scores in individuals undergoing varicose vein surgery. September 2015. *(Presented by SO at the 8th London Surgical Symposium, London)*
7. **Bootun R**, Busuttil A, Lim CS, Lane TRA, Bicknell C, Sritharan K, Franklin IJ, Davies AH. Patient perspective of service provision for the management of varicose vein disease. August 2015. *(Poster Presented at the Union Internationale de Phlebologie (UIP) Chapter Meeting 2015)*
8. **Bootun R**, Busuttil A, Lim CS, Lane TRA, Bicknell C, Sritharan K, Franklin IJ, Davies AH. Patient perspective of service provision for the management of varicose vein disease. July 2015. *(Presented as electronic poster at the European Venous Forum 2015)*

9. **Bootun R**, Lane TRA, Dharmarajah B, Lim CS et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. February 2015. (***Presented at the 27th Annual Meeting of the American Venous Forum 2015***) (also presented as an oral presentation)
10. Hoon K-H, Dharmarajah B, **Bootun R**, Lim CS, Lane TRA, Moore HM, Sritharan K, Davies AH. Comparison of microbubble presence in the right heart during mechanochemical and radiofrequency ablation of varicose veins. (***Presented at the Annual Vascular Society of Great Britain and Ireland (VSGBI) Meeting 2014***)