Outcomes in Varicose Vein Disease

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

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Dedication

The impossible is possible tonight
Billy Corgan, "Tonight Tonight"
Abstract

Introduction

Varicose veins are a common problem with 25-50% of the population symptomatically affected, and chronic venous disease leads to significant impairments in quality of life with substantial health system cost implications. Significant variability exists in the symptoms suffered by patients, the treatment offered and the outcomes achieved. Identification of the optimal treatment pathways for patients remains difficult.

Aims

i. To ascertain primary care disease knowledge.

ii. To assess what affects treatment and identify which patients benefit most.

iii. To generate a predictive model of varicose vein outcomes.

iv. To assess the impact of altering treatment of varicosities in the context of endovenous truncal vein ablation

v. To investigate the early impact of new technologies

Methods

i. Two survey studies were completed:

   - 21 questions assessing venous disease management pathways was disseminated to General Practitioners.

   - 19 questions assessing the management of superficial venous thrombosis and was distributed to General Practitioners and Vascular Surgeons.

ii. A cohort of consecutive patients with symptomatic chronic venous disease were assessed and completed quality of life questionnaires pre and post-intervention.
iii. Uni-variable and multi-variable analysis of patient cohort data to facilitate the creation of generalised model of venous treatment outcomes

iv. A randomised clinical trial assessing the timing of varicosity avulsion in the context of local anaesthetic endovenous truncal ablation.
  - Ambulatory Varicosity avUlsion Later or Synchronised (AVULS) trial.

v. Assessment of new technologies
  - The European Sapheon Closure system Observed ProspectivE (eSCOPE) study a multi-site cohort observational study of cyanoacrylate glue occlusion of truncal vein incompetence
  - The VNUS Versus Clarivein for Varicose Veins (VVCVV) multi-centre randomised clinical trial comparing the procedural pain profile of radiofrequency and mechanochemical ablation.

Results

i. Education outcomes
  - 138 responses were received. The management of chronic venous disease in the primary care setting is disparate and knowledge of current techniques is poor, despite extensive guidance.
  - 369 responses were received, from 197 vascular specialists and 172 primary care physicians. Superficial thrombophlebitis management is shown to be diverse and does not adhere to recent evidence.

ii. 461 patients were recruited. Patients suffering from chronic venous disease suffer from substantial quality of life impairment, including previously under-recognised depressive symptoms. Treatment of the underlying venous condition provides relief from venous symptoms and improves quality of life.
  - Patient symptoms and quality of life do not correlate with anatomical vein diameter, however clinical severity scores do.

iii. Predictive modelling produces models that account for 30-41% of the variability in post-operative scores for disease specific quality of life tools, generic quality of life tools, and clinical severity scores.
iv. The AVULS trial recruited 101 patients. Simultaneous treatment leads to improved clinical outcomes at up to 1 year and early quality of life improvement. Delayed treatment has a significantly increased risk of requiring further treatment (Odds Ratio 27.78, Relative Risk 18.36, p<0.0001). 95% of patients declining randomisation opted for simultaneous treatment.

v. New Technology Outcomes
   - The eSCOPE study recruited 70 patients in Europe with good technical outcomes.
   - The VVCVV trial (ongoing) has recruited 85 patients, with significantly reduced procedural pain found with mechanochemical ablation.

Conclusions

Varicose veins are a widespread problem with effective treatment that leads to a significant improvement in quality of life. Education and communication between community and hospital-based medicine is lacking. Predictive modelling of varicose vein symptoms remains difficult due to the multifactorial nature of the disease. Simultaneous treatment of varicosities during endovenous truncal ablation produces improved outcomes and is the option of choice for most patients. Early data on new technologies show they provide less painful procedures with similar outcomes as the established modalities.
STATEMENT OF ORIGINALITY

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Tristan Lane
19/01/2014
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<tbody>
<tr>
<td>ASVAL</td>
<td>Ambulatory Selective Varices Ablation under Local anaesthesia</td>
</tr>
<tr>
<td>ATV</td>
<td>Anterior Thigh Vein</td>
</tr>
<tr>
<td>AVP</td>
<td>Ambulatory Venous Pressure</td>
</tr>
<tr>
<td>AVULS</td>
<td>Ambulatory Varicosity avUlsion Later or Synchronised</td>
</tr>
<tr>
<td>AVVQ</td>
<td>Aberdeen Varicose Vein Questionnaire</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CBA</td>
<td>Cost-Benefit Analysis</td>
</tr>
<tr>
<td>CCA</td>
<td>Cost-Consequence Analysis</td>
</tr>
<tr>
<td>CCG</td>
<td>Clinical Commissioning Group</td>
</tr>
<tr>
<td>CEAP</td>
<td>Clinical Etiological Anatomical Pathological Score</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-Effectiveness Analysis</td>
</tr>
<tr>
<td>CES-D</td>
<td>Centre for Epidemiological Studies - Depression Score</td>
</tr>
<tr>
<td>CFA</td>
<td>Common Femoral Artery</td>
</tr>
<tr>
<td>CFV</td>
<td>Common Femoral Vein</td>
</tr>
<tr>
<td>CHIVA</td>
<td>Conservatrice et Haemodynamique de l'insuffisance Veinuse en Ambulatoire or Ambulatory Conservative Haemodynamic Management of Varicose Veins</td>
</tr>
<tr>
<td>CMA</td>
<td>Cost-Minimisation Analysis</td>
</tr>
<tr>
<td>CIVIQ</td>
<td>Chronic Venous Insufficiency Quality of Life Questionnaire</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Computed Tomography Venography</td>
</tr>
<tr>
<td>CUA</td>
<td>Cost-Utility Analysis</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability Adjusted Life Year</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Venous Thrombosis</td>
</tr>
<tr>
<td>ET1</td>
<td>Endothelin 1</td>
</tr>
<tr>
<td>eSCOPE</td>
<td>European Sapheon Closure System Observational Prospective Study</td>
</tr>
<tr>
<td>EQ5D</td>
<td>EuroQol 5 Domain Score</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>EVLA</td>
<td>Endovenous Laser Ablation</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GSV</td>
<td>Great Saphenous Vein</td>
</tr>
<tr>
<td>HES</td>
<td>Hospital Episode Statistics</td>
</tr>
<tr>
<td>HVVSS</td>
<td>Homburg Varicose Vein Severity Score</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
</tr>
<tr>
<td>MOCA</td>
<td>Mechanochemical Ablation</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MRV</td>
<td>Magnetic Resonance Venography</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Services</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>PCT</td>
<td>Primary Care Trust</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PFO</td>
<td>Patent Foramen Ovale</td>
</tr>
<tr>
<td>PPG</td>
<td>Photophlethysmography</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>QOL</td>
<td>Quality of Life</td>
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<tr>
<td>RFA</td>
<td>Radiofrequency Ablation</td>
</tr>
<tr>
<td>SFJ</td>
<td>Sapheno-Femoral Junction</td>
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<tr>
<td>SSV</td>
<td>Small Saphenous Vein</td>
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<tr>
<td>STARD</td>
<td>Standards for Reporting of Diagnostic Accuracy Studies</td>
</tr>
<tr>
<td>STS</td>
<td>Saphenous Treatment Score</td>
</tr>
<tr>
<td>SVT</td>
<td>Superficial Venous Thrombosis</td>
</tr>
<tr>
<td>UGFS</td>
<td>Ultrasound Guided Foam Sclerotherapy</td>
</tr>
<tr>
<td>VCSS</td>
<td>Venous Clinical Severity Score</td>
</tr>
<tr>
<td>VD</td>
<td>Maximum Vein Diameter</td>
</tr>
<tr>
<td>VDS</td>
<td>Venous Disability Score</td>
</tr>
<tr>
<td>VEINES-QOL</td>
<td>Venous Insufficiency Epidemiological and Economic Study Quality Of Life and Symptom Severity Questionnaires</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>VS</td>
<td>Vascular Surgeon</td>
</tr>
<tr>
<td>VSDS</td>
<td>Venous Segmental Disease Score</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous ThromboEmbolism</td>
</tr>
<tr>
<td>VV</td>
<td>Varicose Vein</td>
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<tr>
<td>VVCVV</td>
<td>VNUS Versus Clarivein for Varicose Veins</td>
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Chapter 1: Introduction
1.1. Varicose Veins

Varicose veins are defined as subcutaneous dilated veins $\geq$ 3mm in diameter on standing which are normally tortuous in nature (Bergan 2007). They are commonly found on the leg, associated with the saphenous veins (Great Saphenous Vein, GSV and Small Saphenous Vein, SSV), but can be found in the arms or on the trunk in certain circumstances.

1.1.1. Epidemiology

Varicose veins are a common and poorly understood problem, with an extensive history, with documentation of treatment existing in the Ancient Greco-Roman era (Perrin 2011). Varicose veins are dilated tortuous veins and they can cause a constellation of symptoms, from simple cosmesis to severe intractable ulceration and even death (Campbell et al. 2007; Bradbury et al. 1999; Evans et al. 1973; Cocker & Nyamekye 2008).
25-50% of the population suffer from varicose veins (Callam 1994; Beebe-Dimmer et al. 2005) and indeed only 10% of the sample population studied in the Bonn had no signs of venous disease (Rabe et al. 2003). Varicose veins show an increased prevalence with age and are more common in women (Beebe-Dimmer et al. 2005; Dimakakos et al. 2012). However recent work has shown that pregnancy rather than gender is a contributing factor to the development of venous disease (Jawien et al. 2003; Bihari et al. 2011).

Epidemiological studies have been performed but classification criteria has been disparate leading to difficulty assimilating those studies that have been published, leading to limited population level data (Beebe-Dimmer et al. 2005; Clark et al. 2010; Eklöf et al. 2009).

Recent work by international consensus bodies has lead to the formation of unified definitions of anatomy and venous disease (Eklöf et al. 2009; P. Gloviczki et al. 2011; P. Gloviczki & M. L. Gloviczki 2012; Murad et al. 2011; Vasquez & Munschauer 2010). This has lead to firm clinical and symptom scoring systems that allow for comparability between studies (Eklöf et al. 2004; Vasquez & Munschauer 2012; Vasquez et al. 2010). Future studies of epidemiology utilising these systems should provide robust evidence of the true epidemiological status of varicose veins.

Cohort data from the Edinburgh Vein Study, Bochum Study and the Bonn Vein Study (Robertson et al. 2013; Rabe et al. 2010; Schultz-Ehrenburg & Reich-Schupke 2009) has begun to provide data on progression of venous disease - 0.7-2.1% incidence of chronic venous insufficiency per year.
1.1.2. Aetiology

The pathophysiological basis of varicose veins remains unclear with differing theories advanced for the development of a symptomatic condition (Cleave 1972; Cleave 1959; Lim & Davies 2009; Bergan et al. 2008).

The two main competing theories are the descending theory and the ascending theory.

The descending theory was first popularised by Trendelenburg in 1891 (Trendelenburg 1891), with a description of the incompetence of venous valves causing reflux of blood and consequently hydrostatic pressure on the valves below. This causes dilatation of the vein, leading to valvular incompetence. This is purported to lead to a step-wise progression in incompetence down the lower limb. This theory is supported by anatomical studies of cadavers (Cotton 1961), which showed a significant reduction in the number of venous valves present in the incompetent long saphenous vein. The valves themselves have been shown to be hypotrophic and sclerosed (Corcos et al. 1996; Corcos et al. 2000). Additionally, work on venous haemodynamics indicate that venous pressure in varicose veins does not reduce on exercise, in contrast to the normal venous tree (Corley et al. 2010; Broderick et al. 2010; Broderick et al. 2009; Araki et al. 1994). These studies also support an increased venous hydrostatic pressure, which would necessarily come from a column of uninterrupted venous blood in an incompetent vein. Work by Kan and Delis identified improvements in venous volume ejection with exercise which had no effect on the reflux shown in incompetent veins despite a reduced compartment volume and pressure (Kan & Delis 2001) and this was confirmed with longer duration studies (Padberg et al. 2004). This would indicate that incompetent venous valves are the precursor to incompetent veins. This is supported by cohort data from the Bochum study (Schultz-Ehrenburg & Reich-Schupke 2009).
However, with the advent of ultrasonography, patterns of venous reflux which were not consistent with this theory emerged - competent segments existed in refluxing veins and vice-versa as well as incompetent veins anatomically separate from the hydrostatic columns (Labropoulos et al. 1997; Labropoulos et al. 2001; Labropoulos et al. 2005; Labropoulos et al. 2010; Abu-Own et al. 1994; Caggiati et al. 2006). Work describing the deterioration and degradation of the venous wall, leading to venous dilatation and consequently valvular incompetence has been put forward to explain these clinical scenarios. Interestingly, the cadaveric data that supports the descending theory also supports the ascending theory - the sapheno-femoral junction valve (SFJ - the "terminal" valve) was intact in the majority of cases dissected (Cotton 1961). Further cadaveric work has shown that 39.8% of ‘normal' great saphenous veins (GSV) contain segmental narrowing with complete aplasia in 17.4% and these areas had a weaker vein wall (Caggiati & Ricci 2000).

A retrospective study assessing over 4000 individual legs showed that neither the ascending nor descending theories can fully explain the various patterns of reflux seen in the population (Qureshi et al. 2010; Shepherd & Davies 2011; Wing et al. 2010). The complex nature of reflux seen implies that whilst both theories have a role, there is also a potential systemic component to chronic venous disease, which remains elusive despite extensive basic science research (Lim et al. 2012; Lim, Qiao, et al. 2011b; Lim, Gohel, et al. 2011a; Urbanek et al. 2004).

What is clear is that at a crucial point the superficial veins in the leg become dilated and their valves incompetent with a consequent raised venous pressure (Browse 1986; Pollack & Wood 1949). The development of varicose veins is a complex multifactorial pathway, with genetic and environmental variables (Criqui et al. 2007).
1.1.3. Classification of venous disease
Varicose veins have been subject of many differing classification criteria and present a therapeutic challenge as the symptomatology encountered by patients is so diverse (Campbell et al. 2007). Therefore, scoring systems have been developed in an effort to quantify the baseline and post-operative status.

1.1.3.1. Clinical Scoring Systems
Clinical scoring systems exist to provide an objective clinician delivered assessment of varicose vein disease. There have been many attempts to provide a structure on which to hang the difficult signs and symptom spectrum of this common disease (Bergan 2007).

1.1.3.1.1. Widmer Classification
The Widmer Classification or Basle criteria described in 1978 was based on the extensive Basle epidemiological studies performed in Switzerland during the 1960s and 1970s (Zinniker et al. 1978; Widmer et al. 1978; da Silva et al. 1979; Widmer & da Silva 1991).

The classification was blunt, using only 3 stages:
1. Oedema and dilated subcutaneous veins with corona phlebectatica
2. Trophic lesions of the skin with hyper- or depigmented areas
3. A healed or active ulcer.

This criteria lacks finesse due to the minimal differentiation of stages 2 and 3 and the lack of specificity of stage 1 being very broad. However, despite this it has been used in large scale studies such as the Edinburgh vein study which ran between 1994 and 1996 (Bradbury et al. 1999; Evans et al. 1997).

1.1.3.1.2. Hach Grading
Hach theorised that an incompetent GSV would lead to an internal circular shunt, overloading and dilating the deep venous system, leading to deep venous
incompetence as a consequence of superficial incompetence (Hach et al. 1980). In this theory the following four grades were explained in purely anatomical and reflux terms of the GSV:

I. Reflux in the groin  
II. Reflux to above the knee  
III. Reflux to just below the knee  
IV. Total reflux to the ankle

1.1.3.1.3. The Sytchev Criteria

In 1985 Sytchev published the precursor to the currently used classification systems (Sytchev 1985; Bergan 2007), using a combination of clinical stages, aetiology and haemodynamics.

The clinical classes described stages signs such as oedema, time of day of onset and degree of functional change, the aetiology described primary, secondary and congenital and the haemodynamics classified compensated, underloaded or overloaded (Bergan et al. 2007).

1.1.3.1.4. Clinical Etiology Anatomy and Pathology (CEAP)

The CEAP is a clinician completed classification score that allows careful quantification of the clinical status, etiology, anatomical location and pathological status of the patient's venous disease (Eklöf et al. 2004).

The earlier classification attempts prompted an international consensus conference of the American Venous Forum in 1994. This created the CEAP classification - this acronym stands for Clinical, Etiological, Anatomical and Pathophysiological. In 2004 this criteria was modified into the current revised CEAP classification (Eklöf et al. 2004).
The clinical component indicates disease severity, ranging from zero points, for completely asymptomatic patients, up to 6 points for active ulcers. The etiologic component denotes the venous disease as congenital, primary, or secondary in nature. The anatomic classification pinpoints the veins involved as superficial, deep, or perforating. The pathophysiological classification identifies the presence of reflux in the superficial, communicating, or deep systems, as well as the existence of outflow obstruction. The CEAP classification is doctor driven, and highlights the cause of the underlying venous abnormality however it is not sensitive in tracking progressive changes, with only 6 levels covering the whole spectrum of venous disease from its absence (C0) to an active venous ulcer (C6).

Clinical Stages

0: No visible or palpable signs of venous disease
1: Telangiectasia or reticular veins
2: Varicose veins (≥3 mm)
3: Oedema
4: Skin changes
   4a venous eczema or pigmentation
   4b lipodermatosclerosis and/or atrophie blanche
5: Healed ulceration
6: Active ulceration
Figure 2: The Clinical Stages of the CEAP Score

These stages are then further sub-divided with A (asymptomatic) or S (symptomatic)

"Basic" CEAP using all 4 aspects of the scoring system allows a full description of the venous problem in each patient - for example a patient with a symptomatic ulcer, varicosities and swelling due to primary superficial refluxing disease would be C6,3,2,S; Ep; As; Pr. This information is now easily available due to the gold-standard investigation of venous duplex, however is of limited value in most clinical practices and is therefore poorly reported (Eklöf et al. 2004). Often the highest clinical stage reached is the reported term.

An example scoring box is shown in Figure 3:
Figure 3: Example CEAP Scoring Proforma

Examples of the Clinical stages of the CEAP criteria are shown below:

"Advanced" CEAP utilises the full "Basic" CEAP criteria with the addition of named venous segments to allow mapping of the refluxing veins. These are numbered from 1-18 as below (Bergan 2007):

Superficial Veins:
- 1 Telangectasia or reticular veins
- 2 GSV above knee
- 3 GSV below knee
- 4 Small Saphenous Vein (SSV)
- 5 Non-Saphenous Veins

Deep Veins:
- 6 Inferior Vena Cava
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 (Paired)
16 Muscular: Gastrocnemial, Soleal veins, Other

Perforating Veins:
17 Thigh
18 Calf

Therefore, a full description of the above patient with an isolated incompetent GSV to the ankle would be C6,3,2,S; Ep; As; Pr 2,3.

1.1.3.1.5. Venous Severity Score

The Venous Severity Scoring System was designed by consensus of the American Venous Forum ad hoc committee (Rutherford et al. 2000). This was designed to complement and extend the CEAP scoring system by offering reactive scoring instruments. This includes the Venous Clinical Severity Score (VCSS), the Venous Segmental Disease Score (VSDS) and the Venous Disability Score (VDS).

1.1.3.1.5.1. Venous Clinical Severity Score (VCSS)

The VCSS is a clinician-completed tool, which includes 9 hallmarks of venous disease, each scored on a severity scale from 0 to 3. In order to generate a dynamic score, VCSS categories are scored individually (Rutherford et al. 2000). These
categories are pain, use of stockings, swelling skin changes and pigmentation, inflammation and induration, and ulcers (including number, size, and duration).

In 2007, an international ad hoc working group was created to revise the VCSS to update the terminology, simplify the application, and clarify ambiguities which was completed in 2010 (Vasquez et al. 2010).

The value of the VCSS is its ease of use along with an emphasis on the most severe manifestations of venous disease which are likely to show the greatest response to therapy allowing tracking and quantification of improvement (or deterioration) (Vasquez & Munschauer 2012).

1.1.3.1.5.2. Venous Disability Score (VDS)
The VDS is a three point score first introduced in the 1996 as a consensus document (Nicolaides et al. 1996) as part of the initial CEAP scoring system, and then revised in 2000 (Rutherford et al. 2000) as part of the VSS. This clinician completed score provides a blunt assessment tool for the impact chronic venous disease has on the patient.

0 is asymptomatic, 1 symptomatic but able to complete normal activities without compression, 2 dependent on compression therapy to complete normal activities and 3 is unable to complete normal activities despite compression therapy.

Whilst this is a blunt instrument it is easy to separate patients into categories and to assess general improvements. However, it is not very sensitive to change or clinical status (Sritharan et al. 2012).

1.1.3.1.5.3. Venous Segmental Disease Score (VSDS)
The VSDS utilises data derived from duplex ultrasound assessment of the varicose veins of the leg (Rutherford et al. 2000). Segments of refluxing vein are added up
with various weighting factors to provide a score assessing the haemodynamics of the affected leg. This does not represent a clinical assessment but an anatomical assessment.

The score is out of a maximum of 20, with 10 points available for venous reflux and 10 for venous obstruction. The score was developed as an adjunct to the CEAP scoring system using a consensus approach (Rutherford et al. 2000), but has been found to be difficult to interpret and is seldom used in clinical practice (Vasquez et al. 2007; Perrin et al. 2006). Interestingly, despite being developed in conjunction with the VCSS and VDS the correlation between VSDS and VCSS has been found to be statistically significant but very weak (r=0.29, p=0.048 (Kakkos et al. 2003)). Additionally after treatment for venous reflux the score is insensitive to the clinical outcome and successful treatment can lead to static or even increased scores (Kalodiki et al. 2012).

1.1.3.1.6. Saphenous Treatment Score

A newly developed scoring system, the Saphenous Treatment Score (STS) (Lattimer et al. 2012) aims to bridge the gap currently found in venous scoring systems - response to treatment. This would equate to the VCSS, with the CEAP and VSDS scores being less useful for disease change.

The score is derived from duplex ultrasound data, with venous reflux and occlusion scored differently and a composite score providing information on disease progression in a dynamic fashion. It scores and marks Above Knee (AK) and Below Knee (BK) segments separately and then adjusts the score depending on seriousness of the factor.
Table 1: STS Scoring System

<table>
<thead>
<tr>
<th>GSV Status</th>
<th>AK Score</th>
<th>BK Score</th>
<th>Total (=AK+ BK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Occlusion without reflux</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Competency without occlusion or reflux</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Reflux irrespective of occlusion or competency</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

This initial score is then weighted according to the following algorithm

Table 2: STS Scoring Algorithm

<table>
<thead>
<tr>
<th>Explanation</th>
<th>Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 3 present = final score for segment</td>
<td>3</td>
</tr>
<tr>
<td>If 1 present and no reflux precedent.</td>
<td>1</td>
</tr>
<tr>
<td>If no reflux or obstruction = final score. This is the normal &quot;healthy score&quot;</td>
<td>2</td>
</tr>
</tbody>
</table>

The score can be from 2-6. Therefore the normal "healthy" score would be 4, a completely obliterated vein following treatment would be 2 and a vein with reflux both above and below the knee would be 6. Whilst initially difficult to interpret, it is more user-friendly than the VSDS, and can equally be applied to the short saphenous vein.

The STS is designed for ablative techniques, however it has also been modified to allow the use in CHIVA and other saphenous vein sparing treatments where return of competency is the treatment aim (Lattimer et al. 2012).
1.1.3.2. Symptom Scoring Systems

Symptom scoring systems are designed to quantify the subjective improvement of patients varicose vein symptoms. They allow assessment of change due to disease progression and clinical intervention. These scores also assess the impact of the disease on the patient with worsening scores indicating larger impact of the disease in question. As has been found in other fields, the clinical or anatomical status of venous disease is often out of kilter from the patient's symptomatology (Bradbury et al. 2000; Bradbury et al. 1999; Guyatt et al. 1993; Guyatt et al. 1987; Guyatt et al. 1985; Cook et al. 1993).

These scoring systems can be generic and assess the patient as a whole, or they can be disease specific and are termed quality of life assessment (Guyatt et al. 1993).

1.1.3.2.1. Generic Quality of Life Assessment

Quality of life (QOL) is the objective assessment of the level of health and wellbeing a person has at that point in time (Fayers & Machin 2007). It has been extensively developed over the past thirty years to allow quantification of a singularly subjective thing (Watson & Preedy 2010; Romney & Evans 1996; Treurniet et al. 1997; Dolan et al. 1996; Kind & Rosser 1988; Torrance 1986; Fairclough 2010). The development and adjustment of the scales employed are driven by differing interpretations of quality of life using various differing models, such as functional, expectational, needs and satisfaction models in addition to the health status model (Fayers & Machin 2007).

The overall aim of the assessment is to allow the persons state to be defined as a numerical value between 1.00 (perfect health) and 0.00 (death). Negative values are allowed, as some levels of suffering are described as worth than death (Dolan 1997; Dolan et al. 1996). This allows comparison of the sampled group with the population as a whole.
Today’s scales are a very different proposition compared to the Karnofsky Performance Scale in 1948 (Fayers & Machin 2007; Karnofsky et al. 1962), which offered a clinician a scale between 0 (dead) to 100 (alive). This scale evolved into health profile measures such as the Sickness Impact Profile (Bergner et al. 1981) and the Nottingham Health Profile (Hunt et al. 1980; Hunt & McEwen 1980). Health profiles produce scores in differing domains, rather than an overall person score. These domains vary with the profile used, but include mental, physical and social aspects. The Sickness Impact Profile (Bergner et al. 1981) assessed the affect of illness on the patient, but required 136 individual questions covering 12 domains to do so. The Nottingham Health Profile (Hunt et al. 1980) is a more holistic assessment with 38 questions in 6 domains including social isolation and emotional reaction (Fayers & Machin 2007).

The next generation of scoring systems encompass the commonly used Medical Outcomes Study Short-Form Series (now owned by QualityMetric) and the EuroQol questionnaires (Ware & Sherbourne 1992; The EuroQoL Group 1990). These questionnaires were designed to provide sensitive measurement tools but remain simple and short, encouraging completion (Fayers & Machin 2007).

The Short-Form series includes the SF36, SF12, SF8, SF6, with each variation applying to the number of questions asked (Ware & Sherbourne 1992; McHorney et al. 1993; Mutebi et al. 2011; Hurst et al. 1998; Walters & Brazier 2005). These questionnaires remain health profiles, with the SF-36 assessing 8 health domains, split between mental and physical health. Improvements in individual domains are shown, and summary values for physical and mental status are produced. However conversion is required to give a single overall improvement figure (Brazier et al. 1998).
The EuroQol EQ5D and EQ-VAS is a 5 domain 3 or 5 level scoring system with a companion, but independent visual analogue scale (The EuroQoL Group 1990; Brazier et al. 1993; Dolan 1997). Systems of this nature are called "Utilities" and provide a single outcome score. Improvements in QOL can be seen, but the area of improvement is often difficult to identify clearly. The EuroQol EQ5D was designed to be a simple summation tool for use with other tools (The EuroQoL Group 1990; Dolan 1997).

Unlike the extensive Sickness Impact Profile, the modern generic scoring system provide a holistic measurement of QOL at the expense of relative insensitivity to changes in disease status (Guyatt et al. 1993). Good correlation has been shown between the SF-36 and the EQ5D (Brazier et al. 1993).

1.1.3.2.2. Disease Specific Quality of Life Assessment

Disease specific QOL investigates the effect of a disease on the patient. The development of disease specific QOL measures allows comparison of different patients suffering from the disease. The scores do not allow extrapolation to the general population, but does provide quantification of difficult symptomatology (Guyatt et al. 1993; Bradbury et al. 1999; Garratt et al. 1993).

1.1.3.2.2.1. Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ is a 13-question patient completed survey addressing multiple elements of varicose vein disease, first developed in 1993 (Garratt et al. 1993). It is designed for patient self-completion with a timescale of two weeks. Physical symptoms along with social issues, including pain, ankle oedema, ulcers, compression therapy use, and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins. The questionnaire is scored from 0 (no effect) to 100 (severe effect), and utilises a drawn picture of where patients feel affected by their veins.
1.1.3.2.2.2. Venous Insufficiency Epidemiological and Economic Study Quality Of Life and Symptom Severity Questionnaires (VEINES-QOL/Sym)

The VEINES-QOL/Sym is a 26-question patient completed survey developed in 2003, which addresses symptoms, daily life limitations, change in condition and psychological impact of the venous disease. Responses are rated on 2-point to 7-point response scales of intensity, frequency, or agreement. The time frame for questions is the previous 4 weeks. The raw scores are then translated into a standardized scale for comparison (Lamping et al. 2003).

1.1.3.2.2.3. Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ)

The CIVIQ is a 20 or 14 question survey developed in 1996 and then refined in 2011 (Launois et al. 1996), which again assesses patient reported symptoms and the impact of chronic venous disease on quality of life. It has four principle domains and a maximum score of 100 with lower being a better quality of life.

1.1.3.2.2.4. Homburg Varicose Vein Severity Score (HVVSS)

The Homburg Varicose Vein Severity Score (HVVSS) (Rass et al. 2011) is a recently designed venous disease questionnaire comprising of 4 patient completed symptom questions scored from 0-5, 2 clinician completed clinical staging questions scored from 0-5 and one haemodynamic benchmark requiring the use of photoplethysmography, scored from 0-3.

This gives a total score of 0-33, which is then standardised to 100 (via dividing the score by 33 and multiplying by 100).

1.1.3.2.2.5. Specific Quality of Life and Outcome Response – Venous (SQOR-V)

The SQOR-V is a 45-item survey for patient completion, which assesses physical and psychosomatic symptoms providing a score out of 100 for each category. Each item is scored from 1-5 and grouped into 1 of 5 sub-categories with normalization to a maximum score of 20 per sub-category. As quality of life due to venous disease improves the score decreases (Guex et al. 2007; Guex et al. 2010).
1.1.3.2.6. Assessment of Burden in Chronic Venous Disease (ABC-V)

Recently developed, this 39-point survey assesses the burden of venous disease as opposed to the specific quality of life due to venous disease. It has a scale of 0 (best) – 90 (worst). The tool is aimed primarily at population scale assessment (Guex et al. 2010).
1.1.4. Outcome Measures

Outcome measures provide the clinician with four major benefits:

1. Assessment of the interventions value.
2. Opportunity to refine patient treatment
3. Ability to improve patient information and informed consent

In venous treatment, outcome measures in venous treatment can be difficult - which should we use as our gold standard - technical success or patient improvement?

![Diagram of Measuring Venous Disease]

Figure 4: Outcome Measures and Assessment Techniques for Venous Disease

As the above Figure 4 shows, there are many ways to assess venous treatments. Due to this it is difficult to assimilate the many trials performed due to heterogenous reporting (Thakur et al. 2010). This is despite clear guidance given regarding reporting standards (Kundu et al. 2007) and the use of international vein

1.1.4.1. Vein Occlusion Rate

Vein occlusion rates are the standard classical tool for assessment of treatment success (Gohel & Davies 2008; Ulloa 2012; Parente & Rosenblatt 2003; Proebstle et al. 2004; Proebstle et al. 2006). This does not equate to clinical success, as only 10% of the population in some studies have been shown to have no signs of venous reflux, however not all of these patients have venous disease that is symptomatic (Callam 1994; Rabe et al. 2003). This is assessed with formal venous duplex ultrasonography with assessment of vein patency and reflux, as in initial diagnostic scans.

Difficulties have arisen comparing occlusion rates, as different studies have reported different criteria for "occlusion" and "technical success". Some classify success as complete occlusion, some as partially patent but no reflux and some as a short section of patent vessel with reflux (Rasmussen et al. 2010; Rasmussen et al. 2013; Proebstle et al. 2008; Bisang et al. 2012). This has led to the American Venous Forum and Society of Interventional Radiology publishing guidance on reporting standards. This describes that technical success should be complete occlusion without reflux of blood (Kundu et al. 2007; Kundu et al. 2009). It is yet to seen whether this has affected reporting standards with new trials.

1.1.4.2. Recurrence Rate

The rate of recurrence has traditionally been the primary outcome for open stripping procedures especially prior to duplex ultrasound. However, recurrence of varicosities does not depend on the failure of the primary procedure, as it may relate to progressive disease or alternative feeding vessels (Kostas et al. 2004; Allegra et al. 2007; Blomgren et al. 2004).
As the progression rate of venous disease is difficult to determine, utilising recurrence as an outcome measure may lead to conflicted reports (Davies & Lim 2010).

1.1.4.3. Ulcer Prevention

One of the major goals of venous treatment, ulcer prevention is an extremely difficult outcome measure, as progression is difficult to determine (Davies & Lim 2010) and once ulcers have occurred the relative risk of relapse is far greater than the initial risk (Nelzén & Bergqvist 1991). Finally the length of time that ulcers take to heal and recur can prevent adequate results due to duration of follow-up required (Gohel et al. 2007).

Recent work by the Bonn Vein Study has assessed patients 6 years after initial review (Rabe et al. 2003; Rabe et al. 2010). This showed an annual incidence of 2% for varicose veins and also 2% for chronic venous insufficiency. Interestingly, and of great concern on an epidemiological scale, is the number of patients who progress from uncomplicated venous disease (CEAP C2 stage) to chronic venous insufficiency (CEAP C3-6 stages). Over 6 years, 19.8% of those with non-saphenous vein C2 disease progressed (3.3% per year) and 31.8% of those with saphenous vein C2 disease progressed (5.3% per year). With the current climate of rationing of treatment (Audit Commission 2011) this may have extreme consequences on future treatment.

However, reduced recurrence and improved quality of life can be obtained with good treatment (Gohel et al. 2007; Gohel et al. 2005).
1.1.4.4. Health Status Assessment

Health status assessment is designed to allow decisions on an epidemiological scale - are treatments effective and are they beneficial to the patient? It allows assessment beyond simplistic technical success rates to patient success rates.

The driving force behind such assessments is the need to plan and provide appropriate care for all patients, and the difficulty in tallying this with the outputs of hospitals and care providers (Rosser & Watts 1972).

1.1.4.4.1. Quality of Life

Quality of life (QOL) as described before is a key component of Health Status Assessment. With the use of the various generic scoring systems (Guyatt et al. 1993; The EuroQoL Group 1990), and if necessary utility conversion tools (Brazier et al. 1998; Ware 2000), a single summation score can be generated to provide a QOL measure.

1.1.4.4.2. Quality Adjusted Life Year

QOL summation scores can be extrapolated into the QALY - the quality adjusted life year. This is a value of disease burden and represents the quality and quantity of life lived, and is used to assess interventions from a cost-effectiveness viewpoint.

This calculation is performed using a combination of QOL, life expectancy and standardised discount tables producing the value for a QALY (Sugden & Williams 1978; Gudex 1986; Sassi 2006).

1.1.4.4.3. Disability Adjusted Life Year

The Disability Adjusted Life Year or DALY is essentially the inverse of the QALY. It represents the life lost to living with a condition (Murray & Acharya 1997; Arnesen & Nord 1999; Anand & Hanson 1997; Sassi 2006) - the burden of the disease.
1.1.4.5. Economic Analysis

Once a quantification of the quality of life or disability level has been arrived at, the principles of health economic analysis (HEA) can be used to develop outcomes using probability models. The generation of utility scores are required.

This allows cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA) to show whether treatment interventions are of benefit to the wider population (Torrance 1986; Sugden & Williams 1978; Gomes et al. 2010; O'Brien & Briggs 2002; Barshes et al. 2012). The aim of HEA is to provide the best treatment at the best price, but has been unfairly categorised as championing the cheapest treatment (Marsden & Wonderling 2013). Through HEA more expensive treatments with good level improvements can be put forward instead of cheap treatments with minimal improvements (Marsden & Wonderling 2013).

Figure 5: A schematic describing costs and effectiveness for economic assessment.
1.1.4.5.1. Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is defined as "a comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, e.g. Reduced mortality or morbidity" (Facey 2006; Marsden & Wonderling 2013).

It is a key factor in justifying treatment for a patient compared to the population.

The principles include calculating the costs and effects of treatment A and the costs and effects of treatments B and/or C etc. Then the differences in cost and effect are calculated. Finally a cost per unit of effect is calculated (Gray et al. 2011). Whilst this is of general interest, in a comparison of the differences, this is generally converted into an incremental cost-effectiveness ratio (ICER) - the difference in costs divided by the difference in effects.

Whilst the definition of costs is self-explanatory, the definition of effect can vary with the treatment or intervention. For standardisation, the QALY is commonly used to compare different conditions and treatments. The outcome of ICER being £x per QALY is now a standard outcome, with NICE ascribing a ICER of £20,000 per QALY as appropriate (Gohel et al. 2010). New NICE produced guidelines in 2013 performed extensive cost-effectiveness analysis on multiple questions regarding the outcomes of varicose vein intervention. This led to recommendations of endothermal ablation as a first line treatment over surgery, as it is more cost-effective than open surgery {NationalInstituteforHealthandCareExcellence:2013vv}-CITATION_IS_EMPTY.

1.1.4.5.1.1. Cost-Utility Analysis

This can be described as a sub-set of CEA as the process of creating QALYs uses utility theory and utilities to process the QOL values gathered. The use of this
description is mainly to clearly differentiate a study as using generic measures of health outcome (Torrance 1976; Drummond et al. 2005; Gray et al. 2011).

1.1.4.5.2. Cost-Benefit Analysis

This defined by the International Network of Agencies for Health Technology Assessment (INAHTA) as: "A comparison of alternative interventions in which costs and outcomes are quantified in common monetary units" (Facey 2006).

This is a key factor in assessing the economic benefit of a treatment to the population as a whole.

Cost-Benefit Analysis (CBA) attempts to quantify the monetary value of the additional health benefits gained and then to assess whether this is more or less than the costs involved (Gray et al. 2011). This in theory offers an ideal assessment model for health treatment decisions, however due to the difficulty in defining monetary values for human life both from a practical and moral viewpoint, CBA has not been utilised extensively in the medical literature (McIntosh et al. 2010).

1.1.4.5.3. Alternative Methods

Other methods such as Cost-Consequence Analysis and Cost-Minimisation Analysis are available, but are uncommonly used.

Cost-Consequence Analysis presents the data on costs and the data on outcomes separately, allowing the reader to interpret the information. This can be complex data and therefore seldom presented in such a way (Gray et al. 2011).

Cost-Minimization Analysis uses the assumption that all intervention outcomes are equal and therefore aims to reduce costs - the "race to the bottom". This is seldom performed as the assumption of equivalence is difficult to prove and can lead to dangerous mis-leading results (Gray et al. 2011).
1.1.5. Consequences of varicose veins

Varicose veins cause a myriad of symptoms causing significant morbidity. The condition also causes clinical problems.

1.1.5.1. Symptoms

Symptoms of varicose veins can vary extensively but the vast majority of patients report tired heavy legs that ache, itch and can swell. The lumpy varicosed veins can be quite painful and lead to avoidance of activity (Campbell et al. 2007; Bradbury et al. 1999).

Varicose vein disease is complicated in that often the patient reported symptoms are not well correlated with the clinical severity of the disease (Conway et al. 2011), and the size of the incompetent vein is also not a good screening tool (Gibson et al. 2012; Shepherd et al. 2011).
1.1.5.2. **Superficial Thrombophlebitis**

Superficial venous thrombophlebitis or more correctly superficial venous thrombosis (SVT) is inflammation of a superficial vein in the context of thrombus in the vein. Superficial venous thrombophlebitis has previously been described as a benign self-limiting condition, however it is becoming increasingly apparent that it has a significant association with deep venous thrombosis (DVT) and consequently pulmonary embolism (PE) (Decousus et al. 2011). Up to 30% of patients presenting with a SVT has a concomitant DVT. The majority of SVTs have traditionally been treated with non-steroidal anti-inflammatories (such as ibuprofen), however often it is mistaken for an infection and treated with antibiotics and rarely are compression hosiery prescribed.

1.1.5.3. **Deep Venous Thrombosis**

Varicose veins have traditionally been described as benign and without significant morbidity outside of its own disease, however recent work by Heit et al. (Heit et al. 2000) and as previously mentioned Decousus et al. (Decousus et al. 2011) has shown
that not only are varicose veins associated with deep venous thrombosis via superficial thrombophlebitis, but also that they are an independent risk factor, with an Odds Ratio of 4.19 at the age of 40 years. This therefore translates into a significant burden of disease due to deep venous thrombosis and subsequent post-thrombotic syndrome (Heit 2005; Prandoni & Kahn 2009).

1.1.5.4. Skin Changes and Venous Ulceration

Uncomplicated chronic venous disease (CVD) can lead to chronic venous insufficiency (CVI), which via a multifactorial process revolving around increased venous hydrostatic pressure (Pollack et al. 1949; Pollack & Wood 1949; Browse & Burnand 1982; Ghauri & Nyamekye 2010; Bergqvist et al. 1999; Nelzén et al. 1994) lead to cell level changes and essentially a build-up in toxins and cellular by-products that cannot be transported away from the distal dependent areas leading to tissue damage and ultimately tissue breakdown.

This becomes clinically evident when venous skin changes appear (CEAP clinical class C4) - these progress from the early stages of venous eczema, through lipodermatosclerosis, to finally open ulceration. Whilst venous eczema can be reversed with appropriate treatment, lipodermatosclerosis is irreversible. It represents the deposition of fibrin on a microscopic level, which inhibits cellular transport and creates a vicious circle of degradation, which impairs many other signalling and transport pathways (Browse & Burnand 1982; Lim & Davies 2009).

Venous ulceration is the end-point of the disease pathway and is a chronic debilitating wound that is extremely slow to heal without assistance. Epithelial breakdown leads to an oozing, painful smelly wound which has a significant stigmatic and morbidity effect (Palfreyman et al. 2010). Despite effective treatment with compression bandaging (Nelson 2010) the ulcers are slow to heal and relapse frequently. Finally the rate of recurrence without invasive treatment is 35-56% (Marston et al. 1999; Ruckley 1997; Gohel et al. 2007). Surgical treatment in the
context of elderly patients with venous ulceration showed a significant reduction in both ulcer recurrence at 3 years (56% to 31%, p<0.001) and a significant increase in ulcer free time (100 vs 85 weeks, p=0.007) (Gohel et al. 2007).

Compression therapy has been the mainstay of treatment and is extremely expensive - estimated at costing 1% of the NHS total budget per year (Callam 1994; O'Donnell & Balk 2011). The average cost of healing a venous ulcer in a formalised study protocol varies between $1327 for a 2.5 cm diameter ulcer (5 cm²) to $5289 for a 5 cm diameter ulcer (20 cm²) (Marston et al. 1999). Although ulceration can be healed, the scarred skin (in addition to other co-existent skin damage such as atrophie blanche) is at high risk of recurrent ulceration (Magnusson et al. 2006).

It is therefore vital to try and prevent venous ulceration - the aim of the current joint programme of the American Venous Forum and American College of Phlebology is to reduce the rate of venous ulceration in the USA by 50% (O'Donnell & Balk 2011). A new trial investigating the role of endovenous technologies on ulcer healing is underway currently in the UK - the Early Venous Reflux Ablation (EVRA) trial (EVRA Trial Participants 2013).

1.1.5.5. Progression of venous disease

Chronic venous disease and venous ulceration is a disease of the elderly (Heit et al. 2001; Rabe et al. 2003; Criqui et al. 2003) however, venous ulcers do not just appear - they are the end point of the venous incompetence disease spectrum. How and who progress remains difficult to quantify.

Longitudinal studies in varicose vein disease are rare and technically challenging (Heit et al. 2001). To fully encapsulate the disease screening programmes must be performed such as the San Valentino, San Diego or Bonn Vein studies (Rabe et al. 2003; Cesarone et al. 2002; Kaplan et al. 2003; Criqui et al. 2003). Prevalence rates in these studies vary from 7% (Cesarone et al. 2002) to 30% (Rabe et al. 2003;
Kaplan et al. 2003). These studies included duplex ultrasound investigation and found a rate of reflux of 20% in the superficial system and 10% in the deep system (Rabe et al. 2003; Kaplan et al. 2003; Criqui et al. 2003)

Recent studies have confirmed the prevalence rates in other populations such as Greece (15%) (Dimakakos et al. 2012), and Pakistan (34.8%) (Khan et al. 2012) though these studies were based on questionnaire and clinical assessment only.

These studies have all provided point prevalence rates, however rates of progression and therefore indications of at risk populations is lacking. This is likely due to the timescales involved and the highly mobile young population with the initial stages of venous disease. CEAP Class C1 female patients (spider veins and telangiectasia) have been shown to have a reflux rate of 46% (Engelhorn et al. 2007) and 44% even if the leg is asymptomatic (Engelhorn et al. 2007).

Another study from this Brazilian group has assessed 92 female patients with primary varicose veins with two duplex ultrasound scans 33 months apart (Engelhorn et al. 2012). This showed an increase in SSV reflux from 24% to 30% (p<0.001) and a change from isolated segmental to multi-segmental GSV reflux. Additionally normal GSVs and SSVs developed segmental reflux in 25% and 11% respectively. Overall the venous reflux progressed in 33% of GSVs and 13% of SSVs. This would provide an annual progression rate of 11% for GSVs and 4% for SSVs.

The Bonn Vein Study II (Rabe et al. 2010) has re-assessed 64.4% of the original Bonn Vein Study (Rabe et al. 2003) patients (n = 1978/3072) after 6.6 years. The study found that 19.8% of C2 patients with non-saphenous disease progressed to higher CEAP classes and 31.8% with saphenous disease. That produces a progression rate of 3% and 4.8% per annum.
The rate of progression coupled with the falling rate of intervention into varicose veins (Lim et al. 2010) provides sobering information for the elimination or even reduction of chronic venous disease and venous ulceration. With constrained budgets and a lack of understanding from primary care physicians (Lane:2013eo) and vascular specialists (Scurr et al. 2011), this will become a much more important issue in years to come.
1.1.6. Investigations

Due to their complex nature of varicose veins with low flow rates and advanced haemodynamics, a multitude of differing investigations are available to the clinician and researcher.

Contrast venography of the lower limb venous system was originally the only investigation available but was invasive, required the use of iodinated contrast and x-ray imaging. This necessarily limited its use in clinical practice, as did the difficulty in interpreting the ascending and descending venographic imaging in the superficial system (Gloviczki et al. 2011). However it continues to be used for assessment and treatment of deep venous disease.

Computed Tomographic Venography (CTV) and Magnetic Resonance Venography (MRV) are increasingly being used for assessment of central and deep venous abnormalities in conjunction with conventional contrast venography. Venography itself - the previous gold standard - shows a reproducibility of 0.6 (Kalodiki et al. 1998). MRV is of special interest in the assessment of arterio-venous malformations (Gloviczki et al. 2011; Lee et al. 2007).

1.1.6.1. Duplex Ultrasonography

The introduction of duplex ultrasound revolutionised the management and diagnosis of venous incompetence in the context of varicose veins (Gloviczki et al. 2011). Duplex ultrasound uses a combination of B-Mode ultrasound to give an anatomical two dimensional picture linked to colour doppler processing that superimposes pulsed wave ultrasound with Doppler signal processing onto the image and was developed between 1959 and 1974 with further improvements since (Satomura 1959; Strandness 1996; Jaffer & Aslam 2009).
Duplex ultrasound allows anatomical, haemodynamic and reflux details to be extracted at the same time during a non-invasive imaging method without the use of ionising radiation. It remains the "gold standard" investigation for venous disease (Marston 2002; Gloviczki et al. 2011). The clear images obtainable allow measurement of structures at variable depths from the skin's surface. Colour duplex allows clear identification of individual veins that are refluxing or obstructed (Marston 2002; Szendro et al. 1986; Vasdekis et al. 1989).

In the assessment of venous reflux an augmentation of standing venous flow by calf muscle compression is completed. Once the compression is released, a normal reflux time (until the valves close) is defined as < 500 milliseconds (Sarin et al. 1994; Marston 2002; P. Gloviczki & M. L. Gloviczki 2012; Vasdekis et al. 1989). This is then repeated for all veins and all vein segments creating a venous tree diagram of the limb. This is a lengthy procedure even in the most skilled of hands, and requires multiple calf compressions with the patient standing still. This can lead to non-completed scans and less than perfect information. It has been estimated that the experienced vascular scientist will take 40 minutes to perform one venous duplex of a lower limb (Marston 2002). In addition, ultrasound is a dynamic 'online' imaging modality requiring interpretation and completion skills that vary from person to person(Singh et al. 1998; Jaakkola et al. 1996) despite standardised training (The Society for Vascular Technology of Great Britain and Ireland 2012).

However, to counter these difficulties, studies into the reproducibility of the measurements obtained have shown excellent accuracy with very low levels (<10%) of intra- and inter- observer variability (Asbeutah et al. 2005; Vasdekis et al. 1989). In addition compared with the previous "gold standard" diagnostic test - descending digital subtraction venography, duplex ultrasound was found to be far more sensitive - 77% vs 35-44% (Neglén & Raju 1992; Nicolaides 2000).
Venous duplex ultrasound also allows a quantification of venous reflux via the measurement of peak reflux velocity (PRV), peak reflux flow (PRF), reflux time (RT), time averaged flow (TAF), time averaged velocity (TAV) and vessel diameter (VD). However, these values do not all correlate with the clinical scenario found in the patient - RT has been shown to poorly correlate with clinical and haemodynamic outcomes, but peak reflux velocity and flow have been shown to differentiate between clinical stages (Yamaki et al. 2002; Neglén et al. 2004). Additionally these values have not been shown to indicate progression or classify limbs with any greater accuracy than the CEAP clinical staging system, and so are not of benefit outside of the research community.

Advanced calculation techniques assessing the inflow and outflow of the limb have led to some researchers investigating an index called the venous arterial flow index (VAFI). This assesses the flow in the common femoral artery (CFA) and the common femoral vein (CFV) in a supine patient. An index of less than 1 indicates a normal competent venous system with figures above 1.2 indicating chronic venous disease (Kahle et al. 2002). This index has also been shown to improve back to normal levels after treatment (Kahle et al. 2001; Rass et al. 2010; Kahle & Leng 2004). However, it remains a research tool at present with limited literature available and it is yet to be assessed compared to other measures such as clinical scoring systems such as the VCSS or patient reported outcome measures such as the AVVQ or EQ-5D.

Recent studies have shown the presence of a saphenous vein pulsation due to conduction of arterial pressure waveforms through the venous tree, and that that the presence of the pulsation is associated with a worsened CEAP clinical stage (Hingorani et al. 2009; Lattimer et al. 2012). The pulsation is found in 75% of patients with reflux, and reflux was present in 88.9% of those with a pulsation
(Lattimer et al. 2012). These early studies have identified further complex haemodynamics detectable with duplex ultrasonography, and thus this remains a research tool at this stage.

### 1.1.6.2. Ambulatory Venous Pressure

Ambulatory venous pressure represents the gold standard of invasive haemodynamic assessment (Nicolaides & Zukowski 1986; Marston 2002). A cannula is placed in a pedal vein and connected to a pressure transducer. This allows the measurement of a baseline standing pedal venous pressure, the mean ambulatory venous pressure (AVP) and venous refill time (RT). AVP is measured as the steady state achieved after 10 tiptoe movements which empty the calf veins. RT is defined as the time for the pressure to return to 90% of baseline venous pressure.

As is clear from the physics of hydrostatic pressure, the baseline measurement is not of importance and merely related to the column of blood above the cannulation site (i.e. The patient's height) (Nicolaides & Zukowski 1986).

The AVP and RT allow a clear delineation of the whole venous system of the leg. A normal value for AVP is 15-30 mmHg and as the AVP increases, the risk of skin changes, ulceration and increased CEAP grading increases (Nicolaides & Zukowski 1986; Marston 2002). In the worst cases, AVP actually increases with the exercise. This is seen in patients with both deep venous reflux and obstruction. AVP therefore represents a quantifiable measure of venous claudication and can be as high as 110 mmHg (Nicolaides & Zukowski 1986). RT should be longer than 18 seconds in the normal limb, but may reduce down to 3 seconds in the worst deep venous reflux situations (Nicolaides & Zukowski 1986), as this indicates filling from reflux rather than capillary bed inflow.
These measurements are of great interest to the research community as they offer a way of validating offer non-invasive investigation methods, but are invasive and limited value in clinical practice except in the limited cases of venous claudication or deep venous reconstruction.

1.1.6.3. Plethysmography

Plethysmography is the determination of changes in volume, and as such multiple different procedures have been developed.

1.1.6.3.1. Air Plethysmography

Air plethysmography offers a further non-invasive test of venous reflux which allows quantification of reflux in difficult cases where venous duplex is inconclusive. However it can be difficult to perform and interpret (Gloviczki 2007).

Air plethysmography utilises the concept of volume displacement during the reflux filling of varicose veins. The patient is placed supine with the foot to be investigated elevated. An air filled cylinder is placed around the lower leg, connected to a pressure transducer. The air bag is filled to a baseline level air pressure to ensure good leg contact (6 mmHg). This is then calibrated by filling a smaller bag (placed in between the cylinder and leg) with 50 ml increments of body-temperature water (Christopoulos et al. 1987; Lattimer et al. 2013; Lattimer et al. 2012). Then the calibration water is removed and a baseline recording is taken. The device is demonstrated in Figure 7.
Figure 7: The air-plethysmograph consists of a poly-vinyl chloride (PVC) air chamber (5 litre capacity) connected to pressure transducer (P) and a smaller PVC bag (1 litre capacity) used for calibration by injecting known volumes of water (V). Reproduced with Permission from Christopoulus et al (1987)

The patient then stands and on plateauing of the volume a measurement is taken which represents the functional venous volume (VV). The time taken to reach 90% of the VV is the venous filling time 90 (VFT90) with the venous filling index (VFI) representing 90% of the VV divided by the VFT90.

The patient then performs a tiptoe manoeuvre to provide the ejected volume (EV) before then performing 10 tiptoe manoeuvres to produce a the residual volume (RV). This allows calculation of the ejection fraction (EF) and residual volume fraction (RVF). The procedure is demonstrated in Figure 8.
Figure 8: Diagrammatic representation of typical recording of volume changes during standard sequence of posmral changes and exercise. Patient in supine position with leg elevated 45 degrees (a); patient standing with weight on nonexamined leg (b); single tiptoe movement (c); ten tiptoe movements (d); same as in (b)/(e). VV = functional venous volume; VFT = venous filling time; VFI = venous filling index; EV = ejected volume; RV = residual volume; Ef = ejection fraction; RVF = residual volume fraction. Reproduced with Permission from Christopoulus et al. (1987)

Finally, the air plethysmograph is removed and the leg immersed in water with volume displacement measurements being take at the ankle and at the top of where the air cylinder was - this represents the volume of leg inside the cylinder that corresponds to previous measurements (Christopoulos et al. 1987; Christopoulos et al. 1988).

As can be seen from the above methodology this is a complex and lengthy process, but does provide excellent haemodynamic information, with an 80% sensitivity and 99% positive predictive value for abnormal reflux (Marston 2002; Criado et al. 1998). A VFI of <2ml/s is considered normal, with increasing VFI results correlating with increased severity of clinical disease (Marston 2002; Lattimer et al. 2012; Lattimer et al. 2013). A normal VFT 90 is >70 seconds, and RVF 20% (Christopoulos et al. 1987).

Again, after interventional treatment these parameters return to normal and the return of VFI has been shown to be predictive of good clinical outcome (Owens et al. 2000; Ibegbuna et al. 2003).
However, the reproducibility of air plethysmography is controversial, with coefficients of variation ranging from 7.5% to 27%. With repeated measures (3 or more) a variability of 10% or less can be obtained (Yang et al. 1997; Asbeutah et al. 2005).

In view of the length of time taken for each assessment (approx 15-20 minutes (Marston 2002)) this is a tool best used for research and venous disease quantification, especially as venous duplex ultrasound is required for anatomical data in all cases (Gloviczki et al. 2011).

1.1.6.3.2. Strain Gauge Plethysmography

Strain gauge plethysmography utilises the same principle as air plethysmography but instead of a pressure transducer connected to the air chamber, it has air chambers connected to strain gauges which provide a change in electrical resistance in response to a change in leg diameter and therefore strain gauge length (Brakkee & Vendrik 1966; Persson et al. 2009; Rosfors & Blomgren 2013).

An occlusive (60mmHg) cuff is placed around the the thighs of a supine patient with strain gauge wires around the largest part of the calf. When the leg has been filled to a maximum volume the cuff is released and blood is allowed out of the limb (Rosfors & Blomgren 2013). An alternative dynamic method is to measure before, during and after 15 knee bends (Persson et al. 2009).

The observed volume curves (see Figure 9) are obtained and allow the calculation of the Outflow Fraction at 1 second (OF₁) and at 4 seconds (OF₄).
Normal has been quantified as OF$_1$ of 0.2 and OF$_4$ of 0.62 with reduced values indicating outflow obstruction (Persson et al. 2009; Rosfors & Blomgren 2013). Reproducibility variation has been shown to be within 6% (Rosfors & Blomgren 2013).

Strain gauge plethysmography is utilised mainly in the assessment of venous obstruction and remains a research tool due to the complexity of application and the need for an occlusive cuff.

**1.1.6.3.3. Photophlethysmography**

Photophlethysmography (PPG) utilises a light emitting diode to transmit infrared light into the dermis which is then backscattered to a receiver, and this varies with capillary blood flow (Abramowitz et al. 1979; Nicolaides & Miles 1987; Marston 2002). The time taken for the capillaries to refill is an indication of the arterial
inflow and the venous outflow (Sam et al. 2006), and is defined as the venous refill time (VRT).

The PPG probe is attached 10cm above the medial malleolus and then baseline measurements are taken with the patient standing motionless. After 10 tiptoe manoeuvres further measurements are taken with the patient motionless, with automatic calculation of the VRT curve (Sam et al. 2006).

The VRT has been shown to be shortened in patients with venous disease and decreases with CEAP stage (Marston 2002; Darvall et al. 2010). Some studies have defined a normal VRT as >18-20 seconds (Nicolaides & Miles 1987; Darvall et al. 2010), however this is not a standardised measure and dependant on local protocols (Marston 2002). Following treatment VRT normalises in patients who have symptom resolution (Darvall et al. 2010), and those with normal VRT but symptoms do not have symptomatic resolution after treatment (Darvall et al. 2010). Additionally there is no correlation between improvement in VRT and QOL (Shepherd et al. 2011). However, wide ranges of AVP have been demonstrated for similar VRTs (Nicolaides & Miles 1987) and indeed for C3-C6 clinical stages (Darvall et al. 2010), and its use for fine measurement is debatable.

The utility of PPG is limited as it does not offer quantifiable haemodynamic data but does provide a screening test for symptomatic chronic venous insufficiency. Venous duplex ultrasound is still required for anatomical detail.

1.1.6.4. Cross Sectional Imaging

Computed tomographic venography (CTV) and Magnetic Resonance Venography (MRV) are axial imaging techniques that provide intra- and extra-luminal information on the anatomical basis of the venous tree. These techniques require dedicated protocols for timing of contrast and imaging and can be difficult to interpret (Min et al. 2010). They offer excellent anatomical data but no
haemodynamic data and little intra-luminal data (Marston et al. 2011). The use of such cross-sectional imaging is limited to the investigation of deep venous system, which may be the driving force in 10-15% of cases (Arnoldussen et al. 2013).

**1.1.6.4.1. Computed Tomography Venography**

CTV allows the assessment of the central venous system, which is becoming more important with the recognition that iliac vein stenoses and inferior vena cava abnormalities account for a proportion of patients with distal disease and normal leg veins (Smith et al. 2011; Iqbal & Nagaraju 2008).

The concept of stenting the iliac vein abnormalities including deep vein thromboses leading to incompetent but low resistance vessels has emerged with the use of duplex and intravascular ultrasound providing extensive data sets. Raju and Neglen have revolutionised the principles of deep venous intervention (Neglén & Raju 1992; Neglén & Raju 1993; Neglén & Raju 2000; Raju 2013; Raju et al. 2006; Raju et al. 2012; Raju et al. 2002). This has gradually become more accepted worldwide, with further studies confirming initial findings (Rosales et al. 2010; DeRubertis et al. 2013; Delis et al. 2007).

**1.1.6.4.2. Magnetic Resonance Venography**

Magnetic resonance imaging and magnetic resonance venography (MRV) has advanced in recent years with advances in imaging and computing power (Fitzgerald et al. 2006; Wadajkar et al. 2013; Priest et al. 2012; Arnoldussen et al. 2012; Glockner & Lee 2010). Now with the potential to provide dynamic flow images, MRV has become the research tool of choice for deep venous disease. It’s use in the treatment of superficial venous disease is limited to investigating for the presence of proximal stenoses or occlusions, and for planning of deep venous intervention (Fitzgerald et al. 2006). This is due to cost, patient acceptability, access to scan time and the complexity of scanning protocols.
1.1.6.5. Intravascular Ultrasound

Intravascular ultrasound (IVUS) is an invasive test that utilises a 360 degree ultrasound probe inserted into the vein of interest. This provides a multi-planar dynamic assessment of vein segment, with simultaneous digital subtraction venography (Neglén et al. 2007; Raju et al. 2010). This has been popularised by Raju and Neglen with placement of venous stents for demonstrable lesions seen on venography and IVUS (Raju et al. 2002).

Initial work performed by the same authors discovered additional findings with IVUS - intraluminal and mural details that are not possible to see with the so-called "lumen-o-gram" of venography (Neglén & Raju 2002). The diameter and affected cross-sectional areas of the veins can be analysed and calculated and this can allow careful monitoring of the grades of stenosis and outcomes of venoplasty and venous stent placement (Neglén & Raju 2000).

1.1.6.6. Digital Subtraction Venography

Digital subtraction venography allows the visualisation of flow using an invasive test. Use of ascending and descending venograms allow the visualisation of obstruction (ascending) and reflux (descending) pathologies. It also allows intervention in the form of stenting and venoplasty. It is reserved for deep venous investigation.

The use of venography has recently expanded due to the increased knowledge of iliac vein compromise and the beneficial effects of stenting without reflux correction (Raju 2013). However it suffers from a lack of sensitivity in single planes, with the complex nature of haemodynamics and stenoses, additionally the inter-observer agreement (kappa) is only 0.7 (Kalodiki et al. 1998; Phillips et al. 1995; Neglén & Raju 1992). Therefore, multi-planar imaging is needed to identify stenoses.
However, the ability to perform interventions and to provide detailed planning for deep venous bypass procedures means that venography remains in the phlebologists' armoury (Khanna & Singh 2012).

Figure 10: An image from the a digital subtraction venography procedure showing extensive deep venous disease and collateralisation
1.1.7. Current Treatment Methods of Superficial Venous Disease

The treatment of superficial venous disease had been standard for hundreds of years until the recent development of sclerotherapy in the mid 20th century and then ultrasound guided endovenous ablation (Perrin 2011). Prior to this the treatment available was open surgery using segmental avulsion or sapheno-femoral junction ligation and stripping of the long saphenous vein (Mayo 1904; Babcock 1907; Dodd 1955).

These recent advances have greatly changed the patient experience, the logistics of intervention and have provided the opportunity for ambulatory treatment. Treatment has previously been assessed by merely technical means – occlusion and recurrence rates, however patient preference and quality of life assessments are also vital components of treatment analysis. Quality of life assessment pre and post intervention allows a vital stratification of treatment methods (Gohel & Davies 2008).

Due to the lack of a perfect 'one-size-fits-all' solution to superficial venous disease many treatments are available (Lane et al. 2011). This can make it extremely difficult for the clinician to make a fully informed choice between modalities let alone between equipment. With the huge patient population optimum treatment can lead to vast improvements in both individual and population health and well-being, in excess of that offered by optimal treatment of arterial disease (Rasmussen et al. 2011; Gohel et al. 2010; Carradice et al. 2011; Chard et al. 2011). Despite these beneficial outcomes total procedure numbers are falling in the UK – see Figure 11 (Lim et al. 2010). In 2011-2012, the total number of procedures performed had fallen further to 27, 605, a further fall of 26% {HESOnline:2013uk}-CITATION_IS_EMPTY. New guidance from NICE has recently been published advocating treatment for symptomatic varicose veins (Marsden et al. 2013).
Compression therapy using either graduated elastic hosiery or compressive bandaging has become the standard conservative treatment for patients with uncomplicated varicose vein disease. It has also become a screening method for patients with nonspecific symptoms, with a trial of compression hosiery allowing symptom improvement assessment and risk stratification for treatment. Such stratification is becoming especially important in the current age of austerity. The evidence base for compressive hosiery is sparse, and a recent systematic review (Palfreyman & Michaels 2009) showed a heterogeneous evidence base with stockings were shown to improve symptoms, but not to effect progression or recurrence of varicose veins (Carpentier et al. 2011).

Compressive hosiery is not without its own morbidity, leading to poor compliance (Raju et al. 2007). This led over half of those patients randomised to conservative treatment in the large REACTIV randomised controlled trial to chose to withdraw and undergo surgery within 3 years (Michaels et al. 2006). Additionally only patients with adequate arterial systems are eligible for treatment (Mosti et al. 2012).
Unsurprisingly therefore, in the recent publication of guidance from the UK's National Institute for Clinical Excellence (NICE) it was recommended that compression hosiery should not be offered as standalone treatment, unless patients are not suitable for intervention (Marsden et al. 2013).

Compression bandaging is effective but expensive and time consuming. It is therefore reserved for the management of venous ulceration (O'Meara et al. 2012). The technique involves the wrapping of layers of bandage around the leg to invoke increased pressure and improve venous flow. The bandage is routinely changed once or twice a week, and prevents the patient from bathing fully (Moffatt 2006). A randomised clinical trial has shown that four layer bandaging offers the optimum bandaging technique (Moffatt et al. 2003). After completion of ulcer healing, compression hosiery is recommended for life to try and prevent recurrent ulceration of the damaged skin (O'Meara et al. 2012).

Interestingly, in a study of 129 patients who have had an ulcer healed by compression bandaging and for whom lifelong compression hosiery is advocated, only 52% wore them everyday and 16% on most days. The two key factors associated with non-compliance were that patients felt stockings were uncomfortable or unnecessary (Jull et al. 2004).

Surgical intervention has been shown to provide significant quality of life improvement for minimal additional healthcare cost when compared to conservative management (Ratcliffe et al. 2006).

Compression therapy is advocated after intervention, aiming to reduce post-operative pain, haematoma and oedema (Huang et al. 2013). Duration and type of compression are controversial with limited data available (Huang et al. 2013). Huang et al.'s recent meta-analysis on compression after open surgery indicates
that short-term duration of 1 week post-operatively is optimal, as recommended by NICE (Huang et al. 2013; Marsden et al. 2013).

In a recent cost effectiveness study, conservative management was considered to have a cost of zero for comparison with intervention (Gohel et al. 2010). However this does not take into account the significant expenditure in time and materials associated with symptomatic venous disease requiring compression hosiery or bandaging. Intervention was found to be cost-effective even though conservative management was free. Ulcer disease increases the cost of chronic venous insufficiency enormously (Marston et al. 1999). The benefits of intervention to prevent such complications are clear, with 2 million working days lost to venous disease in 2002 (Rabe & Pannier 2010).

1.1.7.2. Neuromuscular Stimulation

Neuromuscular stimulation is a new modification of an old technique, which utilises electrical signals transmitted through the skin to either stimulate the calf muscle bulk or the peroneal nerve to elicit a muscular jerk and pump blood out of the leg. Research is on-going, but these devices may provide a treatment option for patients unable to be treated with compression and unsuitable for venous intervention (Tucker et al. 2010).

1.1.7.3. Intermittent Pneumatic Compression

Intermittent pneumatic compression utilises an inflatable sheath (or boot) which is placed around the lower limb. This is connected to an air pump which inflates bladders in the sheath to produce extrinsic pressure and hence force fluid out of the blood. This increases lymphatic and venous return and arterial inflow (Delis, Slimani, et al. 2000b; Delis, Labropoulos, et al. 2000a; Harfouche et al. 2005; Sheldon et al. 2012; Patterson & Cardullo 2013).
These devices are effective, however they do require the patient to be stationary and can be disturbing due to the recurrent inflation/deflations. The devices are also expensive at £800 for the pump and £80 per pair of sheaths.
1.1.7.4. Open Surgery

Open surgery has been the surgeon's primary armament, and until recent advances in endovenous therapy, surgical intervention was the main treatment option available.

Figure 13: Representation of the Sapheno-Femoral Junction reproduced from Gray's Anatomy (Gray & Lewis 1918)

1.1.7.4.1. Saphenofemoral Junction Ligation and Great Saphenous Vein Stripping

Saphenofemoral Junction ligation and stripping of the great saphenous vein remains the commonest standard treatment, with extensive experience allowing for high quality results including outpatient clinic and local anaesthetic treatment (Rasmussen et al. 2011; Disselhoff et al. 2011; Menyhei et al. 2008; Perrin 2011).
Figure 14: SaphenoFemoral Junction Dissection (a), Ligation (b), Great Saphenous Vein Stripping (c), and Multiple Stab Phlebectomies (d).

Traditional surgery requires open dissection of the groin, identification of the saphenofemoral junction (SJF) and ligation of the junction and major tributaries (a "high-tie" or "crossectomy"). The great saphenous vein (GSV) can be left in situ or "stripped" using a mechanical device or a cryoablation probe (described in more detail below) (Menyhei et al. 2008). Long-term trials have shown a significantly reduced reoperation rate with stripping of the GSV in addition to SFJ ligation, though not recurrent visible varicosities (Jones et al. 1996; Dwerryhouse et al. 1999; Winterborn et al. 2004).
Figure 15: Detail of SFJ Dissection {Scheltinga:ux}-CITATION_IS_EMPT Y.

Figure 16: Detail of Application of PIN stripper at the proximal aspect of the GSV {Scheltinga:ux}-CITATION_IS_EMPT Y.
Different stripping devices such as 'Perforate Invagination' (PIN) strippers have been shown to have equivalent outcomes to standard stripping devices (Durkin et al. 1999).

Varicosed branch veins are then "avulsed" or "phlebectomised" using standard stab incisions and hooking out the vein (Ramelet 2002; Bull & Hiatt 1948).

Ligation and stripping removes the source of reflux, however requires a significant procedure, and can lead to severe post-operative morbidity (Rasmussen et al. 2011). Saphenous nerve lesions are found in approximately 5-15% of cases, though some series have found a rate of 39% if the below knee segment is stripped (Flu et al. 2008; Holme et al. 1990; Kostas et al. 2007).

Recurrence post treatment is relatively common (van Rij et al. 2003), up to 45% at 10 years (Nelzén & Fransson 2013), and predominantly due to either strip-track recurrence or groin neovascularisation (Munasinghe et al. 2007; Egan et al. 2006;
Carradice et al. 2011; van Rij et al. 2003). Additionally due to anatomical variation, careful dissection may still miss important tributaries (Vaz et al. 2013; van Rij et al. 2003).

It remains the most common procedure available (Shepherd et al. 2010) to most UK clinicians. This is due to the relatively low costs of equipment and the procedure (£980 in the UK (Gohel et al. 2010)). The most performance recent data available - 2011-2012; from the Hospital Episode Statistics show that of a total of 27,605 procedures 40% of treatment was open surgery (11,120), 36% was endovenous ablation (9,826) and 16% foam sclerotherapy (4,502) {HESOnline:2013uk}-CITATION_IS_EMPTY. This must be compared to 2006 when 31,642 open procedures were performed (Lim et al. 2010) - a 65% reduction in numbers performed.

The open procedure has extensive patient reported outcome measure data which allows robust conclusions to be drawn that it remains a suitable and appropriate treatment if endovenous treatment is unavailable (Gohel et al. 2010; Lim et al. 2010; Marsden et al. 2013). A demonstration of this is seen in Figure 18 - the proportion of patients treated with open stripping has fallen significantly, however the combined outcome scores have only risen marginally.
Indeed recent long term studies have shown good outcomes for open procedures which are equivalent to endovenous procedures (Rasmussen, Lawaetz, Bjoern, et al. 2013a; Rasmussen, Lawaetz, Serup, et al. 2013b). Patient satisfaction remains high even at ten years (Nelzén & Fransson 2013). In this ten year study of 104 mixed primary and recurrent legs, 85% of patients were satisfied with the outcome, despite a duplex ultrasound proven recurrence rate of 45%. Interestingly, there was no correlation between ultrasound detected recurrence and symptomatology - 65% of those with recurrence reported no symptoms, and 63% described an excellent cosmetic result at 2 years and 10 years (Nelzén & Fransson 2013).

1.1.7.4.2. Varicosity Avulsion - Ambulatory Selective Varices Ablation under Local anaesthetic (ASVAL)

The Ambulatory Selective Varices Ablation under Local anaesthesia or ASVAL technique utilises standard stab avulsion technique to remove all visible varicosities (Pittaluga et al. 2009; Pittaluga et al. 2010). This corrects all visible signs of
varicose vein disease, which leads to a substantial improvement in certain areas of symptom scores however it does not necessarily remove the source of reflux, though in one study (Pittaluga et al. 2010) it has reversed reflux in the truncal vein.

The abolition of the venous reservoir is purported to be the mechanism via which symptoms improve, as without a low resistance tank to fill, the venous blood returns to the heart via normal routes.

1.1.7.4.3. Haemodynamic Normalisation - Conservatrice et Haemodynamique de l'insuffisance Veinuse en Ambulatoire (CHIVA)

Haemodynamic normalisation or Conservatrice et Haemodynamique de l'insuffisance Veinuse en Ambulatoire (CHIVA) is a technique where the truncal veins are preserved but incompetence is tracked and interrupted throughout the leg. The preservation of GSV allows for it to be used as bypass graft conduit in the future. The flow of blood is tracked carefully with ultrasound to elucidate flow loops and abnormal "shunts". These shunts are classified according to location, and direction and then ligated under local anaesthetic to provide appropriate flow from superficial to deep systems (Mowatt-Larssen & Shortell 2010; Franceschi 1992; Mendoza 2002). Six different shunt types have been described, with multiple sub-types. These describe the anatomical and pathological spread of the incompetence seen in most cases (Mendoza 2002).
This procedure leads to good results overall, however the procedures can be intellectually and technically challenging with few centres able to reproduce results (Mowatt-Larssen & Shortell 2010; Maeso et al. 2001; Carandina et al. 2008; Parés et al. 2010). In those centres, the results compete with the best outcomes of other techniques - recurrence rates of 18% at ten years compared to 35% for stripping in the same centre (Carandina et al. 2008).

Additionally, expert ultrasonography in the presence of the treating physician is required to identify the flow loops and to provide information on the appropriate haemodynamic reconstruction.

The process of CHIVA involves multiple steps and these are named "CHIVA 1" and "CHIVA 2", and have more than one step in their completion (Mowatt-Larssen 2010).
Figure 20: Part of the CHIVA Technique. HCP = Hydrostatic pressure column. Reproduced from Pares et al. 2010 (Parés et al. 2010)
1.1.7.5. Endovenous Ablation

The principles of endovenous ablation are the same – minimally invasive destruction of the incompetent veins using either thermal energy or sclerosant and mechanical disruption. This leads to fibrosis of the vein wall and ablation of vessel lumen, thus removing the incompetent vein from the circulation. The advantages of endovenous treatment are faster procedure times, reduced post-operative pain, optional general anaesthesia, patient preference and the possibility of truly ambulant treatment. The various endovenous methods are detailed below. The qualities of endovenous treatment have been reviewed in depth with a meta-analysis of 64 studies, covering over 12,000 treated limbs, with a mean 2.5 year follow-up period in 2009 (VanDenBos:2009dy)-CITATION_IS_EMPTY and again in 2012, with 5 year follow-up data (Siribumrungwong et al. 2012).

Whilst such analyses are hindered by non-standardised reporting (Thakur et al. 2010), it has produced significant positive data for endovenous treatment. Endovenous procedures have been shown to be at least equivalent to open surgery for technical success (Xenos et al. 2009). Coupled with ease of use and patient acceptability, this has led to a huge, increasing practice and success of the procedure.

Figure 21: Endovenous Modalities
These new modalities also offer concurrent treatment of reflux for patients with venous ulceration providing reduced recurrence and relapse rates. The use of these techniques may also offer improved healing rates, however there is currently no significant evidence backing this hypothesis.

All techniques are based on the passage of the treatment catheter inside the vein from an ultrasound guided needle puncture in the caudal aspect of the vein. Standard Seldinger technique \cite{Seldinger:1953tk} under ultrasound guidance is used to gain access to the vein as shown by the schematic Figure 22.

![Figure 22: Seldinger Technique for Endovenous Ablation](image-url)
1.1.7.6. Endovenous Thermal Ablation

Recent work by NICE has recommended that endothermal ablation should be the first line treatment on outcomes of cost-effectiveness analysis. It offers lower cost treatment with improved outcomes (National Institute for Health and Care Excellence 2013).

1.1.7.6.1. Cryoablation

Cryoablation is a hybrid of open and endovenous techniques, utilising an open groin dissection and ligation of the SFJ with tributary ligation before feeding of a cryoprobe down the GSV to the knee. Using either liquid nitrogen dioxide or carbon dioxide fed to the cryoprobe tip cools the tip to -85°C. The cryoprobe is then removed, stripping the vein by cryoadhesion (Breuninger 2001). Whilst it has not been widely adopted, studies have shown equivalent results compared to standard stripping techniques in terms of pain, return to normal activities and recurrence rates (Stotter et al. 2006). Disselhoff et al have shown equivalence between EVLA and cryostripping at 5 years with respect to recurrence and neovascularisation (62%...
versus 51% \( p=0.264 \) and quality of life measures (reduction of AVVQ of 66% versus and 72% \( p=0.72 \), and reduction of VCSS of 69% versus 71%, \( p=0.23 \)) (Disselhoff et al. 2011).

1.1.7.6.2. Endovenous Laser Ablation (EVLA)

This technique utilises a diode laser of varying wavelength transmitted via a glass optic fibre to the area of interest. Laser ablation has been used in certain arterial cases since the 1980’s with limited uptake, and remains a niche procedure (Wissgott et al. 2004; Wissgott et al. 2013; Todd et al. 2013). The laser ablation provides removal of atherosclerotic plaque lesions present in occluded arteries. This technique initially used a bare optical fibre, but due to significant rates of vessel perforation a jacketed tip was developed (Welch et al. 1987; Ashley et al. 1990). However, even in the jacketed tips the temperatures in blood reach 700 °C (Verdaasdonk et al. 1991). The basic principles of arterial laser atherectomy have been modified for use in the venous system. Access sheaths must accommodate 600 nm fibres, and are generally 4-5 French in size (1.35-1.67 mm).

The technique of endovenous laser ablation (EVLA) has advanced greatly since its description in Spanish by Boné in 1999 (Boné 1999) and then in English in 2001 by Navarro et al (Navarro et al. 2001). These studies described local anaesthetic (with and without sedation) treatment of incompetent truncal veins using an 805 nm and 810 nm diode laser.

Following Food and Drug Administration approval, the technique has grown enormously. The major drawback of laser technology is the requirement for a specially shielded; secure treatment room and the requirement for laser goggles for all in that room. In addition, all practitioners must be fully accredited in the safe application of the laser device.
The advancement of technology has lead to a proliferation of different laser wavelengths, with the wavelengths offering different treatment profiles. The wavelengths used for venous treatment were initially based on the absorptive properties of deoxygenated haemoglobin - venous blood (Friebel et al. 2006). Subsequently, however, longer wavelengths have been investigated, as these are absorbed by water in the vein wall cells. In theory this should be a more effective and direct method of treatment and reduce the energy requirement for fibrosis (Almeida et al. 2009). This has led to many different wavelengths being available for use, with 810, 940, 980, 1064, 1320, 1470 and 1540nm lasers available, with 2100nm in the prototype phase (Ash & Moore 2010; Massaki et al. 2013). Longer wavelength lasers have been shown in some studies produce a better post-operative complication profile, with reduced pain being the major benefit (Kabnick 2006; Proebstle et al. 2005; Doganci & Demirkilic 2010; Sadek et al. 2011).

Technical success is highly dependent on energy delivered by unit length (J/cm) with the target for occlusion being > 70 J/cm, but no ill effects of increased energy delivery are seen until 160 J/cm (Carradice et al. 2010; Proebstle et al. 2002).

A meta-analysis in 2009 found that EVLA showed significantly better technical success characteristics, compared to open surgery, sclerotherapy and radiofrequency ablation (VanDenBos:2009dy). However the analysis did produce a surprising improvement in occlusion rates over successive years despite no further intervention, which is difficult to explain. A more recent meta-analysis including modern devices shows no significant difference in occlusion rates (Siribumrungrungwong et al. 2012).

However, the exact mechanism of action of laser treatment is unknown, with multiple theories being put forward:

1. Heat conduction through residual blood in the vein from the fibre tip
2. Direct contact conduction via the vein wall
3. Steam bubble transfer

A recent in vitro experiment found identical temperature profiles for both 940nm and 1470nm lasers (Van Den Bos et al. 2012), indicating that the different treatment profiles found in vivo are more related to procedural differences than wavelength. Further work by Amzayyb et al assessed the deposition of carbon onto laser fibre tips in the presence of blood. This study showed no difference between laser wavelengths (Amzayyb et al. 2010). The data available to compare wavelengths is confusing as some wavelength comparison trials have compared bare tipped forward firing laser fibres with radial firing jacketed tip laser fibres (Almeida et al. 2009; Doganci & Demirkilic 2010). Kabnick's 2006 study using identical fibres demonstrated a reduction in pain and bruising for the 980nm wavelength compared to 810nm (Kabnick 2006), and Proebstle et al.'s 2005 study compared 940nm with 1320nm again with identical fibres and found similar results (Proebstle et al. 2005), however other studies have shown no difference in outcomes between laser wavelengths (980nm vs 1470nm) (Duman et al. 2013).

A major cause of postoperative pain following EVLA is thought to be due to vein perforation and inconsistent pullback speed leading to over and under treatment zones (Schmedt et al. 2006; Proebstle et al. 2002). The use of a special tips to prevent contact with the vein wall have been shown in vitro and in vivo to produce a more even treatment, less wall perforations and lower post-operative pain and bruising (Vuylsteke et al. 2010; Vuylsteke et al. 2012; Massaki et al. 2013). However, unfortunately these tips have also been shown to have worsened occlusion rates (88.9% vs 97.7%, p<0.0001 at 5 months) (Prince et al. 2011). A study by
Schwarz et al. showed improved pain and bruising outcomes with no difference in occlusion when comparing 1470nm bare forward firing and radial firing fibres (Schwarz et al. 2010). Unfortunately, the radial firing group was also treated with a reduced energy delivery and so conclusions on the cause of the improved side-effect profile cannot be drawn. Finally, \textit{ex vivo} models have found that pulsed wave laser treatment provides a different profile of wall damage, with pulsed treatment appearing to reduce the number of wall perforations, except for the 2100nm laser tested (Massaki et al. 2013).

Figure 24: An example of specialised "Tulip" Tip (Vuylsteke et al. 2012)

Long-term outcomes are few in number, due to the young nature of the technique and the constantly changing laser wavelengths available. However, in series reporting follow-up beyond one year, occlusion rates remain high, from 82% at 5 years in 62 legs (Rasmussen et al. 2013) to 97.1% at 4 years in 511 limbs (Desmyttère et al. 2007).

Overall EVLA offers a reliable, technically successful technique for endovenous ablation, which can be done in the day surgery or clinic setting. Current advances in longer wavelength lasers are allowing stepwise progression to the ultimate aim of technical success without post-operative complication.

1.1.7.6.3. Endovenous Radio-Frequency Ablation (RFA)

Endovenous Radiofrequency ablation (RFA) was first described by Goldman et al. in 2000 (Goldman 2000). A systematic review in 2009 outlined the literature and status of the two main competing radiofrequency catheter brands licensed for use in
the UK and Europe – Covidien Venefit (previously named VNUS) and Olympus Celon (Gohel & Davies 2009). In the USA, only the VNUS brand is licensed for endovenous ablation. Worldwide, the catheter choice has expanded from the initial VNUS ClosurePlus™ to include Covidien ClosureFAST™ 7cm and 3cm catheter, the Olympus Celon RFITT™ catheter and the new FCare EVRF™.

1.1.7.6.3.1. Covidien ClosurePlus and ClosureFAST - The Venefit Procedure
The technique is the same as utilised for endovenous laser ablation – ultrasound guided, under tumescent local anaesthesia and Seldinger cannulation technique. General anaesthesia is optional in most cases and the procedures can be done in a clean clinic room environment. The Venefit system requires the use of tumescent anaesthesia to ensure adequate pain relief and adequate compression of the vein to allow secure ablation. It requires access via a 7 French sheath (2.3 mm).

The system has recently been renamed from VNUS to Venefit, with the ClosureFAST catheters changing from VNUS ClosureFAST to Covidien ClosureFAST.

The current Venefit catheters are the second generation of the VNUS Closure Plus™ technology first launched in 2000, and upgraded in 2006. VNUS Closure Plus required a continuous pullback technique whereas the ClosureFAST™ catheter operates in either 7cm or 3cm segments. The 3cm ClosureFAST catheter was launched in 2012. All the VNUS catheters use the same generator - the Covidien ClosureRFG™. The two differing catheter generations represent different energy modalities. Both catheters use a thermocouple in the tip of the electrode to provide a feedback loop to the generator. This then provides variable wattage in real-time to provide a stable therapeutic temperature.

The Closure Plus treatment technique used bipolar radiofrequency energy to cause induction heating to 85°C in the vein wall. This leads to collagen protein
denaturing and constriction of the vein wall. In theory, this does not require
tumescent anaesthesia, but the initial studies produced a 3% rate of full-thickness
skin burns and a 33% rate of paraesthesia (Manfrini et al. 2000). This provoked the
use of tumescent fluid with optional anaesthetic as a requirement of the procedure
(Manfrini et al. 2000). It also requires a slow pullback speed of 3cm/min (0.05cm/s).

![Closure Plus Catheter](image)

Figure 25: The Closure Plus Catheter (Manfrini et al. 2000)

The EVOLVeS study of 86 limbs compared SFJ ligation and stripping with RFA
using the VNUS Closure Plus™ device. This showed improved quality of life
outcomes and reduced pain profiles for the RFA device which persisted at 2 years of
follow-up and a closure rate of 92% (Lurie et al. 2003; Lurie et al. 2005). Gale et al's
study in 2010 compared EVLA and RFA using the Closure Plus catheter and
showed reduced bruising and perioperative pain but a worsened 1 year ablation rate
{Gale:2010ka}-CITATION_IS_EMPTY.

The catheter was refined as the VNUS ClosureFAST™ (now Covidien
ClosureFAST™). This produces a thermocoagulation effect, with a target
temperature of 120°C at the treatment section. The treatment is performed in
segments, with treatment temperature applied over 7cm segments for 20 seconds.
The thermal energy causes protein degradation through conduction. The segmental
approach ensures that all sections of the vein are treated equally. It also improves
treatment speed - sections of 7 cm or 3 cm segments treated per 20 seconds (0.35
cm/s or 0.15 cm/s respectively).
The initial report of treatment of 252 limbs obtained a 99.6% closure rate at 6 months, 96.9% at 1 year and 92.6% at 3 years (Proebstle et al. 2008; Creton et al. 2010; Proebstle et al. 2011). Peri-procedural complications were low with a 0.4% rate of paraesthesia and pigmentation at 3 years. Zero DVTs or PEs were reported (Proebstle et al. 2011). Recent work on 667 limbs has shown the superiority of the newer generation catheter, with a higher rate of occlusion (98% vs 88%, p<0.001) (Zuniga et al. 2012).

The ClosureFAST catheter is limited to veins larger than 2.33mm in internal diameter due to catheter size, however it can be argued that veins smaller than this size are unlikely to produce haemodynamically significant venous reflux, though diameter alone is a poor criterion (Gibson et al. 2012; Perrins et al. 2013).

Several studies have been published showing significantly improved quality of life scores and improved venous clinical severity scores after RFA when compared to laser (Almeida et al. 2009) as well as reduced post-operative pain (Shepherd et al. 2010; Gale et al. 2010; Goode et al. 2010). A 2009 meta-analysis of endovenous treatment found that RFA offered at least equivalent technical success as sclerotherapy and open surgery (VanDenBos:2009dy). A more recent meta-analysis in 2012 showed improved, but not statistically so, rates of occlusion with the ClosureFAST compared to EVLA (Siribumrungrungwong et al. 2012).

1.1.7.6.3.2. Olympus/Celon RFITT™

The RFITT system utilises an induction heating method rather than conduction, so is similar to the original Closure Plus catheter (Boon et al. 2010; Camci et al. 2009; Goode et al. 2010). The RFITT™ system uses the same continuous pullback mechanism as EVLA, which can lead to areas of over and under treatment. It has a recommended pullback speed of <1.5cm/s (Braithwaite et al. 2013). The technique
can be used with or without tumescent anaesthesia due to the inductive nature of treatment (Braithwaite et al. 2013), however due to the earlier results from the Closure Plus studies (Manfrini et al. 2000) most reports in the literature describe the use of tumescent in the majority of patients, whether treated under general, regional or local anaesthetic - up to 85% (Camci et al. 2009; Boon et al. 2010; Braithwaite et al. 2013). The LARA study which compared RFITT to EVLA describes a tumescentless approach as standard in the RFITT arm of the trial. However, of 44 limbs randomised to RFITT, 11 (25%) were treated with tumescent anaesthesia (Goode et al. 2010).

Outcomes are good with this device, with occlusion rates of 92.4% at 1 year, with experienced operators obtaining 98.4% (Braithwaite et al. 2013). Pain profiles and complication rates are similar to ClosureFAST, and improved compared to 810nm EVLA (Goode et al. 2010; Braithwaite et al. 2013; Proebstle et al. 2011). However, no comparative studies between ClosureFAST and RFITT have been performed.

1.1.7.6.3.3. **EVRF**

The EVRF system by F Care Systems was first developed in 2009 and utilises a pulsed radiofrequency 4Hz signal to thermocoagulate the vein wall. It uses different size needles for thread veins (K3i and K6i) and catheters for 1-3 mm veins (CR12i and CR30i) and 4 mm veins and above (CR45i) [EVRF:wg]. There is no peer-reviewed data regarding this device, however, two studies are available from the UK distributor website [ModernAestheticSol:th]. The first pilot study from Belgium describes 40 patients treated in 2011-2012. This achieved a 100% 1 month vein occlusion rate and 92.5% at 6 months (Thomis 2013). The
second study describes 313 limbs treated with EVRF, and described a 99% 1 month occlusion rate and a 97.2% 1 year occlusion rate (Szabo 2013). These initial studies indicate good outcomes and good patient satisfaction, however peer-reviewed publications and comparator studies are required prior to firm decisions being made about this additional device.

Overall, whichever catheter is used, RFA offers a safe, reliable, fast technique for the treatment of varicose veins.

1.1.7.6.4. Steam

The newest of the thermal ablation catheters, the SVS (Steam Varicose System, CermaVEIN, France) has recently been presented as a new and novel technique. Initial pilot studies have shown an encouraging occlusion rate (90% at 6 months in 20 limbs) using small amounts of thermal energy transferred by puffs of steam (Van Den Bos et al. 2011). The catheter transfers pulses of pressurised steam at 120°C to a treatment tip via a narrow (1.2mm diameter) flexible steel catheter. The steam pulses then condense in the area of the tip, transferring energy to the surroundings at a rate of 60 joules per pulse. The technique requires standard tumescent anaesthetic technique as do EVLA and RFA. The catheter tip is positioned 2-3 cm from the SFJ.

Pilot studies in sheep and humans have shown good occlusion rates as above, however 35% had some evidence of non-refluxing recanalisation. The pilot studies used one pulse per cm, or 60 joules/cm, to match equivalent EVLA energy densities (Van Den Bos et al. 2011). Histological studies of animal vein have shown equivalent outcomes to RFA treatment (Van Den Bos et al. 2011).

A recent multi-centre study assessing 88 limbs in 75 patients showed a 6 month occlusion rate of 96% at 6 months and 92% at 12 months, however Kaplan-Meier survival analysis indicates a 86% occlusion rate at 12 months (Milleret et al. 2013).
This study increased the number of pulses to two or three dependent on vein calibre, leading to energy densities of 120-240 joules/cm. Despite the increased energy density, pain >5 on a visual analogue scale was only reported in 10% of patients and the median pain reported was 0.75 (Milleret et al. 2013).

Outside of these two published studies, little literature exists on this catheter due to its recent development and the far greater market penetration of EVLA and RFA. Larger, long-term and comparative studies are required before widespread use of this technique over more established modalities can be justified.

1.1.7.6.5. Summary

Endothermal ablation has many facets, all of which appear to work with similar efficacy, and minor technical differences. Crucially, recent work is building to describe limited differences between modalities (Malskat et al. 2013), confirming clinical experience (Shepherd et al. 2010; Rasmussen et al. 2011; Rasmussen, Lawaetz, Bjoern, et al. 2013a; Rasmussen, Lawaetz, Serup, et al. 2013b). This allows clinicians to continue to treat patients with their preference of device, as their expertise builds with that endothermal ablation device.
1.1.7.7. Sclerotherapy

Sclerotherapy became an avenue of great interest after the development of the hypodermic needle in 1841 by Parvaz (Perrin 2011; van den Bremer & Moll 2010). Liquid sclerotherapy was initially used for injection into aneurysmal sacs by Pravaz, before Chassaignac described its use for varicose veins in 1855 (Tisi et al. 2006). However, due to extremely poor results with infection and even gangrene (Tisi et al. 2006; Perrin 2011) the technique fell out of favour.

Fegan described an effective method of using liquid sclerotherapy using sodium tetradecyl sulfate (STS) and produced excellent results using a diligent empty vein technique to cause vein fibrosis, however his prescription of 6 weeks of compression bandaging might be a limiting factor today (Bergan 2007; Fegan et al. 1964; Fegan 1963). Liquid sclerotherapy produced poor results in general use, requiring very careful application with diligent follow-up protocols (Bergan 2007). Sclerosants are deactivated on contact with blood, requiring direct contact with the vein wall for effect. Due to fluid mixing liquid sclerosants have limited efficacy (Coleridge Smith 2009; Hamel-Desnos et al. 2009).

The liquid sclerotherapy technique was refined into foam sclerotherapy during the 20th century with the Tessari method being most practiced (Jia et al. 2007) and this has lead to improved occlusion and patient satisfaction rates. Foam sclerotherapy is thought to improve occlusion rates with smaller quantities of sclerosant by displacing more blood and improving wall contact. It allows the treatment of varicose veins in a true clinic environment, with no assistance required once skilled at the technique (Coleridge Smith 2009). Due to the simple cannulation nature of the technique, minimal post-procedure morbidity is encountered, leading to high patient acceptance. However, it is highly physician dependent (Coleridge Smith 2009; Cavezzi & Tessari 2009).
At present two sclerosants are licensed and in common use in mainstream European practice - STS and Polidocanol (POL) (Rabe et al. 2013). Both of these are detergents, STS a fatty acid and POL a fatty alcohol. They are available at differing concentrations for differing size veins (Bergan 2007). Sclerosants cause an inflammatory and fibrotic reaction in the vein wall on contact. However, the detergents are deactivated on contact with blood (Bergan 2007; Hamel-Desnos et al. 2011).

The major failing of foam sclerotherapy has previously been occlusion and recurrence rates due to its highly variable technical application. However, with the advent of foam, it has been shown that ultrasound guided foam sclerotherapy (UFGS) has equivalent success but worse recurrence rates compared to open surgery, as shown by recent meta-analyses (Jia et al. 2007; Siribumrungwong et al. 2012) and a recent Cochrane review (Tisi et al. 2006). Sclerotherapy has been found to be less effective than endovenous ablation (Rasmussen et al. 2013), although long-term data are lacking. The relative low cost and low pain profile of sclerotherapy in addition to the ease of retreatment has lead to extensive uptake worldwide.

There is sparse evidence in the literature to guide the actual application of sclerotherapy, with disparate sclerosant volumes, foaming techniques and concentrations used, however Coleridge Smith has published recommendations for clinic requirements and suggested technique (Coleridge Smith 2009) and Bergan's vein book is also illustrative on this subject (Bergan 2007). Diligent technique and follow-up is vital for the optimum outcome for UGFS - due to this the excellent results found in some centres are not necessarily generalisable (Darvall et al. 2011; Darvall, Bate, et al. 2010a; Darvall, Sam, et al. 2010b; Darvall et al. 2009; Lattimer et al. 2012; Frullini et al. 2002).
Overall complications after sclerotherapy are rare, however this much be weighed against the relatively benign nature of varicose veins, and the availability of effective conservative management and other methods of intervention. Major complications include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and transient embolic events. The event rate of these complications is very low, with an event rate of 0.6% for DVT, 2.1% for cerebral events and one previously reported PE (Jia et al. 2007; Sarvananthan et al. 2012). Air embolism is the most feared complication, which can be fatal when associated with gas volumes of > 1 ml/kg injected into the venous system, with 50 ml able to cause significant complications.

Most procedures utilise up to 10 ml of foam, though some report use of up to 30 ml (Forlee et al. 2006) - though this was associated with the one case report of stroke following UGFS (Forlee et al. 2006). The cause of stroke and other transient cerebral events and migraine is not clear, and there are two hypotheses - sclerotherapy microbubbles transferred into the cerebral circulation via a patent foramen ovale or the production of endothelin (Frullini et al. 2011; Frullini et al. 2012; Bush et al. 2008; Sarvananthan et al. 2012). These theories are still undergoing investigation.

European guidelines have been formulated to guide the application of sclerotherapy (Rabe et al. 2013). These recommend a maximum session dose of 10ml of foam to reduce complications.

Overall the risk profile of sclerotherapy is not significantly altered in comparison to surgery and therefore is gives a reasonable alternative for those patients for whom surgery or endovenous ablation is deemed inappropriate or too strenuous.
1.1.7.8. **Endovenous Mechanochemical Ablation - Clarivein**

The ClariVein mechanochemical ablation catheter has recently elicited significant interest in the venous community. The technique utilises a dual-modality catheter – a motorised spinning catheter tip that causes venospasm and abrades the venous endothelium, followed by instillation of liquid sclerosant via the catheter tip. The catheter has a 'hockey stick' profile, allowing for it to be steered up tortuous or difficult veins and requires only a single micro-puncture access (4 French - 1.35mm).

Initial trials have shown a good side-effect profile and effective closure rates (96.7% at 6 months) in both the GSV and SSV (Elias & Raines 2012; van Eekeren et al. 2011; Boersma et al. 2013).

The mechanical component of the mechanochemical ablation procedure has been shown to produce subtle, incomplete damage to the venous endothelium, compared to RFA which produces extensive tissue destruction (Kendler et al. 2013). Theoretically this may produce a reduced peri-procedureal pain profile for the device to match the findings of studies investigating post-procedureal pain (van Eekeren et al. 2013).

Once again, larger scale trials are needed to show the true efficacy of the procedure. It is almost bloodless and fast, but patients do require compression hosiery postoperatively. The device is handheld and portable, and does not require an energy generator or tumescent anaesthesia. Due to the non-thermal nature of the treatment, no tumescent anaesthesia is required. This reduces the procedural time and the number of injections required for anaesthesia. The device does cause a vibration feeling as the vein is treated, which some patients find uncomfortable. The variable speed motor allows reduction in the case of very superficial veins, leading to reduced vibration and in theory discomfort.
Current multi-centre departmental studies are investigating the peri-operative pain profile of mechanochemical ablation versus the Clarivein catheter (VNUS vs Clarivein for Varicose Veins - VVCVV) (ISRCTN Register 2012).

![Clinical Picture of Clarivein Device in Use](image)

**Figure 26: Clinical Picture of Clarivein Device in Use**
1.1.7.9. Endovenous Chemical Occlusion - Sapheon

A new and exciting development, the Sapheon Venaseal product has demonstrated an early 100% occlusion rate with minimal morbidity attached (Almeida et al. 2011; Almeida et al. 2012; Min et al. 2012). It utilises a proprietary glue compound to provide physical occlusion of the vein, which then undergoes fibrosis.

The device uses a standard catheter based delivery technique via a proprietary catheter. This requires 5 French size access (1.67 mm diameter) Treatment protocol uses the injection of 0.08ml 'shots' of the cyanoacrylate into the treatment zone at the tip of the catheter. For the first treatment zone, at the SFJ, the first shot is applied, then the catheter is withdrawn 1cm and a second 'shot' applied. The catheter is then withdrawn 3cm and the two treated zones are compressed for 3 minutes (180 seconds). After this initial treatment zone, one 'shot' of applied and the catheter is withdrawn 3cm and the treatment zone compressed for 30 seconds. This process is repeated for the length of the vein to be treated.

![Figure 27: The Sapheon Closure System](image)

One year follow-up of the initial first-in-man patients has shown a safe, well tolerated procedure with occlusion rates of 92.1%, and no cases of DVT in 38 treated cases (Almeida et al. 2013). 21% of those cases did develop proximal thrombus extension into the deep venous system, but resolved without treatment. This led to
a modification of the positioning of the initial 'shot' to 5cm from the SFJ (Proebstle et al. 2013).

These recent first-in-man and initial studies have indicated a well-tolerated procedure with minimal anaesthetic required and no requirement for compression hosiery. Our unit has shown that it can be used in therapeutically anticoagulated patients, though initial success at 8 weeks did progress to recanalization at 6 months {Lane:2013hg}-CITATION_IS_EMPTY.
1.1.7.10. Deep Venous Stenting

Work by Raju and Neglen in 2003 demonstrated that chronic venous disease is associated with primary proximal deep venous stenoses as assessed by IVUS and venography (Neglén et al. 2003; Raju et al. 2011; Neglén et al. 2010). These findings were confirmed by Gaweesh et al using modified CT venography (Gaweesh et al. 2013). Raju et al have shown good symptomatic improvement with stenting with reasonable long term patency rates of 79% primary and 100% secondary at 6 years in non-thrombotic disease (Neglén et al. 2007).

The role of deep venous stenting in the management of non-thrombotic venous disease remains specialised and limited to careful patient selection. Further disseminated studies are needed to adequately investigate the technique's generalisability. The level of contribution to and causation of chronic venous disease by deep venous stenoses remains unclear and needs further study.
Aims of this thesis

This thesis aims to examine and identify pathways in the invasive treatment of varicose veins, and to provide evidence for the streamlining and improvement of current primary-secondary care interchanges. Through the use of modelling techniques the outcome of interventional treatment will be assessed. This data aims to allow the construction of a prognostic model which aims to identify patients who will benefit most from treatment.
Chapter 2: Venous Disease Education
2.1. Current State of Understanding of Venous Disease

Venous disease is an extensive and common condition with an extensive morbidity as previously described. However due to the fact that it is rarely fatal, training and understanding of the disease has not been extensive.

The creation of dedicated conferences and teaching on venous disease over the past 25 years and more recently the creation of Phlebology curriculae has strengthened the scientific rigour and background for venous medicine. With a complex disease unveiled by duplex ultrasound, both conceptually, and physiologically, this has led to traditional teaching being left behind.

Guidelines are formulated in order to aid non-specialists adhere to current evidence based medicine (Marsden et al. 2013). However, guidelines are difficult to create and implement (Woolf 1993; Woolf et al. 1999; Grol 2001) and there is little evidence to show compliance in the community (Worrall et al. 1997) despite good results in trials (Grimshaw & Russell 1993; Eccles et al. 2002; Wigmore et al. 2007). Physicians must be aware of the guidelines first, before they can adhere to them (Pathman et al. 1996).

Assessing the individual management and outcome of all venous disease patient clinical contacts is an impossible task, and so assessing clinician understanding and compliance with questionnaires is appropriate methodology (Burgers et al. 2003).

2.2. Principles of questionnaire creation and validation

Questionnaires can be and are used to assess many disparate variables, often in qualitative rather than quantative data fields. These methods have been under development for many years leading to extensive literature regarding solely questionnaire formulation (Foddy 1993; American Education Research Association et al. 1999; Jensen 2003; Bradburn et al. 2004; Fayers & Machin 2000).
To achieve a worthwhile questionnaire, one must ensure that the questions asked provide useful information which is reproducible in multiple respondents (Jensen 2003; American Education Research Association et al. 1999).

This means that the questionnaire must be both valid and reliable. To ensure this, multiple prototype versions of questionnaires are produced from expert opinion before being tested on focus groups of the intended respondents (Krause & Backonja 2003).

2.2.1. Validity

Validity of a questionnaire consists of:

• Content Validity
  
  This ensures that the scale used is adequate - i.e. Can the questionnaire cover the full spectrum of the disease of interest (incorporating Face Validity).  

• Construct Validity
  
  This ensures that the questionnaire describes and then assesses the disease of interest adequately.  

• Criterion Validity
  
  This is to ensure that the output of the questionnaire is associated with a single desired outcome measure and is therefore a useful discriminator.

2.2.2. Reliability

The reliability of a questionnaire consists of

• Internal Consistency

  Different questions assessing the same section (or domain) must be consistent. Internal Consistency is used to delineate how closely interrelated different items in the questionnaire are, and utilises Cronbach’s coefficient (Fayers & Machin 2000).  

• Test-Retest Stability

  When the test is repeated the same values should be consistent.
These variables and validation techniques allow the production of reliable, reproducible scales and questionnaires for abstract concepts of quality of life. However, not all aspects of validation are appropriate for all questionnaires. Expert assessment and target group interview leading to iterative improvement using content and face validity assessment are sufficient to generate appropriate items to formulate the questionnaire.
2.3. **General Practitioner Survey of Varicose Vein Management**

2.3.1. **Introduction**

General practitioners (GPs) are the gatekeepers to secondary care in the UK. Standard GP training however does not include any formal teaching on CVD and GPs have variable exposure to the surgical specialties during their medical training (Royal College of General Practitioners 2011). GP trainees do though undergo an extensive apprenticeship with GP trainers and will cover such topics during this period. Interestingly, work by Chassany et al demonstrated the disparity between patient-reported and GP-reported symptom severity with GPs routinely reporting lower levels of pain and quality of life impairment compared to patients (Chassany et al. 2006). Conway et al have also shown that patient reported symptoms are unreliable compared to standardised questionnaires due to the subjectivity of symptoms (Conway et al. 2011). In order to aid GPs in the management and referral of CVD extensive guidelines have been developed in the UK by the National Institute for Clinical Excellence (NICE) (National Institute for Clinical Excellence 2001) and more recently by the Royal Society of Medicine's Venous Forum (Venous Forum of the Royal Society of Medicine et al. 2011). The release of comprehensive...
guidelines in July 2013 have redefined the varicose vein treatment evidence base for primary care physicians (Marsden et al. 2013).

In the US guidelines on management of CVD patients have also been created (Gloviczki et al. 2011). In order to stratify CVD, various clinical scoring systems have also been developed and validated, such as VCSS (Venous Clinical Severity Score) (Eklöf et al. 2004; Vasquez et al. 2010). Despite the existence of guidelines and scoring systems, the treatment of varicose veins has been classified and is viewed of low clinical value by non-medical funding bodies (Audit Commission 2011), leading to the creation of disparate and confusing local guidelines and these are often in contention with national guidelines.

GPs are now also expected to perform routine post-operative follow-up for surgical procedures, such as, varicose veins and hernia repairs (Community Health Partnerships 2008) without appropriate remuneration or support. Previous work surveying patients, GPs and surgeons after post-operative outpatient attendance found that in the context of benign general surgical disease, 95% of patients found follow-up specialist consultations useful, and only 49% would prefer to see their GP. Importantly, management was changed by the specialist in 44% of cases (Gnanalingham & Williams 2004).

Preference for specialty follow-up was mirrored in a similar study by Frew et al. in cancer patients (Frew et al. 2010).

2.3.2. Aims

The aim of this study was to assess patterns of referral and the management of CVD in primary care in the UK.
2.3.3. Methods
Following ethical review and categorisation as service evaluation by the local ethical sub-committee, a 23 question electronic survey was created which assessed different aspects of CVD management and treatment pathways.

The questionnaire was tested and validated for content and validity by GPs and vascular surgeons, with internal, external and independent assessors as previously described (Jensen 2003; Fayers & Machin 2000). Inter and intra-observer reproducibility assessments were not appropriate for this questionnaire and therefore not completed.

In England there are approximately 34,101 GPs. Therefore a subset of these were targeted. Invitations to complete the survey were sent via e-mail to an estimated 300 GPs throughout England (url = http://kwiksurveys.com?u=gpvaricoseveins), at random using local and national mailing lists. Please see Appendix 6 for the complete survey.

Responses were collated by the survey server (KwikSurveys, Dover, UK) over a 6-month period (August 2011 to February 2012) and results were analysed using Microsoft Excel 2011 (Microsoft Corporation, Redmond, USA) and GraphPad Prism (GraphPad Software Inc., La Jolla, USA) software.

2.3.4. Results
138 completed responses were received, representing a response rate of 46%. All received surveys were analysed and none were excluded.

2.3.4.1. Cases Seen:
The vast majority of GPs (85%, p<0.001) stated that they saw less than 50 patients with varicose veins per annum, which is an average of less than one per week. 78%
managed CVD patients conservatively in the community, with 1 providing treatment with sclerotherapy.

If specialist care was required most GPs (78%, p<0.001) referred to a vascular surgeon, 10% to a general surgeon and 11% to a vascular nurse specialist.

2.3.4.2. Reasons for Referral:

40% of GPs would refer a patient at their request and 10% for cosmesis, 43% for venous skin changes and 58% for pain (Figure 30).

![Figure 30: Reasons for referral from primary care (% of GPs)](image)

2.3.4.3. Available Treatments

Figure 31 demonstrates which treatments GPs believe are available to their patients. 33% believed that endovenous treatments were available in their locality, but a surprisingly low figure of 60% believed traditional open surgery to be available as a treatment option, despite its universal availability (33% vs 60%, p<0.001).
2.3.4.4. Guidelines and Scoring Systems

Only one third of GPs (31% vs. 69%, p<0.001) were aware of the NICE Referral Guidelines (published in 2001) for CVD. 61% were aware of local Primary Care Trust (PCT) referral guidelines, but only 36% agreed with these guidelines. 26% of GPs said they were aware of NICE Treatment Guidelines, however these guidelines did not actually exist at the time of survey (and had not been commissioned at that time). Local PCT guidelines do exist and 41% of GPs were aware of these, though again only 26% agreed with them. 11% were aware of clinical scoring systems and 89% were not (p<0.001).

2.3.4.5. How do you manage chronic venous disease?

Overall, for patients with varicose veins, 62% of all treatment was conservative with reassurance (15%), compression hosiery (38%) or compression bandaging (10%). 29% of patients would be referred to a specialist and 8% would undergo further investigation prior to referral. One GP would treat varicose veins with sclerotherapy in the community. 53% of GPs would refer active ulceration (C6), and 41% venous skin changes (C4). Pain symptoms would increase the referral rate for...
CEAP clinical stage C2 disease from 2% to 24% (p<0.001) and from 20% to 55% for C3 disease (p<0.001).

### 2.3.4.6. Role of intervention

Figure 32 illustrates how GPs determined whether there was a role for intervention using sample cases. Pain appeared to be the most important factor in this decision with 16% agreeing that CEAP class C2a (asymptomatic) warranted intervention but with pain (C2s) the referral rate increased to 71% (p<0.001). In patients with leg swelling and varicose veins (C3) 42% felt pain-free patients should have treatment compared to 83% if patients also had pain (p<0.001). Interestingly, only 62% of GPs believed that venous skin changes warranted intervention. Moreover, only 78% believed venous ulceration required intervention compared to 8% who did not and 14% were unsure (p<0.005).

![Figure 32: Role of intervention in example cases (% of GPs)](image)

### 2.3.4.7. Progression, Quality of Life & Cost-Effectiveness

64% of GPs believed that mild CVD would progress to severe disease, compared to 36% who did not (p<0.001). 84% of GPs thought that treating varicose veins would improve a patient's quality of life, and only 26% felt that it was not a cost effective use of NHS resources. The majority (75%) believed that CVD for the purpose of improving quality of life could be managed conservatively.
2.3.4.8. Free Of Charge Treatment

Figure 33 shows which treatments GPs felt should be provided free of charge on the NHS. Interestingly 11% of GPs believed that CEAP class C2a (visible but asymptomatic veins) should be treated free of charge and 8% were unsure. As CEAP class increased the proportion favouring free treatment also increased. Once again the onset of pain vastly increased the favour for free treatment.

![Figure 33: For whom should treatment be free of charge on the NHS? (% of GPs)](image)

2.3.4.9. Follow-Up and "Me Too"?

45% of GPs were happy to provide aftercare for varicose vein intervention; 8% felt no follow-up was required.

In the "Me Too" question 71% of GPs stated they would like invasive treatment if they have varicose veins, with none wanting traditional open surgery

2.3.5. GP Survey Discussion

The management of CVD is a common scenario encountered in general practice. The important aim of treatment is to avoid ulceration. From our results, it is evident that there is no clear consensus on the management of CVD in the community. Whilst the majority of patients are no doubt treated appropriately, there is a reticence of primary care fund holders to allow referral for invasive treatment and consequently the burden of disease remains widespread. From our study, the
treatment options also appear not to be universally available and in addition, there is patchy GP awareness of their availability.

Interestingly GPs saw relatively few patients with CVD – with a 25-50% prevalence the average GP practice should have 1600-3200 patients with the condition (The Health and Social Care Information Centre 2008). This is likely due to a combination of public and medical ignorance of the benefits of treatment.

What has become clear from this survey is that the CVD knowledge base of GPs is limited due to both a lack of exposure to the condition in their training and recent treatment progress. The number of GPs unaware of classification criteria, local and national guidelines, and the treatment options available demonstrates this. A substantial portion of GPs were also unsure of the benefits of treatment on a patient’s quality of life (11%), disease progression (23%) or on cost-effectiveness of treatment (34%), despite extensive literature published on these areas in the past two decades. Our results would also suggest that follow-up should be with the treating physicians, and 92% of GPs felt that this was required, with only 45% were happy to provide post-intervention care themselves.

National advice for referral for patients with CVD recommends referral to a specialist if there is quality of life detriment from prominent varicosities, not for cosmetic reasons or pain specifically. A key finding of the study is that pain is the main discriminator for patients being referred to secondary care. Whilst this is unsurprising, as patients will not attend without symptoms, our study also demonstrates that only about one third of GPs were aware of the NICE Referral Guidelines and that among them only about one third agreed with these guidelines. Crucially 71% of GPs felt that C2 disease with pain (prominent varicose veins) should have intervention compared with 63% (ns) who thought that venous
skin changes warranted treatment. At the point of surveying, pain was not a discriminator in the national referral guidelines.

This is concerning as the treatment of C4 disease is vital in the prevention of venous ulceration. Moreover, CVD intervention is far quicker and cheaper than ulcer treatment.

In an era of austerity and primary and secondary care commissioning there must be improved discourse between venous specialists and primary care physicians. This must include mutual education sessions in order to disseminate recent advances. Surgical exposure in GP training is limited and topics such as venous disease are taught during an 18-month mentorship with GP trainers. It would therefore be prudent to encourage careful updating of these experienced GP trainers by the specialists to whom they refer.

This study is limited by two main factors – numbers and participants. There are approximately 34,101 GPs in England. It was not feasible to contact all GPs and therefore a representative sample of approximately 300 GPs was sought. The study additionally suffers from responder-bias, as those GPs willing to respond to the study are likely to be more engaged with local PCTs and commissioning services. They are also more likely to keep abreast of current treatments. Despite this the disparity between guidelines and practice was significant.

Subsequent to the completion of this study, extensive NICE guidelines have been published with a summary published in the British Medical Journal (Marsden et al. 2013). This guidance addresses many of the knowledge gaps seen in this study and repetition of the study in 5 years may produce extensively different results. In addition, due to reconfiguration of the primary and secondary care commissioning environment there may be improved communication and research dissemination.
2.3.6. GP Survey Conclusion

Despite clear national guidance and advice, referral and treatment patterns are extremely heterogeneous.

This is the driving force behind the formulation of the various guidance documents available. CVD education is also lacking from GP training programmes despite CVD being a common condition, and venous specialists should aim to aid the lifelong learning needs for new and mature GP colleagues.

For the benefit of our patients improved communication with GPs will lead to better patient care. We suggest that this should be sought at a local level with the development of clearer lines of feedback between primary and secondary care. With the development of Clinical Commissioning Groups (Blake & Parker 2012), improved communication and dissemination of cutting edge research should improve. In addition, recent NICE guidelines may drive this improvement and reach those GPs not involved in the commissioning network.
2.4. Management of Superficial Venous Thrombosis

2.4.1. Introduction

Superficial venous thrombophlebitis or more correctly superficial venous thrombosis (SVT) is inflammation of a superficial vein in the presence of a clot. It is a common disease that has traditionally been regarded as benign and there has been little investigation into its prevalence until recently (Leon et al. 2005; Di Nisio et al. 2007; Di Nisio et al. 2012; Decousus, Prandoni, et al. 2010a; Decousus, Quéré, et al. 2010b; Decousus et al. 2011; Hill et al. 2008). Indeed, the 2013 NICE guidance recommends referral of all patients with SVT to their local vascular service {NationalInstituteforHealthandCareExcellence:2013vv}-CITATION_IS_EMPTY.

SVT is a pathology that presents commonly and independently to both primary and secondary care physicians and surgeons. Therefore it acts as an excellent surrogate marker for comparing the understanding of a "simple" disease and its appropriate management between primary and secondary care.

Over the past 10 years extensive work using duplex ultrasound and longitudinal cohort studies have provided robust data on the condition. Its prevalence has been estimated at 3-11% (Decousus et al. 2011; Hill et al. 2008) and as such is more common than deep vein thrombosis (DVT) (Di Minno et al. 2005). SVT has been shown to be a significant risk factor in the development of DVT and consequently PE with an Odds Ratio of 4.3 (Heit et al. 2000; Heit et al. 2002). Up to 30% of patients with a SVT have a concomitant DVT (Decousus et al. 2011), and up to 30% have concomitant pulmonary emboli (PE) (Verlato et al. 1999; Heit et al. 2002). However, SVT has been found not to be a risk factor for major cardiac events or malignancy (Prandoni et al. 2011).

Despite this the literature has previously advised conservative management (London & Nash 2000). This is compounded by the belief that treatment of varicose
veins is a low value procedure (Audit Commission 2011). However, as SVT is a complication of varicose veins, varicose veins are therefore a risk factor for SVT as well as an independent risk factor for DVT (Decousus et al. 2010; Di Minno et al. 2005).

Post-graduate teaching on SVT is sparse and it suffers from falling between the multiple speciality stools of vascular surgery, medicine and general practice. This is despite clear guidance in the form of a recently revised Cochrane review, and now the NICE guidelines.

To investigate this we performed a survey of investigation and management of SVT by GPs and vascular surgeons. The aim of the study was to assess whether current practice followed recent evidence, and whether primary care and secondary management was matched.

2.4.2. Methods
A 19 question electronic survey was created which assessed SVT management, investigation and treatment pathways. This did not require Ethical Approval as it is termed Service Evaluation.

The questionnaire was tested and validated for content and validity by GPs and vascular surgeons, with internal, external and independent assessors as previously described (Jensen 2003; Fayers & Machin 2000).

In England there are approximately 34,101 GPs and 456 members of the Vascular Society in the UK.

Invitations to complete the survey were sent via e-mail to all throughout England (url = http://kwiksveys.com?u=gpvaricoseveins), at random using local and national mailing lists. Please see Appendix 7 for the complete survey.
Responses were collated by the survey server (KwikSurveys, Dover, UK) over a 6 month period and results were analysed using Microsoft Excel 2011 (Microsoft Corporation, Redmond, USA) and GraphPad Prism (GraphPad Software Inc., La Jolla, USA) software.

2.4.3. Results

369 completed responses have been received, from 165 vascular consultants (36% response rate), 172 GPs or GP trainees (14% response rate) and 32 vascular trainees (11% response rate).

Most clinicians saw up to 20 cases per year, with vascular surgeons understandably seeing more cases (Figure 34).

![Figure 34: Number of Patients seen with SVT](image.png)

The majority of clinicians performed with venous duplex as the main investigation, however 40% performed no investigations at all (Figure 35).
Figure 35: Investigations Performed

A worrying disparity was shown in the treatment offered for patients with SVT. At one end of the spectrum almost 10% treated with no treatment for a painful and potentially serious condition or complete bed rest for a thrombotic disease. Fortunately the majority opted for non-steroidal anti-inflammatory drugs (NSAIDs) but only 25% treated with anticoagulation and even fewer with compression hosiery (Figure 36).
An overwhelming majority of clinicians (though significantly different proportions, p=0.007) believed there is indeed an association between SVT and DVT, despite the disparity in treatment offered (Figure 37). The relationships with other conditions is also disparate, although most clinicians felt that SVT was associated with varicose veins – Figure 38 and Figure 39, this was the only non-significantly different spread of opinion between GPs and VCs (p=0.057, ns). All other interpretations of relationships between SVT and PE, Deep Venous Incompetence, Cancer and Infection were significantly different between GPs and VCs.
Figure 37: Is there an association between SVT and DVT?

Figure 38: SVT Association with other conditions
Figure 39: SVT Association with other conditions split amongst speciality
Finally, the approach to follow-up was variable and inconsistent (Figure 40 and Figure 41) - duration of anticoagulation was widely disparate as was the follow-up regime ($p<0.001$).

Figure 40: Duration of Low Molecular Weight Heparin (LMWH) prescribed for SVT

Figure 41: Follow-up for SVT
2.4.4. Discussion

This study demonstrates that the management of SVT is disparate and conflicting despite good level 2 evidence indicating that NSAIDs, LMWH and compression hosiery are effective and reduce the incidence of DVT (Di Nisio et al. 2012). This is likely to be due to the misconceived belief that SVT is a benign self-limiting disease (Decousus et al. 2003), amongst GPs and VCs, despite the increasing literature base that identifies its significant association with DVT (Decousus et al. 2010; Decousus et al. 2011).

The number of cases seen per year (on average <20) appears at odds to the 3-11% prevalence, which would equate to 200-700 cases per year for an average GP practice, and more for a specialised vascular centre (if all were referred) (Decousus et al. 2011; The Health and Social Care Information Centre 2008). The cause of this disparity is probably attributable to a low level of understanding from both the public and from primary care physicians of the condition and its relative importance in the venous thromboembolism spectrum. Venous disease has been shown to have a low level of public exposure in previous work from the our unit, and SVT likely suffers a similar under-exposure {Lane:2013eo}-CITATION_IS_EMPTY.

No national guidelines exist for the management of SVT, however robust level 1 and 2 evidence exist to guide clinicians and with venous thromboembolism prevention being of topical interest aggressive treatment is becoming standardised outside of the UK (Heit 2005; Di Nisio et al. 2012). It is hoped that with the recent NICE guidelines, referral and management in the UK will match this pattern {NationalInstituteforHealthandCareExcellence:2013vv}-CITATION_IS_EMPTY.

2.4.5. Conclusion

The treatment and understanding of SVT is disparate and unclear. Knowledge of the pathophysiology and the risks of are poor. Propagation of the recent advances in the understanding of SVT and its connection with DVT are vital for improving
the outcomes of patients with this condition. From understanding why some patients develop symptomatic SVTs this may be extend our knowledge of symptomatic and asymptomatic DVTs. Guideline formation would improve baseline knowledge however, adherence is often poor {Lane:2013eo}-CITATION_IS_EMPTY.
2.5. Summary of Venous Education

These studies show that whilst an extremely common condition, venous disease is poorly understood by frontline members of the medical community. With the disparate management plans used it is clear that education is severely lacking, and has not kept pace with the extensive advances in the understanding of venous disease.

Careful education and involvement of GPs and non-phlebologists is needed in order to provide patients with optimal treatment with robust evidence. With the aging population this will be become a vital component to an efficient health service.

The formulation of guidelines is an aid but not a remedy as exemplified by the GP survey results. It remains to be seen whether the recent NICE guidelines (Marsden et al. 2013) on covering treatment and diagnosis of varicose veins will affect GP opinion and referral patterns.
Chapter 3: Comparing Quality of Life Questionnaire Scores
3.1. Introduction

The introduction of endovenous treatments has heralded new advances in the management of chronic venous insufficiency over the past decade (Shepherd et al. 2010). Key to understanding the burden of venous disease and the long term efficacy of newer endovascular approaches is the use of outcome measures relevant to the functional status of the patient.

Traditional objective measures of disease severity that focus on the morbidity and mortality of venous disease, whilst readily quantifiable, do not necessarily correlate with the functional status of the patient. To meaningfully capture outcomes in venous disease, the full biopsychosocial consequence of the disease must also be established (Launois et al. 1996). As the role for patient centered care in venous disease increases, the assessment of quality of life (QOL) in venous disease is becoming increasingly important. Currently there are a wide variety of validated outcome measures in use, and these can be divided into generic and disease specific QOL tools.

Generic QOL instruments permit a patient's overall functional status to be measured regardless of their specific disease state, and thus have the advantage of allowing comparison across different studies of different diseases. The EuroQol 5 Domain score (EQ-5D) is a well validated generic QOL score (The EuroQoL Group 1990). Disease specific QOL tools directly assess attributes related to a particular disease. They are increasingly becoming utilized in the study of varicose veins as they are more sensitive for assessing venous disease outcomes. The Aberdeen Varicose Vein Questionnaire (Garratt et al. 1993) (AVVQ) and the ChronIc Venous Insufficiency quality of life Questionnaire (Launois et al. 2012) (CIVIQ-14) are the two most commonly used validated disease specific QoL questionnaires. Other examples of disease-specific QOL tools include the Charing Cross Venous Ulceration Questionnaire (CXVUQ), (Smith et al. 2000) the Venous Insufficiency
Epidemiological and Economic Study instrument (VEINES) (Lamping et al. 2003) and the Specific Quality of Life and Outcome Response- Venous questionnaire (SQOR-V) (Guex et al. 2007).

In a joint statement by the American Venous Forum and the Society of Interventional Radiology, the use of both disease specific and generic QoL tools in conjunction with clinician driven assessment is recommended in all clinical trials investigating venous insufficiency (Kundu et al. 2007; Kundu et al. 2009). There are significant differences in the choice of QOL tools amongst studies, making it challenging for the clinician to make direct comparisons between studies (Thakur et al. 2010). Therefore the correlation between different QOL tools is of huge significance if clinicians are to make valid comparisons between studies. However at present the relationship between the various QOL tools has not been fully characterized.

The aim of this study is to evaluate the relationship between two disease-specific QOL tools; the extensively validated AVVQ and more recently validated CIVIQ-14, to enable better comparison between studies and to compare these tools with generic QOL tools and clinician completed tools (Rutherford et al. 2000).

### 3.2. Methods

#### 3.2.1. Patient selection

Adult patients attending the vascular surgery outpatient clinic at our Institution for management of their varicose veins were prospectively invited to participate in this study. Patients were recruited over a four-month period, from August 2012 to December 2012 in a consecutive manner. Demographic data including patient age and gender was collected.
3.2.2. Intervention

All participants were asked to complete the two disease specific QOL tools, the AVVQ and CIVIQ-14 prior to their outpatient appointment. The AVVQ consists of 13 questions addressing various biopsychosocial attributes of chronic venous disease, including specific signs and symptoms, use of compression stocking and daily functional impact (see Appendix 1) (Smith et al. 1999). The overall score ranges from 0 to 100, with a higher score denoting greater burden of disease. The CIVIQ-14 is a revised version of the well-validated CIVIQ-20 instrument (Launois et al. 1996; Launois et al. 2012), and has shown to be valid in studies of patients across different countries (Biemans et al. 2011). The CIVIQ-14 contains 14 questions covering three QOL dimensions: physical, pain and psychological, and is scored from 0-100, with a higher score denoting a lower QOL (see Appendix 5).

Patients also completed the EuroQol-5D questionnaire (EQ-5D, EuroQoL Group, Rotterdam, the Netherlands) (The EuroQoL Group 1990; Herdman et al. 2011) a generic QOL questionnaire which separately captures the biological, psychological and social aspects of a disease state to generate a numerical overall score.

The clinical severity of venous disease for each patient was stratified using the following clinician driven tools: the Clinical Etiologic Anatomic Pathophysiologic (CEAP) score (Eklöf et al. 2004) and the revised Venous Clinical Severity Score (VCSS) (Rutherford et al. 2000). The VCSS comprises nine characteristics of venous disease and each component is scored independently on a scale from 0 to 3.

3.2.3. Statistical analysis

Outcomes were scored for each patient. In cases of bilateral venous disease, scores were recorded for each leg, and the score of the worst leg was used. Statistical analysis was performed using Prism 5.0a (GraphPad Software, Inc, California). The relationship between the AVVQ and CIVIQ-14 scores was analysed using Spearman's correlation for nonparametric data. Correlation was also analysed
separately for patients with less severe (C1-3) disease and more severe (C4-6) disease.

The AVVQ and CIVIQ-14 scores were analysed against the EQ-5D. Both the AVVQ and CIVIQ-14 were analysed against the VCSS. Spearman's correlation was used to assess the relationship for each analysis. P values less than 0.05 were considered statistically significant.

3.3. Results

3.3.1. Patient demographics
Over a four-month period between August 2012 and December 2012, fully complete questionnaires were collected for 100 patients. There were 44 males (44%) and 56 females (56%). The mean age of participants was 57.5 years (range 22-84 years). 50% of patients were aged 65 years and over. The mean AVVQ score was 25.1 (range 0-74; SD 17.1) and the mean CIVIQ-14 score was 33.8 (range 0-89; SD 21.7).

3.3.2. Relationship between disease-specific QoL tools (AVVQ and CIVIQ-14) and EQ-5D
The EQ-5D score demonstrated a strong negative correlation with both the AVVQ and CIVIQ-14 scores (Figure 42). (r=-0.5; p<0.0001 and r=-0.7; p<0.0001 respectively).

![Figure 42: Relationship between disease-specific QOL Tools (AVVQ and CIVIQ-14) and generic QOL Tool - EQ-5D.](image)
3.3.3. Relationship between disease-specific QoL tools (AVVQ and CIVIQ-14) and VCSS

There was a strong positive correlation between the VCSS and both the AVVQ and CIVIQ-14 scores (Figure 43) \( (r=0.7; p<0.0001 \text{ and } r=0.7; p<0.0001 \text{ respectively}) \).

3.3.4. Relationship between the AVVQ and CIVIQ-14 scores

Strong positive correlation was seen between the AVVQ and CIVIQ-14 scores \( (r=0.8; p<0.0001) \). Strong correlation was maintained for patients with C1-3 disease \( (r=0.7; p<0.0001) \) and C4-6 disease \( (r=0.8; p<0.0001) \).

3.3.5. Conversion Factor

From these data points, a conversion factor was created. The mean AVVQ was 25.10 (SD ± 17.05) with the mean CIVIQ being 33.81 (SD ±21.74). Utilising these data, the following correction factor was formulated:

\[
\text{CIVIQ} = (1.06 \times \text{AVVQ}) + 7.194
\]

The agreement between the observed CIVIQ-14 scores and the predicted CIVIQ-14 scores are shown in Figure 45 and Figure 46.
Wilcoxon testing showed that Predicted and Observed CIVIQ-14 values were not statistically different (Mean difference 0.0097, SD -2.386-2.405, \(p=0.5832\)), and a strong and statistically significant correlation was found (\(p<0.0001\), \(r=-0.7695\)).

### 3.4. Discussion

Measurement of QOL is now commonplace in studies of chronic venous disease. Over the past decade there has been increasing recognition amongst phlebologists that disease specific QOL tools provide a more meaningful correlate of a patient's functional status than objective anatomical or hemodynamic outcome measures (Shepherd et al. 2011; Guex 2008). Reporting guidelines published by the American Venous Forum now recommend the use of disease specific and generic QOL tools along with clinician driven outcome measures in studies of chronic venous disease.
(Kundu et al. 2007; Kundu et al. 2009). In 2005, a review commissioned by the United Kingdom Department of Health recommended the routine use of patient-reported outcome measures after intervention for venous disease (Nesbitt et al. 2012; Smith et al. 2005).

The choice of disease specific QOL questionnaire is crucial to permit both the evaluation of the efficacy of current endovenous treatments, and valid comparison of results from different trials. Currently there are a number of different disease specific and generic QOL tools clinician driven tools being utilized in studies of chronic venous disease (Thakur et al. 2010; Vasquez & Munschauer 2008). The AVVQ and CIVIQ-14 were chosen for evaluation in this study. The AVVQ is a commonly used validated disease specific QOL tool that has been shown to be sensitive in assessing functional outcome after treatment for chronic venous disease (Darwood et al. 2008). The CIVIQ-14 was recently developed as a more stable version of CIVIQ-20 instrument, which itself has been commonly used and validated since 1996 (Launois et al. 1996; Launois et al. 2010; Launois et al. 2012).

This study has established that a strong correlation exists between the two disease specific QOL tools selected for evaluation, the AVVQ and CIVIQ-14, further demonstrating that these disease-specific questionnaires are useful tools in the assessment of QOL in chronic venous disease. The findings from this study show that the relationship between the AVVQ and CIVIQ-14 scores are predictable, thereby supporting the validity of making comparisons between studies regardless of whether the study has utilized the CIVIQ-14 or AVVQ QOL tool. The AVVQ differs in several aspects from the CIVIQ-14 questionnaire. In comparison with the CIVIQ-14, the AVVQ assigns a greater proportion of questions to the physical aspects of chronic venous disease. The CIVIQ-14 is validated for the entire spectrum of chronic venous disease except venous ulcers (Launois et al. 2012), whilst the AVVQ specifically targets varicose veins and includes ulceration (Garratt et al.
1993). Despite these differences, the current study shows that two QOL tools closely correlate, and the correlation is maintained across the spectrum of disease severity, from less severe (C1-3) to more severe disease (C4-6).

Our findings have expanded on the findings from by Shepherd et al. (Shepherd et al. 2011) who found that the AVVQ correlated strongly with another disease-specific QOL tool, the SQOR-V questionnaire. The degree of correlation (Spearman coefficient 0.702) was similar to our findings (Spearman coefficient 0.8). Both the SQOR-V (Guex et al. 2007) and CIVIQ-14 place a greater emphasis on patient-reported symptoms rather than physical signs and this may in part explain the comparable degree of correlation.

Other types of outcome measures utilized to assess chronic venous disease were also shown in this study to correlate with the AVVQ and CIVIQ-14 QOL tools. The study evaluated a generic QOL questionnaire, the EQ-5D, which was shown to correlate strongly with both of the disease specific QOL tools. This is in contrast to findings from previous studies, which have compared different generic QOL questionnaires with disease specific QoL questionnaires. Shepherd et al. (Shepherd et al. 2011) found that the AVVQ only correlated weakly with a generic QOL tool, the Short Form 12 (SF12) questionnaire (Wee et al. 2008). The differences between our findings are not immediately clear, but may be attributed to the difference in construction of health profile-based questionnaires (Short Form series) and preference-based questionnaires (EQ-5D) (Franks et al. 2004). This study also evaluated a clinician-completed assessment tool (VCSS) against the AVVQ and CIVIQ-14. A very strong correlation was found between the clinical scoring system and both of the disease-specific QOL tools. This relationship highlights the sensitivity of the AVVQ and CIVIQ-14 towards the physical aspects of QOL in chronic venous disease. Our results strongly reinforce the findings by Carradice et al. (Carradice et al. 2011), which also found that increasing venous disease severity
was associated with poor disease-specific and generic QOL scores as measured by the AVVQ and EQ-5D, respectively.

The lack of consensus on which disease-specific QOL tool to use for measuring outcomes in chronic venous disease has contributed to an inconsistency in the choice of the QOL tool used in studies of venous disease (Thakur et al. 2010; Jawien 2009). The need to make comparisons between studies using different outcome measures has highlighted the importance of understanding the relationship between these disease specific QOL tools, as well as the relationship with generic QOL and clinician driven tools. Previous work by Carradice et al. investigated the effect of CEAP status on disease-specific quality of life and generic quality of life, and found similar results. This study provides additional evidence of the morbidity associated with chronic venous disease.

The conversion formula has shown good agreement with observed values, providing an option for further meta-analysis and comparison of trials.

A limitation of this study was the relatively small number of participating patients with C1 disease. This may limit the generalizability of our findings. The number of patients with C1 disease treated in secondary care is restricted due to the limitation of referrals from primary care under the United Kingdom National Healthcare System. In the current study, the patient selection was performed in a consecutive manner, and not randomized. This would have been unlikely to impact on the results as the primary purpose of this study was ascertain the correlation between the CIVIQ-14 and AVVQ QOL tools, rather than to compare the outcomes between interventions. What remains to be seen is the relationship of the responsiveness between the disease specific QOL tools, generic QOL tools, and clinician completed outcome measures several weeks post-procedure. It will be important to see if changes in post-procedure AVVQ scores correlate with respective changes in CIVIQ-
14 scores and this will contribute further to our understanding of these QOL tools relative to one other. Further data points are required to improve upon the current conversion formula, throughout the spectrum of disease.

3.5. Conclusion

This study demonstrates that there is a strong and significant linear correlation between two of the main disease-specific QOL tools for varicose veins (AVVQ and CIVIQ-14) across the whole spectrum of disease severity. Strong correlation also exists between these disease-specific QOL tools and the generic EQ-5D QOL tool as well as the clinician-driven VCSS tool. Our findings support the validity of comparisons of results between studies using either the CIVIQ-14 or AVVQ disease-specific QOL tool.
Chapter 4: Venous Disease Cohort Study
4.1. Introduction

Disease cohorts are followed in many fields and provide excellent data on the breadth of disease. The benefits of cohort studies include identification of rare complications and factors, and are not constrained by the limits of RCTs. The level of evidence produced is not as rigorous as RCTs however, pragmatic planning can lead to an excellent evidence base. Venous disease is complex multi-factorial disease and therefore requires large recruitment and analysis for optimal investigation.

Venous disease has been the subject of multiple cohort studies (Widmer & da Silva 1991; Rabe et al. 2003; Evans et al. 1999) which have now started to explore progression of the condition (Rabe et al. 2010; Robertson et al. 2013).

Patients present to vascular services for treatment of symptomatic venous disease. Assessing this sample of the population as a whole offers a different viewpoint to the epidemiological studies of Rabe, Widmer and Evans (Widmer & da Silva 1991; Rabe et al. 2003; Evans et al. 1999). Whilst there is a recruitment bias, it is these patients that require treatment for their disease, as opposed to the asymptomatic majority. The vascular surgery clinic therefore represents a prime opportunity to assess the disease and its components.

4.2. Methods

Regional ethical sub-committee approval was sought and obtained for this study. Patients were recruited between January 2011 and July 2012 (18 months). Patients attending Charing Cross Hospital for secondary care varicose vein investigation and treatment were invited to complete questionnaires relating to the impact their varicose veins had on their lives. This was correlated with clinician completed questionnaires to produce a cohort study group.
Clinicians completed the CEAP, VCSS and VDS. Patients completed the AVVQ, EQ5D-5L and CES-D Depression Score (Appendix 3).

Follow-up review in the host NHS Trust was not funded, and no research funding for follow-up was limited and so patients were followed-up opportunistically during this time.

4.3. Results

The summary patient cohort demographics are illustrated in the following table. 461 patients have been recruited with completed pre-operative questionnaires and 227 with post-operative questionnaires. The mean clinical severity and patient reported symptoms scores are illustrated in table 3 and show a significantly impaired population.

Table 3: The venous patient cohort demographics

<table>
<thead>
<tr>
<th></th>
<th>Pre-Operative</th>
<th>Post-Operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>461</td>
<td>227</td>
</tr>
<tr>
<td>Age</td>
<td>50.66</td>
<td>51.85</td>
</tr>
<tr>
<td>M:F</td>
<td>43:57</td>
<td>42:58</td>
</tr>
<tr>
<td>BMI&gt;30</td>
<td>9%</td>
<td>22%</td>
</tr>
<tr>
<td>Vein Diameter (mm)</td>
<td>8.06</td>
<td>7.346</td>
</tr>
<tr>
<td>VCSS</td>
<td>6.47</td>
<td>3.32</td>
</tr>
<tr>
<td>AVVQ</td>
<td>21.80</td>
<td>13.22</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.718</td>
<td>0.80</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>75.70</td>
<td>80.63</td>
</tr>
<tr>
<td>CES-D</td>
<td>11.27</td>
<td>9.61</td>
</tr>
</tbody>
</table>
The mean VCSS is higher than many previous studies (Carradice et al. 2012; Shepherd et al. 2010) though the AVVQ reported is similar to previous work (Darvall et al. 2010; Shepherd et al. 2010; Rasmussen et al. 2011) and this may indicate the severity of referral guidelines in the community supporting the vascular clinic.

The cohort results compare favourably with that shown by the 2011-2012 NHS Health Episode Statistics Patient Reported Outcome Measures (HES Online 2013) as shown by Table 4.

Table 4: Hospital Episode Statistics Patient Reported Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Pre-Operative</th>
<th>Post-Operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13,278</td>
<td>8,133</td>
</tr>
<tr>
<td>AVVQ</td>
<td>20.19</td>
<td>12.29</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.754</td>
<td>0.848</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>78.50</td>
<td>78.57</td>
</tr>
</tbody>
</table>
4.3.1. Depression Burden in Superficial Venous Disease

4.3.1.1. Introduction

Depression is a common mental health disorder, and affects more than 120 million people worldwide (Lépine & Briley 2011). It is characterised by symptoms of sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration (WHO). These symptoms can become chronic or recurrent impairing an individual's ability to cope with daily life. Depression costs the UK economy over £9 billion in lost working days, and although it can be both reliably diagnosed and treated in a primary care setting only a quarter of patients with depression seek medical advice or are receiving treatment (The ESEMeD/MHEDEA 2000 investigators* et al. 2004).

Overall, 1 in 10 adults in Britain suffer from depression at any one time and depression is approximately 2-3 times more common in patients with chronic physical health problems, compared to those who have good physical health (National Institute for Health and Care Excellence: 2009)-CITATION_IS_EMPTY. This observation led to the development in 2009 of NICE guidelines in the UK, again recommending that all adults, aged 18 years and older, with chronic physical illness be screened for depression.

Varicose veins have been shown to impact on quality of life (QOL), (Smith et al. 1999) with increasing severity of disease having a proportionately greater impact (Carradice et al. 2011). Depression has also been shown to adversely affect QOL (Culpepper 2011). The effect of symptomatic varicose veins on mental health outcomes and on depression specifically is less well defined. The aim of this study was to evaluate the burden of depression in patients with symptomatic uncomplicated and complicated (associated with skin changes which include eczema, lipodermatosclerosis and ulcers) varicose veins presenting to tertiary care for treatment (Abenhaim & Kurz 1997).
4.3.1.2. Centre for Epidemiological Study - Depression (CES-D)

The Centre for Epidemiological Study - Depression Score (CES-D - see Appendix 3) is a validated 20 question screening tool for depressive symptoms. A score of >16 is indicative of depression, and >26 of severe depression (Weissman et al. 1977; Radloff 1977; Lyness et al. 1997; Irwin et al. 1999). A score of 21 has been shown to have a sensitivity of 92% and specificity of 87% for major depression (Lyness et al. 1997; Schulberg et al. 1985). This has led to its use as a popular screening tool (Irwin et al. 1999).

However, as with the majority of screening questionnaires, the CES-D does not equate to a diagnosis but does uncover previously undiagnosed cases (Weissman et al. 1977; Lyness et al. 1997; Irwin et al. 1999; Noyes et al. 2011).

4.3.1.3. Methods

4.3.1.3.1. Patient selection

All patients referred by their General Practitioner (GP) to the vascular surgery outpatients clinic at Charing Cross Hospital, London, for management of their varicose veins, over a 6 month period from January to June 2011, were invited to complete a validated questionnaire relating to disease-specific quality of life, using the Aberdeen Varicose Veins Questionnaire (AVVQ) (Garratt et al. 1993) and health-related QOL, using the EuroQoL-5D questionnaire (EQ-5D, EuroQol Group, Rotterdam, The Netherlands) and EuroQol-Visual Analogue Score (EQ-VAS). The presence of depressive symptoms was determined using the Centre for Epidemiological Studies Depression Scale (CES-D Scale) (Weissman et al. 1977) - Table 5. A 20 item self-reporting scale which has been shown to be both a sensitive and valid screening tool for detecting depressive symptoms (Weissman et al. 1977) across different populations (McCallum et al. 1995).
Table 5: An overview of the questionnaires used in this study

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Number of items</th>
<th>Parameters evaluated</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberdeen Varicose Vein Questionnaire</td>
<td>13</td>
<td>- Physical symptoms&lt;br&gt;- Compression therapy use&lt;br&gt;- Limitations of disease on daily and social activities</td>
<td>0 (no effect) to 100 (severe effect)</td>
</tr>
<tr>
<td>EuroQol-5D (EQ-5D)</td>
<td>5</td>
<td>- Mobility&lt;br&gt;- Self-care&lt;br&gt;- Pain/Discomfort&lt;br&gt;- Anxiety/Depression</td>
<td>n/a</td>
</tr>
<tr>
<td>EuroQol-Visual Analogue Score (EQ-VAS)</td>
<td>n/a</td>
<td>This is a 20 cm subjective visual analogue scale relating to health-related quality of life</td>
<td>100-0</td>
</tr>
<tr>
<td>Centre of Epidemiological Studies Depression Score (CES-D)</td>
<td>20</td>
<td>This is a sensitive and validated self-reporting depression-symptom scale</td>
<td>0-60&lt;br&gt;&gt;16 suggests depression&lt;br&gt;&gt;26 suggests severe depression</td>
</tr>
<tr>
<td>Clinical Stage of the Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification</td>
<td>6</td>
<td>- C0 — no visible varicose veins&lt;br&gt;- C1 — spider or reticular veins&lt;br&gt;- C2 — Varicose veins&lt;br&gt;- C3 — Oedema&lt;br&gt;- C4 — Skin Changes&lt;br&gt;- C5 — Healed ulcer&lt;br&gt;- C6 — Active ulcer</td>
<td>Maximum score of 27</td>
</tr>
<tr>
<td>Venous Clinical Severity Score (VCSS)</td>
<td>9</td>
<td>Evaluates for presence of skin changes and pigmentation, inflammation and induration, presence of ulcers and use of compression hosiery</td>
<td>0-3</td>
</tr>
<tr>
<td>Venous Disability Score (VDS)</td>
<td>1</td>
<td>Based on the ability to work an 8-h day with or without the requirement for external compression hosiery support</td>
<td>0-3</td>
</tr>
</tbody>
</table>

No patients were excluded from the study. Ethics approval was obtained from the Local Research Ethics Committee (LREC), and the study was termed Service Evaluation. Questionnaires were administered in a clinic setting following the consultation and prior to any intervention.

Questionnaires typically took 30 min to complete. Patients did not receive any direction regarding how they should be filled, but were provided standardised guidance notes and given the opportunity to ask questions.

Generic QOL measurement tools, such as the EuroQol (EQ-5D), are divided into domains of interest. They thereby allow mental, physical and social aspects of QOL to be evaluated independently. Disease-specific QOL measurement tools, such as the AVVQ, (Garratt et al. 1993) attempt to quantify the change in QOL due to an individual disease state. In combination, these two types of tool provide a powerful and robust method for assessing both the baseline QOL and disease-specific QOL and were therefore both utilised in this study.

Patient age, occupation, gender, medical co-morbidity and history of previous intervention for varicose veins were also determined. The clinical severity of venous disease was established by the treating physician using the Clinical Etiologic
Anatomic Pathophysiologic (CEAP) classification, Venous Clinical Severity Score (VCSS) and Venous Disability Score (VDS) (Rutherford et al. 2000). Once completed, all questionnaires were collated and analysed. Patients with CES-D scores of >16 were referred to their GP for further management.

4.3.1.3.2. Statistical analysis

Univariate linear correlation analysis was used to assess the relationship between two independent variables. Mann-Whitney- U test was used to assess the difference between two independent groups. Statistical significance was expressed as both p values and 95% confidence intervals. A p value <0.05 was considered statistically significant.

4.3.1.4. Results

4.3.1.4.1. Demographic data

A hundred patients were recruited from a total of 125 eligible patients (80% uptake) over the 6 months study period. There were 37 men (37%) and 63 women (63%). All questionnaires were fully completed and included in the analysis. The mean age of patients was 52.7 years (range, 24-91 years), 72% of patients were under the age of 65 and 28% were aged 65 years or more. There was no significant correlation between CES-D score and patient age (p = 0.30, r2 = 0.011). There was no difference in depression scores between those patients aged over 65 years and those aged less than 65 years old (p = 0.60). Twenty-nine per cent of all patients had CES-D scores greater than 16 and 5% of patients had CES-D scores greater than 26. No patient had previously been diagnosed or treated, or were on current treatment for depression.

In terms of past medical history, no patient had co-existing peripheral vascular disease. Thirty-three patients (33%) had previously undergone intervention for their varicose veins. There was no significant difference in CES-D scores in patients who
had previously undergone treatment for their varicose veins, compared to those who had not (p = 0.94).

4.3.1.4.2. Depression and quality of life

A weak positive correlation was seen between CES-D score and disease-specific QOL as evaluated using the AVVQ (p = 0.0009, r² = 0.11) (Figure 47).

![Figure 47: Correlation between CES-D and disease specific quality of life as indicated by the AVVQ score (p = 0.0009, r² = 0.11).](image)

A significant negative correlation was seen between CES-D score and health-related QOL as indicated by EQ-5D (p < 0.0009, r² = 0.32) and EQ-VAS scores (p < 0.0009, r² = 0.25) (Figure 48 and Figure 49). Higher EQ-5D and EQ-VAS, unlike the AVVQ score, indicate better QOL and lower EQ-5D and EQ-VAS scores worse QOL.

![Figure 48: Correlation between CES-D and health-related quality of life as indicated by the EQ-5D (p < 0.0001, r² = 0.32) and EQ-VAS scores (p = 0.0009, r² = 0.25).](image)
4.3.1.4.3. Depression and clinical severity of venous disease

Patients with severe depression (n = 5) were observed to have venous disease of clinical stage 4-6, as defined by the CEAP classification. However, overall there was no difference in CES-D scores with varying clinical stage (p = 0.30). CES-D score did not correlate with the VCSS (p = 0.07, r² = 0.03) or VDS (p = 0.75) (Figure 50 and Figure 51).
4.3.1.4.4. Depression and Response to Treatment

After initial assessment of the depressive burden, data continued to be collected, including after intervention, as part of the venous disease cohort study.

Recruitment of completed CES-D questionnaires totalled 284 pre-operative patients and 195 post-operative patients.

Figure 52: Pre and Post-Operative CES-D score

Mean pre-operative score was 11.27 (±9.117) and showed a significant improvement to 9.61 (±8.997) post-operatively (p=0.049), a drop of 14.7%.
4.3.1.5. Discussion

The presence of depression in patients with varicose veins has undergone only limited investigation previously. In contrast, QOL status in patients with varicose veins has been extensively investigated, (Garratt et al. 1993; Biemans et al. 2011) (Kaplan et al. 2003; Kurz et al. 2001) and is an accepted outcome measure used both in clinical practice and in clinical trials investigating varicose vein treatment (Carradice et al. 2011; Shepherd et al. 2010; Darvall et al. 2010). QOL measures are also shown to be better correlated with symptomatology and patient satisfaction than anatomical or technical measures (Shepherd et al. 2011).

Varicose veins are common with a reported incidence of 20-25% in women, and 10-15% in men (Beebe-Dimmer et al. 2005; Maurins et al. 2008). A number of studies have shown an increased incidence of depression and anxiety in patients with venous ulcers, with reported incidences ranging from 40 to 60% (Palfreyman et al. 2010; Ratcliffe et al. 2007). Our study reports an incidence of depression in patients with symptomatic varicose veins of 29% and this falls to 26% when patients with healed or active venous ulcers are excluded. This is twice the reported prevalence of depression within the general population (Demyttenaere et al. 2004), but is similar to that reported in patients with chronic physical health problems.

Esteban et al, in a Spanish study of 7341 subjects aged >15 years with a variety of chronic medical diseases, found that depression had a significant impact on health-related QoL (Esteban y Pena et al. 2010). When looking specifically at the impact of venous disease on mental health, Smith et al in their study found no significant difference in the mental health domain of the SF-36 in patients with varicose veins compared to those without, (Smith et al. 1999) but following treatment with open surgery there was a significant improvement in the mental health domain. In our study, depressive symptoms correlated with disease-specific and health-related QoL outcomes, however, we failed to demonstrate any correlation with clinical disease
severity. A possible explanation is that depression may alter a patient's perception of the severity of venous disease. Chronic physical health problems are also seen to precipitate and exacerbate depression and this may be true for varicose veins (Moretti et al. 2011).

In our study similar depression scores were reported amongst men and women. This is in contrast to the incidence within the general population, where women are twice as likely to suffer from depression compared to men (Murakumi 2002). The reasons for this are unclear. In addition, there was no correlation with depression and age as documented in other studies of depression in the general population. However, there were few patients in our study over the age of 65 years (27%).

Both depression and varicose veins are treatable once diagnosed. Work by Chassany et al (Chassany et al. 2006) showed that general practitioners routinely under-estimate the quality of life impairment due to venous disease whilst over-estimating that from peripheral arterial occlusive disease. Notably, no patients in our study had previously been diagnosed or were on treatment for their depression.

The aim of this study was to assess the burden of disease in ambulatory patients with symptomatic varicose veins, who have presented to their GP and subsequently to a vascular surgeon for treatment. However, this group of patients may not reflect the burden of depression in varicose veins patients within the general population. Moreover, the influence of socioeconomic factors and ethnicity on depression scores was not ascertained in this study.

Further work has been completed with extended numbers of patients since completion of the initial discrete study. This has provided a larger cohort of pre- and post-intervention scores, which have shown a significant drop after intervention. This would be in keeping with resolution of physical symptoms improving holistic wellbeing (Katon et al. 2007), and also agree with our findings of
strong correlation between CES-D and quality of life (both generic and disease specific) prior to treatment.

With the large burden of disease associated with depression simple treatments of physical conditions may be a key component in the population level treatment of depression.

**4.3.1.6. Conclusion**

Patients with symptomatic varicose veins are at increased risk of depression compared to the general population. This study reports a high incidence of previously unreported and undiagnosed depression in this group of patients. Further investigation of a patient's wellbeing and a more holistic approach in the management of patients with venous disease is therefore recommended. Additionally, this work has shown that intervention for varicose veins reduces patients scores on the CES-D depression screening questionnaire, further strengthening the rationale for venous treatment.
Chapter 5: Vein Diameter Relationships
5.1. Introduction

Varicose veins are a common but often underestimated condition (O'Hare & Earnshaw 2009; Rabe & Pannier 2010). Epidemiological estimates give a prevalence of 25-50% (Beebe-Dimmer et al. 2005) and there is extensive evidence that intervention provides significant cost-effective improvements in quality of life (Rasmussen et al. 2011; Gohel et al. 2010; Nesbitt et al. 2011). Modern treatments offer minimally invasive procedures with low morbidity (Lane et al. 2011).

Due to financial constraints and the ageing population, rationing of treatment has become accepted as a necessary evil (Broqvist & Garpenby 2011), and is best assessed on cost effectiveness of the treatment itself (Grassi & Ma 2011) and need (Cuff et al. 2012). Varicose veins have long been classed as a condition with low priority (Lindsey:2006vo)-CITATION_IS_EMPTY, partly due to the prevalence and partly due to the wide spectrum of symptoms (Campbell et al. 2007).

There has been a recent movement towards using vein diameter to stratify patients suitable for treatment and indeed reimbursements in some countries depend on vein diameter criteria being met, including the UK (NHS North West London 2011). This is despite clear referral recommendations against such rationing (National Institute for Clinical Excellence 2001; Venous Forum of the Royal Society of Medicine et al. 2011).

The evidence base for this assumption is sparse, and often made on the presumption of traditional surgical operations (Abbott et al. 2011). There is some evidence to show that chronic venous insufficiency (CVI - CEAP classification C4-C6) is associated with worse disease specific quality of life scores (Aberdeen Varicose Vein Questionnaire - AVVQ) and a larger vein diameter (VD), when compared to chronic venous disease (C1-C3) (Conway et al. 2011; Gibson et al. 2012). Previous work in our unit showed no association between anatomical reflux
(venous segmental disease score - VSDS) or haemodynamic assessments (venous refill time - VRT) and outcomes (Shepherd et al. 2011).

The aim of this study was to assess the association between clinical grading (CEAP), clinical severity score (Venous Clinical Severity Score - VCSS), disease specific quality of life score (AVVQ) and vein diameter (VD).

5.2. Methods

Regional ethical sub-committee approval was sought and obtained for this study. Patients were recruited from those attending a tertiary referral vascular clinic for assessment and treatment of varicose veins between January 2011 and July 2012 (18 months).

Patients underwent duplex ultrasound scans of the venous tree in the standing position and were then assessed according to the CEAP and VCSS clinical scoring systems and were invited to complete a questionnaire assessing disease specific quality of life (AVVQ). Patients were follow-up opportunistically after treatment due to lack of funding for follow-up visits in the NHS clinic.

Maximal vein diameter, CEAP, VCSS and AVVQ scores were collated on a database (Access 2010, Microsoft, Richmond) and underwent statistical analysis (SPSS v21, IBM, Armonk, USA). Data was analysed using three separate methods - as one group (1), as groups dependent on VD (2) and as clinically graded CEAP groups (3).

(1) formed one group which underwent analysis using Spearman's Correlation Coefficient
(2) formed five groups surrounding the mean VD using t tests
(3) formed two groups (C1-3 and C4-6) which underwent analysis using Mann-Whitney tests comparing VD, AVVQ and VCSS
Additional unpublished and unanalysed data from a previous randomised controlled trial (Shepherd et al. 2010) was included in the full dataset (recruitment period July 2008 - July 2009).

5.3. Results

5.3.1. Demographics

The demographics for patients recruited to the vein diameter assessment (including previously unpublished data from the VALVV study) are presented in Table 6.

Table 6: Vein Diameter Cohort Demographics

<table>
<thead>
<tr>
<th></th>
<th>Pre-Operative</th>
<th>Post-Operative</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>461</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.66</td>
<td>51.85</td>
<td>ns</td>
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<tr>
<td>M:F</td>
<td>43:57</td>
<td>42:58</td>
<td>ns</td>
</tr>
<tr>
<td>BMI&gt;30</td>
<td>9%</td>
<td>22%</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Vein Diameter</td>
<td>8.06 mm</td>
<td>7.346</td>
<td>ns</td>
</tr>
<tr>
<td>VCSS</td>
<td>6.47</td>
<td>3.32</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>AVVQ</td>
<td>21.80</td>
<td>13.22</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.718</td>
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<td>EQ VAS</td>
<td>75.70</td>
<td>80.63</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>CES-D</td>
<td>11.27</td>
<td>9.61</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

5.3.2. Overall Comparisons

There was no significant correlation between VD and AVVQ \( (r=0.060, r^2=0.011, \ p=0.160) \), however there was a weak but significant positive correlation between VD
and both VCSS ($r=0.169$, $r^2=0.017$, $p=0.001$) and CEAP ($r=0.169$, $r^2=0.020$, $p=0.008$). These results are displayed in Figure 53, Figure 54 and Figure 55.

Figure 53: Vein diameter vs AVVQ. Correlation $r = 0.060$, $p = 0.111$, ns; Linear Regression $r^2 = 0.011$

Figure 54: Vein diameter vs CEAP. Correlation $r = 0.169$, $p<0.001$; Linear Regression $r^2 = 0.020$
Figure 55: Vein diameter vs VCSS. Correlation $r = 0.164$, $p=0.001$; Linear Regression $r^2 = 0.017$

Figure 56: Vein Diameter vs EQ5D QOL ($r=-0.57$, $r^2=0.003$, $p=0.181$) and EQ5D VAS ($r=-0.46$, $r^2=0.003$, $p=0.230$)

There was no significant correlation found with generic quality of life as seen in Figure 56.
5.4.2. Stratification by Clinical CEAP Grade

The results were divided into two groups depending on clinical grading - CEAP score – see Table 7. Group one represented mild venous disease - C1-C3 (telangectasia to leg swelling); and group two represented more severe venous disease - C4-C6 (skin changes to active ulceration). 55% of patients were graded as having mild disease (254 of 461) and 45% as severe. The severe group had a significantly higher mean age (57 years vs 49 years, p<0.001) and proportion of men in the group (55.1% vs 32.7%, p<0.001).

Table 7: Study population stratified by CEAP Classification into groups C1-C3 (mild venous disease) and C4-C6 (severe venous disease).

<table>
<thead>
<tr>
<th></th>
<th>CEAP C1-C3</th>
<th>CEAP C4-C6</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.28</td>
<td>57.29</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Proportion Female (%)</td>
<td>67.3</td>
<td>44.9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>11.1%</td>
<td>7.5%</td>
<td>ns</td>
</tr>
<tr>
<td>Vein Diameter (mm)</td>
<td>7.605</td>
<td>8.640</td>
<td>p=0.04</td>
</tr>
<tr>
<td>VCSS</td>
<td>6.41</td>
<td>12.65</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>AVVQ</td>
<td>19.016</td>
<td>25.190</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EQ-5D QOL</td>
<td>0.686</td>
<td>0.750</td>
<td>p=0.004</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>76.57</td>
<td>74.83</td>
<td>ns</td>
</tr>
<tr>
<td>CES-D</td>
<td>10.25</td>
<td>12.26</td>
<td>ns</td>
</tr>
</tbody>
</table>

The severe group were found to have significantly larger mean maximal vein diameters (8.6 mm vs 7.6mm, p=0.04), higher mean AVVQ scores (25.190 vs 19.016, p<0.001) and higher mean VCSS (12.65 vs 6.41, p<0.0001). These are displayed in table 7.
5.4.3. Stratification by Gender

Male patients had a significantly higher CEAP clinical stage (4 vs 3, p=0.001), but significantly improved QOL both disease specific and generic - AVVQ (19.485 vs 23.472, p=0.001), EQ5D QOL (0.759 vs 0.682, p=0.001) and EQ5D VAS (78.34 vs 73.44, p=0.006). There was no significant difference between genders in VCSS scores (p=0.058), vein diameter (p=0.129), or CES-D (p=0.285).

5.4.4. Receiver Operator Curve Analysis of Vein Diameter

As there is no diagnostic test for varicose veins and as patients recruited into this cohort are by definition patients with symptomatic varicose veins, surrogate markers for a positive diagnosis have to be used. Therefore, Receiver Operator Curve (ROC) analysis was performed on the maximum vein diameter to access it's specificity and sensitivity as a diagnostic test.

Previous studies have suggested that the AVVQ be used as a rationing tool to indicate patients qualifying for treatment (Ward et al. 2013; Lattimer et al. 2013). Therefore, ROC analysis was performed at the following AVVQ points - 10, 15, 20, 25 and 30. The ROC graphs are shown in Figure 57. All of the curves produced showed very poor accuracy using maximal diameter as a diagnostic test.
Figure 57: ROC curves for AVVQ = 15-30 cut-offs. Area under curve: 10=0.522, 15=0.517, 20=0.529, 25=0.509, 30=0.558.

Many local referral guidelines suggest using CEAP scoring as a rationing tool, and so the ROC analysis was also performed for CEAP classes 3 and 4. CEAP 2 was not used due to the absence of C1 or C0 patients in this cohort (a limitation previously seen in (Carradice et al. 2011)). The CEAP ROC graphs are shown in Figure 58.
Figure 58: ROC curves for CEAP 3 and 4 cut-offs. Area under curve: 3=0.616, 4=0.589.

Finally, VD cut-offs at 6mm, 8mm, 10mm and 12mm were assessed. These are displayed below in Figure 59 and Figure 60 show poor accuracy.

Figure 59: ROC curves for Vein Diameter 6mm and 8mm cut-offs. Area under curve - all less than 0.550
5.4.3. Response to treatment

Treatment has previously been shown to be successful in improving clinical status, disease specific QOL scores and generic QOL scores. 227 patients have completed post-intervention questionnaires. A summary of the results is shown in Table 6.

5.4.3.1. Clinical Outcomes

5.4.3.1.1. CEAP

CEAP scores are not designed to assess treatment and are therefore relatively insensitive to change of disease. Whilst the median CEAP did not change pre- and post-intervention, the proportional makeup did (p<0.001). CEAP was not correlated with VD post-intervention.

Table 8: CEAP Scores for Venous Disease Cohort Pre and Post Intervention

<table>
<thead>
<tr>
<th>CEAP Stage</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9%</td>
<td>18.6%</td>
</tr>
<tr>
<td>2</td>
<td>28.4%</td>
<td>24.8%</td>
</tr>
<tr>
<td>3</td>
<td>25.3%</td>
<td>13.8%</td>
</tr>
<tr>
<td>4</td>
<td>37.3%</td>
<td>30.5%</td>
</tr>
<tr>
<td>5</td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
5.4.3.1.2. VCSS
The clinician scoring system showed a significant improvement from 6.47 to 3.32 (p<0.001). No correlation was seen between VCSS and VD.

5.4.3.2. Generic Quality of Life

5.4.3.2.1. EQ-5D QOL
Mean EQ-5D QOL improved from 0.718 to 0.800 (p<0.001). No correlation was seen with post-intervention EQ-5D QOL and VD.

5.4.3.2.2. EQ-5D VAS
Mean EQ-5D VAS improved from 75.70 to 80.63 (p<0.01). No correlation was seen between EQ-5D VAS and VD.

5.4.3.3. Disease Specific Quality of Life

5.4.3.3.1. AVVQ
AVVQ improved significantly from 21.80 to 13.22 (p < 0.001). AVVQ post-intervention was negatively correlated with VD (r=-0.140, r²=0.019, p=0.043).
Figure 61: Maximal vein diameter vs AVVQ post-intervention.

No correlation was found between VD and change in AVVQ at any time point.

5.4. Discussion

This study shows that there is a significant correlation between VD and clinical scoring systems (VCSS and CEAP). However, this correlation is extremely weak and not clinically significant. Crucially there is no correlation between VD and symptomatology suffered by patients (AVVQ). However, and more importantly, patients with more advanced disease - CEAP clinical classes C4-6, have a larger mean vein diameter. This indicates that vein diameter may be an independent risk factor for complicated varicose vein disease. If so, progression to severe venous disease may be preventable by treatment of enlarged veins. However, this process would be complicated by the fact that symptomatology is not associated with VD and so patients at risk may not attend - screening would be required, which would not be feasible or appropriate on the current evidence base as asymptomatic veins
would not benefit from treatment unless individuals at high risk can be accurately identified.

Extensive work has shown that varicose vein treatment works and is cost-effective, and these treatment pathways offer all types of treatment as day cases whether open surgery or endovenous treatment. Due to the population size, many healthcare systems are attempting to limit treatment to those who most need it. This rationing has been achieved with the use of VD as a hurdle. In the UK many PCTs have utilised 3 mm, as have insurers in the UK and US. Whilst this is sensible from a technical viewpoint - cannulating a small vein takes considerable skill and radiofrequency treatment catheters for example are over 2mm in diameter, it has no basis in the literature. As endovenous skills increase and devices become smaller, this "technical" boundary recedes in importance. Additionally, due to the nature of the saphenous vein, it is a hidden vein. Therefore, if VD is used as a rationing tool, it would require the primary care use of venous duplex ultrasound to ascertain whether the vein is large enough for referral - this would engender far more ultrasound scans, leading to a much higher cost.

From this study it is clear that not only does this "treat the scan not the patient" approach ignore the patient and their symptoms; from the ROC analyses performed, it is clear VD has no role as a rationing tool. Additionally, the true nature of progression of venous disease and vein diameter changes are not known (Engelhorn et al. 1997; Engelhorn et al. 2007; Engelhorn et al. 2012) - treating a small vein now may prevent more costly treatment and extensive morbidity in the future (Lane et al. 2013).

From a patient perspective, patients seek medical treatment not due to the size of the truncal vein but due to symptoms. There is no evidence linking varicose surface tributary diameter with truncal vein diameter. Indeed there is evidence of
non-saphenous varicosity reflux in isolation (Labropoulos et al. 2001). This prevents clinicians from making accurate diagnosis on examination alone. Therefore, clinical history and validated questionnaires are crucial methods of assessing outcomes from this extremely common but relatively benign disease. The use of national Patient Reported Outcome Measures (PROMs) data enables conclusions to be drawn from population level venous treatment (Nesbitt:2012bl)-CITATION_IS_EMPT, however there is little data published by the Department of Health of the impact of the endovenous revolution.

Interestingly, this data agrees with the general trend for men to present with worse health conditions than women (Doyal 2001; Farrimond 2012). Men are over-represented by in the severe disease group (C4-6) compared to the total group (55.1% vs 32.3%, p<0.001). Whether this is because of delayed presentation or a general susceptibility is difficult to hypothesis.

Previous work (Gibson et al. 2012) has shown that great saphenous vein diameter does not correlate with patients symptoms and quality of life impairment in a study of 91 patients, however only 10 patients had severe disease (C4-6), which means assessment of effect of VD on CEAP is unavailable. Conway et al's work (Conway et al. 2011) supports the findings of this study that whilst vein diameter does not correlate with quality of life scores it is positively associated with increased CEAP category. Unfortunately the Conway study did not include VCSS scoring, but did have a robust data set with 85 C4 - C6 patients. A recently published retrospective cohort study of 55 limbs with maximal GSV diameter < 5mm compared with 116 limbs of maximal GSV diameter > 5mm found similar improvement between in both groups, according to VCSS and CEAP (Perrins et al. 2013). This study did not assess AVVQ, the groups were significantly different in terms of BMI, age, and CEAP and follow-up was limited to 3 months.
This main strength of this study is the large numbers involved with data collected in a prospective manner, with both clinical and quality of life scoring systems utilised. However, limitations exist due to lack of follow-up post-procedure data. Most crucially this study does not answer the question of whether large vein diameter is associated with the development of venous skin changes and ulceration. This would necessitate a large multi-centre long term follow-up study to be completed, such as the Bonn or Edinburgh Vein Studies (Rabe et al. 2003; Robertson et al. 2013). Patients in this cohort have already developed the peak of their condition prior to treatment, which then causes regression. A long-term cohort study of these patients would enable assessment of recurrence and/or progression of the disease.

Multivariable analysis of the vein diameter data will allow clarity on whether the size of incompetent vein is a truly an independent risk factor for treatment outcome, which will be discussed in the modelling section of this manuscript.

5.5. Conclusion

Whilst vein diameter is associated with clinical stage of venous disease, it has no significant bearing on patient symptoms and experience. Therefore it has no role as a diagnostic or rationing test. It should be used as a component of patient selection for treatments (Goode et al. 2009) rather as a blunt rationing tool.
Chapter 6: Modelling Outcomes in Superficial Venous Disease
6.1. Introduction

Varicose veins are subject to increasing pressure due to limitations on funding and an inaccurate perception that the treatment is superfluous (Audit Commission 2011). Varicose veins are the most common operation in vascular surgery, but also the most commonly litigated (Ray 2005; Markides et al. 2008; Campbell et al. 2002), this is despite evidence that over 90% of primary and 75% of recurrent varicose vein patients being satisfied with treatment (Gandhi et al. 2010). Additionally, historic anecdotal evidence of significant pain post-operatively with open surgery biases patient viewpoints despite extensive studies demonstrating good tolerability and low pain scores (Leopardi et al. 2009).

The risk of litigation has been reduced with the use of pre-operative duplex ultrasound scans providing key haemodynamic data (Campbell et al. 2002; Ray 2005; Markides et al. 2008; J. R. H. Scurr & J. H. Scurr 2007).

Therefore, assessing which patients improve and which do not is vital in raising the awareness of this debilitating disease.

Extensive work has previously been completed to model the pre-intervention impact of venous disease on patients and to assess the utility of treatment both from QOL and economic viewpoints (Carradice et al. 2011; Gohel et al. 2010). This data has been used to help form the 2013 NICE guidelines {NationalInstituteforHealthandCareExcellence:2013vv}-CITATION_IS_EMPTY. These studies have utilised pre-operative data (Carradice et al. 2011) and previously published RCT data (Gohel et al. 2010), to create predictive models. Modelling of longitudinal data aims to identify key variables that influence patient outcomes with the benefit of pre-operative and comparative post-operative outcome data.
The principle aim of this study is to assess and describe these key factors via the cohort of patients that have completed patient outcome questionnaires.

6.2. The Development of a Rationing Tool

The pragmatic purpose for model creation is to predict which patient benefit most from treatment. This is to improve the overall outcomes of varicose vein treatment by selecting the most appropriate patients. Additionally it helps to identify patients who do not improve and reasons why.

Once these factors have been discovered, a rationing tool can be developed to ensure that patients who will not benefit do not receive inappropriate treatment.

6.3. Principles of modelling

Modelling data uses statistical tools to provide a prospective estimation of outcomes.

6.3.1. Multivariable Analysis

Multivariable statistics deal with multiple inputs to one single outcome - i.e. Many independent variables but one outcome dependent variable (Katz 2003).

6.3.1.1. Regression

Linear regression concerns a method of examining causal association between an independent and dependent variable, and the degree of association (Bland & Altman 1994; Bowers 2008). Multiple linear regression concerns a examining multiple independent variables and one dependent variable (Bowers 2008). Linear regression requires linear continuous variables for appropriate model construction.

However, in clinical practice patients may present as symptomatic or not - a binary outcome. This cannot be readily examined with linear regression and so logistic regression is an appropriate method to examine relationships. The benefit of logistic regression is to produces an Odds Ratio for the relationship - i.e. The odds
that if you have the appropriate risk factor then you will have the disease in question (Bowers 2008). Again logistic regression can be expanded into multiple logistic regression

Proportional hazards regression assesses longitudinal studies and provides a hazard ratio of reaching a discrete endpoint over a timescale (often the endpoint is death) (Bowers 2008; Katz 2011).

6.3.2. Univariate and multivariate analysis

Univariate analysis is the assessment of one independent variable in the sample data. Using this method the effect of individual factors can be adjusted and modelled.

Multivariate analysis utilises the interplay of many independent variables to adjust and formulate a model for factor analysis and risk factor assessment (Katz 2011; Hair 2010).

6.3.2.1. Factor Analysis

The aim of factor analysis is to reduce large number of seemingly independent factors to a smaller number of truly independent factors, which then allow for true modelling assessment with the use of assumptions and constant values (Hair 2010).

6.3.3. The Markov Chain and the Monte Carlo Method

The Markov Chain is a decision tree, which has probabilities at each Markov or chance node (Gohel et al. 2010). This provides a probability of reaching each endpoint of the decision tree. Each node has a options whose sum probability is 1. This allows all possibilities to be modelled, and the probabilities are constructed using available experimental data. An example is shown in Figure 62. The probability of A->B->C->A = 0.6x0.7x0.8 = 0.336
The Monte Carlo method is a statistical process of running repeat simulations of decision tree to test validity, variance and uncertainty (Spiegelhalter et al. 2004; Gohel et al. 2010). Whilst these simulations can be extremely complex and accurate, it must be remembered that they are artificial approximations based on real-life study data probabilities. These testing methods are best used in situations where multiple variables are present and many assumptions have to be made, essentially where measurements are not possible or feasible (Rogers 2006; Nguyen et al. 2013; Hempel et al. 2013; Oono et al. 2013).

6.4. Response to treatment

The aim of factor analysis is to reduce large number of seemingly independent factors to a smaller number of truly independent factors, which then allow for true modelling assessment with the use of assumptions and constant values.
6.5. Capacity to benefit

The ability of patients to benefit from venous treatment is key. Some patients suffer from significant recurrences at short time periods, whereas others have a single treatment that lasts the rest of their lifetime (Allegra et al. 2007; Blomgren et al. 2004). Differentiating between the groups is key to offering a pragmatic bespoke service. It also prevents patients from having multiple gradually more complex procedures for minimal benefit.

Whilst the majority of the difference in the patient groups is phenotypic and genetic (Lim & Davies 2009), isolating individual variables is key to the optimisation of the treatment pathway.
6.6. Vein Cohort Data Model

The Venous Disease patient cohort data previously described has been utilised in advanced statistical analysis using a senior statistician’s assistance to provide models looking at 3 main outcomes - symptomatic benefit (AVVQ), Clinician Deemed Benefit (VCSS) and Overall Quality of Life Benefit (EQ-5D). The aim is to elucidate key independent variables that affect the outcome of patients.

All patients in this cohort undergo treatment, and therefore a good model should be able to predict the outcomes. The model is created on the pre-intervention data and then assessed against the post-intervention data, which was measured at 6 weeks, 6 months and 1 year.

6.6.1. Symptomatic Benefit

The Symptomatic Benefit of treatment is assessed using the patient completed AVVQ, which as described earlier is a patient completed symptom score, allowing outcomes of the surgery to be assessed from the patient viewpoint. The baseline data was assessed to identify factors associated with the outcome, and from these predictive models were created.

6.6.1.1. Model 1

6.6.1.1.1. Introduction

The first model was created using baseline data from the venous patient cohort to predict the AVVQ outcome.

6.6.1.1.2. Statistical methods:

Initial analysis was performed using linear regression, as AVVQ is measured on a continuous scale. The AVVQ outcome distribution showed a positive skew and was therefore log transformed. Repeated univariable analyses then investigated the baseline variables for association with the outcome.
Those variables which had shown significant association (p<0.02, allowing for correction for multiple comparisons) were then subjected to multivariable analysis, and using a backwards selection procedure all non-significant values were removed leaving only significant variables in the final model.

This technique was used as it allows for the effects of each variable to be adjusted for the other variables, which better clarity of the underlying associations between these variables. Only those variables which have a significant effect on the outcome variable are then assessed in the multivariable analysis as allows for simplification, which is then continued with the incremental removal of all none significant variables in the backwards selection procedure. This should provide only significant variables of interest for the final model.

The model was then evaluated with the follow-up data as observed values to compare with the predicted values from the model.

6.6.1.1.3. Results:

Table 9: Results of AVVQ univariable analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>1.42 (1.06, 1.99)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.53 (1.14, 2.04)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>1.08 (0.93, 1.26)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.60 (0.48, 0.74)</td>
<td></td>
</tr>
<tr>
<td>Age (**)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>1.00 (0.93, 1.08)</td>
<td>0.98</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Category</td>
<td>Ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td>Left</td>
<td>1.06 (0.79, 1.43)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.42 (1.06, 1.92)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.73, 1.28)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.18</td>
</tr>
<tr>
<td>Yes</td>
<td>1.21 (0.91, 1.61)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>1</td>
<td>0.24</td>
</tr>
<tr>
<td>SSV</td>
<td>1.22 (0.87, 1.70)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.90 (0.57, 1.42)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable
(**) Ratio reported for a 10-unit increase in predictor variable

The results of the univariable analysis indicate that when examined separately only CEAP, sex and leg were significantly associated with AVVQ (Table 9).

The CEAP results indicate as found before that increasing CEAP leads to increasing AVVQ. Patients with CEAP 4-6 had AVVQ scores just over 50% higher than CEAP 0-2.

Patient gender showed reduced AVVQ scores for men compared to women, with men's scores on average only 60% of the women's scores.

Leg results indicated minimal difference between left and right leg single symptomatic patients but a 40% increase in symptomatology in bilateral symptomatic leg patients.
Following multivariable analysis and backwards selection, only CEAP and sex were independently associated with AVVQ scores as shown in Table 10, with laterality now longer being significant.

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
<th>Regression Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP 0-2</td>
<td>1</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.27 (0.94, 1.72)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.56 (1.20, 2.02)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.59 (0.48, 0.73)</td>
<td>-0.53</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-</td>
<td>2.90</td>
<td></td>
</tr>
</tbody>
</table>

This was then converted into a predictive model for AVVQ, and this can be expressed as:

\[ AVVQ = \exp(2.90 + (0.24 \text{ if CEAP} = 3 + 0.44 \text{ if } CEAP \geq 4 - 0.53 \text{ if Male}) \]

i.e. The model would predict in a 50 year old man with CEAP 3 disease the following:

\[ AVVQ = \exp(2.90+0.24-0.53) = \exp(2.61) = 13.599. \]

This model was then compared with the follow-up data in Figure 63 - a plot of AVVQ - Observed vs AVVQ - Predicted. The diagonal line represents perfect agreement.
The accuracy of the model is also explained in Figure 64 showing differences in predicted and observed values.

6.6.1.1.4. Discussion:

The two plots suggest a poor predictive ability of this first AVVQ model. Predictions are all between 10-30, whereas observed values range from 0-50. The model discrimination of high and low AVVQ is poor. The likely explanation is the small number of variables found to be significantly associated with the outcome in
the baseline data. In addition, these variables were categorical and so are not very discriminatory.

Additionally, the majority of predictions were 78% higher than those observed, and this is likely to be due to the reduction in AVVQ post-intervention. This will likely cause any baseline model to over-predict, however a good model should still be able to discriminate between high and low scores. The second plot explains that the high values were under-predicted and the low values over-predicted.

Overall, there were only two variables independently associated with AVVQ from the baseline data. This predictive model did not adequately predict the AVVQ scores observed at follow-up. This reinforces the known literature that symptoms of varicose veins are often difficult (Bradbury et al. 1999) to quantify and may be out of proportion to anatomical or clinical features. This first model attempted to predict outcomes wholly independently of outcome, which as shown above leads to over-estimation due to treatment and consequent reduction of symptomatic status. This model may be suitable to ascribe predicted AVVQ scores to new patients presenting to the department prior to completion of the scoring questionnaires. To test this model would however require a separate cohort of patients, ideally from the same geographical location.

6.6.1.2. Model 2

6.6.1.2.1. Introduction

The first model used baseline values to predict values at follow-up. This was shown to not be particularly effective, mainly as follow-up values were lower than those at baseline. So in the second model the follow-up values were considered as the outcome in the analyses.
6.6.1.2.2. Statistical Methods

There are three follow-up timepoints, and due to the decrease in AVVQ values over time, in order to obtain any reliable predictions, each timepoint was considered separately. To create this second model the AVVQ values at 6 weeks were treated as the outcome values in the analysis. The patient characteristics at baseline were considered to be the predictor variables.

As before, AVVQ was measured on a continuous scale and so was again initially analysed using linear regression. Once more the distribution suggested a positive skew and so the AVVQ values were log transformed prior to analysis. This analysis was again performed in two stages:

- Firstly the separate association between each variable and the outcome was assessed separately in a series of univariable analyses.
- Secondly the joint association between the variables and the AVVQ score was assessed in a multivariable analysis.

As the baseline data are the predictor variables and the follow-up data the outcome values, there is no independent data on which to test the fit of a predictive model. A statistic which can be used to measure of the fit of the model is the $R^2$ statistic, which measures the amount of total variability in the outcome explained by the model, and which is expressed as either a proportion, or a percentage. A high value would imply a good model fit, and thus a better likelihood of good predictions in the future.

6.6.1.2.3. Results

6.6.1.2.3.1. AVVQ at 6 weeks

Initially the separate association between each of the patient characteristics and the AVVQ score at 6 weeks was examined in a series of univariable analyses. The
results are summarised in Table 11. Due to the log transformation of the AVVQ scores, the results are presented in the form of ratios. For the categorical variables, this gives the ratio of AVVQ values in each category relative to the values in a baseline category. For the continuous variables the relative change in AVVQ is reported for a given increase in each variable. Associated confidence intervals are reported for each ratio, along with p-values indicating the significance of the results.

Table 11: Results of Univariable comparison for AVVQ at 6 weeks.

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.22 (1.13, 1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>1.50 (0.81, 2.78)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.61 (0.94, 2.76)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td>0.93 (0.72, 1.20)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>0.60 (0.40, 0.91)</td>
<td></td>
</tr>
<tr>
<td>Age (**)</td>
<td>1.05 (0.91, 1.20)</td>
<td>0.53</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Left</td>
<td>0.97 (0.57, 1.63)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.64 (0.98, 2.76)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.73</td>
</tr>
<tr>
<td>Yes</td>
<td>1.09 (0.68, 1.74)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>1.86 (1.14, 3.03)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td>LSV</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 12

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSV</td>
<td>1.34 (0.75, 2.38)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.95 (0.41, 2.22)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable  
(**) Ratio reported for a 10-unit increase in predictor variable

The results showed that, when variables were examined separately, AVVQ at baseline, sex and previous VV surgery were all significantly associated with AVVQ at 6 weeks. There was also some evidence of a difference in AVVQ scores between legs, although this difference was not statistically significant. The remaining variables were not found to be associated with this outcome at 6 weeks.

Higher AVVQ scores at baseline were associated with higher scores at 6 weeks. A 5-unit increase in the score at baseline was associated with a 22% increase in scores at 6 weeks.

The gender differences suggested lower scores for males relative to females. Scores for males were only 60% as large as those for females.

Patients with previous VV surgery had higher scores at 6 weeks, on average 86% higher than those with no previous surgery.

The second stage in the analysis was to examine the joint association between the variables and AVVQ scores at 6 weeks in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the final model is summarised in Table 12.
Table 12: Results of Backwards Selection for AVVQ at 6 weeks

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.21 (1.13, 1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>1.78 (1.14, 2.78)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable

The multivariable analysis indicates that only AVVQ at baseline and previous VV surgery were independently associated with the AVVQ scores at 6 weeks. After adjusting for these two variables, there was no longer any significant association between sex and this outcome. Again patients with higher AVVQ scores at baseline and those undergoing previous VV surgery had higher AVVQ scores at 6 weeks.

The regression coefficients from the final model were then calculated, and used to create down a predictive model for AVVQ at 6 weeks, which can be expressed as follows:

\[
\text{AVVQ 6 weeks} = \exp(1.27 + 0.039 \times \text{AVVQ baseline} + 0.58 \text{ if previous surgery})
\]

This is shown in Figure 65.
Figure 65: Demonstration of AVVQ at 6 weeks model

The $R^2$ value from the final model is 0.30 (or 30%). This suggest that 30% of the variation in the AVVQ scores at baseline is due to the two variables in the final model. This suggests that whilst the variables have some predictive ability, there is a lot of variation (70%) which is unexplained by the model. Therefore the model is unlikely to give extremely reliable predictions of AVVQ at 6 weeks.

6.6.1.2.3.2. AVVQ at 6 months

Following creation of the model for AVVQ at 6 weeks the same technique was completed for the AVVQ values at 6 months.

Again the separate association between each of the patient characteristics and the AVVQ score at 6 months was examined in a series of univariable analyses. The results are summarised in Table 13. Due to the log transformation of the AVVQ scores, the results are presented in the form of ratios. For the categorical variables, this gives the ratio of AVVQ values in each category relative to the values at baseline. For the continuous variables the relative change in AVVQ is reported for a given increase in each variable.
Table 13: Results of Univariable comparison for AVVQ at 6 months.

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.25 (1.16, 1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1</td>
<td>0.30</td>
</tr>
<tr>
<td>3</td>
<td>1.23 (0.67, 2.25)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.50 (0.89, 2.55)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>0.95 (0.73, 1.22)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>0.66 (0.44, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Age (**)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>1.00 (0.87, 1.15)</td>
<td>0.98</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>0.42</td>
</tr>
<tr>
<td>Left</td>
<td>1.15 (0.70, 1.91)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.40 (0.84, 2.35)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>Yes</td>
<td>1.42 (0.87, 2.27)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>Yes</td>
<td>1.31 (0.81, 2.11)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>SSV</td>
<td>1.36 (0.78, 2.37)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.78 (0.26, 2.30)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable
(**) Ratio reported for a 10-unit increase in predictor variable

From the invariable analysis, only AVVQ at baseline and sex were significantly associated with AVVQ at 6 months. Higher AVVQ scores at baseline were associated with higher scores at 6 months. A 5-unit increase in the score at
baseline was associated with a 25% increase in scores at 6 months. The gender differences suggested lower scores for males relative to females, with scores a third lower for males compared to females.

The second stage in the analysis was to examine the joint association between the variables and AVVQ scores at 6 months in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the final model is summarised in Table 14:

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.26 (1.17, 1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Yes</td>
<td>1.55 (1.04, 2.33)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable

The results of the multivariable analysis indicates that AVVQ at baseline and obesity were independently associated with the AVVQ scores at 6 months. After adjusting for these two variables, there was no longer any significant association between sex and this outcome. Again patients with higher AVVQ scores at baseline had higher AVVQ scores at 6 months.

Obesity was not significant in the univariable analyses. However, after adjusting for the AVVQ score at baseline, this was now significant. Obese patients had higher values, on average 55% higher than those who were not obese.

The regression coefficients from the final model were also obtained, and then used to create the predictive model for AVVQ at 6 months, which can be expressed as follows:
$AVVQ\ 6\ months = \exp(1.06 + 0.046\times AVVQ\ baseline + 0.44\ if\ obese)$

This is shown in Figure 66:

![AVVQ 6 Months Model](image)

**Figure 66: Demonstration of AVVQ at 6 months model**

The $R^2$ value from the final model is 0.36 (or 36%). This suggests that 36% of the variation in the AVVQ scores at 6 months is due to the two variables in the final model. This suggests that whilst the variables have some predictive ability, there is a lot of variation (64%) which is unexplained by the model. Therefore once again, the model is unlikely to give extremely reliable predictions of AVVQ at 6 months.

6.6.1.2.3.3. AVVQ at 12 months

The final AVVQ outcome examined was the AVVQ scores at 12 months, using the same procedure as before.

Initially the separate association between each of the patient characteristics and the AVVQ score at 12 months was examined in a series of univariable analyses, and the results are summarised in Table 15.
### Table 15: Results of Univariable comparison for AVVQ at 12 months.

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.36 (1.22, 1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>1.31 (0.56, 3.03)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>2.45 (1.19, 5.04)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td>0.62 (0.41, 0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0.43</td>
</tr>
<tr>
<td>Male</td>
<td>0.79 (0.44, 1.43)</td>
<td></td>
</tr>
<tr>
<td>Age (***)</td>
<td>1.04 (0.83, 1.29)</td>
<td>0.73</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>Left</td>
<td>0.90 (0.45, 1.80)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.74 (0.83, 3.66)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.55</td>
</tr>
<tr>
<td>Yes</td>
<td>1.24 (0.61, 2.50)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>2.31 (1.22, 4.35)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>SSV</td>
<td>0.85 (0.36, 2.01)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.27 (0.31, 5.26)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable

(**) Ratio reported for a 10-unit increase in predictor variable

The results suggest that, when each variable is examined separately, AVVQ at baseline, CEAP, vein diameter and previous VV surgery are all significantly
associated with AVVQ at 12 months. The remaining variables were not found to be associated with this outcome at this timepoint.

Higher AVVQ scores at baseline were associated with higher scores at 12 months. A 5-unit increase in the score at baseline was associated with a 36% increase in scores at 12 months.

The results for CEAP suggested that patients with higher values had higher AVVQ scores. Those with a score of 4-6 had AVVQ values at 12 months that were 2.5 times higher than patients with CEAP value of 0-2.

Increased vein diameter was associated with lower AVVQ scores at 12 months. A 5-unit increase in vein diameter was associated with a decrease in values of just over a third.

Patients with previous VV surgery also had higher AVVQ scores at 12 months. On average, these were 2.3 times greater than for patients with no previous surgery.

The second stage in the analysis was to examine the joint association between the variables and AVVQ scores at 12 months in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the final model is summarised in Table 16.

<table>
<thead>
<tr>
<th>Category</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVVQ at baseline (*)</td>
<td>1.33 (1.20, 1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Yes</td>
<td>1.73 (1.06, 2.84)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Ratio reported for a 5-unit increase in predictor variable
The multivariable analysis indicates that only AVVQ at baseline and previous VV surgery were independently associated with the AVVQ scores at 12 months. After adjusting for these two variables, there was no longer any significant association between either CEAP or vein diameter and the outcome at this timepoint. Again patients with higher AVVQ scores at baseline and those undergoing previous VV surgery had higher AVVQ scores at 12 months.

The regression coefficients from the final model can also be obtained, and used to write down a predictive model for AVVQ. This can be expressed as follows:

\[ AVVQ\ 12\ months = \exp(0.59 + 0.057 \times AVVQ\ baseline + 0.55 \text{ if previous surgery}) \]

This is shown in Figure 67:

![AVVQ 12 Months Model](image)

**Figure 67: Demonstration of AVVQ at 12 months model**

The R² value from the final model is 0.36 (or 36%). This suggest that 36% of the variation in the AVVQ scores at 12 months is due to the two variables in the final model. This suggests that whilst the variables have some predictive ability, there is
a lot of variation (64%) which is unexplained by the model. Therefore the model is unlikely to give extremely reliable predictions of AVVQ at 12 months.

### 6.6.2. Clinician Deemed Benefit

Clinician deemed benefit was assessed using the VCSS which as described earlier is a clinician completed clinical scoring system which allows assessment of treatment success from a physician standpoint.

Using the methods from the assessment of the symptomatic benefit modelling process, this was repeated for the VCSS outcome for the 6 week, 6 month and 12 month time points, with a view to create a predictive model from baseline data.

### 6.6.2.1. Statistical Methods

The second outcome assessed was the VCSS scores. An examination of the follow-up scores suggested that the scores varied over the follow-up period. As a result, a separate analyses was performed for each follow-up time period. The analysis of this outcome was performed using linear regression. On examination, the distribution of the VCSS scores were not perfectly normally distributed, however the assumptions of the regression methods were met in all analyses.

As described previously, the analysis was performed in two stages, with both a univariable and multivariable analysis performed.

### 6.6.2.2. Results

#### 6.6.2.2.1. Overall VCSS score

The scores at the three follow-up time-points were examined, and summaries of the scores at each time-point are given in Table 17. The figures reported are the mean and standard deviation, as well as the median and inter-quartile range.
Table 17: Overall VCSS Values

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>3.0 (2.2)</td>
<td>3 (1, 4)</td>
</tr>
<tr>
<td>6 months</td>
<td>2.5 (2.3)</td>
<td>2 (0, 4)</td>
</tr>
<tr>
<td>12 months</td>
<td>2.0 (2.4)</td>
<td>1 (0, 3)</td>
</tr>
</tbody>
</table>

The results suggested decreasing values over the course of the follow-up period. As a result, the data from each follow-up timepoint was analysed separately.

6.6.2.2.2. VCSS at 6 weeks

Initially the separate association between each of the patient characteristics and the VCSS scores at 6 weeks was examined in a series of univariable analyses. The results are summarised in Table 18 as regression coefficients, along with corresponding confidence intervals. For the categorical variables, this gives the difference in VCSS values in each category and the values in a baseline category. For the continuous variables the change in VCSS score is reported for a given increase in each variable. P-values indicating the significance of the results are also presented.

Table 18: Results of Univariable comparison for VCSS at 6 weeks.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCSS baseline **</td>
<td>-</td>
<td>0.4 (0.2, 0.5)</td>
</tr>
<tr>
<td>CEAP</td>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.6 (-0.7, 1.9)</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>1.6 (0.5, 2.8)</td>
</tr>
<tr>
<td>Vein diameter *</td>
<td>-</td>
<td>0.2 (-0.4, 0.8)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Category</td>
<td>Coefficient (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Male</td>
<td>-0.4 (-1.3, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Age (***)</td>
<td>0.6 (0.3, 0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Left</td>
<td>0.7 (-0.5, 1.8)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.5 (0.4, 2.7)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.42</td>
</tr>
<tr>
<td>Yes</td>
<td>0.4 (-0.6, 1.5)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Yes</td>
<td>1.6 (0.6, 2.6)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>SSV</td>
<td>0.3 (-0.9, 1.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0.71</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.3 (-1.5, 2.2)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Coefficient reported for a 5-unit increase in predictor variable

(**) Coefficient reported for a 10-unit increase in predictor variable

When each variable was examined separately, the VCSS score at baseline, CEAP, age, leg and previous VV surgery were significantly associated with values at 6 weeks.

Higher VCSS scores at baseline were associated with higher scores at follow-up. A 10-unit increase in the score at baseline was associated with a 0.4 unit increase in scores at follow-up.

The CEAP score results suggested higher VCSS values for increased scores. Patients with a score of 4-6 at baseline had the highest values, with VCSS scores at 6-weeks, on average, 1.6 units higher than for those with a score of 0-2.
Older patients also had higher scores, with a 10-year increase in age associated with a 0.6 unit increase in outcome. Additionally those having previous surgery also had higher values, on average 1.6 units higher.

The leg results suggested the lowest scores in the right leg group, with the highest scores in those in the both leg group. The both group had VCSS scores that were 1.5 units higher than the right leg group.

The second stage in the analysis was to examine the joint association between the variables and VCSS scores at 6 weeks in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the results are summarised in Table 19.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCSS baseline (**)</td>
<td>-</td>
<td>0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td>Age (**)</td>
<td>-</td>
<td>0.4 (0.1, 0.6)</td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.2 (0.3, 2.1)</td>
</tr>
</tbody>
</table>

(**) Coefficient reported for a 10-unit increase in predictor variable

The results of the multivariable analysis indicated that VCSS score at baseline, age and previous VV surgery were independently associated with VCSS score at 6 weeks. After adjusting for these variables, there was no longer any significant association between CEAP or leg and the outcome.
Again patients with higher VCSS scores at baseline, older patients and those with previous surgery all had higher values at 6 weeks.

The regression coefficients from the final model were obtained, and used to write down a predictive model for the VCSS score at 6 weeks and expressed as follows:

\[
\text{VCSS 6 weeks} = -1.56 + 0.32 \times \text{VCSS baseline} + 0.036 \times \text{age} + 1.18 \text{ if previous surgery}
\]

The R\(^2\) value from the final model is 0.35 (or 35%). This suggest that 35% of the variation in the VCSS scores at 6 weeks is due to the three variables in the final model.

### 6.6.2.2.3. VCSS at 6 months

Next the VCSS scores at 6 months were considered. Initially the separate association between each of the patient characteristics and the VCSS scores was examined in a series of univariable analyses. The results are summarised in Table 20.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCSS baseline (**)</td>
<td>-0.3 (0.1, 0.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>-0.1 (-1.5, 1.3)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.7 (0.5, 3.0)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td>-0.1 (-0.7, 0.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Male</td>
<td>-0.5 (-1.6, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Age (**</td>
<td>-0.5 (0.2, 0.8)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
The results suggest that, when each variable was examined separately, the VCSS score at baseline, CEAP, age, leg and previous surgery were significantly associated with values at 6 months. There was also some evidence of an association with the outcome for vein treated, but this result was not quite statistically significant.

Higher VCSS scores at baseline were associated with higher scores at 6 months. A 10-unit increase in the score at baseline was associated with a 0.3 unit increase in scores at 6 months.

The CEAP score results suggested little difference between those with a score of 3 and those with a score of 0-2. However, patients with a score of 4-6 had increased values, on average 1.7 units higher than those with a score of 0-2.
Older patients had higher scores at 6 months, as did patients in the both leg group. Higher scores were also observed in patients with previous surgery, on average 1.6 units higher than patients with no previous surgery.

The second stage in the analysis was to examine the joint association between the variables and VCSS scores at 6 weeks in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the results are summarised in Table 21.

**Table 21: Results of Backwards Selection for VCSS at 6 months**

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEAP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>-0.4 (-1.7, 0.9)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.4 (0.2, 3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (</strong>)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>0.3 (0.0, 0.6)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Previous VV surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>1.4 (0.3, 2.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Vein treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>SSV</td>
<td>1.3 (0.0, 2.5)</td>
<td></td>
</tr>
</tbody>
</table>

(**) Coefficient reported for a 10-unit increase in predictor variable

The results of the multivariable analysis indicated some evidence that CEAP score, age, previous VV surgery and vein treated were independently associated with the VCSS score at 6 months. After adjusting for these variables, there was no additional effect of VCSS score at baseline or leg upon the 6 month scores.
As in univariable analyses patients with CEAP scores of 4-6, older patients, and those with previous surgery all had higher VCSS scores.

Vein treated was not quite significant in the univariable analyses. However, after adjusting for the other variables in the multivariable analysis, this variable was now statistically significant. Patients with a SSV vein treated had higher scores at 6 months, on average 1.3 units higher.

The regression coefficients from the final model can also be obtained, and used to write down a predictive model for the VCSS score at 6 months. This can be expressed as follows:

\[
\text{VCSS 6 months} = -0.38 - 0.42 \text{ if CEAP 3 } + 1.36 \text{ if CEAP 4-6 } + 0.032 \times \text{ age} + 1.42 \text{ if previous surgery } + 1.29 \text{ if vein SSV}
\]

The $R^2$ value from the final model is 0.32 (or 32%). This suggest that 32% of the variation in the VCSS scores at 6 months due to the three variables in the final model.

6.6.2.2.4. VCSS at 12 months

The final analysis examined factors associated with the VCSS score at 12 months. A summary of the univariable analysis results is given in Table 22.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCSS baseline (**)</td>
<td>-</td>
<td>0.3 (0.0, 0.6)</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>-0.3 (-2.4, 1.8)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.7 (-0.1, 3.5)</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Coefficient (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td>-0.4 (-1.3, 0.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Male</td>
<td>0.8 (-0.6, 2.2)</td>
<td></td>
</tr>
<tr>
<td>Age (**)</td>
<td>0.7 (0.2, 1.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Left</td>
<td>0.1 (-1.5, 1.8)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>2.0 (0.3, 3.8)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Yes</td>
<td>1.0 (-0.7, 2.6)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>Yes</td>
<td>2.2 (0.6, 3.7)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>0</td>
<td>0.35</td>
</tr>
<tr>
<td>SSV</td>
<td>1.0 (-1.2, 3.1)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoker</td>
<td>-1.5 (-5.0, 1.9)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Coefficient reported for a 5-unit increase in predictor variable

(**) Coefficient reported for a 10-unit increase in predictor variable

The results suggested that, when each variable was examined separately, the VCSS score at baseline, CEAP, age, leg and previous VV surgery were significantly associated with values at 12 months. The remaining variables were not found to be associated with VCSS values at 12 months.

Higher VCSS scores at baseline were associated with higher scores at 12-months. A 10-unit increase in the score at baseline was associated with a 0.3 unit increase in scores at 12-months.
The CEAP score results suggested that patients with a score of 4-6 had higher outcome values compared to those with lower scores.

Older patients had higher VCSS scores at 12 months, with a 10-year increase in age associated with a 0.7 unit increase in score.

There was little difference in outcome between the left and right leg group. However, the both leg group had higher values, 2.0 units higher than the right leg group.

Patients with previous VV surgery had VCSS scores at 12 months that were, on average, 2.2 units higher than the group having no surgery.

The second stage in the analysis was to examine the joint association between the variables and VCSS scores at 12 months in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the results are summarised in Table 23.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>-1.0 (-2.8, 0.9)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>1.0 (-0.6, 2.7)</td>
<td></td>
</tr>
<tr>
<td>Age (**</td>
<td>0.6 (0.1, 1.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Yes</td>
<td>1.7 (0.3, 3.2)</td>
<td></td>
</tr>
</tbody>
</table>

(**) Coefficient reported for a 10-unit increase in predictor variable
The results of the multivariable analysis indicated that CEAP score, age and previous VV Surgery were independently associated with the VCSS score at 12 months. After adjusting for these variables, VCSS score at baseline and leg were not found to be additionally statistically significant.

The results for CEAP score again suggested highest values in group with a score of 4-6. As in the univariable analyses, older patients and those with previous surgery also had higher scores.

The regression coefficients from the final model can also be obtained, and used to write down a predictive model for the VCSS score at 6 weeks, which is:

\[
\text{VCSS 12 months} = -1.90 - 0.97 \text{ if CEAP 3} + 1.03 \text{ if CEAP 4-6} + 0.060 \times \text{age} + 1.72 \text{ if previous surgery}
\]

The R\(^2\) value from the final model is 0.39 (or 39%). This suggest that 39% of the variation in the VCSS scores at follow-up is due to the three variables in the final model.

### 6.6.3. Overall Quality Of Life Benefit

The final component to outcomes assessment of varicose vein treatment, after disease specific symptom effect and disease specific clinical score is the outcome for the overall well-being of the patient - the generic QOL assessment. These were assessed using the EQ-5D QOL and EQ-VAS assessment tools.

Using the methods from the assessment of the symptomatic benefit modelling process, this was repeated for the EQ-5D QOL and EQ-VAS outcomes for the 6 week, 6 month and 12 month time points, with a view to create a predictive model from baseline data.
6.6.3.1. **EQ-5D QOL**

6.6.3.1.1. **Statistical Methods**

An examination of the follow-up values indicated that there was little variation in the scores between the follow-up time periods. As a result it was chosen to consider a single analysis for all time-points. Data from all follow-up time-points was treated as the outcome values in the analysis, with the patient characteristics at baseline considered to be the predictor variables.

As all time-points were considered in a single analysis, there are up to three measurements from each subject in the analysis. It is likely that two values from the same patient are more similar than values from different patients, which violates the assumption of many statistical methods (Goldstein et al. 2002; Goldstein 2011). To allow for this multilevel statistical methods were used for the analysis, which can account for multiple responses from each patient (Goldstein et al. 2002; Goldstein 2011). Two level models were used with individual results nested within patients.

The EQ-5D QOL scores were measured on a continuous scale, and as a result multilevel linear regression was used for the analysis. An examination of the distribution of the values suggested that these had a negatively skewed distribution. It is difficult to transform such data to be more normally distributed. However, the assumptions of the statistical methods were met despite this distribution, and therefore the distribution was not transformed.

The analysis was performed in two stages. Firstly the separate association between each variable and the outcome was assessed separately in a series of univariable analyses. Subsequently the joint association between the variables and the EQ-5D QOL score was assessed in a multivariable analysis. To reduce the number of variables in this stage of the analysis, only those variables showing some evidence
of an association with the outcome in the univariable analyses (p<0.02) were considered for this stage of the analysis. The final model was produced by using a backwards selection procedure. This involves removing non-significant values one at a time, until all remaining variables were statistically significant.

Again there is no independent data on which to test the fit of a predictive model, and therefore the R² statistic was again used as measure of the model's fit.

6.6.3.1.2. Results
The scores at the three follow-up time-points were examined, and summaries of the scores at each time-point are given in Table 24. The figures reported are the mean and standard deviation, as well as the median and inter-quartile range.

<table>
<thead>
<tr>
<th>Time</th>
<th>EQ-5D QOL Mean (SD)</th>
<th>EQ-5D QOL Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>0.82 (0.21)</td>
<td>0.84 (0.75, 1.00)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.82 (0.19)</td>
<td>0.84 (0.74, 1.00)</td>
</tr>
<tr>
<td>12 months</td>
<td>0.84 (0.17)</td>
<td>0.84 (0.74, 1.00)</td>
</tr>
</tbody>
</table>

The results suggested almost identical values at the three follow-up timepoints. As a result, the data from all timepoints was analysed together.

Initially the separate association between each of the patient characteristics and the EQ-5D scores was examined in a series of univariable analyses. The results are summarised in Table 25. This shows the regression coefficients. For the categorical variables, this gives the difference in QOL values in each category and the values in a baseline category. For the continuous variables the change in QOL score is reported for a given increase in each variable.
### Table 25: Results of Univariable comparison for EQ-5D QOL

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL score baseline (†)</td>
<td>0.05 (0.03, 0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>-0.09 (-0.19, 0.01)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>-0.05 (-0.14, 0.04)</td>
<td></td>
</tr>
<tr>
<td>Vein diameter (*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>0.01 (-0.04, 0.05)</td>
<td>0.76</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Male</td>
<td>0.07 (0.00, 0.14)</td>
<td></td>
</tr>
<tr>
<td>Age (**)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-0.02 (-0.04, 0.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td>0.27</td>
</tr>
<tr>
<td>Left</td>
<td>-0.05 (-0.15, 0.03)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>-0.07 (-0.17, 0.02)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.09</td>
</tr>
<tr>
<td>Yes</td>
<td>-0.06 (-0.014, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Previous VV surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>Yes</td>
<td>-0.06 (-0.15, 0.02)</td>
<td></td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>SSV</td>
<td>-0.08 (-0.18, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.00 (-0.14, 0.14)</td>
<td></td>
</tr>
</tbody>
</table>

(†) Coefficient reported for a 0.1-unit increase in predictor variable

(*) Coefficient reported for a 5-unit increase in predictor variable

(**) Coefficient reported for a 10-unit increase in predictor variable

The results suggest that, when each variable was examined separately, only the EQ-5D QOL score at baseline was strongly associated with values at follow-up.
However, there was some evidence that sex, age, obesity and vein treated showed a trend towards significance, although results for these variables were not quite statistically significant. The remaining variables were not found to be associated with QOL values at follow-up.

Higher QOL scores at baseline were associated with higher scores at follow-up. A 0.1-unit increase in the score at baseline was associated with a 0.05 increase in scores at follow-up.

The gender differences suggested higher scores for males relative to females. Scores for males were 0.07 units higher, on average, for males than for females.

QOL decreased with increased age. A 10-year increase in age was associated with a 0.02 unit decrease in QOL scores at follow-up.

Obese patients also had a lower quality life scores, on average 0.06 units lower than for non-obese patients. Patients whose SSV vein was treated also had lower quality of life at follow-up.

Patients with previous VV surgery had higher scores at 6 weeks, on average 86% higher than those with no previous surgery.

The second stage in the analysis was to examine the joint association between the variables and QOL scores at follow-up in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables, and the final model is summarised in Table 26.
Table 26: Results of Backwards Selection for EQ-5D QOL

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL score baseline (†)</td>
<td>- 0.05 (0.04, 0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (**</td>
<td>-0.02 (-0.04, 0.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vein treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSV</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>SSV</td>
<td>-0.07 (-0.15, 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

(†) Coefficient reported for a 0.1-unit increase in predictor variable
(**) Coefficient reported for a 10-unit increase in predictor variable

The results of the multivariable analysis indicated some evidence that QOL score at baseline, age and vein treated were independently associated with the QOL score at follow-up. The results for vein treated were not quite statistically significant, but it was chosen to retain these variables in the final model. As in the univariable analyses, patients with higher baseline values had higher values at follow-up, whilst older patients and SSV patients had lower quality of life scores.

The regression coefficients from the final model can also be obtained, and used to write down a predictive model for the QoL score. This can be expressed as follows:

\[
\text{EQ-5D QOL follow-up} = 0.62 + 0.50 \times \text{EQ-5D baseline} - 0.0023 \times \text{Age} - 0.074 \text{ if SSV}
\]

The R² value from the final model is 0.29 (or 29%), suggesting that 29% of the variation in the EQ-5D QOL scores at follow-up is due to the three variables in the final model. This suggests that whilst the variables have some predictive ability, there is a lot of variation (71%) which is unexplained by the model. Therefore the model is unlikely to give extremely reliable predictions of QOL score at follow-up.
6.6.3.2. EQ-VAS

The final outcome considered was the EQ-5D VAS scores. An examination of the follow-up values indicated that there was little variation in the scores between the follow-up time periods. As a result it was chosen to consider a single analysis for all timepoints. Data from all follow-up timepoints was treated as the outcome values in the analysis, with the patient characteristics at baseline considered to be the predictor variables. As all timepoints were considered in a single analysis, the analysis was performed using multilevel linear regression, as described previously (Goldstein et al. 2002; Goldstein 2011).

An examination of the distribution of the outcome was assessed. Although these were not perfectly normally distributed, the assumptions of the regression methods were met in all analyses.

The scores at the three follow-up timepoints were examined, and summaries of the scores at each timepoint are given in Table 27. The figures reported are the mean and standard deviation, as well as the median and inter-quartile range.

<table>
<thead>
<tr>
<th>Time</th>
<th>EQ-VAS Mean (SD)</th>
<th>EQ-VAS Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>79.5 (15.8)</td>
<td>80 (70, 90)</td>
</tr>
<tr>
<td>6 months</td>
<td>79.1 (16.8)</td>
<td>85 (70, 90)</td>
</tr>
<tr>
<td>12 months</td>
<td>78.0 (24.9)</td>
<td>85 (70, 96)</td>
</tr>
</tbody>
</table>

The results suggested similar values at the three follow-up timepoints. As a result, the data from all timepoints was analysed together.
Initially the separate association between each of the patient characteristics and the EQ-5D VAS scores was examined in a series of univariable analyses. The results are summarised in Table 28 as the regression coefficients. For the categorical variables, this gives the difference in VAS values in each category and the values in a baseline category. For the continuous variables the change in VAS score is reported for a given increase in each variable.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS score baseline</strong> (***)</td>
<td>-</td>
<td>6.6 (5.0, 8.1)</td>
</tr>
<tr>
<td>CEAP</td>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-13.3 (-23.2, -3.4)</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>-6.1 (-14.8, 2.6)</td>
</tr>
<tr>
<td><strong>Vein diameter (*/)</strong></td>
<td>-</td>
<td>-3.3 (-7.7, 1.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>3.6 (-3.5, 10.7)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (</strong>*)**</td>
<td>-</td>
<td>-0.3 (-2.7, 2.0)</td>
</tr>
<tr>
<td><strong>Leg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>-2.3 (-11.4, 6.8)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>-3.2 (-12.4, 6.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Obese (BMI &gt; 30)</strong></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>-3.8 (-12.2, 4.6)</td>
</tr>
<tr>
<td><strong>Previous VV surgery</strong></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>-1.8 (-10.3, 6.7)</td>
</tr>
<tr>
<td><strong>Vein treated</strong></td>
<td>LSV</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SSV</td>
<td>2.5 (-7.4, 12.4)</td>
</tr>
<tr>
<td>Category</td>
<td>Coefficient (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0</td>
<td>0.79</td>
</tr>
<tr>
<td>Smoker</td>
<td>-2.0 (-17.0, 12.9)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Coefficient reported for a 5-unit increase in predictor variable
(**) Coefficient reported for a 10-unit increase in predictor variable

The results suggested that, when each variable was examined separately, only the EQ-5D VAS score at baseline and CEAP were significantly associated with values at follow-up. The remaining variables were not found to be associated with VAS values at follow-up.

Higher VAS scores at baseline were associated with higher scores at follow-up. A 10-unit increase in the score at baseline was associated with a 6.6 unit increase in scores at follow-up.

The CEAP score results suggested a slightly inconsistent picture. Patients with a score of 3 at baseline had the lowest values, with those with a score between 0 and 2 the highest values. Those with scores of 4-6 had values in the middle of the two other groups. Values for patients with a score of 3 were, on average, 13 units lower than those for patients with a score of 0-2.

The second stage in the analysis was to examine the joint association between the variables and VAS scores at follow-up in a multivariable analysis. A backwards selection procedure was used to retain only the statistically significant variables. The results of two different models are presented in Table 29. The first considers CEAP score as three categories. However, due to the lack of a consistent trend, the analysis was repeated categorising the patients into only two CEAP groups, and this revised analysis is seen in the second part of Table 29.
Table 29: Results of Backwards Selection for EQ-VAS. Analysis 1 and 2.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS score baseline (**)</td>
<td>- 6.3 (4.8, 7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>-9.8 (-16.9, -2.8)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>-3.4 (-9.3, 2.6)</td>
<td></td>
</tr>
<tr>
<td>Analysis 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS score baseline (**)</td>
<td>- 6.2 (4.7, 7.8)</td>
<td></td>
</tr>
<tr>
<td>CEAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>3-6</td>
<td>-5.4 (-11.2, 0.5)</td>
<td></td>
</tr>
</tbody>
</table>

(**) Coefficient reported for a 10-unit increase in predictor variable

The results of the multivariable analysis indicated some evidence that VAS score at baseline and CEAP score were independently associated with the VAS score at follow-up. The results for CEAP score not quite statistically significant when considered in two categories, but it was chosen to retain this variable in the final model. As in the univariable analyses, patients with higher baseline values had higher values at follow-up, whilst those with higher CEAP scores had lower values at follow-up.

The regression coefficients from the final model can also be obtained, and used to write down a predictive model for the VAS score. Considering CEAP score in two categories, this can be expressed as follows:

\[
\text{EQ-VAS follow-up} = 36.4 + 0.62 \times \text{EQ-VAS baseline} - 5.4 \text{ if CEAP} \geq 3
\]
The R² value from the final model is 0.41 (or 41%), suggesting that 41% of the variation in the EQ-VAS quality scores at follow-up is due to the two variables in the final model.

6.6.4. Discussion

This study has assessed the predictive ability of a standardised proforma (see Appendix 1) to predict the outcome of varicose vein treatment, when measured using patient reported outcome measures (PROMS - AVVQ, EQ-5D QOL and EQ-VAS) and when measured by clinicians (VCSS). Previous work by Carradice et al. (Carradice et al. 2011) demonstrated the complexity of venous disease and illustrated that increasing clinical severity led to worsening QOL, in the context of primary unilateral single trunk venous incompetence. The key finding from the different models created is that the most important factor in delineating outcome was the symptom or clinical score pre-operatively. Whilst patients with higher symptom score or clinical score pre-operatively have the greatest potential to benefit, to do so those patients also had to have the greatest improvement, from a standardised treatment. The evidence from this study shows that these patients fare worse, symptomatically (AVVQ), with post-operative scores increasing exponentially with pre-operative scores. Despite an larger actual reduction in AVVQ score, the proportion improvement is decreased. It is likely that this represents increasingly persistent symptomatology - i.e. Worse symptoms are more difficult to resolve. This exponential increase is not seen in the VCSS and EQ-5D QOL and EQ-VAS models, indicating a linear relationship, with worse clinical scores or generic quality of life leading to an increased improvement (but a constant proportion). This variance may be explained by two main reasons - firstly, that the treatment resolves the anatomical situation and as is seen in symptom studies the anatomical data does not correlate well with symptomatology (Bradbury et al. 1999; Campbell et al. 2007; Conway et al. 2011; Gibson et al. 2012). The second reason is that the generic quality of life measure may not be sufficiently sensitive to detect the persistence of disease symptoms that the AVVQ can detect.
This study used 461 individual patient data sets pre-operatively and 227 post-operatively to produce models that showed a fit of between 30 and 41%. No model was able to explain >41% of the variability seen in the outcomes with the data collected pre-operatively. This underlines the difficulty found in previous studies (Bradbury et al. 1999; Campbell et al. 2007) - varicose veins are difficult to quantify and explain with anatomical or physical data poorly correlating with symptomatology (Conway et al. 2011; Gibson et al. 2012).

Some authors are suggesting that patient reported outcome measures could be used as a rationing or triage tool (Staniszewska et al. 2013; Ward et al. 2013). This is a flawed approach as not only does it lead to manipulation of the scores by patients (Fayers & Machin 2007) and is subject to selection bias (Rupp et al. 2002), it also ignores the fact that symptomatic benefit and symptoms themselves worsen with time (Carradice et al. 2011; Rabe et al. 2010; Robertson et al. 2013). Additionally, recent work by Black et al. has shown that increasing the number of procedures (i.e. the reverse of rationing) does not lead to a significant reduction in symptom severity pre-operatively (Black et al. 2013). This indicates that the NHS is not fully treating the affected population, and that treatment numbers should be increased. The study supports this viewpoint with increased symptomatology having a relatively worse outcome.

The principle aim of this study was to attempt to create a predictive model from a comprehensive data set. The model which has been created provides a first predictive model for varicose vein outcomes. Unfortunately this model is of limited accuracy and the predictive model requires further work with an increased number of variables collected to try and identify the key variables that drives outcomes.
The major limitations are firstly the lack of 100% follow-up of the cohort, which impairs the creation of the model, and prevented formal testing on independent data, due to low number of independent data points. To enable formal testing, a new cohort of patients must be collected and analysed. This would also allow for a refinement and extension of the data collected and improvement of the model, and cover the second major limitation - the initial baseline dataset is inadequate to fully explain the outcome. This could not have been avoided prospectively, and will help to guide further prospective cohort data collection.

6.6.5. Conclusion

This study demonstrates the complexity and individuality of varicose veins, and provides the first predictive model of varicose vein treatment outcomes in the context of endovenous ablation under local anaesthetic. The model is limited in accuracy, and needs further refinement with independent data provided by a further prospective cohort. Interestingly, it has unveiled further evidence that varicose vein symptomatology is difficult and non-linear, which should hopefully guide future work.
Chapter 7: Adjunctive Procedures for the treatment of varicosities
7.1. Introduction

Adjunctive procedures in the treatment of varicose veins are the treatment of non-truncal varicose veins - the small tortuous dilated veins that are commonly referred to as varicose veins by the lay public. These are treated with either sclerotherapy or phlebectomy (avulsion).
7.2. Systematic Review of the Use of Adjunctive Procedures

7.2.1. Introduction

Traditional treatment of varicose veins involved general anaesthetic, SFJ ligation and stripping of the GSV. At this point phlebectomies or multiple stab avulsions were completed to remove the varicosities present. This enabled complete treatment of the pathological venous system in one sitting and became the standard of care.

7.2.1.1. Local anaesthesia and patient choice

With the advent of minimally invasive endoluminal procedures, treatment pathways have changed with patient comfort and experience coming to the fore (Gandhi et al. 2010; Shepherd, Gohel, Lim, Hamish & Davies 2010b; Shepherd, Gohel, Lim, Hamish & Davies 2010a). However, the majority of interventional treatments still remove the incompetent GSV or SSV, with either physical removal, ablation, sclerosant or occlusion (Lane et al. 2011).
Tumescent local anaesthesia has allowed extensive venous treatments with patients awake but comfortable (Do & Kelley 2007; Lane et al. 2011). This has led to a move from the operating theatre into the procedure room (McLafferty 2006). Procedure rooms may not have the facility for phlebectomy treatment, and historically phlebectomies were felt to be too painful for local anaesthetic treatment. With the emergence of tumescent local anaesthesia this consensus is changed and the ASVAL technique and its variants offer excellent evidence of acceptability of local anaesthetic phlebectomies (Pittaluga et al. 2009; Onida et al. 2012). Additionally studies have shown the safety of foam sclerotherapy during endovenous ablation (Yilmaz et al. 2011).

Previous work has assessed patient preference for hernia repair showed 47% of patients opted for general anaesthetic, compared to 33% for local (Gnanalingham & Budhoo 1998), however, in the context of varicose veins patients preferred local anaesthetic treatment (71%) and single session treatment (63%) (Shepherd et al. 2010).

7.2.1.2. Reflux/Varicosities

The clinician therefore has a choice - to treat the varicosities at the first sitting or to arrange two treatment session, and consequently has led to debate over the treatment of the varicosities left behind (Mowatt-Larssen 2010; Passman 2011). Following the removal of the feeding truncal vein, the varicosities should from descending haemodynamic theory shrink down and become asymptomatic due to reduced flow, however recurrence may evolve despite technical success (Perrin et al. 2000). For some patients, the initial treatment is sufficient, but not for others. Recent evidence has shown that even techniques with robust occlusion and success rates can incur early recurrence (Lattimer et al. 2012; Kalodiki et al. 2012), which effects long term treatment needs.
7.2.1.3. Study Aim
This study aims to systematically review and perform a meta-analysis of the literature regarding the timing adjunctive procedures for the treatment of varicose tributaries in the context of incompetent truncal vein ablation.

7.2.2. Methods

7.2.2.1. Search Strategy
A search of the published literature was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009). The searches were performed by two authors (T.L. and S.O). The Medline and EMBASE online databases were searched from 1948 to July 2013 using the OVID online portal. In cases of dispute a third review was asked to independently assess the article (AHD).

Search terms used were:
- Varicose veins (MeSH Search Term) AND Phlebectomies OR Avulsions OR Secondary Interventions
- Concomitant AND Phlebectomies OR Avulsions OR Secondary Interventions

7.2.2.2. Search Criteria
Inclusion criteria were
- Studies assessing the timing and outcome of phlebectomies in the context of ablation of the GSV for the treatment of varicose veins.

Exclusion criteria were:
- Those studies with no clear phlebectomy selection procedure
- Those studies where all patients were treated with either simultaneous or delayed adjunctive procedures.
- Those studies which did not compare phlebectomy timing in the context of varicose vein treatment
- Those studies not related to varicose veins
No limits, filters or language exclusions were applied. Case reports, review articles and letters were excluded if they did not meet the inclusion criteria. Additional hand-searching of reference lists from full-text included publications was undertaken.

7.2.2.3. Study Analysis

After title and abstract screening, full-text articles were assessed independently for clinical heterogeneity and methodological quality by two reviewers (T.L., S.O.), assessing according to the Consolidated Standard of Reporting Trials (CONSORT) (Moher et al. 2010), and the Cochrane Collaboration assessment tools (Revman v5, Cochrane Collaboration, Oxford, UK).

Data was extracted into Comprehensive Meta-Analysis v 2.2.064 (Biostat, Englewood, USA) and OpenMetaAnalyst for statistical analysis (TL) using the Fixed Effects Inverse Variance Meta-Analysis model.

7.2.3. Results

7.2.3.1. Search Outcomes

Search outcomes are shown in Figure 69. Few studies investigated the principle study question of varicosity treatment timing, excluding many well-conducted trials. Studies included are described in Table 30 and risk of bias is demonstrated in Figure 70.
Figure 69: PRISMA diagram for phlebectomies review. Three clinical questions were identified from the literature search - need for further procedure, QOL and rate of DVT.
### 7.2.3.2. Risk of bias summary

![Risk of bias summary](image)

**Figure 70**: Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. Green dots equate to low risk of bias, red dots equate to high risk of bias, blank spaces indicate unknown risk of bias.
### 7.2.3.3. Included Study Summary Table

Table 30: Included Study Characteristics. Phleb = Phlebectomy. EVLA = Endovenous laser ablation. UGFS = Ultrasound Guided Foam Sclerotherapy. RCT = Randomised Clinical Trial. DVT = Deep Vein Thrombosis. QOL = Quality of Life

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Participants (Simultaneous / Delayed)</th>
<th>Follow-Up Duration (Weeks)</th>
<th>Intervention</th>
<th>Anaesthesia</th>
<th>Outcomes Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theivacumar (2008)</td>
<td>RCT</td>
<td>68 (22/46)</td>
<td>12</td>
<td>EVLA ± UGFS</td>
<td>LA</td>
<td>Phleb/QOL/DVT</td>
</tr>
<tr>
<td>Puggionni (2009)</td>
<td>Case Series</td>
<td>293 (90/203)</td>
<td>7</td>
<td>EVLA ± Phlebectomies</td>
<td>GA/LA</td>
<td>DVT</td>
</tr>
<tr>
<td>Marsh (2010)</td>
<td>Case Series</td>
<td>2820 (2470/350)</td>
<td>1</td>
<td>EVLA ± Phlebectomies</td>
<td>GA/LA</td>
<td>DVT</td>
</tr>
</tbody>
</table>
7.2.3.4. Need for further procedures

Only four studies were eligible for analysis based on study methodology - these were the only studies to have separate groups based on phlebectomy timing. Two studies were formal randomised controlled trials investigating adjunctive intervention delay in the context of laser ablation with either phlebectomy (n=50) (Carradice et al. 2009) or foam sclerotherapy (n=68) (Theivacumar et al. 2008). Two studies were retrospective cohort studies assessing the need for secondary interventions after endovenous ablation with either radiofrequency (n=184) (Welch 2006) or laser (n=265) (Kim et al. 2009). However, whilst Welch's 2006 study included both groups, 177 were delayed and only 7 were simultaneous, it was therefore excluded. Kim et al. Described a large study with even groups of 132 patients (simultaneous) and 133 patients (delayed) with 12 and 11 patients requiring further treatment respectively. Carradice et al. is the only randomised clinical trial (RCT) assessing the timing of varicosity treatment in the context of endovenous ablation. This study had 64% of patients in the delayed group needing further treatment, compared to 4% in the simultaneous arm. Theivacumar et al. was a RCT assessing the outcome of differing treatment protocols for the below knee GSV in the context of EVLA. 46 patients received EVLA alone, with 18 (39%) requiring further treatment, compared to 22 patients receiving EVLA and UGFS combined, with 8 (36%) requiring further treatment.

The subsequent forest plot of three studies assessing need for further procedure is demonstrated in Figure 71, and publication bias in Figure 72.
Figure 71: Forest plot of Need for Further Procedures. Sim = Simultaneous Phlebectomy, Del = Delayed Phlebectomy. Fixed Effects Inverse Variance Model. Odds Ratio=0.734, Z-Value=-0.957, p=0.339. I²=81.45, p=0.005

Figure 72: Funnel Plot of Need for further procedure studies

These figures show that there is no significant difference in need for further procedure, although the statistical heterogeneity is high at 81%. This statistical variability provides a large confidence interval surrounding the Odds Ratio of 0.734. Isolating the randomised clinical trials produces a more clinically homogenous group, but due to the different findings of the trials, the statistical heterogeneity increases as shown in Figure 73.
However, there is a trend (p=0.092) towards simultaneous treatment offering a reduced Odds Ratio (0.443) of needing further treatment, though this is not statistically significant.

7.2.3.5. Quality Of Life Outcomes

Both of the randomised trials assessed quality of life at 6 and 12 weeks post treatment. The forest plot of the QOL outcome at 6 weeks is displayed in Figure 74. Carradice et al. found a much improved AVVQ at 6 weeks in the simultaneous compared to Theivacumar et al. This may be secondary to the differences in number of patients requiring further treatment.
Figure 74: Forest plot of QOL outcomes at 6 weeks. Sim = Simultaneous Phlebectomy, Del = Delayed Phlebectomy. Fixed Effects Inverse Variance Model. Odds Ratio=0.460, Z-Value=-2.177, p=0.029. I²=84.89, p=0.010.

The pooling of the data shows that there is a significant improvement in AVVQ at 6 weeks for the simultaneous group, with an Odds Ratio of 0.460 (p=0.029).

AVVQ outcomes at 12 weeks, after all further treatments are concluded, is shown in Figure 75.

Figure 75: Forest plot of QOL outcomes at 12 weeks. Sim = Simultaneous Phlebectomy, Del = Delayed Phlebectomy. Fixed Effects Inverse Variance Model. Odds Ratio 0.688, Z-Value=-1.073, p=0.283. I²=18.70, p=0.267.

This data shows no significant difference between simultaneous and delayed varicosity treatment by 12 weeks (Odds Ratio 0.688, p=0.283).
8.2.3.6. Incidence of DVT or EHIT

Three studies have examined the role of combined phlebectomy and venous ablation on the incidence of deep venous thrombosis (DVT). All are retrospective analyses of changing practice from operating theatre to procedure room, and from general anaesthetic (GA) to local anaesthetic (LA) (Puggioni et al. 2009; Marsh et al. 2010; Knipp et al. 2008).

The first study of 293 limbs by Puggioni et al (Puggioni et al. 2009) showed a significantly increased occurrence of thrombotic events in the combined phlebectomy and radiofrequency ablation group, of 22% (20/90) versus 9% (18/203) (overall incidence of 38/293 = 13%). Of these thrombotic events, 5% were DVTs (2.5% calf vein and 2.5% common femoral vein), with 8% more correctly termed endovenous heat induced thrombosis (EHIT) (Kabnick et al. 2006) with extension into but not occlusion of the Sapheno-Femoral junction. However, the combined phlebectomy group procedures were all performed under general anaesthetic, with the delayed procedures under local anaesthetic. Neither groups received pharmaceutical DVT prophylaxis. This study also does not report on the number of procedures required after the initial treatment.

Other studies have indicated a much lower incidence of DVT after endovenous ablation (Anwar et al. 2012; Dexter et al. 2012), including the second study by Knipp et al (Knipp et al. 2008) which examines DVT in the context of combined and non-combined procedures.

This study represents 456 limbs, with an overall DVT incidence of 0.7% (3/456) and an EHIT incidence of 7% (32/456). 177 procedures were completed under GA, 107 with pharmaceutical DVT prophylaxis and 74 without. There were 4 treatment failures which were not analysed. 321 limbs were treated with EVLA alone and 135 had combined EVLA and phlebectomy. DVT and EHIT rates were not significantly
different between GA and LA or between prophylaxis groups. When assessing the combined EVLA and phlebectomy group with the EVLA solely groups, it was found that rates of DVT increased with phlebectomy (2.2% versus 0%) but EHIT was unchanged (5.9% versus 7.8%, p=0.554). This gave a DVT or EHIT rate of 12/135 in the concomitant group and 23/321 in the delayed group.

Finally Marsh et al. (Marsh et al. 2010) retrospectively assessed 2820 endovenous procedures, 2470 RFA under GA with concomitant phlebectomies and 350 EVLA under LA with delayed phlebectomies. All patients received pharmacological DVT prophylaxis. An overall DVT or EHIT rate of 0.7% was described (21/2820), with 17 post RFA(7%) and 4 post EVLA (1%). There was no significant difference between treatment groups. However, in 567 RFA GA procedures short saphenous ligation was performed simultaneously with ablation and phlebectomies. These cases accounted for 7/21 of the thrombotic events. If these cases are excluded, the appropriate comparison would be 7/1903 (0.37%) versus 4/350 (1.14%). In this study the EHIT categories were 2-4 (Kabnick et al. 2006), which would classify them as DVT. Overall, the rate of any thrombotic event was extremely low throughout.

These studies are pooled in Figure 76 and Figure 77.

Figure 76: Forest plot of DVT incidence studies. DVT = Deep Venous Thrombosis, EHIT = Endovenous Heat Induced Thrombosis. Fixed Effects Inverse Variance Model, Odds Ratio=1.519, p=0.078 (Odds Ratio >1 favours Delayed Treatment). I²=80, p=0.007.
Figure 77: Funnel plot of DVT incidence studies

This indicates no significant difference in risks of DVT or EHIT between simultaneous and delayed phlebectomy treatment strategies (Odds Ratio 1.519, p=0.078), though there is a trend in favour of delayed varicosity treatment. Statistical heterogeneity is extremely high at 80, and indeed clinical heterogeneity between groups (but not studies) is also high, with combined procedures under GA and endovenous only under LA. Fernandez et al (Fernández et al. 2008) found a DVT rate of 0.13% after 1985 combined EVLA and phlebectomy procedures under LA. This may indicate that the increased risk found in the other studies is as a consequence of the GA approach rather than the actual procedure itself, with the three studies above reporting a rate of 7-22% under GA.

The three studies looking at need for further procedures post endovenous ablation identified no DVT's in either group (0/250), with Carradice et al. and Theivacumar et al. both performing treatment under local anaesthetic only and Kim et al. offering general anaesthetic, regional spinal anaesthetic or local anaesthetic. If
these three studies are added into the meta-analysis the resulting analysis is obtained (Figure 78).

![Forest plot of DVT incidence studies.](image)

Figure 78: Forest plot of DVT incidence studies. DVT = Deep Venous Thrombosis, EHIT = Endovenous Heat Induced Thrombosis. Fixed Methods Inverse Variance. Odds Ratio=1.508, p=0.077 (Odds Ratio > 1 favours Delayed Treatment). I²=50, p=0.076

With the addition of these further cases, the statistical heterogeneity is reduced to 50 (non-significant, p=0.076), and there remains no significant difference in rate of EHIT or DVT between simultaneous or delayed varicosity treatment (Odds Ratio of 1.508, p=0.077, Odds Ratio > 1 favours Delayed Treatment).

7.2.4. Discussion

This review of the literature has shown that despite extensive work assessing the impact of endovenous treatments on varicose vein outcomes from both a technical occlusion viewpoint and a patient centred quality of life outlook, little literature exists on the technicality of secondary interventions. The evidence that does exist, whilst including level 2 evidence (Carradice et al. 2009; Theivacumar et al. 2008) only serves to fuel the controversy. There is a non-significant trend towards simultaneous phlebectomies in the context of avoiding secondary procedures and early quality of life improvements. However, this is limited by the low numbers available in the literature, and the fact that both treatment groups offer good and equivalent QOL and disease improvement at one year.

The technique described in Theivacumar et al is catheter directed foam sclerotherapy to the distal GSV rather than direct varicosity treatment (with either phlebectomy or needle injection). This may limit the applicability of its results in comparing delayed and simultaneous varicosity treatment. However, due to the
dispersing nature of foam sclerotherapy and the average length of vein treated (19cm), tributaries of treated vein will have received foam sclerotherapy treatment, as has been shown in other studies (Williamsson et al. 2012). Additional treatments were either repeat injection via catheter or direct injection (Theivacumar et al. 2008).

Interestingly this review has found large retrospective single-centre studies showing that combined phlebectomy and ablation and delayed phlebectomy treatment pathways have similar risks of DVT or EHIT. Another study suggested that the VT risk may be greater in patients treated with concomitant phlebectomy, although the use of general anaesthetic and the lack of thromboprophylaxis may have also significantly influenced this study’s DVT rates.

Modern day practice facilitates vein procedures to be performed under LA unless there are specific patient concerns and this is evidenced by the excellent results gathered in randomised trials (Rasmussen et al. 2011; Rasmussen et al. 2010; Rasmussen et al. 2013). These trials include phlebectomies or foam sclerotherapy of varicosities. With tumescent anaesthesia now widespread and accepted at levels of up to 35-55 mg/kg (Do & Kelley 2007), it is clear that multiple extensive procedures are acceptable and well-tolerated under local anaesthetic.

In light of the lack of clear answer in the literature regarding the optimal treatment pathways, the recent NICE guidelines (Marsden et al. 2013) for the management of varicose veins have posed as a research topic whether or not adjunctive procedures are required for the optimal patient treatment pathway. Before clear evidence is obtained the guidelines also recommend that clinicians should consider offering patients simultaneous treatment.
7.2.4.1. Limitations
This review of the literature and summary of outcomes is limited by the paucity of studies assessing a crucial component of varicose vein treatment. The randomised studies available provide level 2 evidence, but only cover 118 procedures. Many studies were identified that assessed various treatment methods for truncal veins however very few assessed the need for phlebectomies in their work. This leads to concerns regarding the generalizability of this analysis.

The larger non-randomised retrospective studies are limited by their methodology, but offer good procedure numbers. These studies have a confounding factor of a change from GA to LA procedure, reflecting the change in venous practice. This may have affected the outcomes, and so the analysis outcome should be approached with caution. However, with such low rates of thrombotic events found, the need for large registry style data is required to investigate the clinical question in the era of full tumescent anaesthesia.

7.2.5. Conclusion
This study has shown that evidence guiding varicose vein adjunctive procedure timelines is sparse, with no significant difference in need for further procedure between combined ablation and varicosity treatment and ablation alone. QOL outcomes after treatment is improved in both groups, but significantly higher with simultaneous varicosity treatment at 6 weeks, though this is not maintained through to 12 weeks. Rates of DVT are low in both settings with no significant difference seen between treatment strategies.

Larger randomised clinical trials investigating the role of phlebectomies in local anaesthetic ambulatory vein treatment (such as AVULS - ISRCTN76821539) are needed to provide evidence to guide clinicians in the future. These may or may not support the previous work by Carradice et al. and Theivacumar et al. (Carradice et al. 2009; Theivacumar et al. 2008).
With the advent of venous registries (European Venous Forum et al. 2012; American Venous Forum 2012) and many centres moving to predominantly local anaesthetic procedures, large patient series assessing the role of phlebectomies in the modern era should be available, with outcomes including QOL, need for further procedures and complications key to improvements.

Patient preference must also be taken into account - many patients prefer one-stop treatment, a trend that has persisted for over a decade (Campbell et al. 1998; Shepherd et al. 2010). This limits the generalizability of sequenced treatment trial data due to patients opting out.

Overall, there is not conclusive evidence for or against combined venous ablation and varicosity treatment and so clinician judgement in combination with clinician and patient preference is the key to formulating satisfactory venous treatment pathways.
7.3. Ambulatory Varicosity avULsion Later or Synchronised (AVULS): A Randomised Clinical Trial

7.3.1. Introduction

With the advent of techniques described earlier in this manuscript, the treatment of the incompetent truncal veins has been intensively investigated with multiple studies showing benefit (Rasmussen et al. 2011; Carradice et al. 2012; Shepherd et al. 2010). This has led to clinicians moving away from surgical ligation of the saphenofemoral junction and stripping of the great saphenous vein, towards less invasive options. However the issue of residual varicosities has not been conclusively investigated and remains a matter of debate (Mowatt-Larssen 2010).

Varicosities can be treated at the same sitting as truncal veins, either with phlebectomy or foam sclerotherapy; alternatively treatment of varicosities can be delayed for 6-12 weeks, when, in a number of patients the need for treatment will be reduced following truncal vein treatment.

The proportion of patients who are adequately treated with solely truncal vein treatment is unclear, and the additional benefit of simultaneous treatment of varices in the context of radiofrequency ablation has not been investigated in depth.

There are two schools of thought with regard to treating varicosities in those patients undergoing truncal vein ablation. The first suggests simultaneous truncal treatment and phlebectomy as a single procedure (Mekako et al. 2006; Theivacumar et al. 2008). The second advises delayed phlebectomy after monitoring for varicosity regression. If still present, these varicosities or REVAS (REsidual Varicosities After Surgery) can be addressed with either ambulatory phlebectomies or foam sclerotherapy (Monahan 2005).

Previous work in laser ablation has shown that approximately 40% of patients with delayed phlebectomies require a second procedure, which was matched in a non-
randomised cohort study in radiofrequency ablation (Carradice et al. 2009; Monahan 2005). Both studies present similar data, however this is used to support different positions. Carradice et al. showed that there was no difference in long-term QOL outcome between the delayed or simultaneous varicosity treatment.

Advocates of the first option suggest that immediate treatment of surface varicosities is advantageous in that it ensures patients are treated in a single session and reduces the varicosity reservoir. However, this may increase operative time (Carradice et al. 2009), and could be over-treating patients whose varicosities may regress.

Those in favour of delayed phlebectomies claim that this treatment is shorter, saving operative time. However, a variable number of patients do come back with troublesome residual varicosities, which require secondary procedures. The evidence of the timing for phlebectomy is at best confusing. Carradice et al.’s 2009 study showed that while there was no sustained difference in QOL measures between delayed and simultaneous phlebectomy in the context of EVLA treatment, 66% of patients in the truncal ablation only group required secondary interventions (Carradice et al. 2009). Monahan et al. suggested that after RFA, 13% of patients had spontaneous varicosity regression and 41% of patients did not require further treatment, suggesting that monitoring for regression is the best option (Monahan 2005).

This appears confusing and contradictory, but both EVLA and RFA truncal ablation have been shown to save 30 – 40% of patients from having needless phlebectomies. Part of the issue is that the literature is very heterogeneous, making comparisons between studies challenging (Thakur et al. 2010). Variations exist in the reporting standards for surgical versus EVLA/RFA or foam sclerotherapy both in terms of vein classification, as well as length to follow-up, objective assessments and
questionnaires. Studies looking at specifically immediate versus delayed phlebectomies are few in number (Mekako et al. 2006; Carradice et al. 2009; Monahan 2005). Most randomised studies into catheter type or modality to date have used standardized delayed or simultaneous phlebectomies across their study groups, with no clear definition of the trigger to varicosity treatment. This makes comparison difficult.

Furthermore, there are a number of variables that confound the picture. Patient factors such as age, body habitus and mobility will influence the result of any intervention on the venous system. Patient preference and expectations, as well as operator experience, may have an effect on patient and operator satisfaction. Pain levels experienced have been assessed only in Carradice's study, which showed no statistical difference in pain or return to normal activities (Carradice et al. 2009).

Finally the anatomy of the venous system and its preoperative haemodynamic state (Cappelli et al. 2004; Cappelli et al. 2006) will also influence the outcome of any intervention, as will the condition of the patient and the venous calf pump. These factors need to be considered when considering treatment options, with the appreciation that any alteration in the venous tree will lead to haemodynamic changes (Blomgren et al. 2005). Indeed the ASVAL technique solely removes varicosed tributaries, leaving incompetent truncal veins in situ. This has also been shown to produce good results and implies a significant factor is the incompetence venous reservoir found in each patient (Pittaluga et al. 2009).

Ultimately, the aim of procedures for residual venous disease is to provide the maximum symptomatic relief for as long as possible. An ideal treatment would be minimally invasive, safe, effective from a functional and cosmetic point of view, have low recurrence rates and be cost-effective. However, the goal of ambulatory
minimally invasive treatment should not preclude the full management of the disease. Recent studies have shown that radiofrequency ablation has equivalent closure rates to laser ablation and has a reduced pain profile (Shepherd et al. 2010; Rasmussen et al. 2011).

7.3.2. Aim
The aim of this study was to ascertain the outcomes of delayed or simultaneous phlebectomy in the context of truncal vein ablation.

7.3.3. Methods
AVULS is a single centre randomised controlled trial recruiting 240 patients into 2 equal sized groups – one with simultaneous local anaesthetic treatment of truncal veins with endovenous ablation and varicosity treatment with phlebectomy; and the other with delayed varicosity avulsion.

7.3.3.1. Ethical Approval and Trial Registration
Ethical approval has been granted for the AVULS Trial by Brighton Research Ethics Committee Reference Number 11/H1107/3.

The trial was registered with Current Controlled Trials - ISRCTN76821539 (Lane 2011).

7.3.3.2. Patient Selection
Consecutive patients presenting with symptomatic primary varicose veins due to reflux in the great saphenous vein (GSV), or small saphenous vein (SSV) were invited to participate. The study was set in the Department of Vascular Surgery at Charing Cross Hospital. Patients were followed up for 12 months post-procedure, with repeated quality of life measures at 6 weeks, 6 and 12 months and technical success appraisal at 6 months.
Patients were eligible if they had treatable single truncal vein incompetence and visible varicosities in the distribution of the target vein.

Patients were consented and complete a quality of life questionnaire incorporating the AVVQ, EQ-5D 5L and VAS, CES-D and SF-12. The consenting clinician completed the VCSS, CEAP, VDS and also estimated the number of avulsions required.

7.3.3.3. Power Calculations

7.3.3.3.1. Aberdeen Varicose Vein Questionnaire:
Based on previous randomised clinical trials, an improvement of 10 points is predicted at 6 weeks with a standard deviation of 10 in patients who have concomitant phlebectomies. A difference of 5 points at 6 months is considered clinically significant.

At 90% power and 5% significance, 64 patients per arm would be required. Allowing for loss to follow-up and protocol violation, target recruitment was set at 120 per arm, or 240 in total.

7.3.3.4. Reasons for declining AVULS
Patients who did not want to participate in the AVULS study were invited to offer a reason for not entering into the study.

7.3.3.5. Randomisation
Following consenting and recruitment patients were randomised into concomitant or delayed phlebectomy groups on the day of treatment.

Randomisation was via computerised allocation at a remote location provided by a randomisation service (Sealed Envelope, London, UK).
7.3.3.6. Treatment

Treatment was then performed according to standardised endovenous thermal ablation using radiofrequency ClosureFAST catheters under tumescent local anaesthetia using standard Covidien Venefit procedure (Creton et al. 2010) and multiple stab phlebectomies according to treatment arm.

Number of phlebectomies and length of treatment were recorded.

The treatment was non-blinded as the use of phlebectomies cannot be hidden from either the practitioner or patient. Patients then received standardised compression hosiery for 2 weeks post-operatively.

7.3.3.7. Follow-up

Patients were seen in the research clinic at 6 weeks, 6 months and 1 year post-operatively. At each clinic visit, clinical review was completed as were complete the quality of life questionnaires.

At the 6 week visit, the patient was assessed for the need for further intervention by independent clinicians unaware of the initial treatment group. This was offered as either foam sclerotherapy or multiple stab phlebectomies under local anaesthetic. However, as patients had healing scarring after phlebectomies this was not full blinding. All further treatments were completed as soon as possible after the 6 week visit and all before the 6 month visit.

At the 6 month follow-up a certified duplex ultrasound scan was completed to ensure closure of the treated truncal vein. This is categorised as fully occluded, predominantly occluded, predominantly patent and fully patent. The duplex was performed by an independent vascular scientist who is blinded to the treatment allocation.
7.3.3.8. **Primary Endpoint**

The primary endpoint of this study was disease specific quality of life improvement at 6 months post procedure assessed by the AVVQ.

7.3.3.9. **Secondary Endpoints**

- The need for further procedures over the 6 month period
- Clinical disease severity assessed using the Venous Clinical Severity Score (VCSS)
- Generic quality of life assessed using the EQ-5D
- Anatomical success assessed with colour duplex at 6 months
- Level of depression assessed using CES-D
7.3.3.10. AVULS Throughput Diagram

**Screening**
Symptomatic patients with varicose veins assessed >0.5 seconds on colour duplex

**Suitability**
Patients with truncal venous disease and varicosities in one distribution

**Recruitment**
Consenting Patients complete AVVQ, EQ-5D, VCSS and CES-D

**Randomisation**

**Simultaneous Group**
Endovenous Ablation of Truncal Vein with Phlebectomy

**Delayed Group**
Endovenous Ablation of Truncal Vein without Phlebectomy

**6 Weeks**
AVVQ, EQ-5D, VCSS and CES-D Assessment for further intervention

**Further Intervention**
Phlebectomy or Foam Sclerotherapy as required

**6 Months**
AVVQ, EQ-5D, VCSS and CES-D Closure Duplex Scan

**12 Months**
AVVQ, EQ-5D, VCSS and CES-D

*Figure 79: AVULS Throughput Diagram*
7.3.3.11. Statistical Methods

All data was entered into a bespoke database created in Microsoft Access version 14 (Microsoft, Redmond, Washington, USA). Statistical analysis was performed on SPSS version 22 (IBM, Armonk, New York, USA), Prism version 6 (Graphpad, La Jolla, California, USA) and Wizard Pro version 1.3.5 (Evan Miller, Chicago, Illinois, USA).

7.3.4. Results

From April 2011 until November 2012, 393 consecutive patients presenting to the Charing Cross Local Anaesthetic Varicose Vein Unit for treatment were screened for inclusion in the AVULS trial. 221 patients were suitable for the trial.
Figure 80: AVULS Trial Consort Diagram
The 172 patients ineligible for the trial included those with no visible varicosities but truncal reflux (88 = 23%), patients with visible varicosities but no truncal reflux (71 = 19%), and patients with mixed truncal disease with venous anatomy unsuitable for endovenous treatment.

Of the 221 patients eligible, 101 patients consented to randomisation. Of those refusing to participate in the trial, 95% gave wanting single sitting treatment as the reason for declining.

The final trial sample was 26% of the screened population and 46% of the suitable population.

The baseline demographics are shown below in Table 31, and as can be seen the groups were well-matched, with no significant differences:
Table 31: AVULS Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Delayed</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>101</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Age</td>
<td>52.9</td>
<td>53.9</td>
<td>52.0</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>24%</td>
<td>26%</td>
<td>22%</td>
</tr>
<tr>
<td>BMI</td>
<td>28.28</td>
<td>29.13</td>
<td>27.52</td>
</tr>
<tr>
<td>CEAP (Median)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Maximal Vein Diameter</td>
<td>9.04</td>
<td>8.97</td>
<td>9.11</td>
</tr>
<tr>
<td>AVVQ Baseline</td>
<td>22.52</td>
<td>21.80</td>
<td>23.20</td>
</tr>
<tr>
<td>VCSS Baseline</td>
<td>7.56</td>
<td>7.80</td>
<td>7.30</td>
</tr>
<tr>
<td>EQ-5D QOL Baseline</td>
<td>0.691</td>
<td>0.695</td>
<td>0.688</td>
</tr>
<tr>
<td>EQ-5D VAS Baseline</td>
<td>75.68</td>
<td>74.76</td>
<td>77.30</td>
</tr>
<tr>
<td>CES-D Baseline</td>
<td>11.68</td>
<td>12.26</td>
<td>11.14</td>
</tr>
</tbody>
</table>

Treatment characteristics are shown below in Table 32. No differences were seen between groups. All treatments were completed as per protocol.

Table 32: AVULS Completed Treatment Details

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Delayed</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>101</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Trunks Treated (Median)</td>
<td>1.10 (1)</td>
<td>1.08 (1)</td>
<td>1.11 (1)</td>
</tr>
<tr>
<td>Cycles Completed (Median)</td>
<td>6.71 (7)</td>
<td>6.93 (7)</td>
<td>6.49 (6)</td>
</tr>
<tr>
<td>Vein Length Treated (Median)</td>
<td>46.97 (49)</td>
<td>48.51 (49)</td>
<td>45.43 (42)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Delayed</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Pre-Operative Estimated Phlebectomies (Median)</td>
<td>9.00 (8)</td>
<td>9.76 (10)</td>
<td>8.24 (6)</td>
</tr>
<tr>
<td>Phlebectomies Completed (Median)</td>
<td>6.84 (6)</td>
<td>-</td>
<td>6.84 (6)</td>
</tr>
<tr>
<td>Further Phlebectomies (Median)</td>
<td>7.33 (9)</td>
<td>7 (9)</td>
<td>10 (10)</td>
</tr>
</tbody>
</table>

### 7.3.4.1. Primary Outcome - AVVQ

Mean AVVQ decreased following treatment as shown by Figure 82. The mean baseline AVVQ was 22.54 (standard deviation, SD, 12.40), decreasing to 13.57 (12.04) at 6 weeks, 11.19 (10.08) at 6 months and 8.56 (7.83) at 1 year, which represents an symptomatic improvement of 62%. (p<0.001).

![Graph showing AVVQ over the course of treatment](image)

**Figure 82: Aberdeen Varicose Vein Questionnaire (AVVQ) over the course of treatment.**

Mean change at 6 weeks, 6 months and 12 months was -8.86 (11.30), -10.00 (10.24) and -11.54 (7.76) respectively (negative change equates to an improvement in symptoms).

Both groups showed a significant improvement in symptoms from baseline at all time points (p<0.0001). There was a significant difference seen at 6 weeks, with the
simultaneous group showing a 5.48 point improvement (p=0.029). However there was no significant difference at 6 months or 12 months. Table 33 demonstrates the AVVQ values.

<table>
<thead>
<tr>
<th>AVVQ</th>
<th>Overall</th>
<th>Delayed</th>
<th>Simultaneous</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.54 (12.40)</td>
<td>22.69 (11.67)</td>
<td>22.39 (13.17)</td>
<td>0.30</td>
<td>0.908</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>13.57 (12.04)</td>
<td>16.34 (12.62)</td>
<td>10.86 (10.91)</td>
<td>5.48</td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>6 Months</td>
<td>11.19 (10.08)</td>
<td>12.93 (11.05)</td>
<td>9.46 (8.80)</td>
<td>3.47</td>
<td>0.120</td>
</tr>
<tr>
<td>12 Months</td>
<td>8.56 (7.83)</td>
<td>9.48 (9.61)</td>
<td>7.60 (5.43)</td>
<td>1.88</td>
<td>0.387</td>
</tr>
</tbody>
</table>

This is shown in Figure 83 and Figure 84.

![Figure 83: Aberdeen Varicose Vein Questionnaire (AVVQ) over the course of treatment showing delayed and simultaneous groups.](image-url)
When assessed between patients who did not need any further treatment after 6 weeks there was no significant difference seen between the groups at any time point as shown in Figure 85, Figure 86 and Table 34.

Table 34: AVVQ outcomes when no further treatment is required.

<table>
<thead>
<tr>
<th></th>
<th>Delayed &amp; No Further Treatment</th>
<th>Simultaneous &amp; No Further Treatment</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21.62 (10.97)</td>
<td>22.37 (13.31)</td>
<td>0.75</td>
<td>0.795</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>13.78 (11.36)</td>
<td>10.85 (11.04)</td>
<td>2.93</td>
<td>0.279</td>
</tr>
<tr>
<td>6 Months</td>
<td>11.47 (11.19)</td>
<td>9.40 (8.91)</td>
<td>2.07</td>
<td>0.405</td>
</tr>
<tr>
<td>12 Months</td>
<td>8.75 (9.00)</td>
<td>7.60 (5.43)</td>
<td>1.15</td>
<td>0.605</td>
</tr>
</tbody>
</table>
Figure 85: Comparison of AVVQ between delayed and simultaneous groups when no further treatment required.

Figure 86: Comparison of AVVQ between delayed and simultaneous groups when no further treatment required.
When comparing the groups who did and did not need further treatment a large significant difference of 8.1 AVVQ points was found at 6 weeks ($p=0.004$). Though those requiring Further Treatment remained at higher symptom scores throughout, this difference was not statistically significant at 6 months or 12 months and is demonstrated by Figure 87 and Figure 88 and Table 35. Further treatment was completed before the 6 month review.

Table 35: AVVQ for no further treatment needed and further treatment needed groups.

<table>
<thead>
<tr>
<th>AVVQ</th>
<th>No Further Treatment Needed</th>
<th>Further Treatment Needed</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.08 (12.38)</td>
<td>24.70 (12.63)</td>
<td>2.62</td>
<td>0.937</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>11.97 (11.18)</td>
<td>20.07 (13.53)</td>
<td>8.1</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>6 Months</td>
<td>10.24 (9.86)</td>
<td>15.48 (10.26)</td>
<td>5.24</td>
<td>0.069</td>
</tr>
<tr>
<td>12 Months</td>
<td>8.05 (6.98)</td>
<td>10.73 (10.96)</td>
<td>2.68</td>
<td>0.335</td>
</tr>
</tbody>
</table>
Figure 87: Comparison of AVVQ between further treatment required and further treatment not required.

Figure 88: Comparison of AVVQ between further treatment required and further treatment not required.
The final comparison for the AVVQ quality of life score was between those in the delayed group who needed further treatment compared to the simultaneous group. This showed a large significant difference at 6 weeks and 6 months in favour of simultaneous treatment. This is shown in Table 36, Figure 89 and Figure 90.

Table 36: AVVQ values for the Delayed and requiring further treatment group and the simultaneous group

<table>
<thead>
<tr>
<th></th>
<th>Delayed &amp; Further Treatment Needed</th>
<th>Simultaneous</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24.76 (13.04)</td>
<td>22.39 (13.17)</td>
<td>2.37</td>
<td>0.534</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>20.56 (13.77)</td>
<td>10.86 (10.91)</td>
<td>9.7</td>
<td>0.005</td>
</tr>
<tr>
<td>6 Months</td>
<td>15.74 (10.59)</td>
<td>9.46 (8.80)</td>
<td>6.28</td>
<td>0.033</td>
</tr>
<tr>
<td>12 Months</td>
<td>10.73 (10.96)</td>
<td>7.60 (5.43)</td>
<td>3.13</td>
<td>0.258</td>
</tr>
</tbody>
</table>

Figure 89: Comparison of AVVQ between Simultaneous Group and Delayed Group Further Treatment Required.
7.3.4.2. Secondary Outcomes

7.3.4.2.1. Need for Further Procedure

There was a significant difference in need for further treatment between the delayed and simultaneous groups - 18 (36%) required further treatment in the delayed group compared with 1 (2%) in the simultaneous group (p<0.001).

The odds ratio and relative risk of patients in the delayed group requiring further varicosity treatment were 27.78 and 18.36 respectively (p<0.0001).

There was no difference between estimated number of multiple stab phlebectomies required prior to intervention (9.76 vs 8.24, p=0.171) in the patient groups and there was no significant difference between the number of phlebectomies estimated as necessary prior to intervention and the number performed in patients requiring further treatment (9.0 vs 7.33, p=0.3479).
All procedures were completed as soon as feasible after the 6 week review and no further procedures were needed after 6 months or 1 year.

7.3.4.2.2. Technical Success

At 6 months, 93.75% of patients had truncal vein treatment success, termed as complete venous ablation and absence of any flow on colour duplex or predominant venous ablation with small areas of isolated colour flow (<5cm).

6.25% of patients had partially treated veins with >5cm of colour flow. No patient needed truncal retreatment and no cases of complete patency and reflux were found.

There was no difference in treatment success between groups (p=0.849).

7.3.4.2.3. Generic Quality of Life

There was a significant improvement in generic quality of life as measured by the EQ-5D QOL from baseline to 6 weeks (0.691 to 0.820, p<0.0001) but not as measured by the EQ-VAS (76.24 to 79.45, p=0.157). The significant improvement in EQ-5D QOL was maintained through to 12 months however there were no further significant differences seen between time groups. This improvement equates to a 21% improvement in QOL. This is shown in Figure 91.
Overall, EQ-5D results showed the same trends as found for the primary outcome of AVVQ.

Between treatment groups there was a significant difference in EQ-5D QOL at 6 weeks (Delayed 0.773, Simultaneous 0.866, p=0.033) but this difference was lost as the follow-up progressed, as shown in Figure 92 and Figure 93. There was no significant difference seen between groups for the EQ-VAS score, as shown in Figure 94.
Figure 92: EQ-5D Generic Quality of Life Outcomes for Simultaneous and Delayed Groups

Figure 93: EQ-5D Generic Quality of Life Outcomes for Simultaneous and Delayed Groups
For those patients not requiring further treatment, there was no significant differences seen between treatment arms as shown in Table 37, Figure 95 and Figure 96.

### Table 37: EQ-5D QOL outcomes when no further treatment is required.

<table>
<thead>
<tr>
<th>EQ-5D QOL</th>
<th>Delayed &amp; No Further Treatment</th>
<th>Simultaneous &amp; No Further Treatment</th>
<th>Difference</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.689 (0.248)</td>
<td>0.689 (0.221)</td>
<td>0.00</td>
<td>0.995</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>0.807 (0.189)</td>
<td>0.870 (0.201)</td>
<td>0.63</td>
<td>0.191</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.825 (0.151)</td>
<td>0.830 (0.212)</td>
<td>0.005</td>
<td>0.917</td>
</tr>
<tr>
<td>12 Months</td>
<td>0.846 (0.147)</td>
<td>0.850 (0.142)</td>
<td>0.004</td>
<td>0.929</td>
</tr>
</tbody>
</table>
Figure 95: EQ-5D QOL Outcomes for patients requiring no further treatment for Simultaneous and Delayed Groups.

Figure 96: EQ-5D QOL Outcomes for patients requiring no further treatment for Simultaneous and Delayed Groups.
Comparing those requiring further treatment to those not requiring further treatment showed a significant difference at 6 weeks, with those needing further treatment having a significantly worse QOL (0.719 vs 0.846, \( p=0.018 \)). This difference was not seen at 6 months or 12 months and is shown in Figure 97 and Figure 98.

![Figure 97: EQ-5D QOL Outcomes for patients comparing no further treatment with further treatment required.](image1)

![Figure 98: EQ-5D QOL Outcomes for patients comparing Further Treatment Required and No Further Required.](image2)
Comparing those in the delayed group who required further treatment to the simultaneous group shows a similar picture - a significant difference at 6 weeks in favour of simultaneous treatment (0.720 vs 0.866, p=0.024) however this difference in QOL was not seen at 6 months or 12 months. This is shown in Figure 99 and Figure 100.

Figure 99: EQ-5D QOL Outcomes for patients comparing Further treatment in the delayed group and the Simultaneous Groups.
Figure 100: EQ-5D QOL Outcomes for patients comparing Further treatment in the delayed group and the Simultaneous Groups.

7.3.4.2.4. Clinical Disease Severity

7.3.4.2.4.1. CEAP

CEAP is a non-reactive clinical staging measure, however, it does provide an overview of the cohort.

Median CEAP at baseline was 4 (inter-quartile range 3-4), decreasing to 2 (2-4) at 6 weeks, 2 (1-4) at 6 months and 1(1-3) at 12 months. This was a significant improvement from baseline (p<0.0001), and is shown in Figure 101.
Figure 101: Overall CEAP status of the treated cohort.

This represents an improvement in clinical signs from venous eczema to thread veins at 1 year.

When looking at the simultaneous and delayed groups, there was a significantly higher CEAP score at 6 weeks (p=0.006) and 6 months (p=0.003), however by 1 year this was no longer significantly different (p=0.117). This is shown in Figure 102.
Figure 102: CEAP for the Delayed and Simultaneous Treatment Arms.

This represents an improvement for the delayed group from venous eczema to varicosities, compared to from venous eczema to thread veins in the simultaneous group.

7.3.4.2.4.2. VCSS

Treatment led to a significant reduction in VCSS from a baseline of 7.368 (2.556) to 3.011 (2.193) at 6 weeks, 2.557 (2.319) at 6 months and 1.978 (2.390) at 12 months (p<0.0001) (Figure 103). This represents a 73% decrease in clinical score.

Table 38: VCSS Outcomes over duration of follow-up.

<table>
<thead>
<tr>
<th>VCSS</th>
<th>Overall</th>
<th>Delayed</th>
<th>Simultaneous</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.32 (2.55)</td>
<td>7.65 (2.59)</td>
<td>7.00 (2.50)</td>
<td>0.65</td>
<td>0.212</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>2.99 (2.191)</td>
<td>3.76 (2.18)</td>
<td>2.26 (1.96)</td>
<td>1.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Months</td>
<td>2.56 (2.356)</td>
<td>3.20 (2.45)</td>
<td>1.90 (2.09)</td>
<td>1.30</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Figure 103: VCSS Scores for whole cohort

Treatment groups were well matched at baseline (Delayed 7.696 versus Simultaneous 7.061, p=0.229) and showed a significant difference in VCSS levels at all follow-up points as shown in Figure 104 and Figure 105 (p=0.001 at 6 weeks, p=0.012 at 6 months and p=0.011 at 12 months).
Figure 104: Mean VCSS in Delayed and Simultaneous Treatment Groups

Figure 105: Mean VCSS in Delayed and Simultaneous Treatment Groups
When comparing those patients who needed no further treatment, a significant difference between the delayed and the simultaneous groups was again seen at 6 weeks (3.72 vs 2.22, p=0.004), 6 months (3.21 vs 1.90, p=0.022) and 12 months (2.83 vs 1.14, p=0.013), again in favour of the simultaneous group. This is shown in Figure 106 and Figure 107.

**Figure 106: Mean VCSS in Delayed and Simultaneous Groups not requiring any further treatment**
Assessing those patients who did and did not require further treatment, no statistical difference was seen at any follow-up time-point. At 6 weeks the further treatment group scored 3.82 vs 2.8 (p=0.082), at 6 months scored 3.07 vs 2.34 (p=0.371) and at 12 months scored 2.27 vs 1.80 (p=0.537). This is shown in Figures 108 and 109.
Finally, assessing the group of the delayed arm that required further treatment versus the simultaneous arm, a significant difference in favour of the simultaneous
arm was found at 6 weeks (3.81 vs 2.26, p=0.006), but at 6 months (3.15 vs 1.90, p=0.080) and 12 months (2.27 vs 1.14, p=0.088) this was no longer significant (p=0.080 and p=0.088). This is demonstrated in Figure 110 and Figure 111.

![Figure 110: Comparison of VCSS between the Simultaneous Group and Delayed Group requiring Further Treatment](image1)

![Figure 111: Comparison of VCSS between the Simultaneous Group and Delayed Group requiring Further Treatment](image2)
7.3.4.2.5. Depressive Symptoms - CES-D

CES-D results are tabulated in Table 39. There was no significant difference seen between baseline and 6 weeks for the CES-D score, though there was a 24% reduction (p=0.0636). There was a significant improvement between baseline and 6 months (24%, p=0.0199). However, at 12 months this difference had reduced and was not significant (17%, p=0.2657).

No significant difference was seen during follow-up in the delayed group. There was a significant improvement at 6 weeks in the simultaneous group (p=0.0361) but this was no longer significant by 6 months (p=0.0796) or 12 months (p=0.6600). No significant difference was seen between groups at any time point during follow-up.

Table 39: CES-D Scores during Follow-up.

<table>
<thead>
<tr>
<th>CES-D</th>
<th>Overall</th>
<th>Delayed</th>
<th>Simultaneous</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11.68 (10.32)</td>
<td>12.26 (11.41)</td>
<td>11.14 (9.29)</td>
<td>1.12</td>
<td>0.598</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>8.85 (10.14)</td>
<td>10.81 (10.53)</td>
<td>7.02 (9.53)</td>
<td>3.79</td>
<td>0.082</td>
</tr>
<tr>
<td>6 Months</td>
<td>8.22 (9.07)</td>
<td>8.82 (8.96)</td>
<td>7.65 (9.26)</td>
<td>1.17</td>
<td>0.574</td>
</tr>
<tr>
<td>12 Months</td>
<td>9.66 (10.02)</td>
<td>9.32 (8.16)</td>
<td>9.96 (11.58)</td>
<td>0.64</td>
<td>0.829</td>
</tr>
</tbody>
</table>
Figure 112: CES-D Scores during follow-up.

Figure 113: CES-D Scores during follow-up for Delayed and Simultaneous Groups
7.3.4.3. Complications

Two episodes of superficial venous thrombosis occurred, one in each group. No other complications were reported by patients.

7.3.5. Discussion

Endovenous management of varicose veins in the outpatient setting is a successful and safe procedure with increasing uptake (Anon 2013; McLafferty 2006). This study provides further evidence of excellent results with endovenous ablation at up to 1 year after treatment in both clinical (73% improvement) and disease specific QOL (62% improvement) scoring systems. Additionally generic QOL scores improved by 21%. Both simultaneous phlebectomy and delayed phlebectomy groups showed excellent overall improvements. Minimal complications were seen, with only two SVT episodes observed, one in each group. This study provides further evidence that both simultaneous and delayed treatment pathways are safe and feasible.

The main finding of this study is that simultaneous treatment of incompetent truncal veins and varicose tributary veins provides improved clinical outcomes which persist up to one year after treatment. Quality of life values are improved at 6 weeks in both disease specific and generic scoring systems. These changes normalise by 6 months after adjunctive treatment was completed. The simultaneous group showed an improved VCSS score out to 1 year compared to the delayed group and even when comparing only those patients who did not require further treatment. Understandably, no significant difference was seen in the QOL tools, as these patients were happy with their outcome. Most interesting is how the "under-treated" group fared - those in the delayed group who underwent further treatment. In these 18 patients whilst the clinical score was no longer significantly different to the simultaneous arm after further treatment (p=0.080 at 6 months and 0.088 at 12 months), the AVVQ remained significantly worse until 1 year.
Depression screening scores (CES-D) improved overall at 6 months by 24%, before regressing to 17% improvement, a non-significant improvement on pre-treatment values. Interestingly, delayed patients displayed no significant difference in scores at the time points, with simultaneous patients only improved at 6 weeks. This may indicate that patients experience a greater mental-health "bounce" from a larger procedure, and the improvement offered by delayed treatment is too gradual to be assessed with the numbers achieved in this study.

Patients undergoing delayed treatment in this study had a significantly higher rate of further intervention (36% vs 2%, Relative Risk 18.36). Advocates of delayed phlebectomies cite "over-treatment" as a prime concern (Welch 2006), however in a time of austerity (Lane et al. 2013) one must also consider "under-treatment" and its sequelae as shown by this study's worse outcomes in those patients needing further treatment. With recent long term cohort data indicating that superficial venous disease has a progressive nature (Schultz-Ehrenburg & Reich-Schupke 2009; Rabe et al. 2010; Robertson et al. 2013), and good outcomes from ascending theory evangelists (Pittaluga et al. 2009), the fact that patients receive both better clinical outcomes and the treatment that they prefer with simultaneous treatment may become a key driver to better healthcare.

This study provides further evidence that simultaneous treatment of truncal veins and varicosities leads to improved early disease specific quality of life with improved clinical status as found by Carradice et al in the previous randomised study specifically addressing this question (Carradice et al. 2009). That study of 50 patients using laser ablation found that clinical severity (as assessed by VCSS) was not significantly different at 1 year, but did show early improvement in favour of simultaneous treatment. Our present study replicates these outcomes with early QOL improvement but adds extended clinical improvement.
The odds ratio of patients undergoing adjunctive procedures in the delayed phlebectomy group in the Carradice trial was 16.67 (66% in delayed group vs 4% in simultaneous group) with a relative risk of 16.67, which is in keeping with the risk profile seen in our current study. In our study, patients who underwent delayed treatment had an Odds Ratio of 28.125 (p<0.0001) and Relative Risk of 18.360 (p<0.0001) of requiring further treatment, with 36% requiring further treatment compared to 2% in the simultaneous group. It is interesting that despite a decrease in overall percentage requiring re-intervention the risk statistics are in fact increased. The patient demographic reported by Carradice et al had a far lower disease burden than that reported in this study (AVVQ 13 vs 23 and VCSS 4 vs 7.4). This may be secondary to change in referral practice in the intervening 5 years or a different burden of disease in our local geographical area.

This study was powered to detect a 5 point difference in AVVQ at 6 months between groups, and thus required a recruitment target of 128 patients with 100% follow-up. Allowing for loss to follow-up, target recruitment was 240. 81% of recruited patients were follow-up up to the primary endpoint at 6 months. A significant limitation of this study is the failure to reach target recruitment over the 18 month recruitment period. The target was not achieved due to patient preference for single sitting treatment despite equipoise from the researchers and careful consenting for both the trial and the procedure - >50% of the suitable population refused randomisation due to a preference for simultaneous treatment. At 6 weeks the difference in AVVQ was 5.48 and at 6 months 3.47. It is possible therefore that this lack of significance is a Type 2 error. Alternatively, as all patients requiring further treatment would have both received and recovered from the second intervention by 6 months, it may not be possible to achieve this difference. A clearer picture may have been found if a further review at 6 weeks post re-intervention had been undertaken. Carradice et al. also set their re-intervention review at 6 weeks, with this trial using a similar protocol, however using 3 months
as a further intervention decision point may have offered better differentiation between groups.

No specific assessment of operating time or efficiency was completed in this study, however all patients participating in the trial were scheduled as ± phlebectomies and booked onto standardised morning lists in single slots. The morning day case lists catered for a maximum of 6 patients per session, based on one surgeon completing all tasks (consent, positioning, preparation and treatment including ultrasonography). Those undergoing adjunctive procedures were booked into similar single slots, however previous work on anaesthetic time reduction in general anaesthetic cases has found that large reductions in treatment time are required to allow extra case throughput (Dexter et al. 1995; Dexter & Macario 1999), due to the logistical time involved in moving, positioning and preparing the patient. This is even more vital in the context of local anaesthetic procedures where the patient must not feel rushed.

Initial adjunctive procedures were not completed with foam sclerotherapy, though this is standard in some centres (King et al. 2009; Yilmaz et al. 2011). This may provide a more time-efficient option, especially as tumescentless ablation techniques become more accepted and commonplace, as phlebectomies would render the major selling point of the techniques obsolete.

7.3.6. Conclusion

This study lends further weight to the argument that one stage treatment is not only the patient’s preference but also in their best interests with improved early quality of life and prolonged improved clinical status. The clinical improvement is upheld even in those in the delayed group who do not need further varicosity treatment.
This study would therefore suggest that simultaneous treatment of truncal veins and varicosities represents the optimal management of patients with symptomatic varicose vein disease. However, larger scale studies are required to confirm these results, and this may be difficult due to patient preference.

Further work into cost-effectiveness, operating time and pain profile would allow clear guidance on not only the patient's ideal treatment pathway, but also the most efficient.

Crucially the final decision on treatment pathway remains with the clinician and the patient as both simultaneous and delayed pathways offer good outcomes overall with excellent complication profiles.
Chapter 8: Assessing New Technologies
8.1. Introduction

With the advance of technology, the evidence base must move with it. Efficacy and safety are assessed first, followed by long-term reliability and patient experience. Over time the endpoints of treatment move from technical and objective measures (Lurie et al. 2005) to quality of life and patient assessment (Rasmussen et al. 2011).

New techniques are driven by new devices and vice versa. The target of bloodless, painless varicose vein surgery remains elusive, however minimally invasive techniques are becoming more common and more advanced (Lane et al. 2011; McBride 2011; Onida et al. 2013). In order to truly examine each device many outcome measure need to be assessed, from initial clinical safety assessments and technical success to long-term occlusion and QOL results.

Varicose veins pose a difficult disease question as progression and recurrence are relatively common, and may not be related to the treatment modality used. Therefore RCTs between different modalities and "gold standards" are required. However, the pace of development often outstrips the follow-up required in these trials. This can easily be seen in the EVLA modality with the multiple different wavelengths being developed at rapid intervals (Ash & Moore 2010; Massaki et al. 2013).

It is also important to fully investigate previous generations of devices, those that are in common use at present, as concerning features are often not visible until long term follow-up and generalised acceptance is available. Additional theories concerning complications seen in other modalities need further exploration to assess their generalisability and occurrence under different circumstances.
8.2. Echocardiography during Radiofrequency Ablation of Varicose Veins

8.2.1. Introduction

Chronic venous insufficiency presents with lower limb varicosities, ankle swelling, skin changes and in severe cases venous ulceration (Callam 1994). Over the last 15 years, the practice of treating varicose veins has moved towards minimally invasive endovenous techniques, which can be performed under local anaesthetic in an ambulatory, outpatient based setting (Nael & Rathbun 2009; Lane et al. 2011). Two commonly used endovenous modalities of varicose vein treatment are foam sclerotherapy and endothermal ablation, which have been described before. Modern ultrasound guided foam sclerotherapy (UGFS) has good technical efficacy, low cost and low morbidity (Coleridge Smith 2009; Bradbury et al. 2010) and is a generally accepted treatment modality for varicose veins. Endothermal ablation is now also a mainstay of clinical practice (van den Bos & Proebstle 2013). The thermal energy causes damage of the venous wall leading to fibrosis and occlusion of the refluxing vein, however, the exact mechanism is still unclear (Van Den Bos et al. 2009; Malskat et al. 2013).

Both UGFS and endothermal ablation are associated with few complications (Anwar et al. 2012; Dexter et al. 2012; Cavezzi & Parsi 2012), however, neurological events ranging from auras and headaches to transient ischaemic attacks and strokes have been reported in association with UGFS in approximately 2% of patients (Hartmann et al. 2009; Regan et al. 2011; Rathbun et al. 2012). Sarvananthan et al. (2011) (Sarvananthan et al. 2012) stated that the mechanism behind such adverse events was unclear and, there may potentially be more than one cause.

One of the principal hypotheses is the migration of bubbles (Bush et al. 2008; Picard et al. 2010; Parsi 2011), which are introduced as part of the foam sclerosant, to the brain, possibly by passing through a patent foramen ovale. These bubbles may be
responsible for cerebral vessel occlusion working as emboli. However, studies with carbon dioxide bubble formation has shown varied results with a reduced incidence of cerebral symptoms in one study, but not another, when compared to conventional air based foam (Parsi 2011). Significant bubble migration has been shown through a variety of imaging modalities during sclerotherapy and some bubbles are able to reach the middle cerebral artery, as detected by Morrison et al. (Morrison et al. 2008) through the use of transcranial Doppler studies. Bubbles have also been found in the middle cerebral artery of patients who did not suffer from neurological complications.

A principle theory behind the mechanism of action of endothermal ablation is heat transfer by bubble formation. It has been shown previously that endothermal ablation produces steam bubbles at the tip of the catheter (Proebstle, Lehr, et al. 2002a; Proebstle, Sandhofer, et al. 2002b). However, there have been no reported incidences of neurological complications (Anwar et al. 2012) nor have there been any investigations into whether the bubbles dissipate or are able to persist throughout the circulation in a fashion akin to those produced in foam sclerotherapy (Guex et al. 2010).

8.2.2. Aim

The aim of this safety study was to determine whether microemboli present at the catheter tip during endothermal ablation of varicose veins are seen in the right side of the heart.

8.2.3. Methods

8.2.3.1. Study Design and Size

Research Ethics Committee approval was sought and obtained (11/LO/1358) and all patients gave written informed consent. Ethical approval had initially been obtained for the investigation of up to 32 patients allowing the prevalence to be
calculated to the nearest 3%, however, it was deemed both unnecessary and unethical to proceed after the first 16 patients were scanned. Patients undergoing elective endothermal ablation of the great saphenous vein under local anaesthesia using a VNUS ClosureFast Catheter (VNUS Medical Technologies, San Jose, USA) took part in the study. Only those undergoing long saphenous vein ablation were considered as they would be in the appropriate supine position. Those undergoing an ablation of the short saphenous vein are positioned in the prone position in our institution and therefore were unable to undergo transthoracic echocardiography.

8.2.3.2. Inclusion and Exclusion Criteria

Consecutive patients over 18 years of age presenting for endothermal ablation of the long saphenous vein were invited to take part in the study. The following patients were excluded:

- Those unable to consent.
- Those undergoing other venous procedures
- Those with recurrent varicose veins (especially with prior high-tie)

8.2.3.3. Training Phase

Transthoracic echocardiography provides a sensitive, well validated method to identify and quantitatively grade the presence of microbubbles in the right atrium and ventricle, as evidenced by its common use in the diagnosis of a patent foramen ovale (Attaran et al. 2006). Prior to scanning the patient population of the study, a sonographer was observed performing bubble echocardiography on four patients by the independent consultant cardiologist. The model used was a Philips iU22 system with an X3 curvilinear echo transducer.

8.2.3.4. Main Study Phase

Consecutive patients undergoing elective endothermal ablation of varicose veins under local anaesthetic underwent intra-procedural echocardiographic monitoring
from March 2012 to May 2012. A B-mode apical four chamber view was acquired throughout the procedure. The settings for the ultrasound machine were as follows:

- Mechanical index: 1.1
- Compression: 72
- Persistence: Off
- Focal depth set to visualise right atrium (12±2cm)
- Gain optimised to ensure blood appeared black

The GSV was successfully cannulated, catheter advanced to 2cm distal to the SFJ and tumescent local anaesthetic instilled as standard protocol for endovenous ablation (Creton et al. 2010). Several, standardised loops of footage were saved for each patient:

- A loop of 30 seconds of the patient's heart prior to the start of the procedure serving as a negative control (no microemboli present)
- A 30 second loop of footage captured as a 10ml saline flush was introduced through the sheath at the site of cannulation to serve as a positive control
- A third loop of 30 seconds prior to commencement of heating to confirm no circulating bubbles remained after the flush.
- Radiofrequency ablation was commenced at a 2 minute interval after flushing, and only after no remaining bubbles were present. Loops taken during endovenous ablation itself were then recorded. The number of loops captured was dependent on the number of heating cycles performed (usually three or four cycles per procedure).
- Finally, one minute after the ablative treatment had ended, a loop of footage was captured. It was deemed unethical to perform a Valsalva procedure as this may have induced symptoms. Phlebectomies were then completed as clinically indicated. The patient was monitored for an hour post procedure for neurological phenomena.
The raw DICOM data was exported as AVI format. The AVI loops were then independently scored for quality and presence of bubbles at a later date by an independent consultant cardiologist. The grading system (Figure 114) used was a modification from the International Consensus Criteria grading guidelines (Lao et al. 2008) used to assess the bubble density seen in a cardiac shunt test.

![Grading Scale](image)

Figure 114: A visual depiction of the grading scale that was devised. The numbers indicate the grade assigned to each particular presence of microbubbles in the right heart. Grade 0 = no detectable bubbles, grade 1=solitary bubbles, grade 2=stream of bubbles, grade 3=opacification of right heart

8.2.4. Results

16 patients consented to the study during the recruitment period of March 2012-nay 2012. However, 2 declined to proceed during the procedure itself, as detailed in the Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram (Figure 115), and the scans of 3 patients were deemed to be non-diagnostic, as both the right ventricular walls and the mitral valve were not clearly visible throughout the procedure.
The mean age of the patients scanned was 49 years old (SD = 14) and the cohort was predominantly female (8 Females to 3 Males, 73%:23%). No adverse events were noted in any of the cohort during the procedures themselves or after a one hour period of observation in the unit.

Microbubbles were absent in the pre-procedure scan in all the 11 patients scanned. However in the heating phase, 5 patients (45±9%) had acoustic reflectors, moving from the right atrium into the right ventricle. As shown in Table 40, 4 patients had solitary microbubbles visible, and 1 patient had a visible stream of microbubbles.

Figure 116 represents a still image from a video loop from patient #2. Bubbles were noted to persist from 20 seconds to up to 5 minutes after the ablation had begun, however, this varied widely between patients. No patient reported any neurological symptoms.
Table 40: Baseline demographics, visualised bubbles and the occurrence of neurological complications

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnostic Bubble Grade</th>
<th>Neurological symptoms at 1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>0</td>
<td>Nil</td>
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8.2.5. Discussion

This study provides the first documented presence of microbubbles in the right atrium and ventricle during endothermal ablation of varicose veins. Despite the fact that this was a common finding, no neurological complications ensued. These results suggest that the presence of microbubbles in the right heart may be an incidental finding.

Ceulen (2008) (Ceulen et al. 2008) cast doubt on the theory that microbubbles play a major role in the development of neurological complications as he showed that 100% of the 33 patients who had undergone UGFS had bubbles present in the right side of the heart, but it was noted that only 7% of their cohort suffered from neurological complications. If transient bubbles are the primary causative agent in the pathogenesis of the neurological complications, one would, in theory, expect to see
neurological complications quickly arise in every patient with a PFO, which is estimated to have a prevalence of approximately 17% in the general population (Schwerzmann et al. 2005). This, however, is not the case and therefore suggests that these neurological complications may be either unrelated to the sole presence of bubbles or are part of a multi-factorial aetiological process. In addition, patients undergoing investigation for the presence of a PFO have agitated saline with air bubbles injected into a peripheral vein. There is some controversy as to whether neurological complications occurring during the test can be attributed to the bubbles (Romero et al. 2009), but during a large multi-centre study no neurological complications were reported and it is routinely carried out for the investigation of a right to left cardiac shunt (Tsivgoulis et al. 2011).

It is likely that there are inherent differences between the micro-emboli witnessed in this study and the bubbles seen in the systemic circulation of patients undergoing foam sclerotherapy. For example, bubbles formed by foam sclerotherapy may be more stable, or more likely to coalesce than the bubbles formed by endothermal ablation, due to the presence of the sclerosant detergent. Epstein and Plesset initially suggested that air bubbles in dynamic biological systems do not usually have the potential to persist for extended periods of time (Epstein & Plesset 1950; Plesset & Sadhal 1982) and work by Peterson and Goldman has shown that the half-life of foam bubbles was 25-28 seconds and 86-91 seconds using carbon dioxide and room air respectively (Peterson & Goldman 2011). However, bubbles produced by foam sclerotherapy have the potential to persist for up to 32 minutes beyond the commencement of treatment (Regan et al. 2011). This prolonged persistence may have a role to play in the neurological complications.

An alternative hypothesis currently gaining momentum is that the action of the sclerosant on the endothelium leads to the production of Endothelin 1 (ET1), which is able to initiate many pathogenic pathways, including those related to migraines
and auras. Frullini et al (Frullini et al. 2011; Frullini et al. 2012) showed there is an increased production of ET1 following UGFS in murine models, and that levels correlate closely with the severity of the neurological events experienced. Initial recent human work has also shown that increased ET1 levels are found in patients who have undergone UGFS. However, ET1 levels have yet to be measured in patients post endothermal ablation for comparison. It may be that thermal ablation technique destroys any endothelin produced during treatment, or that thermal ablation does not cause the release of endothelin. These results may shed light on why neurological complications are almost exclusive to foam sclerotherapy.

8.2.6. Conclusion

This study demonstrates that microemboli are commonly found in the right heart during endothermal ablation of the GSV but without immediate neurological sequelae, and may therefore be an incidental finding. This evidence suggests that that neurological complications experienced after foam sclerotherapy are not solely due to microemboli, but may be due to differing bubble stability or the production of endothelin.
8.3. Clarivein - Mechanochemical Ablation

8.3.1. VNUS Versus Clarivein for Varicose Veins - A Randomised Clinical Trial

8.3.1.1. Background

Varicose veins are characterised by dilated, tortuous superficial veins in the legs and affect approximately 25% of men and women in the United Kingdom (Callam 1994; Evans et al. 1999; Robertson et al. 2008).

The introduction of minimally invasive endovenous techniques has resulted in a rapid increase in their use throughout the UK and worldwide (Lane et al. 2011). Of the 27,000 procedures, of which over 9,000 (36%) were endovenous ablation a change from 15% of procedures in 2008-2009 (Edwards et al. 2009; Shepherd et al. 2010).

Advantages of endovenous techniques including thermal (laser, radiofrequency or steam) and chemical ablation (foam sclerotherapy) include the fact that they are routinely performed under local anaesthesia in an outpatient setting (Darwood & Gough 2009) and result in less post procedural discomfort and allow a more rapid recovery compared to traditional surgery (Darvall et al. 2009; Rasmussen et al. 2011) with low complication rates, they are therefore highly desirable for patients and clinicians. Efficacy has been shown to be equivalent between all treatment modalities (Rasmussen et al. 2013).

Covidien Venefit is the most frequently used radiofrequency device world-wide and allows rapid thermal ablation of truncal veins (Proebstle et al. 2011). Treatments are performed under tumescent local anaesthesia (Klein 1996) to provide a heat sink for the thermal energy around the vein, to compress the vein around the catheter, reducing the energy requirements and provides anaesthesia for the patient, and allowing the use of the outpatient setting (Bisang et al. 2012).
technique can be performed under general anaesthetic, but still requires the instillation of local anaesthetic.

Clarivein is a relatively new device which combines mechanical and chemical ablation to achieve vein closure (Elias et al. 2013). Potential advantages include the fact that no tumescent anaesthesia is required, reducing the discomfort experienced by the patient and the time to perform the procedure. It also reduces risk of skin or nerve damage as can be encountered with thermal ablation therapies (Dexter et al. 2012; Anwar et al. 2012).

In addition, the combination of chemical sclerosant and mechanical abrasion of the vein wall has been shown to achieve closure rates comparable to those achieved with thermal ablation (Elias & Raines 2012). Early results have shown 6 month occlusion rates to be 96% in all studies, 94% at 1 year (Boersma et al. 2013) in one study and 96% in the original study (Elias et al. 2013). These results are therefore comparable with thermal ablation results - 93% at 3 years (Rasmussen et al. 2013).

Each endovenous technique has specific advantages and disadvantages, the ideal therapy would provide long term success rates at a competitive cost, it should be quick and simple to perform with minimal discomfort to the patient. At present there is limited data comparing endovenous treatment modalities and this study proposes to compare Clarivein with RFA. By eliminating the need for tumescent anaesthesia, is it thought that Clarivein will be significantly less painful than RFA to perform, due to a reduction of tumescent anaesthesia injections counter-balanced by the feeling of the Clarivein device.

**8.3.1.2. Methods**

Patients referred for treatment of symptomatic varicose veins who are found to have primary great or small saphenous vein reflux on colour duplex imaging will be studied. In patients with bilateral disease, the leg which is most symptomatic
according to the patients will be randomised and both legs will receive the same treatment.

8.3.1.2.1. Inclusion Criteria

Adults over 18 years of age
Symptomatic long or short saphenous vein reflux < 0.5 seconds on colour duplex.

8.3.1.2.2. Exclusion Criteria

• Current 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

8.3.1.2.3. Patient allocation and randomisation

Two potential allocations are available:

1. VNUS Closure FAST™
2. Clarivein™

Patients will be randomised to receive one of the possible treatment options.
Treatments will be completed local anaesthetic with concomitant phlebectomy if necessary. Randomisation will be via an internet randomisation service (Sealed Envelope, London, UK).

8.3.1.2.4. Measurement of outcomes

8.3.1.2.4.1. Primary outcome

The primary outcome of pain during the procedure will be measured using a validated patient reported Visual Analogue Score (VAS) (Appendix 2)
8.3.1.2.4.2. Secondary Outcomes

- Improvement in the AVVQ score at 30 days and 6 months compared to baseline (Appendix 1)
- Improvements in generic quality of life measured using the EQ-5D at 30 days and 6 months (Appendix 1)
- Technical success/saphenous vein occlusion at 30 days and 6 months measured using colour duplex by an accredited vascular scientist
- Clinical success at 30 days and 6 months according to the VCSS
- Number of days taken to resume work and normal activities
- Cost effectiveness of the treatment regimes in terms of quality adjusted life years

8.3.1.2.5. Operative details

The length of the specific vein ablated, the amount of local anaesthesia used and the number of phlebectomies performed will be recorded at the time of operation. Patients are treated under local anaesthetic with standard mechanochemical ablation protocol via a 4 French sheath (Elias et al. 2013) or with standard radiofrequency ablation protocol with tumescent anaesthesia via a 7 French sheath (Creton et al. 2010).

8.3.1.2.6. Recruitment

Eligible patients who have been referred by their GP with primary symptomatic varicose veins will be identified at their first out patient appointment by the clinical team. They will be informed of the study and provided with an information sheet. Willing patients will sign a consent form agreeing to participate in the trial.

8.3.1.2.7. Participating Sites

The study was initially approved as a one site study - Charing Cross Hospital in London (Imperial College Heathcare NHS Trust) and was then expanded into a three site study incorporating Northwick Park and Central Middlesex Hospitals in
London (North West London Hospitals NHS Trust) and Addenbrookes Hospital in Cambridge (Cambridge University Hospitals NHS Trust).

8.3.1.2.8. Proposed sample size

Power calculations were based on the primary outcome measure of pain during the procedure and were based upon detection of a 20mm difference in maximum pain score with a standard deviation of pain score of 20mm, which was considered to be a significant clinical difference.

To attain 90% power at the 5% significance level, a minimum target sample size of 47 legs per group was required.

This figure was increased to allow for loss to follow up or protocol violation. This resulted in an overall target recruitment of 170 patients (85 per group).

The trial protocol is below.
Ethical approval was sought and gained from the National Research Ethics Service Committee London-Chelsea, identifier 12/LO/0570. This was initially approved as a one site study then amended to a three site study with local NHS Research and Development approval locally at Imperial College NHS Trust and North West London Hospitals NHS Trust (Imperial College NHS Trust approval identifier JRC0HH0431 and North West London Hospitals NHS Trust approval identifier...
RD13/032). Cambridge University Hospitals NHS Foundation Trust local approval is pending.
The trial is registered at Current Controlled Trials with the identifier ISRCTN06552809 (ISRCTN Register 2012).

8.3.1.3. Interim Results

After one year of recruitment, 85 patients (50% of target) have been successfully randomised over 2 sites since January 2013. As 50% of the recruitment has been achieved an interim analysis has been performed to ensure data quality and patient safety.

85 patients (46% male) with a mean age of 51 years have been recruited and treated, with 43 Clarivein procedures completed. 1 protocol violation occurred due to intolerance of the VNUS procedure, which necessitated conversion to Clarivein treatment.

Initial primary outcome results indicate that there is currently a significant difference in maximum intraoperative discomfort and average intraoperative discomfort scores between Clarivein and VNUS treatments (Maximum: 13.9 mm vs 33.7 mm, p<0.001; Average 9.6 mm vs 22.4 mm, p=0.002) as shown in Figure 118 and Figure 119. Median numerical pain score values were also significantly different between mechanochemical and radiofrequency ablation for both maximum and average intraoperative discomfort (Maximum 2 vs 4, p<0.001; Average 1 vs 3, p=0.005).
Figure 118: Visual Analogue Scale (VAS) scores in millimetres for maximal discomfort experienced.

VAS Maximum Discomfort (mm)
Clarivein versus VNUS

Clarivein

9.59 ± 3.987

VNUS

22.362 ± 7.224

Figure 119: Visual Analogue Scale (VAS) scores in millimetres for average pain experienced
No significant difference has thus far been seen between Clarivein and VNUS groups for the time taken to return to normal activities (3.6 days vs 4.8 days, p=0.417, Figure 120) and to return to work (4.1 vs 5.4, p=0.435, Figure 121). Additionally, no difference has been seen for disease specific or generic QOL tools at 30 days (AVVQ – 14.8 vs 14.3, p=0.897; EQ-5D - 0.80 vs 0.79, p=0.902).

No thromboembolic complications (SVT, DVT or PE) have been reported nor have any local complications (infection, nerve injury or skin burns).
The first patients recruited are beginning to complete follow-up. It is anticipated that recruitment will be completed by June 2014, with the trial completed by December 2014.

8.3.1.4. Discussion

These early outcomes from this ongoing study lend further weight to previous evidence that treatment with the Clarivein mechanochemical ablation device is safe and efficacious. The primary outcome of this study is to demonstrate the differing pain profiles of radio frequency and mechanochemical ablation. Interim analysis has shown that mechanochemical ablation has a significantly lower maximum intraoperative discomfort score, both statistically and clinically. Average perioperative discomfort was also significantly reduced in the mechanochemical ablation group.

Recent work in the Netherlands on 68 patients has shown that post-operative pain after GSV treatment is significantly improved for mechanochemical ablation compared to radiofrequency ablation (van Eekeren et al. 2013). Interestingly, the peri-operative discomfort score seen in the two groups was 22mm (Clarivein) and 27mm (radiofrequency) (van Eekeren et al. 2013), with the same group obtaining a 20mm average peri-operative discomfort for SSV mechanochemical ablation and the early safety study from the same group for GSV mechanochemical ablation produced a mean pain score of 4/10 (van Eekeren et al. 2011). Our study’s values show an reduced pain score for the Clarivein mechanochemical technique, compared to relatively static radiofrequency pain scores. This indicates that with the maturation of the technique and increased familiarity improved procedural outcomes can be obtained. This stable level of peri-operative pain for radiofrequency ablation is likely to be due to the tumescent anaesthesia application, with technique having reached a plateau.
8.3.1.5. Conclusion

Completion of this study should provide level 1 evidence to guide clinicians on improving their patient's experience and pathway during endovenous treatment.
8.4. Sapheon - Cyanoacrylate Ablation

8.4.1. European Sapheon Closure System Observational Prospective Study

8.4.1.1. Introduction

The Sapheon Cyanoacrylate Closure System is a new device that treats incompetent truncal veins by instillation of cyanoacrylate into the treated vein. It builds on the experience of using thermal and mechanochemical ablation techniques (Proebstle et al. 2005; Lohr & Kulwicki 2010; Elias et al. 2013). This "arms race" aims to simplify the endovenous treatment paradigm and reduce complications such as thermal injury and reduce the need for protective tumescent anaesthetic (Dexter et al. 2012; Anwar et al. 2012).

This has led to the production of the Sapheon Closure System as shown in Figure 122 and Figure 123.

Figure 122: Sapheon Closure System
Figure 123: Sapheon Cyanoacrylate

The kit consists of a proprietary glue and a proprietary catheter system. The cyanoacrylate glue is a tissue adhesive which is used extensively in other applications and has been modified for superficial venous treatment (Morrison 2013). The cyanoacrylates rapidly polymerise on contact with water or blood (Kamer & Joseph 1989).

The superficial venous treatment system requires no tumescent anaesthesia and no compression. In theory this should provide a reduced pain experience for patients undergoing treatment, in line with other modality advancements and studies assessing previous technologies and other tumescentless treatments (Nordon et al. 2011; Shepherd et al. 2010).

This study attempts to treat and observe the first large cohort of treated patients across 7 different participating sites and clinical teams.
8.4.1.2. Methods

This observational study recruited symptomatic C2-C4 chronic venous disease patients from multiple sites in the UK and Europe from March-June 2012. Imperial College London and Imperial College Healthcare NHS Trust was the lead UK centre and only NHS centre, responsible for ethical approval, NHS Research and Development approval and trial registration. Additionally the first UK Sapheon cases were performed at Charing Cross Hospital in the training phase of the study.

Patients were suitable for recruitment if they had primary incompetent long saphenous veins, with a reflux time of >0.5 seconds on colour duplex ultrasonography.

Patients were treated with the standard Sapheon Venaseal cyanoacrylate treatment pathway as previously published (Almeida et al. 2011; Lane et al. 2013). Standard endovenous Seldinger technique is used for access via a 5 French sheath and then the patient is placed in the standard reverse-Trendelenburg position. The catheter is passed to 5 cm distal to the saphenofemoral junction. Compression is applied at the saphenofemoral junction using the ultrasound probe in cross-section (transverse). Then one injection using the catheter system is completed before the catheter is withdrawn 1 cm and the second injection completed. The catheter is withdrawn a further 3 cm and 3 minutes of light compression is applied to the treated area. Then further injections with 3 cm withdrawals and 30 seconds of compression are completed. The compression times allow for polymerisation of the glue. Occlusion is confirmed on duplex ultrasound.

Patients were reviewed at 48-72 hours, 1 month, 3 months, 6 months, 12 months, 24 months and 36 months with a duplex ultrasound and a standardised questionnaire.
including AVVQ and EQ-5D QOL and EQVAS. A pain diary was completed for the first month. 2 year and 3 year follow-up is ongoing.

No additional procedures were completed at the initial treatment, and were only allowed after the 3-month review.

8.4.1.2.1. Number of Study Sites and Subjects
This multi-centre study consisted of 7 centres that specialize in the diagnosis and treatment of peripheral venous disease:

1. Private Clinic Proebstle in Mannheim, Germany
2. Charing Cross Hospital, Imperial College London and Imperial College Healthcare NHS Trust, London, UK - Lead UK Centre and NHS site.
3. Vein Center, Ouderkerk, Netherlands
4. The Danish Vein Center, Naestved, Denmark
5. The Whiteley Clinic, Guildford, UK
6. Vein Solutions, Spire Cheshire, UK
7. Dermatologikum, Hamburg, Germany

8.4.1.2.2. Study Outcomes

8.4.1.2.2.1. Primary Outcomes
• Vein closure at 1 year as assessed by duplex ultrasound - defined as no patent segments >10 cm.

8.4.1.2.2.2. Secondary Outcomes
• Venous Clinical Severity Score
• Quality of life and pain
  - Specific QOL – AVVQ
  - Generic QOL - EQ-5D
  - Pain during the procedure, diary (VAS) on use of analgesics
  - Pain reported during the first 30 days by patient diary VAS
8.4.1.2.3. Inclusion Criteria

- Age ≥18 years and ≤ 70 years of age
- Symptomatic primary GSV incompetence diagnosed by clinical symptoms, with or without visible varicosities, and confirmed by duplex ultrasound imaging
- CEAP classification of C2, C3 or C4
- Ability to walk unassisted
- Ability to attend follow-up visits
- Ability to understand the requirements of the study and to provide written informed consent
- GSV on standing pre-procedure Doppler US ≥3mm and ≤10mm (maximum diameter)

8.4.1.2.4. Exclusion Criteria

- Life expectancy < 1 year
- Regular pain medication
- Anticoagulation including Heparin or Warfarin
- Previous DVT
- Previous superficial thrombophlebitis in GSV
- Previous venous treatment on target limb
- Known Hyper-coagulable disorder
- Conditions which prevent routine vein treatment like:
  - Acute disease
  - Immobilization or inability to ambulate
  - Pregnancy
  - Tortuous GSV, which in the opinion of the Investigator will limit catheter placement (no 2 primary access sites allowed)
  - Incompetent ipsilateral small saphenous or anterior accessory great saphenous vein
  - Known sensitivity to the cyanoacrylate (CA) adhesive
- Current participation in another clinical study involving an investigational agent or treatment, or within the 30 days prior to enrollment

8.4.1.2.5. Ethical Approval

Ethical approval was obtained in the United Kingdom for NHS sites (sites 2, 5 and 6) from the NHS Lothian South East Scotland Research Ethics Committee 02 with the unique identifier of 12/SS/0028. The study is registered with ClinicalTrials.gov with the record number: NCT01570101. Local site specific approval was gained from NHS Research and Development Offices (Imperial College NHS Trust Approval Number: JR0HH0356) and local private hospital approval offices.

8.4.1.3. Results

69 patients have been recruited throughout Europe, with 6 month data and early 12 month data available.

3 (4%) patients have been recruited from Charing Cross Hospital Venous Unit. All 3 have shown excellent results with good vein closure and reduction in symptoms at 1 years post-treatment.

The three patients baseline demographics and outcomes are presented in Table 41.

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<th>Table 41: Imperial College eSCOPE Participants Demographics and Outcomes</th>
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<td>GSV Maximal Diameter (mm)</td>
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<td>0</td>
<td>2</td>
<td>0.67</td>
</tr>
<tr>
<td>AVVQ</td>
<td>3.26</td>
<td>10.46</td>
<td>12.03</td>
<td>8.58</td>
</tr>
<tr>
<td>EQ-5D QOL</td>
<td>1.000</td>
<td>1.000</td>
<td>0.837</td>
<td>0.946</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>100</td>
<td>98</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Vein Occluded</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEAP</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (Median)</td>
</tr>
<tr>
<td>VCSS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (-5.67 = 100% improvement)</td>
</tr>
<tr>
<td>AVVQ</td>
<td>0</td>
<td>16.93</td>
<td>13.65</td>
<td>10.19 (-7.58 = 43% improvement)</td>
</tr>
<tr>
<td>EQ-5D QOL</td>
<td>1</td>
<td>0.837</td>
<td>1.000</td>
<td>0.946 (+0.109 = 13% improvement)</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100 (+3.66 = 3.81% improvement)</td>
</tr>
<tr>
<td>Vein Occluded</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100%</td>
</tr>
</tbody>
</table>

These three patients showed excellent and persisting improvement in symptoms and disease status.

Two patients (66%) required treatment of persisting symptomatic varicose tributaries performed between the 3-month and 6-month follow-up. Both patients underwent foam sclerotherapy. No complications were encountered.
This small sample is part of the eSCOPE study, with the 6-month results displayed below.

8.4.1.3.1. eSCOPE Results

70 GSVs in 70 patients have been treated, with a median follow-up of 3 months. 6-month complete vein occlusion figures are satisfactory at 93.75%, indicating technical success in 45/48 cases, with partial recanalisation seen by 3 months in 2 cases and by 6 months in the third case. No complete treatment failures have been seen to date. Figure 124 shows the Kaplan Meier Curve with occlusion rates of 95% at 3 months (Confidence Interval 88.5-100%) and 90% at 6 months (78.9%-100%).

![Figure 124: Kaplan-Meier curve showing vein closure rates for the Sapheon Venaseal device](image)
The clinical outcomes have shown good improvements. Figure 125 shows improvement in VCSS scores after treatment from a baseline of 4.4 (SD 2.3) to 1.8 (1.6) at 1 month and to 0.2 (2.2).

![Figure 125: VCSS Outcomes for the eSCOPE Study](image)

6 cases (8.7%) of phlebitis were reported during follow-up, which were treated with non-steroidal anti-inflammatories for 7 days. One case (0.7%) of thrombus extension beyond the SFJ into the common femoral vein was reported. This was treated with anticoagulation and resolved without intervention.

8.4.1.4. Discussion

As can be seen from both the local and European results, the Sapheon Venaseal cyanoacrylate occlusion device shows a good efficacy and safety profile. This will need to be examined with further randomised comparative trials in the future and long-term follow-up of this initial cohort of patients is ongoing. This will be key in describing the long-term effect of glue instillation for the treatment of varicose veins.

The benefits of the technique are patient experience - no tumescent injection and no compression hosiery. However, with combined truncal ablation and varicosity phlebectomy under local anaesthetic a common procedure, the benefits may not be
as obvious as initially thought. The compatibility of the cyanoacrylate device with foam sclerotherapy has yet to formally investigated, although delayed adjunctive procedures have been performed without complication thus far. The high unit cost of the proprietary cyanoacrylate will hinder adoption, especially in developing countries.

A randomised study between all 5 truncal ablation techniques (radiofrequency, laser, steam, Clarivein and Sapheon) would be the optimum outcome to provide the evidence base for device differentiation. The first randomised study - the VeClose study in the USA, has recruited 242 patients, comparing Sapheon Venaseal with Covidien ClosureFAST (Sapheon Inc 2013). This study has completed recruitment and is in follow-up, and should report in Spring 2014. Total follow-up duration of the VeClose trial is planned at 3 months.

8.4.1.5. Conclusion

Cyanoacrylate glue appears to be a safe, feasible option with promising initial ablation success. It provides a further modality for treatment, but requires further longer term follow-up and randomised trials to confirm these initial results. The VeClose study allows initial success assessment and comparison with the current gold standard, but further long-term studies and repetition is required prior to blanket adoptance of the technique.
Chapter 9: Final Discussion and Conclusion
9.1. Final Discussion

The world of venous disease and treatment has changed significantly since the start of the 21st Century, in terms of understanding of pathophysiology and haemodynamics, and of investigation and management. The emergence of duplex ultrasound imaging has been pivotal in guiding the development of the surgeon's armamentarium and their understanding of an superficially simple but significantly complex disease (Labropoulos et al. 1997; García-Gimeno et al. 2009). With the knowledge and concepts introduced, ultrasound assessment of varicose veins has paved the way for refinements to surgical treatments (Smith et al. 2002; Blomgren et al. 2005), the birth of the endovenous revolution (Navarro et al. 2001; Lohr & Kulwicki 2010) and the evolution of vascular trainees education and expectations (Scurr et al. 2011; Karthikesalingam et al. 2012).

The endovenous revolution has led to a predominantly local anaesthetic based treatment for varicose veins, increasing the pool of patients suitable for treatment. It has also enabled clinicians to select different options for their patients, safe in the knowledge that all interventions offer good outcomes with good improvements in symptomatology (Rasmussen et al. 2011; Rasmussen et al. 2013). A body of evidence is beginning to form examining the long-term outcomes of venous disease, which is shining the light on the consequences of under-treatment. However, despite this burgeoning literature base, it is clear that non-vascular specialists are yet to be carried forth on the endovenous wave (Lane et al. 2013) with many continuing to deem varicose veins of little import (Audit Commission 2011) despite the morbidity experienced. The knowledge and understanding of the options for local services by GPs (now Clinical Commissioning Groups) is relatively poor, and cost is held as the reason for rationing treatment in many cases. It is hoped that the new NICE guidance (National Institute for Health and Care Excellence 2013) will improve this education level. These guidelines expound the future of venous treatment with minimally invasive treatments to the fore and endothermal
treatment first line due to its lower level of complications with similar efficacy (Biemans et al. 2013). With evidence existing for the past decade of the benefits of endovenous techniques, it is surprising that it is not universally-offered in the NHS (Lees et al. 1999; Subramonia & Lees 2007; Edwards et al. 2009). This may be due to the generational effect seen previously with laparoscopic surgery, and as the procedures become more widespread in senior clinicians then trainee experience and NHS uptake will follow outside of cutting-edge centres.

A difficulty interpreting research into varicose veins and its treatment has been the multiplicity of different assessment tools, both clinician derived and patient reported. Since the international consensus regarding CEAP and VCSS classification (Eklöf et al. 2004; Vasquez et al. 2010; Gloviczki et al. 2011), reporting standards have improved in clinical trials, making comparisons easier and more reliable. This allows meta-analyses to be more significant and robust. Currently the PROM outlook remains less clear, with differing countries preferring specific questionnaires. Fortunately, as our study demonstrates, well-constructed questionnaires show a high correlation and allow relative ease of comparison. This may enable easier comparison in the future, especially as the advent of tablet computers and smart-phones allow for easy entry of data online. This reduces the workload for analysis, however is limited by difficulty with electronic drawing (Ward et al. 2013; Lane et al. 2013). With different PROM tools requiring differing input methods such as the CIVIQ, an optimum option might be to use this tool in preference to the AVVQ, with previous scores converted. Alternatively, with progress in software, the AVVQ may remain a viable option with patient completed online drawings, as is completed in some trials currently underway (Sapheon Inc 2013).

With this progression of reporting standards, PROMs have become the key outcome of interest in most studies. This is partly due to equivalent technical outcomes with
most treatments in experienced hands, but also due to the understanding that even partial technical "failure" may lead to an improved and satisfactory outcome for one patient, and a complete technical "success" may be of zero benefit for another patient (Brake et al. 2013). This variability has led to many studies trying to isolate the principle cause of the symptomatology. The venous disease cohort and modelling work presented in this thesis shows that currently collected data (demographic, clinical and symptoms) is only a part of the cause. More extensive demographic data needs to be collected in further research cohort studies in order to tease out the key variables, which can then streamline data collection for registry entry. With national publication of surgeon level data on abdominal aortic aneurysms and carotid endarterectomies (Vascular Services Quality Improvement Programme et al. 2013), it is only a matter of time until funding groups and patients will expect all outcomes to be published at local levels as opposed to national levels with the Hospital Episode Statistics programme (Anon 2013). The American Venous Forum has already created a modular registry (American Venous Forum American Venous Forum 2012), based on previous work for the International Venous Registry (European Venous Forum et al. 2012) and has begun to link it to the pre-existing Society for Vascular Surgery's Vascular Quality Initiative registry (Society for Vascular Surgery American Venous Forum 2013). This collaborative effect will lead to large cohort data evidence, but this is only of use if the data quality is good and the data collected is appropriate. At present our work suggests that this standard demographic data collected needs to be expanded to enable good outcome prediction with these population sized cohorts.

Previous work on the timing of varicosity treatment has been sparse, as shown by Chapter 7. The previous work available has shown a significant early improvement in quality of life after simultaneous treatment, but heterogenous findings with respect to re-intervention, and similar rates of deep venous thrombosis. This may explain the lack of widespread adoption of simultaneous treatment despite excellent
outcomes from the single randomised clinical trial explicitly examining the timing question. The AVULS trial showed early symptomatic benefits and persistent clinical benefits. Additionally, the group of patients in the delayed treatment arm that required further treatment suffered from symptoms out to 6 months from initial treatment. Finally, patients undergoing delayed procedures were significantly more likely to need further intervention (Odds Ratio 16). Recruitment for AVULS study was less successful than expected with only 46% of those eligible participating over the 18 month recruitment window. Follow-up was within expectations, with 80% at 6 months (primary endpoint). 12 month follow-up was below expectations (56%) but within the bounds of previous trials (Nordon et al. 2011). The total population examined in the AVULS trial was 26% of the screened population. To reach minimum target recruitment of 128 it is likely to have required a further 6 months of recruitment, and to reach 240 it would have required some 28 further recruitment months. This highlights the difficulty encountered in generalising trial results into the wider population - the sample may not be a truly random constituent of the target population. The data from the Hospital Episode Statistics (Anon 2013) suggest that our patients were slightly more symptomatic than the general population, and much more symptomatic than the population assessed by Carradice et al. (Carradice et al. 2009). This is reassuring that our results are applicable to the National Health Service generally. Many institutions do not have the logistical support to allow for combined phlebectomy and endovenous truncal ablation, and though foam sclerotherapy of the varicosities is an appropriate alternative, the evidence base for that approach is sparse. This leads to many clinicians being unable to offer combined treatment in the public sector despite the evidence base and public preference. Further work is needed to compare the outcomes of foam sclerotherapy in the endovenous ablation context.

The advance of technology has led to the emergence of tumescent-less techniques and these devices once again alter the geography of treatment (Lawson et al. 2013;
Indeed, some may suggest that they have rendered the question of adjunctive treatment moot as whilst phlebectomy can easily be performed during ablation (as in the VVCVV trial (ISRCTN Register 2012)), the need for further anaesthetic reduces the benefits offered by these new devices. Additionally, the use of foam sclerotherapy and mechanochemical ablation may be limited due to sclerosant safety limits; whilst there is no published data describing the use of cyanoacrylate and sclerosant simultaneously. These safety concerns allied to the lack of extensive long-term data limit the applicability of the newer devices outside of the research environment. Long-term evidence of equivalence of the different endothermal modalities is beginning to emerge (Rasmussen et al. 2013; Proebstle et al. 2011) and ex vivo work is explaining the differences in complications whilst reassuring that there is a similar method of action (van den Bos & Proebstle 2013; Malskat et al. 2013). The new devices must satisfy the conditions of equivalence to current techniques that the endothermal devices have achieved previously with surgery.
9.2. Conclusion

Endovenous ablation has revolutionised the treatment of varicose veins allowing virtually all patients appropriate treatment. With improved techniques and technology and long-term follow-up, endovenous treatment is now the "gold standard" against which other treatments must be compared. This is not due to improved technical outcomes but improved pain profiles, reduced logistical requirements and improved complication rate. These benefits also make endovenous ablation a cheaper solution overall, with a much preferred patient experience, despite higher initial equipment costs. The differing thermal ablation devices available all offer excellent treatments, and work is now focussed on the final 1-2% of treatment optimisation. The development of non-thermal ablation systems offers further refinement and improvement of the patient pathway.

Primary care management of venous diseases is severely behind this forefront of venous treatment, which is understandable from a generalists viewpoint. However, with the advent of Clinical Commissioning Groups, these very primary care physicians are the key decision makers. With the release of the first National Institute for Health and Care Excellence guidance on varicose vein management it is hoped that this deficit in understanding will be reduced.

Patient reported outcome measures have been accepted as the key tool for assessment of success, with technical achievement almost a secondary aim. Management and treatment of the patient rather than the anatomy has become the target for venous specialists. Previously studies have reported disease specific quality of life with differing scales causing confusion in interpretation. Fortunately, the two most commonly used scales have been shown to have excellent correlation, and therefore interpretations can be made confidently. Anatomical data has classically been a focus point for surgeons dealing with varicose veins, with the belief that the largest veins cause the most problems, which has been shown to be
inaccurate, with symptomatology being poorly associated with vein diameter. This leads to a more patient centred consultation with management of expectations key.

Simultaneous treatment of varicosities during truncal vein ablation leads to significantly improved and persistent clinical outcomes with significantly improved early quality of life. Delayed treatment leads to a significantly increased risk of further treatments, and those delayed treatment patients requiring further intervention have a significantly worse outcome. In large retrospective studies delayed and simultaneous treatments have been shown to have equivalent rates of deep venous thrombosis or endovenous heat induced thrombosis.

Modelling of varicose vein outcomes remains a complex and difficult field with many key variables currently unclear. The isolation of those patients who will have the best outcomes is still elusive, however, it is clear that worsened symptoms equate to worse outcomes, and so by inference early treatment is key. Further careful work to identify further key variables is necessary to provide robust and accurate predictive models. The varicose vein population is extensive and disparate, and some of the multiple variables needed to explain the variation in symptomatology may remain hidden until further population scale cohorts studies are undertaken.
Chapter 10: Future Work
10.1. Future Work in Treatment Devices

As part of ongoing assessment of different treatment devices, the currently running VVCVV trial is assessing the peri-procedural pain profile of the mechanochemical ablation and radiofrequency thermal ablation (ISRCTN Register 2012). The eSCOPE trial is also in long-term follow-up (Sapheon Inc 2012).

Following this study, long term studies comparing mechanochemical ablation, thermal ablation (using modern laser and radiofrequency devices) and chemical occlusion are planned to provide detailed experience of the safety and efficacy of the devices. This would provide robust data to complement that by recently published comparing UGFS, EVLA, RFA and open surgery (Rasmussen et al. 2011; Rasmussen et al. 2013).

Assessment of microemboli seen in other mechanochemical ablation (which uses detergent sclerosant) is a further study to be completed as this would allow possible identification of equivalent bubble propagation to foam sclerotherapy. This would be completed using the previous protocol for standardisation (Sounderajah et al. 2012).

10.2. Future Work in Simultaneous Treatment

The AVULS trial (Lane 2011) examined the timing of adjunctive treatments in the context of endothermal ablation of truncal venous incompetence. However, due to patient preference this trial under-recruited. Additionally the recommendation of simultaneous treatment may not be feasible due to local treatment pathways. Further evidence would be needed to provoke change, as local centres have preferred methods of operation, which often have not changed with recent evidence.

To this end, a further study AVULS 2 is planned with multi-centre recruitment. This would extend follow-up to 2 years post treatment to allow for assessment of
progression and recurrence. The study would aim to recruit in the region of 500 patients from 8 separate clinical institutions to provide extensive and reliable data for further modelling work and pathway optimisation. In order to be able to proceed with this study, a grant to the Health Technology Assessment Programme of the National Institute for Health Research is in the initial stages, as it is anticipated that the study will cost in the region of £2,000,000 to complete.

**10.3. Further Work in Venous Education**

The recent publication of the NICE guidelines (National Institute for Health and Care Excellence 2013) for the management of varicose veins aim to improve the baseline knowledge of clinicians regarding varicose veins. This will need to investigated and assessed for effectiveness. It is therefore proposed that a repetition of the GP survey (Lane et al. 2013) assessing management of varicose veins should be completed 1 year after the publication of the guidelines, to allow for assimilation into clinical practice.

A survey of vascular surgeons to assess current venous treatment and surgical practice would be appropriate following the launch of the Vascular Surgery speciality in 2013. This would ideally be completed in 2015 to allow for initial trainees to commence and for settling of the new speciality. This would then be compared to previous work (Shepherd et al. 2010), and compared to the outcome of a recently published survey of vascular trainees (Karthikesalingam et al. 2012).

**10.4. Further Work in Venous Cohort and Modelling**

The venous cohort data is planned to be repeated and expanded with a new cohort of patients, with further demographic details recorded at baseline. The aim of this work is to improve the predictive model created from the current venous patient cohort and reduce the unexplained variance. It would also allow the independent testing of long-term modelling.
Of great importance is discovering the minimally important clinical difference (Revicki et al. 2008), and so as part of this work, a patient satisfaction questionnaire will be completed to discover how much of an improvement in QOL scores is clinically significant. This will greatly help both the predictive model and interpretation of future trial results.
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Appendices
Appendix 1. AVVQ

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

![Diagram of legs viewed from front and 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)

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>None at all</td>
<td>☐</td>
</tr>
<tr>
<td>Between 1 and 5 days</td>
<td>☐</td>
</tr>
<tr>
<td>Between 6 and 10 days</td>
<td>☐</td>
</tr>
<tr>
<td>For more than 10 days</td>
<td>☐</td>
</tr>
</tbody>
</table>

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

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

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

   | None at all | ☐ | ☐ |
   | Slight ankle swelling | ☐ | ☐ |
   | Moderate ankle swelling (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)

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>☐</td>
</tr>
<tr>
<td>Yes, those I bought myself without a doctor's prescription</td>
<td>☐</td>
</tr>
<tr>
<td>Yes, those my doctor prescribed for me which I wear occasionally</td>
<td>☐</td>
</tr>
<tr>
<td>Yes, those my doctor prescribed for me which I wear every day</td>
<td>☐</td>
</tr>
</tbody>
</table>
6. In the last two weeks, have you had any itching in association with your varicose veins?
(Please tick one box for each leg)

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes, but only above the knee</td>
<td></td>
</tr>
<tr>
<td>Yes, but only below the knee</td>
<td></td>
</tr>
<tr>
<td>Both above and below the knee</td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes, but it does not require any treatment from a doctor or district nurse</td>
<td></td>
</tr>
<tr>
<td>Yes, and it requires treatment from my doctor or district nurse</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>R Leg</th>
<th>L Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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 |
## VCSS

<table>
<thead>
<tr>
<th>Appendix 2: VCSS</th>
</tr>
</thead>
</table>

| Pain or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning) | None: 0 | Mild: 1 | Moderate: 2 | Severe: 3 |
| Presumes venous origin | Occasioned pain or other discomfort (i.e. not restricting, regular daily activity) | Daily pain or discomfort (i.e. interfering with but not preventing regular daily activities) | Daily pain or discomfort (i.e. limits most regular daily activities) |
| Varicose veins | Mild: 1 | Moderate: 2 | Severe: 3 |
| *Varicose* veins must be ≥3 mm in diameter to qualify | Few, scattered (i.e. isolated branch varicosities or clusters) | Confined to calf or thigh | Involves calf and thigh |
| Venous oedema | Moderate: 2 | Extends above ankle but below knee | Extends to knee and above |
| Presumes venous origin | Limited to foot and ankle area | Diffuse over lower third of calf | Severe: 3 |
| Skin pigmentation | Limited to perimalleolar area | Wider distribution above lower third of calf |
| Presumes venous origin | None or focal | |
| Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e. vasculitis purpura) | |
| Inflammation | None: 0 | Mild: 1 | Moderate: 2 | Severe: 3 |
| More than just recent pigmentation (i.e. erythema, cellulitis, venous eczema, dermatitis) | Limited to perimalleolar area | Diffuse over lower third of calf | Wider distribution above lower third of calf |
| Induration | None: 0 | Mild: 1 | Moderate: 2 | Severe: 3 |
| Presumes venous origin of secondary skin and subcutaneous changes (i.e. chronic oedema with fibrosis, lymphedema) | Limited to perimalleolar area | Diffuse over lower third of calf | Wider distribution above lower third of calf |
| Includes white atrophy and lipatrodermatosclerosis | |
| Active ulcer number | 0 | 1 | 2 | 3 |
| Active ulcer duration (longest active) | <3 months | >3 months but <1 year | ≥3 months | Not healed for >1 year |
| Active ulcer size (largest active) | Diameter <2 cm | Diameter 2–6 cm | Diameter >6 cm |
| Use of compression therapy | 0 | 2 | 3 |
| Not used | Intermittent use of stockings | Wears stockings most days | Full compliance: stockings |

N/A, not applicable
### Appendix 3. CES-D

**Center for Epidemiologic Studies Depression Scale (CES-D), NIMH**

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

<table>
<thead>
<tr>
<th>Week</th>
<th>During the Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely or none of the time (less than 1 day)</td>
<td>Some or a little of the time (1-2 days)</td>
</tr>
<tr>
<td>1. I was bothered by things that usually don’t bother me.</td>
<td>[ ]</td>
</tr>
<tr>
<td>2. I did not feel like eating; my appetite was poor.</td>
<td>[ ]</td>
</tr>
<tr>
<td>3. I felt that I could not shake off the blues even with help from my family or friends.</td>
<td>[ ]</td>
</tr>
<tr>
<td>4. I felt I was just as good as other people.</td>
<td>[ ]</td>
</tr>
<tr>
<td>5. I had trouble keeping my mind on what I was doing.</td>
<td>[ ]</td>
</tr>
<tr>
<td>6. I felt depressed.</td>
<td>[ ]</td>
</tr>
<tr>
<td>7. I felt that everything I did was an effort.</td>
<td>[ ]</td>
</tr>
<tr>
<td>8. I felt hopeful about the future.</td>
<td>[ ]</td>
</tr>
<tr>
<td>9. I thought my life had been a failure.</td>
<td>[ ]</td>
</tr>
<tr>
<td>10. I felt fearful.</td>
<td>[ ]</td>
</tr>
<tr>
<td>11. My sleep was restless.</td>
<td>[ ]</td>
</tr>
<tr>
<td>12. I was happy.</td>
<td>[ ]</td>
</tr>
<tr>
<td>13. I talked less than usual.</td>
<td>[ ]</td>
</tr>
<tr>
<td>14. I felt lonely.</td>
<td>[ ]</td>
</tr>
<tr>
<td>15. People were unfriendly.</td>
<td>[ ]</td>
</tr>
<tr>
<td>16. I enjoyed life.</td>
<td>[ ]</td>
</tr>
<tr>
<td>17. I had crying spells.</td>
<td>[ ]</td>
</tr>
<tr>
<td>18. I felt sad.</td>
<td>[ ]</td>
</tr>
<tr>
<td>19. I felt that people dislike me.</td>
<td>[ ]</td>
</tr>
<tr>
<td>20. I could not get &quot;going.&quot;</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**SCORING:** zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.
## Appendix 4. CEAP

<table>
<thead>
<tr>
<th>CEAP</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C₁</td>
<td>Telangiectases or reticular veins</td>
</tr>
<tr>
<td>C₂</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>C₃</td>
<td>Edema</td>
</tr>
<tr>
<td>C₄</td>
<td>Pigmentation and/or eczema</td>
</tr>
<tr>
<td>C₅</td>
<td>Lipodermatosis and/or atrophic blanche</td>
</tr>
<tr>
<td>C₆</td>
<td>Healed venous ulcer</td>
</tr>
<tr>
<td>C₇</td>
<td>Active venous ulcer</td>
</tr>
<tr>
<td>C₈</td>
<td>Symptoms, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction</td>
</tr>
<tr>
<td>C₉</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>E₀</td>
<td>Congenital</td>
</tr>
<tr>
<td>E₁</td>
<td>Primary</td>
</tr>
<tr>
<td>E₂</td>
<td>Secondary (postthrombotic)</td>
</tr>
<tr>
<td>E₃</td>
<td>No venous etiology identified</td>
</tr>
<tr>
<td>A₀</td>
<td>Superficial veins</td>
</tr>
<tr>
<td>A₁</td>
<td>Perforator veins</td>
</tr>
<tr>
<td>A₂</td>
<td>Deep veins</td>
</tr>
<tr>
<td>A₃</td>
<td>No venous location identified</td>
</tr>
<tr>
<td>P₀</td>
<td>Reflux</td>
</tr>
<tr>
<td>P₁</td>
<td>Obstruction</td>
</tr>
<tr>
<td>P₂</td>
<td>Reflux and obstruction</td>
</tr>
<tr>
<td>P₃</td>
<td>No venous pathophysiology identifiable</td>
</tr>
</tbody>
</table>
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 |
CIVIQ-14

SELF-QUESTIONNAIRE PATIENTS

In English language for UK

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.

<table>
<thead>
<tr>
<th></th>
<th>No pain</th>
<th>Slight pain</th>
<th>Moderate pain</th>
<th>Considerable pain</th>
<th>Severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>No trouble</th>
<th>Slight trouble</th>
<th>Moderate trouble</th>
<th>Considerable trouble</th>
<th>Severe trouble</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Fairly often</th>
<th>Very often</th>
<th>Every night</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
### CIVIQ-14

**SELF-QUESTIONNAIRE PATIENTS**

*In English language for UK*

<table>
<thead>
<tr>
<th>No trouble</th>
<th>Slight trouble</th>
<th>Moderate trouble</th>
<th>Considerable trouble</th>
<th>Could not do it</th>
</tr>
</thead>
<tbody>
<tr>
<td>4) Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5) Crouching, Kneeling down</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6) Walking at a brisk pace</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7) Going out for the evening, going to a wedding, a party, a cocktail party...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8) Playing a sport, exerting yourself physically</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

During the past four weeks, how much **trouble** have you experienced **carrying out the actions and activities** listed below **because of your leg problems**?

For each statement in the table below, indicate how much trouble you have experienced by circling the number chosen.
C I V I Q-14

SELF-QUESTIONNAIRE PATIENTS

*In English language for UK*

---

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>A lot</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>9) I have felt nervous/tense</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10) I have felt I am a burden</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11) I have felt embarrassed about showing my legs</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12) I have become irritated easily</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13) I have felt as if I am handicapped</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14) I have not felt like going out</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Leg problems can also affect your mood. How closely do the following statements correspond to what you have felt during the past four weeks?

For each statement in the table below, circle the number that applies to you.
Appendix 6. Management of varicose veins in the community survey

Survey of Superficial Venous Disease Management in Primary Care

Superficial Venous Disease (Varicose Veins) is a common condition with a varied presentation. Many treatment options are available. The purpose of this survey is to look at referral patterns for the treatment of varicose vein disease in the community.

The below questionnaire is a service evaluation/audit of current practice in primary care. The aim is to identify what GPs think of chronic venous insufficiency (and varicose veins), what the level of knowledge is regarding new advancements in varicose vein treatment. This information will be utilised to improve the co-ordination of primary and secondary care. In the current era of proposed GP commissioning it is vital that such co-ordination is as efficient and up to date as possible, in both directions. We aim to provide an extensive primary care viewpoint which will be disseminated to both primary care and secondary care.

* How many patients do you see on average per year with Superficial Venous Disease (Varicose Veins)?
  - < 10
  - 10-50
  - 51-100
  - 101-200
  - > 200

* Do you manage or treat Superficial Venous Disease (Varicose Veins) in the community (e.g. compression hosiery or injection sclerotherapy)?
  - Yes
  - No

* If you do refer patients with Superficial Venous Disease (Varicose Veins), to whom do you refer?
  (please select all that apply)
  - Vascular Surgeon
  - General Surgeon
  - Dermatologist
  - Vascular Nurse Specialist

* What presenting symptoms would you refer to a specialist (please select all which apply)
  - Prominent varicose veins
  - Bleeding veins
  - Leg swelling
  - Thrombophlebitis
* What treatments options do you discuss with your patients for the management of varicose veins?

* Which of the following treatment options are available for your patients in your area? (please select all which apply)

- Compression hosiery
- Sclerotherapy
- Endovenous laser ablation
- Endovenous radiofrequency ablation
- Open tradition vein stripping surgery
- Do not know

* Are you aware of NICE Guidelines for the referral of Superficial Venous Disease (Varicose Veins) to specialist care?

- Yes
- No

If yes, do you follow them?

* Are you aware of Local PCT Guidelines for the referral of Superficial Venous Disease (Varicose Veins) to specialist care?

- Yes, and I agree with them
- Yes, but I do not agree with them, please specify
- No
* Are you aware of NICE Treatment Guidelines for the management of Superficial Venous Disease (Varicose Veins)?
  - Yes
  - No

* Are you aware of Local PCT Treatment Guidelines for the management of Superficial Venous Disease (Varicose Veins)?
  - Yes, and I agree with them
  - Yes, but I do not agree with them, please specify
  - No

* Are you aware of any clinical scoring systems for Superficial Venous Disease (Varicose Veins)?
  - Yes
  - No

* Below are a number of treatment options (A-F), how would you treat the following patients if they presented to your GP surgery?

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>A patient with non-painful but visible varicose veins?</th>
<th>A patient with painful visible varicose veins?</th>
<th>A patient with leg swelling?</th>
<th>A patient with varicose veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hosiery, Please Specify which class or type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression Bandaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral to a specialist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, please specify</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A patient with varicose veins, leg swelling, & pain?

A patient with venous skin changes?

A patient with a venous ulcer?

In the above cases, do you think there is a role for operative/invasive/endovenous management?

Yes  No  Don't Know

A patient with non-painful but visible varicose veins?

A patient with painful visible varicose veins?

A patient with leg swelling?

A patient with varicose veins and leg swelling

A patient with varicose veins and leg swelling, and pain?

A patient with venous skin changes?

A patient with a venous ulcer?

Do you think that mild Superficial Venous Disease (Varicose Veins) will progress over time to more severe disease unless treated?

Yes, but can be managed conservatively  Yes and needs invasive treatment

No  Don't Know

Do you think that by treating Superficial Venous Disease (Varicose Veins) you will improve a patient's quality of life?

Yes, but can be managed conservatively  Yes and needs invasive treatment

No  Don't Know
Any comments?

* Do you think that treatment of Superficial Venous Disease (Varicose Veins) is a cost-effective use of NHS resources?
  - Yes, but can be managed conservatively
  - Yes and needs invasive treatment
  - No
  - Don't Know

Any comments?

* In the following cases, do you think all treatment should be provided free-of-charge by the NHS?

A patient with non-painful but visible varicose veins?
A patient with painful visible varicose veins?
A patient with leg swelling?
A patient with varicose veins and leg swelling
A patient with varicose veins and leg swelling, and pain?
A patient with venous skin changes?
A patient with a venous ulcer?

Any specific comments?

* If a patient has had invasive treatment, are you:
  - Happy to provide the aftercare
  - Feel that aftercare should be provided by the specialist
  - Feel no aftercare is required

Any comments?

* If you had Superficial Venous Disease (Varicose Veins) how would you like them treated?

What best describes your medical practice?
- Single-handed GP
- Salaried GP
Where is your medical practice located? (please tick all that apply)

- Rural
- South West
- London
- West Midlands
- East of England
- Yorkshire and the Humber
- Scotland
- Urban
- South East
- Wales
- East Midlands
- North West
- North East
- Northern Ireland

Do you have any comments on aspects of care that have not been covered or you would like to make the researchers aware of?

If you would like further information with results of the survey please provide your e-mail address below (this will not be used for any other purposes nor released to third parties)

For further information please refer to the Royal Society of Medicine’s Venous Forum Recommendations

Thank you very much for considering and participating in our survey. We appreciate the time you have spent on it. All results are held confidentially, and are not identified to individuals. If you have submitted your e-mail address as part of the survey, this will only be used for dissemination of the survey results. It is not obligatory. The e-mail address and the survey answers are not linked and your responses are not personally identifiable.

If you would like any further information, including the recently published RSM Venous Forum Guidelines, or recent study publications, please contact me at tristan.lane@imperial.ac.uk.
Appendix 7. Management of superficial venous thrombosis in primary and tertiary care survey

Dear colleague,

Many thanks for visiting our survey. This is a replacement survey which has been made on a new server following the collapse of our previous host. If you have previously completed the survey then thank you very much.

We are investigating the management and care of patients with superficial venous thrombosis or superficial venous thrombophlebitis (SVT).

This is a 20 question survey which should not take more than 10 minutes to complete.

We would be grateful for your help in completing this survey. Please help to disseminate this survey to GP and vascular consultant colleagues.

Kind Regards,

Tristan

tristan.lane@imperial.ac.uk
Tristan Lane, Kaji Sritharan, Mr Ian Franklin and Professor Alun Davies
Academic Section of Vascular Surgery, Imperial College London

1) Are you a:

GP
GP Trainee
Consultant Vascular Surgeon
Vascular Trainee
Other (Please Specify):

2) Which country do you practice in?

UK
Europe
Other (Please Specify):
3) How many patients do you see each year with superficial thrombophlebitis?

<table>
<thead>
<tr>
<th>Option</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td></td>
</tr>
<tr>
<td>6 - 10</td>
<td></td>
</tr>
<tr>
<td>11 - 20</td>
<td></td>
</tr>
<tr>
<td>21 - 30</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td></td>
</tr>
</tbody>
</table>

4) When you encounter a patient with superficial thrombophlebitis, do you:

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat the patient yourself</td>
</tr>
<tr>
<td>Refer ALL patients elsewhere</td>
</tr>
<tr>
<td>Refer select cases</td>
</tr>
<tr>
<td>Other (Please Specify):</td>
</tr>
</tbody>
</table>

5) If you refer the patient, who do you refer to? (Please select all which apply)

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Surgeon</td>
</tr>
<tr>
<td>Dermatologist</td>
</tr>
<tr>
<td>General Physician</td>
</tr>
<tr>
<td>Haematologist</td>
</tr>
<tr>
<td>Nurse-Led DVT Clinic</td>
</tr>
<tr>
<td>Do Not Refer On</td>
</tr>
<tr>
<td>Other (Please Specify):</td>
</tr>
</tbody>
</table>

6) Do you think there is an association between superficial thrombophlebitis and deep vein thrombosis (DVT)?

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Don't Know</td>
</tr>
</tbody>
</table>
7) If yes, what percentage of patients with superficial thrombophlebitis in your experience have a co-existing deep vein thrombosis (DVT) at presentation?

<table>
<thead>
<tr>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>75%</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Don't Know</td>
</tr>
</tbody>
</table>

8) If yes, what percentage of patients with superficial thrombophlebitis in your experience will develop a deep vein thrombosis (DVT) at 3 months?

<table>
<thead>
<tr>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>75%</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Don't Know</td>
</tr>
</tbody>
</table>

9) Do you think there is an association between superficial thrombophlebitis and the following?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolus (PE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicose Veins (VV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep Venous Incompetence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10) In your assessment of the patient, which of the following would you perform? (Please select all which apply)

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia Screen</td>
</tr>
<tr>
<td>Venous Duplex</td>
</tr>
<tr>
<td>CT Venography</td>
</tr>
<tr>
<td>MR Venography</td>
</tr>
<tr>
<td>Conventional Venography</td>
</tr>
<tr>
<td>None of the above</td>
</tr>
<tr>
<td>Other (Please Specify):</td>
</tr>
</tbody>
</table>

11) How would you treat a patient with superficial thrombophlebitis? (Please select all which apply)

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment required</td>
</tr>
<tr>
<td>Compression Hosiery</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Topical Heparinoids</td>
</tr>
<tr>
<td>Low Molecular Weight Heparin</td>
</tr>
<tr>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Leg Elevation</td>
</tr>
<tr>
<td>Bed Rest</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Other (Please Specify):</td>
</tr>
</tbody>
</table>
12) If Low Molecular Weight Heparin (LMWH) is commenced, for what duration?

- 2 weeks
- 4 weeks
- 6 weeks
- 3 months
- Depends on specialist advice
- Varies according to care
- Other (Please Specify):

13) Would your management be different if the patient had recurrent (more than one episode) thrombophlebitis?

- No
- Don't Know
- Yes, How?

14) In your experience what proportion of patients experience recurrent episodes of thrombophlebitis?

- < 5%
- 10%
- 25%
- 50%
- 75%
- All patients
- Don't know

15) Would the distribution (i.e. SSV or Above Knee or Below Knee GSV) of the superficial thrombophlebitis influence your treatment?

- No
- Don't Know
- Yes, How?
### 16) How do you follow-up patients with superficial thrombophlebitis?

<table>
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<tr>
<th>Option</th>
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<tbody>
<tr>
<td>No follow-up is performed</td>
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<tr>
<td>Follow-up only in selected cases</td>
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<tr>
<td>Weekly</td>
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<tr>
<td>Fortnightly</td>
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<tr>
<td>Monthly</td>
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<tr>
<td>Other (Please Specify):</td>
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</table>

### 17) At follow-up do you perform any imaging?

<table>
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<tr>
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<tbody>
<tr>
<td>No follow-up undertaken</td>
</tr>
<tr>
<td>No, no imaging performed</td>
</tr>
<tr>
<td>Yes, venous duplex</td>
</tr>
<tr>
<td>Yes, CT venography</td>
</tr>
<tr>
<td>Yes, MR venography</td>
</tr>
<tr>
<td>Yes, Other (Please Specify):</td>
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</table>

### 18) If surgery is performed, what are the indications? (please select all of those which apply)

- Don't know - would take specialist advice
- Persistent pain
- Cosmesis
- Failure of conservative/medical measures
- Propagation of thrombus
- Thrombus in close proximity to the deep venous system - please specify minimum acceptable distance from junction if this is one of your criteria
19) In your personal experience, is there a seasonal variation in the incidence of superficial thrombophlebitis?

<table>
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<tr>
<th>Option</th>
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<tr>
<td>No</td>
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<tr>
<td>Don't Know</td>
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<td>Yes, (Please Specify):</td>
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20) Is there anything else that you would like to tell us?

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Appendix 8. Grants

2013: Graham-Dixon Charitable Trust Research Grant
Modelling Varicose Vein Outcomes
£8,000

2012: Sapheon Inc. Commercial Grant
European Sapheon Closure System Observational Prospective Study
£47,000

2012: Vascular Insights Commercial Grant
VNUS Versus Clarivein for Varicose Veins (VVCVV) Randomised Controlled Trial
£225,000

Appendix 9. Fellowships and Awards

2013: 3rd Place Presentation
ESVS:EVST Stars of the Future
Charing Cross Symposium, London, UK

2013: Servier Travel Grant
American Venous Forum Annual Meeting, Phoenix, USA

2013: Runner-Up Prize for Oral Presentations (Author not presenter)
Australasian College of Phlebology, Hobart, Australia

2013: Norman Williams Prize (Author not presenter)
Society for Academic and Research Surgery, London, UK

2012: 3rd Place
Spring Meeting Prize Session
Royal Society of Medicine Venous Forum, London, UK

2012: Cook Medical Bursary
London Cardiovascular Symposium

2012: Vascutek Travel Grant
Veith Conference, New York, USA
2011: Glaxo Travelling Fellowship - 2nd Place
   Norman Tanner Prize Session
   Royal Society of Medicine Surgery Section, London, UK

2011: International Travelling Fellowship
   American College of Phlebology, Los Angeles, USA
Appendix 10. Research Related Journal Publications

Appendix 10.1. Journal Articles:


Appendix 10.2. Letters:


Appendix 10.3. Abstracts:

1. Lane TRA, Varatharajan L, Kelleher D, Franklin IJ, Davies AH. Clinical and Quality of Life Outcomes are Improved with Simultaneous Phlebectomies at 6 weeks - Early Results of the AVULS Randomised Clinical Trial. International


Appendix 11. Research Related Book Chapters


6. Lane TRA, Shepherd AC, Davies AH. It matters not a jot or tittle which method is used to thrombose the superficial varicose vein by heat - the result is the same. In: Greenhalgh RM, editor. Vascular and Endovascular Controversies Update. 34 ed. London: BIBA Medical; 2012. pp. 546–52.


Appendix 12. Research Related Presentations

Appendix 12.1. Oral Presentations:


4. **Lane TRA**, Varatharajan L, Kelleher D, Franklin IJ, Davies AH. Clinical and Quality of Life Outcomes are Improved with Simultaneous Phlebectomies at 6 weeks - Early Results of the AVULS Randomised Clinical Trial. 17th World Congress of the International Union of Phlebology. Boston, USA; 2013.


14. Lane TRA, Varatharajan L, Kelleher D, Franklin IJ, Davies AH. Early Results of the AVULS Trial - Both Clinical and Quality of Life Outcomes at 6 weeks are improved with simultaneous phlebectomies. Royal Society of Medicine Venous Forum Spring Meeting. London, UK; 2013.


17. Moore HM, Sounderajah V, Thapar A, Lane TRA, Fox KF, Franklin IJ, et al. Microemboli are visible in the right heart during endothermal ablation of

19. **Lane TRA**. Opinions of varicose veins in primary care. Winter Ski Meeting of Royal Society of Medicine, Surgery Section. Champoluc, Italy; 2013.


29. **Lane TRA**, Sritharan K, Franklin IJ, Davies AH. Referral Patterns for Chronic Venous Disease in Primary Care. American College of Phlebology 25th Annual Congress. Los Angeles, USA; 2011.


33. **Lane TRA**, Sritharan K, Franklin IJ, Davies AH. Referral Patterns for Chronic Venous Disease in Primary Care. European Chapter Meeting of International Union of Phlebology. Prague, Czech Republic; 2011.


35. Shepherd AC, **Lane TRA**, Davies AH. The relationship between great saphenous vein diameter, quality of life and physician assessment of venous...


Appendix 12.2. Posters of Distinction (Poster with Oral Presentation):


7. Sritharan K, **Lane TRA**, Franklin IJ, Davies AH. Depression is Common in Patients with Chronic Venous Disease - Implications for Management. American College of Phlebology 25th Annual Congress. Los Angeles; 2011.


**Appendix 12.3. Posters:**


Appendix 13. Publication Full-Texts
IVC Filters for Prevention of Venous Thromboembolism in Obese patients undergoing Bariatric Surgery: A Systematic Review

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Conflicts of Interest and Source of Funding

There are no conflicts of interest to declare
Abstract

Objective The use of Inferior Vena Cava (IVC) filters for prevention of Venous Thromboembolism (VTE) in bariatric surgery is a contentious issue. We aim to review the evidence for the use of IVC filters in bariatric surgical patients, describe trends in practice and discuss challenges in developing evidence-based guidelines.

Summary Background Data The incidence of VTE in modern bariatric procedures with traditional methods of thromboprophylaxis, such as sequential calf compression devices and perioperative low molecular weight heparin, is approximately 2%.

Methods A systematic review of the literature was conducted according to PRISMA guidelines. We searched Medline up until July 2013 with the terms ‘bariatric filter’ and ‘gastric bypass filter’. Two investigators independently screened search results according to an agreed list of eligibility criteria.

Results 18 studies were included. There were no randomised controlled trials. Data from controlled cohort studies suggest that those who undergo IVC filter insertion pre-operatively may be at higher risk of developing DVT and PE. A small cohort of patients with multiple risk factors for VTE benefitted from reduced PE-related mortality following pre-operative IVC filter insertion. Data from twelve case series reporting VTE outcomes from a total of 497 patients who underwent pre-operative IVC filter insertion demonstrated DVT rates of 0-20.8% and PE rates ranging from 0-6.4%.
Conclusions Published data reporting the safety and efficacy of IVC filter use in bariatric surgical patients is highly heterogeneous. There is no evidence to suggest that the potential benefits of IVC filters outweigh the significant risks of therapy.

Mini-Abstract
Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in the bariatric surgical population. Although most would agree that there is a role for both pre- and post-operative pharmacoprophylaxis, the use of Inferior Vena Cava (IVC) filters remains a contentious issue. In this systematic review we summarise evidence for the insertion of pre-operative IVC filters to prevent pulmonary embolism in patients undergoing bariatric surgery.
Background

The World Health Organisation (WHO) estimates that there are more than 500 million obese individuals worldwide.\(^1\) Morbid obesity, defined as a body mass index (BMI) >40kg/m\(^2\), is associated with significant co-morbidities including cardiovascular disease, obstructive sleep apnea, an increased risk of cancer and the metabolic syndrome.\(^2\)-\(^4\) This population is at high risk of developing venous thromboembolism (VTE). Indeed risk of VTE may be directly proportional to BMI.\(^5\)

Bariatric surgical procedures have been shown to be the most effective treatment modality for morbid obesity and its co-morbid conditions.\(^6\)-\(^7\) Procedures include laparoscopic or open Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG). They are thought to work through the so-called ‘BRAVE’ effects: (Bile flow alteration; Reduction of gastric size; Anatomical gut rearrangement and altered flow of nutrients; Vagal manipulation; and Enteric gut hormone modulation).\(^4\) Bariatric procedures are increasingly performed worldwide and there is growing evidence that they may represent a sustainable cost-effective long-term solution for the treatment of morbid obesity.\(^8\)

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in the bariatric surgical population.\(^9\) Historically, the incidence of symptomatic VTE in open bariatric surgery has been reported as high as 3.4%.\(^10\) In modern practice with the use of perioperative thromboprophylaxis and pneumatic calf compression devices, VTE may still occur in greater than 2% of all open procedures.\(^11\) Those undergoing revisional surgery are potentially at greater risk still. The introduction of laparoscopic bariatric
surgery has been associated with reduced rates of VTE. A recent meta-analysis of published literature demonstrated that the overall incidence of symptomatic VTE in modern laparoscopic bariatric procedures is less than 1% with a further 1% thought to have subclinical disease. These figures suggest that conventional methods of thromboprophylaxis such as the use of sequential calf compression devices and perioperative low molecular weight heparin may be adequate for the bariatric surgical population as a whole. However in many cases this approach is seen to be inadequate due to the presence of multiple risk factors for VTE or the presence of a contraindication to pharmacological prophylaxis. This has led to the increased use of inferior vena-caval filters in modern bariatric surgical practice.

Currently there is a lack of consensus on the most effective strategy for prevention of venous thromboembolism in patients undergoing bariatric surgery. A recent survey of predominantly North American surgeons suggests that more than 92% of bariatric surgeons routinely use preoperative pharmacological prophylaxis. The majority of surgeons prescribe sequential compression devices in high-risk patients (96.3%) and pharmacological prophylaxis is used post-operatively by 97% however the duration and dose of therapy is highly variable. In patients perceived to be high risk, routine use of IVC filters is reported by 28.1% of surgeons, with more than half of these patients receiving additional pharmacoprophylaxis on discharge. At present there is no cross-sectional data available to describe strategies employed in other parts of the world. In the United Kingdom the National Institute of Clinical Excellence (NICE) recommends mechanical prophylaxis with 5-7 days of pharmacological therapy after bariatric surgery however the role of IVC filters is not discussed. Although most would agree that there is a role
for both pre- and post-operative pharmacoprophylaxis, the use of IVC filters remains a contentious issue among bariatric surgeons worldwide.

To date there are no randomised trials investigating the role of IVC filters for prevention of venous thromboembolism in bariatric surgical patients. We aim to review the evidence for the use of IVC filters in bariatric surgical patients, describe trends in practice and discuss challenges in developing evidence-based guidelines.

Methods

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We searched Medline up until July 2013 with the terms 'bariatric filter' and 'gastric bypass filter' and reviewed reference lists to identify additional publications. Two investigators separately assessed search results according to an agreed list of eligibility criteria. Articles were eligible for inclusion if they described rates of venous thromboembolism in patients who had undergone IVC filter insertion before bariatric surgery and were written in English. We excluded duplicate articles, review articles, case studies, editorials, and letters. Two investigators independently assessed the methodological quality of each study using the QUADAS-2 tool. Where there were differences in ratings a joint assessment was performed in order to reach a consensus. Data was extracted systematically under the following headings: Study Design (eg. Randomised Controlled Trial, Registry Review, Cohort study etc.), Study Population (Dates of recruitment, Number of patients, Age, Sex, BMI), Indications for IVC filter insertion, Pharmacological prophylaxis, Surgical Procedure, Operative Time, Filter insertion time, Type of Filter, and
Follow-up Period. Outcomes data was collected to assess rates of pulmonary embolism (PE), deep vein thrombosis (DVT), PE-related mortality, all-cause mortality, filter related complications, as well as rates and timings of filter removal.

Results

Figure 1 summarises results from our systematic review of the literature. The search terms 'bariatric filter' and 'gastric bypass filter' returned 39 and 29 results respectively. Following exclusion of duplicates 46 titles were screened leaving 41 abstracts for review. Six further results were excluded on abstract screening leaving 35 manuscripts for full review. 18 manuscripts were found to contain outcomes data for patients who had undergone bariatric surgery with pre-operative insertion of IVC filter and were included in this systematic review. Quality assessment using the QADAS-2 tool demonstrated at least a low risk of bias in at least one domain in all included studies. A high risk of bias was found in more than one domain in several studies.

There were no randomised controlled trials evaluating the benefit of IVC filters for prevention of venous thromboembolism in obese patients undergoing bariatric surgery. Table 1 summarises data from controlled cohort studies. There were two large registry reviews reporting VTE outcomes in patients with IVC filter and no IVC filter. In a study of prospectively collected data from 1077 patients with an equal number of propensity-matched controls Birkmeyer et al. reported that both PE (0.84% vs 0.46%) and PE-related mortality (0.37% vs 0%) tended to be higher in patients who had pre-operative placement of IVC filter than those who did not, although results were not statistically significant. Rates of DVT (1.20% vs 0.37%) and serious complications
(5.8% vs 3.8%) also tended to be higher in the IVC filter cohort, but again were not statistically significant. Li et al. reported VTE outcomes from a retrospective registry review of 97,218 patients, of which 322 had pre-operative filter insertion. IVC filter patients had a higher incidence of DVT (0.93% vs 0.12%; p<0.001) and tended to suffer from PE more frequently (0.31% vs 0.12%), although this was not statistically significant. Death from suspected PE was also higher in the IVC filter cohort (0.31% vs 0.03%; p=0.003). In this study patients in the IVC filter cohort had a greater pre-operative risk of VTE due to higher rates of previous VTE, impairment of functional status, lower extremity oedema, obstructive sleep apnea, and pulmonary hypertension. Patients in the IVC filter cohort were also more likely to be male, had a higher BMI, and more frequently underwent open surgery with a longer operative time. Statistical analysis was performed using a multivariate logistic regression model to address the aforementioned differences in VTE risk factors.

There were 3 further controlled cohort studies describing VTE outcomes in patients who had pre-operative IVC filter insertion. Obeid et al. reported symptomatic DVT rates of 1.21% in a cohort of 246 ‘high risk’ patients who had pre-operative IVC filter insertion. DVT rates of 0.8% were found in the remaining bariatric surgical population (n=1848), who acted as unmatched controls. PE rates were higher in the IVC filter cohort (0.8% vs 0.6%) however differences were not statistically significant. In a prospective cohort study of 330 patients Overby et al. reported DVT numbers identified by duplex screening at 6-weeks follow-up. DVT rates were again higher in the IVC filter cohort (3.13% vs 2.35%; p=0.744) however those without an IVC filter more frequently suffered from pulmonary embolism (2.94% vs 0.63%; p=0.216). A cohort of non-IVC filter patients were again more likely to suffer from PE in a prospective study by Gargiulo et al. (28% vs
0%; p<0.05). PE related mortality was less than 1% in these three studies with the exception of Gargiulo et al who reported rates as high as 11% in certain subgroups. National Survival outcomes have been estimated for bariatric surgical patients with and without IVC filter who developed VTE. According to the Nationwide Inpatient Sample, which captures around 20% of US non-federal short-term hospitals, mortality in patients who developed DVT in hospital was lower in those who had undergone IVC filter insertion (0/510) compared to those who did not (80/5970; p=0.009). No significant difference in PE-related mortality was found between the two cohorts.

Table 2 summarises observational data describing population demographics and rates of venous thromboembolism in patients who had undergone prophylactic IVC filter insertion prior to bariatric surgery. Data presented is largely from retrospective series and as a result there is significant heterogeneity in both patient demographics and thromboprophylaxis protocol. Carmody et al. report the largest series of 145 patients with data collected over a 24-year period. Patients had a mean BMI of 57 kg/m² and mean age of 47 years with a 2.1% PE rate. This was the only series to report PE related mortality in a patient who had pre-operative IVC filter insertion (1/145 patients). Piano et al. reported VTE outcomes from a cohort of 58 patients who had a Gunther–Tulip filter placed before undergoing Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) or Duodenal switch. There was a mean age of 43 years and mean BMI of 61 kg/m² with 17% male population. PE occurred at a rate of 1.7% with no DVT identified on routine lower limb duplex scanning performed prior to filter retrieval at a mean of 63 days post-operatively. The highest rates of PE were reported as 6.4% and 4.2% in cohorts of 31 and 24 patients respectively who had Gunther-Tulip filter insertion prior to either open or laparoscopic Roux-en-Y Gastric Bypass surgery. These cohorts were followed-up for a mean of
262 days and 16 months respectively. Symptomatic DVT rates were also relatively high, reported as 20.8% and 3.1% respectively. In the remaining eight observational studies results from 239 patients were reported with no PE.\textsuperscript{23, 25-27, 30-32, 34} DVT rates in these studies were less than 5% with the exception of the study by Vaziri et al. which reported a rate of 21% in a cohort of 29 patients who were followed up for a mean of 16 days following insertion of an Optease filter prior to LRYGB (16), LAGB (9), or open RYGB (4).

Our search identified three published case series describing outcomes specifically after Laparoscopic Roux-en-Y Gastric Bypass surgery.\textsuperscript{30, 31, 34} There were two retrospective cohort studies and one prospective study. 81 patients underwent LRYGB between December 2004 and July 2009 with mean follow-up of 16, 204 or 356 days according to the series in question. Types of IVC filters utilised included Gunther Tulip, Bard G2, and Optease. These were used in combination with subcutaneous heparin, sequential calf compression devices, and early ambulation. Pharmacoprophylaxis was not continued after discharge. Mean operative time was highly variable ranging from 93 minutes to 175 minutes. There was no reported incidence of pulmonary embolism but a minimum of five examples of deep vein thrombosis. There was one minor complication of IVC filter insertion (haematoma). Filter retrieval rates were not reported.

There was one case series identified describing procedure specific rates of venous thromboembolism after open RYBG surgery in morbidly obese patients who underwent insertion of IVC filter.\textsuperscript{23} 58 patients underwent surgery with IVC filter insertion at a single institution between 1999 and 2007. This represented 10% of all morbidly obese patients undergoing open RYGB. In the IVC filter cohort there was a mean age of 37 years with 38% males. Mean BMI was 62kg/m\textsuperscript{2}. There were 35 TrapEase filters, 9
Simon-Nitinol, 2 Greenfield, and 12 Bard Recovery filters placed with an average additional operating time of 20+/−5 minutes. In addition all patients received sequential calf compression, subcutaneous heparin therapy (50units/Kg) pre- and post-operatively twice daily until ambulating four hours per day. All patients underwent pre-operative and post-operative venous duplex examination as a screening test for DVT. After a mean follow-up of 65±12 months there were no examples of pulmonary embolism and two cases of DVT, one fatal. Only one IVC filter was removed and this was at one year post-operatively with no reported filter-related complications. There were no case series reporting procedure specific data for patients who underwent adjustable gastric banding or sleeve gastrectomy with placement of prophylactic IVC filter. Table 3 summarises published literature detailing DVT, PE and PE related mortality rates in patients who underwent IVC filter insertion before laparoscopic vs open RYGB.

IVC filter-specific complications, not including failure to retrieve, occurred at a rate of 0-11·1%. (Table 4) There was one report of a DVT forming at the insertion site of the IVC filter and another report of PE occurring secondary to thrombus formation within the filter itself. Other major complications included device migration requiring cardiac valve replacement, development of contrast induced nephropathy, and haemopericardium.18,19 Minor complications included haematoma formation (three), malposition (three), cellulitis (one) and severe pain (one). In five of the twelve case series there were no filter-specific complications reported. Planned filter retrieval was attempted in ten of the twelve studies with retrieval rates reported in six of these. In the largest study to report retrieval rates 90% of filters were removed from 58 patients at a mean of 63 days post-operatively.28 In all cases failure to retrieve was due to technical difficulties secondary to
filter tilt. In this series a further six retrievable filters were converted to permanent filters due to patient preference. Halmi et al. demonstrated that a retrieval rate of 96·3% can be achieved, indeed only one filter remained due to an unrelated illness.26 High retrieval rate (100%) was also demonstrated to be possible in a small UK study of five patients.32 Schuster et al. and Vaziri et al. reported 83% and 72% filter retrieval respectively with one filter in each cohort remaining in place due to technical failure in retrieval.29, 34 The lowest filter retrieval rate was reported as 68·3% by Vaziri et al. in a cohort of 29 patients.30 This series also reported the longest time to filter removal (mean 204 days). There were no technical failures during retrieval. Of those patients who did not have their IVC filter retrieved, two refused, three were advised against retrieval due to DVT, and one patient had died from an unrelated cause.

Discussion

This systematic review of the literature describing VTE outcomes in bariatric surgical patients with and without IVC filter demonstrated a heterogeneous dataset comprising of controlled and un-controlled cohort studies. There were no randomised controlled trials. Data from controlled cohort studies suggest that those who undergo IVC filter insertion pre-operatively may be at higher risk of developing DVT and PE. A small cohort of patients with multiple risk factors for VTE may have benefitted from reduced PE-related mortality following pre-operative IVC filter insertion. However there is no evidence at present to suggest that this potential benefit outweighs the significant risks associated with IVC filter use. Data from twelve case series reporting VTE outcomes from a total of 497 patients who underwent pre-operative IVC filter insertion demonstrated
DVT rates of 0-20.8% and PE rates ranging from 0-6.4%. PE-related mortality however was rare with only one reported case. Of these twelve series there were three studies reporting LRYGB specific outcomes with no PE-related mortality.

In recent years the use of IVC filters for prevention of VTE has been limited by safety concerns, which have been described in detail by a 2010 report from the United States Food and Drug Administration. Serious complications include filter migration and embolisation, thrombosis and occlusion of the filter, IVC perforation, and filter fracture. Much of the available data is from case reports and there is a paucity of data describing filter-specific complications in the bariatric population. The risk of radiation and contrast exposure during filter insertion and removal must also be considered. In our study filter related complications were rare however the authors recognise that publication bias may have influenced our findings. Data from the aforementioned 2010 FDA report suggests that there may be significant under-reporting of complications in the medical literature. Further, complications of therapy are often described as case reports, a format that is not captured by the systematic review process. Serious complications of IVC filter occurred most frequently in patients with prolonged filter exposure, which may occur when patients are lost to follow-up or where there is technical failure during retrieval. We recommend filter retrieval at the earliest possible opportunity in order to reduce risk of complications. This recommendation is supported by recent evidence suggesting increased risk of technical failure during retrieval when the first attempt is delayed. Until evidence based protocols are available the risks and benefits of filter retrieval should be considered on a case-by-case basis.
Given the risks of IVC filter insertion, bariatric surgeons only consider their use in patients believed to be at increased risk of venous thromboembolism. Within the published literature factors consistently believed to increase risk of VTE include a history of prior VTE or deep vein thrombosis, pulmonary hypertension, personal or family history of coagulopathy, chronic severe immobility, and evidence of pre-operative lower limb venous stasis. The presence of obstructive sleep apnea is considered an independent risk factor by some bariatric surgeons. Those with the highest BMI are considered to be at increased risk of VTE in all case series to date however there is apparent disagreement between surgeons regarding the level at which raised BMI should be deemed as an independent risk factor. BMI of 50kg/m², 55kg/m², 60kg/m² have each been used as cut-off points. According to analysis of retrospective data at a single institution those with a BMI >55 may have significantly increased risk of venous thromboembolism (relative risk 10·2) compared to those with BMI <55 kg/m².

It should be noted that this recommendation is based on data obtained from patients who underwent open bariatric surgery, which has been largely superseded by minimally invasive techniques in modern bariatric surgical practice. However the findings by Gargiulo et al. may still be relevant to those undergoing revisional surgery, which may often be performed via an open approach. A survey of 385 surgeons from the United States reported that 44% consider the presence of one risk factor as an indication for IVC filter insertion. 54·7% believed that at least two risk factors are required before IVC filter insertion and 47·4% require the presence of three risk factors. Finks et al. have demonstrated that individual risk factors may have unequal significance in bariatric surgical patients, suggesting that an empirically based risk calculator may be the most appropriate method of risk stratification. Such an approach has been applied successfully in other cohorts of patients. A recent statement by the ASMBS has
suggested that IVC filters should be considered only in high-risk patients, however there continues to be a lack of consensus regarding risk stratification for morbidly obese patients and indications for IVC filter.\textsuperscript{39}

Development of evidence based guidelines for use of IVC filter in bariatric surgical patients is challenging given the significant heterogeneity in published series. In current series thromboprophylaxis regimen are not standardised\textsuperscript{40} and a wide range of IVC filter models have been employed. It should be noted that much of the published data describes VTE outcomes after open surgery. Laparoscopic bariatric surgery, now considered gold standard, is associated with shorter operative time and reduced rates of VTE.\textsuperscript{41} Physicians should also consider that in published series IVC filters have been used exclusively in subjects deemed to be at relatively high risk of VTE. Without randomized controlled trial study design it is not possible to assess outcomes if IVC filters had not been inserted in these high risk groups. Whilst investigators have attempted to address this issue by the inclusion of propensity matched controls and statistical correction for example, it cannot be excluded that experienced clinicians in fact correctly predicted those at highest risk, and that the outcome might have been much worse had no filter been inserted. Such factors are important when considering whether the benefits of therapy outweigh the significant risks associated with IVC filters. Further evidence is required to evaluate the risks of VTE and IVC filter use in modern bariatric units. Whilst randomised controlled trials provide the ideal evidence source the issue may be more successfully addressed with non-randomised large multicentre prospective trials with well-defined patient cohorts. Such trials should include long-term follow-up in order to identify complications of therapy. Until such evidence is available, data from well-maintained national registries may provide a basis for future recommendations.\textsuperscript{22, 42}
Given the lack of evidence to demonstrate any significant benefit of IVC filter use over alternative approaches, it could be argued that appropriate national or local guidance for surgical thromboprophylaxis may represent the safest option. Indeed it has been demonstrated that extended pharmacological therapy with early ambulation and perioperative sequential calf compression can all but eliminate the risk of VTE in some bariatric surgical cohorts.43

Conclusions

Published data reporting the safety and efficacy of IVC filter use in bariatric surgical patients is highly heterogeneous and lacks randomized controlled trial evidence. Given the shift towards laparoscopic surgery and ongoing developments in filter technology current evidence may not be directly applicable to modern bariatric surgical practice. At present we would recommend that pre-operative IVC filter insertion should only be considered for prevention of VTE in high-risk bariatric surgical patients. It is important to consider the potential for significant harm resulting from IVC filter insertion. The benefits of therapy are unlikely to outweigh the risks unless there are multiple risk factors for VTE, which may include super-morbid obesity, previous VTE, pulmonary hypertension, a history of coagulopathy, chronic severe immobility, obstructive sleep apnea, or evidence of pre-operative lower limb venous stasis. Where IVC filters are used there is evidence to suggest that early retrieval will increase technical success and reduce long-term complications. Given the significant challenges in performing a randomised controlled trial in this population, large multicentre prospective trials with well-defined patient cohorts should be designed to investigate the role of IVC filters in modern bariatric surgery.
Legends.

Figure 1. PRISMA Literature Search Results

Table 1. Controlled cohort studies describing venous thromboembolism after bariatric surgery with and without pre-operative IVC filter insertion. (NS=Not Specified; RYGB=Roux-en-Y Gastric Bypass; LRYGB=Laparoscopic Roux-en-Y Gastric Bypass; AGB=Adjustable Gastric Band; LGB=Laparoscopic Gastric Band; GB=Gastric Band; DS=Duodenal Switch; SG=Sleeve Gastrectomy; IVCF=Inferior Vena Cava Filter; Hx=History; DVT=Deep vein thrombosis; PE=Pulmonary Embolism; HTN=Hypertension; BMI=Body Mass Index; LMWH=Low molecular weight heparin; SCD=Sequential Compression Device)

Table 2. Case series describing venous thromboembolism after bariatric surgery with pre-operative IVC filter insertion. *Gariguolo 2010 reports long-term Follow-up data from cohort by Gargiulo et al. 2006, presented in Table 1. (NS=Not Specified; RYGB=Roux-en-Y Gastric Bypass; LRYGB=Laparoscopic Roux-en-Y Gastric Bypass; LGB=Laparoscopic Gastric Band; DS=Duodenal Switch; LSG=Laparoscopic Sleeve Gastrectomy; BMI=Body Mass Index; LMWH=Low molecular weight heparin; SCD=Sequential Compression Device)

Table 3. Summary of published literature detailing DVT, PE and PE related mortality rates in patients who underwent IVC filter insertion before Laparoscopic vs Open.

IVC Filters in Bariatric Surgery
IVC Filters in Bariatric Surgery

Table 4. Complications of Inferior Vena Cava Filters in Bariatric Surgical Patients

(Published Case Series) NS=Not Specified. N/A=Not Applicable.

References


42. British Society of Interventional Radiology Caval Filter Registry [database online]. Insert City of Publication Here see notes.

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Indication for IVC Filter</th>
<th>Procedure</th>
<th>Cohort</th>
<th>No. Patients</th>
<th>Age (Mean Years)</th>
<th>Male Sex %</th>
<th>BMI</th>
<th>PE</th>
<th>DVT (Screened or Symptomatic?)</th>
<th>PE related mortality</th>
<th>Mortality All Cause (%)</th>
<th>Thromboprophylaxis</th>
<th>Anticoagulation post-discharge</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkmeyer et al. 2013</td>
<td>Propensity-matched cohort study</td>
<td>NS</td>
<td>AGB 15%, SG 12%, RYGB 73%, DS 0.7%</td>
<td>IVCF</td>
<td>1077</td>
<td>48</td>
<td>32</td>
<td>58</td>
<td>0.80</td>
<td>1.2% (NS)</td>
<td>0.37%</td>
<td>0.70%</td>
<td>Pre-Op Heparin: unfractionated, 60% LMWH. Post-op Heparin: unfractionated 7%, LMWH 70%</td>
<td>72%</td>
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<td></td>
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<td>49</td>
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<td>57</td>
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<td>0.4%</td>
<td>(NS)</td>
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<td>Pre-Op Heparin: unfractionated, 54% LMWH. Post-op Heparin: unfractionated 10%, LMWH 68%</td>
<td>66%</td>
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<tr>
<td>Gargiulo et al. 2006</td>
<td>Retrospective Cohort</td>
<td>Hx DVT or PE, pulmonary HTN, BMI&gt;55kg/m2 not an indication</td>
<td>Open RYGB</td>
<td>IVCF</td>
<td>8</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>SCD, thromboembolic devices (TEDs), and weight-adjusted subcutaneous heparin (50 U/kg) injections before surgery and every 12 hours after surgery until ambulating more than 4 hours per day.</td>
<td>NS</td>
<td>2.5 years (1-42 months)</td>
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<td>Prospective Cohort</td>
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<td>2.5 years (1-42 months)</td>
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<td>2.5 years (1-42 months)</td>
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<td>Study</td>
<td>Cohort Description</td>
<td>Treatment</td>
<td>IVCF</td>
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<td>Age</td>
<td>BMI</td>
<td>Incidence</td>
<td>NS</td>
<td>Incidence</td>
<td>NS</td>
<td>Duration</td>
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<td>Patient Choice, BMI&gt;55, Hx DVT, PE, Pulmonary HTN</td>
<td>Open RYGB</td>
<td>IVCF</td>
<td>17</td>
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<td>NS</td>
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<td>18</td>
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<td>16.7</td>
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<td>2.5 years (1-42 months)</td>
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<tr>
<td>Obeid et al. 2007</td>
<td>Poor mobility, BMI&gt;60, lower limb venous disease, personal or FHx or thrombophilia. (Data only available for 36% of cohort.)</td>
<td>LRYGB (12); Open RYGB (234); Lap GB (0)</td>
<td>IVCF</td>
<td>246</td>
<td>46.6</td>
<td>23.6</td>
<td>60</td>
<td>0.80%</td>
<td>NS</td>
<td>0.81%</td>
<td>NS</td>
<td>30 days</td>
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<td>LRYGB (132); Open RYGB (1689); Lap GB (27)</td>
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<td>1848</td>
<td>44.7</td>
<td>14</td>
<td>38.8</td>
<td>0.60%</td>
<td>NS</td>
<td>4.00%</td>
<td>NS</td>
<td>30 days</td>
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<tr>
<td>Overby et al. 2009</td>
<td>Evidence of thrombophilia (all patients underwent full screening), poor ambulation, severe venous disease, pulmonary HTN, severe OSA, obesity hypoventilation</td>
<td>RYGB (NS)</td>
<td>IVCF</td>
<td>162</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.63%</td>
<td>NS</td>
<td>3.13% (Screened)</td>
<td>NS</td>
<td>SCD, S/C Heparin 5000-7500U2 TDS.</td>
<td>No</td>
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<tr>
<td>Variable</td>
<td>RYGB (NS)</td>
<td>No IVCF</td>
<td>NS</td>
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<td>NS</td>
<td>2.94%</td>
<td>2.35% (Screened)</td>
<td>0.61%</td>
<td>NS</td>
<td>SCC, S/C Heparin 5000-7500U2 TDS</td>
<td>No</td>
<td>6 weeks</td>
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<tr>
<td>Li et al. 2012</td>
<td>Retrospective Cohort Comparative Database Review</td>
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<tr>
<td>LRYGB 179 (55.59%); Open RYGB 69 (21.43%); LGB 74 (22.98); 0</td>
<td>322</td>
<td>47</td>
<td>31.4</td>
<td>45.3</td>
<td>0.31%</td>
<td>0.93%</td>
<td>NS</td>
<td>0.31%</td>
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<td>NS</td>
<td>90 days</td>
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<tr>
<td>LRYGB 51,648 (53.35%); Open RYGB 45,800 (4.73%); LGB 40,538 (41.88%); Open GB 40 (0.04%)</td>
<td>No IVCF</td>
<td>9680</td>
<td>46</td>
<td>21.1</td>
<td>44.5</td>
<td>0.12%</td>
<td>0.12%</td>
<td>NS</td>
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<td>Variable</td>
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<td>Procedure</td>
<td>No. Patients</td>
<td>Age (Mean)</td>
<td>Male Sex %</td>
<td>BMI (Kg/m²)</td>
<td>Time to Filter Retrieval</td>
<td>Mean Operative time (minutes)</td>
<td>PE %</td>
<td>DVT %</td>
<td>PE related mortality</td>
<td>Mean (StANDARD Error) Additional Operating Time (minutes)</td>
<td>Thromboprophylaxis</td>
<td>Anticoagulation post-discharge</td>
<td>Follow-Up</td>
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<td><em>Gargiulo et al. 2010</em></td>
<td>Open RYGB</td>
<td>58</td>
<td>37</td>
<td>38</td>
<td>62</td>
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<td>0</td>
<td>3.40% (Screened)</td>
<td>0</td>
<td>20 +/- 5</td>
<td>SCD, Subcut Heparin 50u/kg pre op and post-op BD until ambulating 4hrs per day</td>
<td>NS</td>
<td>65 +/- 12mths</td>
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<tr>
<td>Kardys et al. 2008</td>
<td>LRYGB (8); Open RYGB (23)</td>
<td>31</td>
<td>43</td>
<td>8.3</td>
<td>71</td>
<td>NS</td>
<td>NS</td>
<td>6.40%</td>
<td>3.10%</td>
<td>0</td>
<td>NS</td>
<td>Pre-op: 5000u Heparin. Post-op: SCD, Enoxaparin 40mg BD Day 1, Enoxaparin for 2/52 if BMI&gt;60</td>
<td>Only if BMI&gt;60</td>
<td>262 +/- 38 days</td>
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<tr>
<td>Trigilio Black et al. 2007</td>
<td>LRYGB (14/41); Open RYGB (20/41); LGB (1); LSG (5/41); Open Jej-ileal bypass (1)</td>
<td>41</td>
<td>47.3</td>
<td>29.2</td>
<td>64.2</td>
<td>Not retrieved, by design</td>
<td>172.3 +/- 45</td>
<td>0</td>
<td>2.40%</td>
<td>0</td>
<td>34.3 +/- 9</td>
<td>Pre-op: LMWH, Post Op Lovenox 30mg S/C</td>
<td>No</td>
<td>Mean 16 months</td>
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<tr>
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<td>Procedure</td>
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<td>BMI</td>
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<td>Post-op Heparin</td>
<td>Risk Factor</td>
<td>Anticoagulation Details</td>
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<tr>
<td>Halmi et al. 2007</td>
<td>Mini’ RYGB (Open)</td>
<td>27</td>
<td>47</td>
<td>33.3</td>
<td>18-21 days</td>
<td>0</td>
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<td>Brent et al. 2005</td>
<td>LRYGB=11; Open RYGB=3</td>
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<td>49.1</td>
<td>14.3</td>
<td>56.5</td>
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<td>Piano et al. 2007</td>
<td>LRYGB or DS (NS)</td>
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<td>43</td>
<td>17</td>
<td>61</td>
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<td>0</td>
<td>(Screened)</td>
<td>NS</td>
<td>SC, SCD, Intraoop Heparin infusion 500U/Hr in BMI&lt;50, 750U/Hr BMI&gt;50. LMWH 1 week post-op. Yes for 1 week</td>
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<td>Schuster et al. 2007</td>
<td>RYGB (NS)</td>
<td>24</td>
<td>50</td>
<td>58</td>
<td>57</td>
<td>NS</td>
<td>4.20%</td>
<td>20.80%</td>
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<td>Vaziri et al. 2011</td>
<td>LRYGB</td>
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<td>0</td>
<td>(Screened)</td>
<td>0</td>
<td>5000U S/C Hep Preop, Post-op: S/C Heparin TDS, SCD. No</td>
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Mean FU: 204+/−160 days
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<th>Age</th>
<th>Gender</th>
<th>Median Age</th>
<th>BMI</th>
<th>Weight</th>
<th>% Loss</th>
<th>Follow-up</th>
<th>Anticoagulant Protocol</th>
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</thead>
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<tr>
<td>Escalante et al. 2008</td>
<td>LRYGB</td>
<td>24</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>93</td>
<td>0</td>
<td>NS</td>
<td>5000u SCH on induction, repeated 8hrly for initial 24hrs post-op, then 40mg enoxaparin sodium BD until discharge. SCD intraoperatively and until patient fully mobile. No 2, 8, 12, 24 and 52 weeks</td>
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<tr>
<td>Chan et al. 2013</td>
<td>NS - Lap</td>
<td>5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>5-6 weeks</td>
<td>0</td>
<td>0</td>
<td>Tinzaparin 50 U/kg/40-80 mg Enoxaparin (dose according to weight) OD 1 day before surgery 2 weeks post surgery. SCD. Yes for 2 weeks NS</td>
</tr>
<tr>
<td>Carmody et al. 2006</td>
<td>Various</td>
<td>145</td>
<td>47</td>
<td>NS</td>
<td>57</td>
<td>NS</td>
<td>NS</td>
<td>2.10%</td>
<td>NS</td>
<td>40mg Enoxaparin OD. No NS</td>
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<tr>
<td>Vaziri et al. 2009</td>
<td>LRYGB (16), LAGB (9), Open RYGB (4)</td>
<td>29</td>
<td>49</td>
<td>41</td>
<td>49</td>
<td>NS</td>
<td>165+-/65</td>
<td>0</td>
<td>20.70% (Screened)</td>
<td>5000U unfractionated heparin S/C pre-op then TDS post-op, SCD until ambulatory. No 16+/-18 days</td>
</tr>
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</table>

SCD: Superior Cervical Dissection
LRYGB: Laparoscopic Roux-en-Y Gastric Bypass
LAGB: Laparoscopic Adjustable Gastric Banding
RYGB: Roux-en-Y Gastric Bypass
<table>
<thead>
<tr>
<th>Procedure</th>
<th>DVT (Screened)</th>
<th>PE</th>
<th>PE related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic Roux-en-Y Gastric Bypass $^{30,34}$</td>
<td>7.0% (4/57 patients)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Open Roux-en-Y Gastric Bypass $^{23,34}$</td>
<td>6.7% (4/60 patients)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Reference</td>
<td>Type of IVC Filter</td>
<td>Device related Complications</td>
<td>Technical failure to retrieve</td>
</tr>
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<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Gargiulo et al. 2010</td>
<td>TrapEase=35, Simon-Nitinol=9, Greenfield=2, Bard Recovery=12</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Kardys et al. 2008</td>
<td>NS</td>
<td>6.4% (Malposition)</td>
<td>NS</td>
</tr>
<tr>
<td>Trigilio Black et al. 2007</td>
<td>9 Optease (retrievable); 31 Greenfield (non-retrievable); 1 Gunther-Tulip (retrievable)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Halmi et al. 2007</td>
<td>Gunther Tulip Cook</td>
<td>11.1% (Haematoma (2), cellulitis (1))</td>
<td>0</td>
</tr>
<tr>
<td>Brent Keeling et al. 2005</td>
<td>13 Greenfield, 1 VenaTech LGM</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Piano et al. 2007</td>
<td>Gunther Tulip Cook</td>
<td>0</td>
<td>9.3% (5/54 Filter Tilt)</td>
</tr>
<tr>
<td>Schuster et al. 2007</td>
<td>Gunther Tulip Cook</td>
<td>4% (1 PE from thrombus in filter)</td>
<td>4%</td>
</tr>
<tr>
<td>Vaziri et al. 2011</td>
<td>Gunther Tulip/Bard G2</td>
<td>4.8% (pain, malposition)</td>
<td>0</td>
</tr>
<tr>
<td>Escalante-Tattersfield et al. 2008</td>
<td>NS</td>
<td>4.2% (Haematoma)</td>
<td>NS</td>
</tr>
<tr>
<td>Chan et al. 2013</td>
<td>NS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carmody et al. 2006</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Vaziri 2009 et al.</td>
<td>Optease</td>
<td>3.4% (DVT at device insertion site)</td>
<td>3.40%</td>
</tr>
</tbody>
</table>
Pubmed searched using terms
'bariatric filter'
'gastric bypass filter'
(n = 68)

Records after duplicates removed
(n = 46)

Titles screened
(n = 46)

Records excluded
(n = 5, No IVCF outcomes data)

Abstracts screened
(n = 41)

Full-text articles excluded,
(n = 6, no relevant outcomes data)

Full-text articles assessed for eligibility
(n = 35)

Studies included in qualitative synthesis
(n = 18)

Full-text articles excluded,
(n = 17, no relevant outcomes data)
The Disparate Management of Superficial Venous Thrombosis in Primary and Secondary Care
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Table Count: 2
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Key Words:
Superficial venous disease, venous thromboembolism, primary care, secondary care

Running Title
SVT Management in primary and secondary care
The Disparate Management of Superficial Venous Thrombosis in Primary and Secondary Care
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Abstract:

Objectives
Superficial Venous Thrombosis (SVT) is common and traditionally considered a benign condition requiring only symptomatic treatment. Recent evidence however advocates more aggressive management. Extensive guidance is available but actual practice is unknown. This study aimed to assess the management of SVT by General Practitioners (GPs; primary care physicians) and Vascular Surgeons.

Methods
A 19 question validated electronic survey was created and circulated by e-mail to GPs and Vascular Surgeons in the United Kingdom. The survey evaluated presentation, investigation and treatment of SVT.

Results
369 surveys were returned from 197 vascular surgeons and 172 GPs. Most clinicians saw < 20 cases a year, with 40% of clinicians not performing any investigations. Venous duplex was the investigation of choice in over 55%. Treatment with anti-inflammatory drugs was widespread, but anticoagulation and compression were seldom prescribed. Follow-up and treatment duration were disparate.

Discussion
The management of SVT varies widely despite good levels of evidence and guidance. Investigation and treatment of SVT shows marked differences both between and within groups. Improvements in education are required to optimise the treatment pathway and advance patient care.
The Disparate Management of Superficial Venous Thrombosis in Primary and Secondary Care
Tristan R A Lane*, Kaji Sritharan*, J Ros Herbert§, Ian J Franklin*, Alun H Davies*

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Introduction
Superficial venous thrombophlebitis or more correctly superficial venous thrombosis (SVT) is thrombus formation within a superficial vein, associated with inflammation within the surrounding tissue. It typically presents with pain, tenderness, induration, and/or erythema extending along the vein. In addition, there is often a palpable cord which suggests the presence of thrombus. SVT is a common disease that has traditionally been regarded as benign and until recently, its pathophysiology has been poorly characterised.

It has an estimated prevalence of between 3% and 11% [1-7], and thus it is more common than deep vein thrombosis (DVT) [8]. Moreover, SVT has been shown to be a significant risk factor in the development of DVT and consequently PE with an Odds Ratio of 4.3 [9,10]. Between 6% and 44% of patients with a SVT have a concomitant DVT [2], and up to 30% have a concomitant asymptomatic pulmonary emboli (PE) [10,11]; 2% to 13% have a symptomatic PE.

Despite this association, the literature in the past has advocated conservative management [12]. This is compounded by the belief that treating varicose veins is of low value [13]. Varicose veins are a risk factor for SVT and an independent risk factor for DVT [7,8].

Clear guidance regarding the management of SVT is provided by a recently revised Cochrane review [3,5,14]. Despite this, post-graduate teaching on the management of SVT is anecdotally sparse. This may be because SVT falls between the stools of multiple specialities which include vascular surgery, medicine and general practice.

The aim of our study was to assess the investigation and management of SVT by both GPs and vascular surgeons in the UK.
Methods

A 19 question electronic survey was created which assessed SVT management, investigation and treatment pathways (Appendix 1). This did not require Ethical Approval as it is termed Service Evaluation by the United Kingdom National Research Ethics Service.

The questionnaire was tested and validated for content and validity by GPs and vascular surgeons, with internal, external and independent assessors as previously described [15-17].

In England there are approximately 34,101 GPs and 456 members of the Vascular Society in the UK. 456 Consultant Vascular Surgeons, 290 vascular trainees and 1,000 GPs (including GP Registrars) were contacted.

Invitations to complete the survey were sent via e-mail to potential participants (url = http://kwiksveys.com?u=Thrombophlebitis and subsequently url = http://freeonlinesurveys.com/s.asp?id=hqi8rbxblw7i8h387978) using local and national mailing lists.

Responses were collated by the survey server (KwikSurveys, Dover, UK and FreeOnlineSurveys, UK) over a 6-month period and results were analysed using Microsoft Excel 2011 (Microsoft Corporation, Redmond, USA) and IBM SPSS (v21, IBM Software, Armonk, USA).

Results

369 completed responses have been received, from 165 vascular consultants (36% response rate), 172 GPs or GP trainees (17% response rate) and 32 vascular trainees (11% response rate).

Most clinicians see fewer than 20 cases per year of SVT, with vascular surgeons seeing more cases compared to their GP colleagues (See Figure 1).

The overwhelming majority of clinicians (though significantly different proportions, p=0.007) believed there to be an association between SVT and DVT. There was however a disparity between this view and the treatment offered – Table 1. The belief of a relationship between
SVT and other conditions is also varied. Clinicians consistently across all groups felt there was an association between SVT and varicose veins. Beliefs of a relationship between SVT and PE, Deep Venous Incompetence, Cancer or Infection were significantly different between GPs and VCs.

The majority of clinicians performed a venous duplex as their main investigation, but 40% performed no investigations at all (See Figure 2).

A large disparity was shown in the treatment offered for patients with SVT. Almost 10% offered no treatment at all for this painful and potentially serious condition. Moreover, complete bed rest was advocated by a few clinicians for this thrombotic disease. The majority opted for non-steroidal anti-inflammatory drugs (NSAIDs) but only 25% treated with anticoagulation. The duration of anticoagulation was widely disparate as \( p < 0.001 \). Even fewer (<20%) prescribed compression hosiery (See Figure 3).

Finally, the approach to follow-up was variable \( p < 0.001 \) and inconsistent as shown in Figures 4, with 23.8% of GPs and 13.3% of VCs providing no follow-up at all; and 57% of GPs and 39% of VCs providing follow-up in select cases only.

**Discussion**

This study demonstrates that the management of SVT is disparate despite good level 2 evidence indicating that NSAIDs, LMWH and compression hosiery are effective and reduce the incidence of DVT [5]. This is likely to be due to the continued misconception amongst GPs and VCs that SVT is a benign self-limiting disease [18].

The number of cases seen per year (on average <20) appears at odds to the estimated 3-11% reported prevalence of SVT. This should equate to 200-700 cases per year given the average list size of a GP, and 7,500 cases per year for a VC [2,19]. The discrepancy in prevalence and cases seen, may be due to failure of these patients to present to their doctor, or more likely due to poor recognition or a low level of understanding of both the condition and its relative importance in the context of venous thromboembolism.
Whilst the majority of clinicians believed there to be an association between SVT and DVT, a fifth of all clinicians believed there to be no association at all despite the increasing literature base to the contrary [2,6]. Moreover, the majority of clinicians (40% GPs vs 57% VCs) who did believe in an association between DVT and SVT, significantly underestimated that risk. This once again highlights the need for focussed postgraduate education into this condition.

Venous disease has been shown to have a low level of public exposure in previous work from the our unit, and SVT is likely to suffer from a similar under-exposure [17]. A concerning feature from our study, is the low level usage of compression hosiery which is a simple, symptom relieving measure that is poorly utilised. Moreover, the use of compression hosiery in SVT has been shown to significantly reduce SVT progression and is associated with lower rates of VTE.

Antibiotics were prescribed by approximately 20% of clinicians. The use of antibiotics for the treatment of a sterile inflammation leads to no symptomatic improvement for the patient, misdiagnosis and potentially antibiotic resistance [20]. However, their use is perhaps not surprising given the belief held by 72% of GPs and 48% of VCs, of an association between infection and SVT.

SVT and DVT share similar predisposing factors, once again suggesting a similar or linked pathophysiology. Despite this, less than 20% of clinicians performed a thrombophilia screen as part of their work-up. In addition, a third of clinicians did not perform any imaging at presentation. Baseline imaging would have usefully excluded a concomitant DVT and allow for objective assessment of thrombus propagation.

No national guidelines exist for the management of SVT, however robust level 1 and 2 evidence exist to guide clinicians. The goal of management is not only geared towards symptom control, but also aimed at prevention of thrombus propagation, reduction in SVT recurrence and venous thromboembolism (VTE) prevention. The latter is the key driver for more aggressive and standardised treatment [5,21]. The use of guidelines to help construct an optimal patient pathway should in theory be of benefit, but evidence from other conditions has shown that guideline formulation does not lead to significant changes or improvements in practice in both a first and third world setting [17,22-28]. Education regarding the full gamut of VTE and venous
disease would provide holistic improvements in treatment pathways, however, this would be
costly and time consuming, and would be difficult to achieve. Intensive methods in
cardiovascular medicine have led to improved guideline adherence over a period of 9 years [29].

**Conclusion**

The treatment and understanding of SVT is disparate and unclear in the UK. If the potentially
devastating thromboembolic sequelae of SVT are to be avoided, better awareness of the
pathophysiology of SVT and education regarding its management is mandatory. The creation of
Guidelines and the development of clearer referral pathways would both give SVT a higher
clinical profile and over time improve patient care.

**Competing Interests:**
All authors declare: no conflict of interest.

**Acknowledgements:**
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Research Centre based at Imperial College Health-care NHS Trust and Imperial College London.
The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the
Department of Health.

**Contributions:**
AHD, KS and TRAL conceived the study.
AHD, KS, JRH, TRAL and IJF collected the data and analysed the data.
TRAL and KS wrote the first draft.
TRAL, KS, JRH, IJF and AHD reviewed, amended and agreed the final draft.

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Appendix 1:
Superficial Venous Thrombophlebitis Survey 2012 (File SVT Survey 2012.pdf)
Table 1: Is there an association between SVT and DVT, what percentage of patients suffer from DVT and association between SVT and other conditions split amongst speciality

<table>
<thead>
<tr>
<th>Are you a:</th>
<th>GP</th>
<th>Vascular Consultant</th>
<th>Vascular Trainee</th>
<th>GP Trainee</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Column N %</td>
<td>Count</td>
<td>Column N %</td>
<td>Count</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and DVT?</td>
<td>Yes</td>
<td>126</td>
<td>66%</td>
<td>122</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24</td>
<td>33%</td>
<td>23</td>
<td>30.3%</td>
</tr>
<tr>
<td>If yes, what percentage of patients with SVT in your experience have a co-existing DVT at presentation?</td>
<td>&lt;=5%</td>
<td>66</td>
<td>42%</td>
<td>94</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>&gt;5%</td>
<td>20</td>
<td>40</td>
<td>29</td>
<td>17.6%</td>
</tr>
<tr>
<td>If yes, what percentage of patients with SVT in your experience will develop a DVT at 3 months?</td>
<td>&lt;=10%</td>
<td>12</td>
<td>33%</td>
<td>11</td>
<td>29.7%</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>15</td>
<td>33%</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and Pulmonary Embolus (PE)?</td>
<td>No</td>
<td>12</td>
<td>9%</td>
<td>11</td>
<td>9.2%</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>45</td>
<td>25%</td>
<td>21</td>
<td>17.3%</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and Valvular Versa?</td>
<td>Yes</td>
<td>158</td>
<td>97%</td>
<td>154</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>3%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and Deep venous incompetence?</td>
<td>Yes</td>
<td>158</td>
<td>97%</td>
<td>154</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>3%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and Cancer?</td>
<td>Yes</td>
<td>26</td>
<td>64%</td>
<td>158</td>
<td>95.6%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>152</td>
<td>36%</td>
<td>27</td>
<td>4.4%</td>
</tr>
<tr>
<td>Do you think there is an association between SVT and Infection?</td>
<td>Yes</td>
<td>118</td>
<td>72%</td>
<td>79</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>46</td>
<td>28%</td>
<td>53</td>
<td>51%</td>
</tr>
<tr>
<td>Are you a:</td>
<td>GP</td>
<td>Vascular Consultant</td>
<td>Vascular Trainee</td>
<td>GP Trainee</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----</td>
<td>---------------------</td>
<td>------------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>Column N%</td>
<td>Count</td>
<td>Column N%</td>
<td>Count</td>
</tr>
<tr>
<td>How do you follow-up patients with SVT?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Follow-Up</td>
<td>39</td>
<td>23.8%</td>
<td>22</td>
<td>13.3%</td>
<td>3</td>
</tr>
<tr>
<td>Weekly</td>
<td>23</td>
<td>14.0%</td>
<td>11</td>
<td>6.7%</td>
<td>4</td>
</tr>
<tr>
<td>Fortnightly</td>
<td>7</td>
<td>4.3%</td>
<td>13</td>
<td>7.9%</td>
<td>6</td>
</tr>
<tr>
<td>Monthly</td>
<td>1</td>
<td>0.6%</td>
<td>3</td>
<td>20.6%</td>
<td>6</td>
</tr>
<tr>
<td>6-12 Weeks</td>
<td>0</td>
<td>0.0%</td>
<td>20</td>
<td>12.1%</td>
<td>2</td>
</tr>
<tr>
<td>Follow-up only in selected cases</td>
<td>94</td>
<td>57%</td>
<td>65</td>
<td>39%</td>
<td>11</td>
</tr>
<tr>
<td>Yes - Venous Duplex</td>
<td>15</td>
<td>9.1%</td>
<td>104</td>
<td>63%</td>
<td>23</td>
</tr>
<tr>
<td>No - No Imaging</td>
<td>87</td>
<td>53%</td>
<td>30</td>
<td>18.2%</td>
<td>4</td>
</tr>
<tr>
<td>No - No Follow-Up</td>
<td>55</td>
<td>33.5%</td>
<td>23</td>
<td>13.9%</td>
<td>4</td>
</tr>
<tr>
<td>Depends on Clinical Context</td>
<td>7</td>
<td>4.3%</td>
<td>8</td>
<td>4.8%</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Follow-up for SVT table
Are you a:
- GP
- Vascular Consultant

How many patients do you see each year with superficial thrombophlebitis?

150x129mm (72 x 72 DPI)
Figure 4: Duration of LMWH prescribed for SVT
Retrograde mechanochemical ablation of the small saphenous vein for the treatment of a venous ulcer

Hayley M Moore, Tristan RA Lane, Ian J Franklin and Alun H Davies

Abstract

We present the first case of retrograde ablation of the small saphenous vein to treat active venous ulceration. A 73-year-old gentleman with complicated varicose veins of the left leg and a non-healing venous ulcer despite previous successful endovenous treatment to his left great saphenous vein underwent mechanochemical ablation of his small saphenous vein with the ClariVein® system, under local anaesthetic, using a retrograde cannulation technique. Post-operatively the patient had improved symptomatically and the ulcer size had reduced. This report highlights that patients with small saphenous vein incompetence and active ulceration can be treated successfully with retrograde mechanochemical ablation.

Keywords

ClariVein, varicose veins, endovenous ablation, mechanochemical ablation, ulcer

Introduction

Venous ulceration is generally treated with compression therapy, but work by Gohel et al.1 showed that surgical intervention was effective at preventing ulcer recurrence. More recent evidence from Kulkarni et al.2 and Pang et al.3 demonstrated that ultrasound-guided foam sclerotherapy improved ulcer healing rates compared to historical data. Mechanochemical superficial vein ablation using the ClariVein® (Vascular Insights LLC of Madison, CT, USA) catheter does not require tumescent anaesthesia and has good treatment outcomes.4 Twenty two percent of patients with venous ulceration have small saphenous vein (SSV) incompetence.5 In the presence of active ulceration, open surgery and distal endovenous ablation techniques requiring cannulation and tumescent anaesthesia may risk the introduction of infection. The use of ultrasound-guided foam sclerotherapy has been described, however ablation rates are variable.2,6-8

In this report, we present the first case of retrograde ablation of the SSV to treat active venous ulceration.

Case report

A 73-year-old gentleman presented to the clinic at Charing Cross Hospital with complicated varicose veins of the left leg, with a non-healing 4-cm diameter venous ulcer present for more than 1 year. He had a Clinical Etiological Anatomical Pathological (CEAP) score of C6bS Ep Asd Pr, an Aberdeen Varicose Vein Questionnaire (AVVQ) score of 23.85,9 an EQ-5D 0.666, EQ-VAS 7010 and a VCSS of 16.11 He had a history of type II diabetes mellitus and a past history of prostate cancer, which had been treated with radiotherapy. A venous duplex ultrasound revealed refluxing (>0.5 seconds reflux time) disease of both the great saphenous vein (GSV) and SSV as well as an incompetent deep venous system. The GSV was 7.2 millimetres in maximal diameter and the SSV maximal diameter was 12 millimetres in maximal diameter. He underwent endovenous treatment to his left GSV, following which his pain improved and the size of the ulcer reduced from 4 cm to 2 cm diameter. However, after 6 months of adequate compression with the three-layer bandaging technique, the ulcer had failed to fully heal and his symptoms worsened. A repeat venous duplex scan...
demonstrated occlusion of the GSV and persisting reflux in the SSV and the femoral and popliteal veins. The patient underwent mechanochemical ablation of his SSV under local anaesthetic in August 2012. The procedure was as follows:

The SSV was cannulated under ultrasound guidance at the SSV fascial curve in the popliteal fossa and the ClariVein\textsuperscript{\textregistered}/C213 catheter was passed distally using standard Seldinger technique in a prone reverse Trendelenberg position. The patient angle was then flattened. Using standard mechanochemical ablation technique\textsuperscript{4} and 4 ml 2\% Fibrovein\textsuperscript{\textregistered} (sodium tetradecyl sulphate), 20 cm of the SSV was ablated. The puncture site was closed with a Steri-Strip dressing (3M, St. Paul, Minn) and a cannulation site plaster (Mepore; Mölnlycke Health Care, Gothenburg, Sweden) without sutures. A schematic of the technique is demonstrated by Figure 1, with a clinical photo of the equipment in Figure 2. Adequate compression with the three-layer bandaging technique was continued until ulcer healing.

At 3-month follow up, subjectively, he had experienced no post-operative pain or inflammation. The patient had improved symptomatically, increasing his daily activities due to a reduction in the pain from his ulcer. The ulcer size had reduced to 3 mm with evidence of granulating tissue at the base. His AVVQ had not improved – 24.82 (5\% deterioration) – however, the EQ-5D 0.735 (10\% improvement) and EQ-VAS of 80 (14\% improvement) were both markedly improved and his VCSS score was improved to 12 (25\% improvement). Repeat venous duplex ultrasound at 3 months showed successful SSV occlusion and a competent deep venous system.

**Figure 1.** Schematic of retrograde ClariVein procedure.

**Figure 2.** Clinical picture of ClariVein mechanochemical ablation device in use.
Discussion

In this report, we demonstrate that retrograde venous ablation using a non-thermal modality is feasible with a catheter-based technique such as the ClariVein® device. A mechanochemical catheter device allows distal treatment without the risk of nerve damage due to thermal injury. This retrograde technique ensures that the cannulation site is distant from the site of ulceration, which may reduce the risk of infection, with the added benefit that no additional skin punctures are required for tumescent anaesthesia. However, the current rate of infection during ablation runs at 0.3% and so the improvement will be minor. Historic infection rates of 4–8% have been reported in the context of general anaesthetic with simultaneous adjunctive phlebectomies and the one notable report of sepsis after endovenous treatment was treatment of an ulcer with endovenous ablation and phlebectomies under general anaesthetic.

The segment of vein underlying the area of ulceration can also be treated using this technique, meaning a longer segment of vein can be ablated. The technique could also be applied to treat both the distal GSV in the presence of ulcerations and in the future may allow precise access to problematic incompetent veins extending under active ulceration.

Further patients have also been treated with this approach with good closure rates and improvements in symptomatology and ulcer status. The normalisation of deep venous reflux on treatment of superficial reflux has been previously described after surgery.

Use of the ClariVein® device for retrograde treatment has a good margin of safety as the amount of liquid sclerosant used is small and the active treatment area is 2 cm distant to the cannulation site to prevent skin damage. Coupled with a vein in spasm and a catheter impeding flow, proximal passage of sclerosant into the deep venous system before deactivation by blood is highly unlikely.

Conclusion

This report highlights the expanding possibilities for treatment of venous ulceration. Patients with SSV incompetence and active ulceration can be treated successfully with retrograde mechanochemical ablation whilst maintaining sterility.

Conflict of interest

None declared

Funding

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References


Socio-economic impact of endovenous thermal ablation techniques

Damian Kelleher · Tristan R. A. Lane · Ian J Franklin · Alun H Davies

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Abstract Varicose veins are common and cause extensive morbidity; however, the value of treatment is under-appreciated. Many procedures allow the treatment of varicose veins with minimal cost and extensive literature supporting differing minimally invasive approaches. In this article, we investigate the current literature regarding treatment options, clinical outcome and the cost-benefit economics associated with varicose vein treatment. The practice of defining clinical outcome with quality of life (QOL) assessment is explained to provide valid concepts of treatment success beyond occlusion rates.

Keywords QOL · QALY · Varicose veins · Cost-effectiveness

Varicose veins are an extremely common and affect over 25% of the population with the majority of patients presenting with varicose veins being young and otherwise systemically well [1, 2].

There are widespread misconceptions held by both the general public and primary care physicians with regards to varicose veins; the public fear that there is an increased likelihood of DVT, or that chronic venous changes are a common cause of limb amputation [3], whilst primary care physicians are often mistaken in believing that varicose veins are merely a cosmetic concern and so, leading to a reduced rate of referral for treatment, and even the skin changes of chronic venous insufficiency (a precursor to ulceration) are often deemed inconsequential [4, 5]. Additionally, knowledge on current treatment methods in the primary care sector is poor, leading to denial of referral for treatable patients [4, 6].

Health-care costs are spiralling; in the UK, they have doubled over the last decade to £126 billion annually [7], with a similar picture seen in the USA where spending is now $1.2 trillion/year [8], equivalent to over 8% GDP, a value seen throughout Europe as well [9, 10].

Whilst costs and value for money have always had a role in the decision-making processes, these increasing financial pressures at the hospital, regional and national levels have caused hospital managers to look at ways to cut costs at all levels. Varicose veins have been labelled as a “procedure of low clinical value” due to the low mortality rates associated with this benign disease, leading to a reduced rate of referral for treatment [5]. Varicose vein surgery in the National Health Service is an obvious target for exclusion to reduce costs, as some may see this surgery as not essential.

Varicose vein assessment

Varicose vein symptoms are often vague and non-specific but include aching, discomfort, pruritus and muscle cramps [11]; however, there are more obvious and objective symptoms which include varicose eczema, pigmentation, bleeding and ulceration [12]. There is a wealth of evidence which demonstrates that venous disease significantly impairs quality of life. Patients with varicose veins have been shown to have lower scores than UK population norms for domains relating to pain and physical function and an increased prevalence of depression [13–19].

There are many definitions of quality of life and as many ways to measure it, including instruments completed by the patient or physician. For a quality of life instrument to be a valuable measure of what is intended, it must be reliable and valid, and probably most importantly, it must also be practical.
Quality of life instruments include both generic and disease-specific surveys. Generic surveys assess global states of well-being and provide a subjective measure of treatment efficacy, whilst disease-specific surveys focus on elements associated with particular disease processes and treatment effects [20–22]. These instruments are helpful when attempting to determine cost-effectiveness in an era of limited resources.

Patient reported outcome measures are intended to provide a direct measure of the success of medical interventions, as judged by patients, to enable clinical teams to benchmark their performance and research the success of different treatment options. The results of the returned questionnaires will be available to the public on the NHS choices website allowing comparison between centres from a patient perspective [23–28].

CEAP classification

Varicose veins have often not been adequately defined and have variously been described as being visible subcutaneous veins, to dilated palpable subcutaneous veins generally larger than 3 mm in the upright position. Due to this lack of consensus in the reporting and classification in the published literature, the clinical severity, aetiology, anatomy and pathophysiology (CEAP) classification for chronic venous disorders (CVD) was developed in 1994 by an international ad hoc committee of the American Venous Forum, endorsed by the Society for Vascular Surgery, and this classification became incorporated into “Reporting Standards in Venous Disease” in 1995, with further refinements made to it in 2004 [29]. This classification has become universally adopted and so allows a direct comparison between studied modalities.

This is a clinician-implemented categorisation tool. The clinical component indicates disease severity, ranging from 0 points, for completely asymptomatic patients, up to 6 points for active ulcers. The etiologic component denotes the venous disease as congenital, primary or secondary in nature. The anatomic classification pinpoints the veins involved as superficial, deep or perforating. The pathophysiological classification identifies the presence of reflux in the superficial, communicating or deep systems, as well as the existence of outflow obstruction. The CEAP classification is doctor-driven and highlights the cause of the underlying venous abnormality; however, it is not sensitive enough to track progressive changes.

Venous Clinical Severity Score (VCSS)

The VCSS is a clinician-completed tool, which includes nine hallmarks of venous disease, each scored on a severity scale from 0 to 3. In order to generate a dynamic score, VCSS categories are scored individually. These include skin changes and pigmentation, inflammation and induration, and ulcers (including number, size and duration). In 2007, an international ad hoc working group was created to revise the VCSS to update the terminology, simplify the application and clarify ambiguities, which was completed in 2010 [30].

The value of the VCSS is its ease of use along with an emphasis on the most severe manifestations of venous disease which are likely to show the greatest response to therapy allowing tracking and quantification of improvement (or deterioration) [12].

Disease-specific assessment—Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ is a 13-question patient-completed survey addressing multiple elements of varicose vein disease, first developed in 1993 [31]. It is designed for patient self-completion with a timescale of 2 weeks.

Physical symptoms along with social issues, including pain, ankle oedema, ulcers, compression therapy use and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins. The questionnaire is scored from 0 (no effect) to 100 (severe effect).

Disease-specific assessment—Venous Insufficiency Epidemiological and Economic Study Quality of Life and Symptom Severity Questionnaires (VEINES-QOL/Sym)

The VEINES-QOL/Sym is a 26-question patient-completed survey developed in 2003, which addresses symptoms, daily life limitations, change in condition and psychological impact of the venous disease. Responses are rated on two-point to seven-point response scales of intensity, frequency or agreement. The time frame for questions is the previous 4 weeks. The raw scores are then translated into a standardised scale for comparison [32].

Disease-specific assessment—Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ)

The CIVIQ is a 20- or 14-question survey developed in 1996 and then refined in 2011 [33, 34], which again assesses patient-reported symptoms and the impact of chronic venous disease on quality of life. It has four principal domains and a maximum score of 100, with lower scores indicating a better quality of life.
Disease-specific assessment—Specific Quality of Life and Outcome Response—Venous (SQOR-V)

The SQOR-V is a 45-item survey for patient completion, which assesses physical and psychosomatic symptoms providing a score out of 100 for each category. Each item is scored from 1 to 5 and grouped into 1 of 5 subcategories with normalisation to a maximum score of 20 per subcategory. A quality of life due to venous disease improves the score decreases [35, 36].

Disease-specific assessment—Assessment of Burden in Chronic Venous Disease (ABC-V)

Recently developed, this 39-point survey assesses the burden of venous disease opposed as the specific quality of life due to venous disease. It has a scale of 0 (best)–90 (worst). The tool is aimed primarily at population scale assessment [37].

Generic assessment—Short Form Health Survey (SF-36, SF-12, SF-8)

A widely used and well-validated generic health quality of life assessment tool is the Short Form Health Survey (QualityMetric, Lincoln, RI, USA), developed over time with questions in physical and mental health. These two categories have been broken down into eight domains that include physical and social functioning, role limitations due to physical or emotional problems, mental health, pain, vitality and health perception. The survey generates a score ranging from 0 to 100, with higher scores indicating better general health perception with a time coverage of 4 weeks.

Generic assessment—EuroQOL 5 Domain (EQ-5D)

The EuroQOL 5 Domain survey (Euroqol, Rotterdam, The Netherlands) is an alternative validated patient-completed generic health quality of life questionnaire that measures mobility, self-care, usual activities, pain and anxiety domains at the time of questioning. The domains generate a unique quality of life outcome between −0.594 and 1, with 1 being perfect health.

It also provides a separate visual analogue scale (VAS) rendering of global health status, from 0 to 100, with higher scores indicating better health [21, 38].

Treatment of varicose veins

The treatment of patients with superficial venous reflux has changed in recent years following the widespread acceptance of minimally invasive, endovenous modalities including ultrasound-guided foam sclerotherapy (UGFS), radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) [6, 39]. Recent thermal and non-thermal modalities have emerged in the past 2 years including steam ablation, mechanochemical ablation (ClariVein) and pharmacological occlusion (Sapheon) [40–42]. All endovenous interventions are aimed at principally abolishing truncal reflux and then removing or occluding any incompetent varicosities. Many open techniques exist such as traditional sapheno-femoral ligation (crossectomy) with or without vein stripping [43], cryostripping [44, 45], varicosity avulsion (ASVAL) [46] and haemodynamic correction (CHIVA) [47]. Traditional open surgery remains the gold standard against which other modalities must be measured [6, 48, 49].

Endovenous ablation

In the past decade, the introduction of minimally invasive endovenous ablation therapy has revolutionised the treatment of varicose veins.

Endovenous laser ablation (EVLA) treatment is designed to cause thermal damage to the vein lining. During laser activation, light energy is transmitted through an optical fibre to the tip, usually producing a fine beam within the vein. This beam either exits the fibre at the end (end firing) or from the side of the fibre tip (radial firing).

Lasers used for EVLA may be either diodes or solid-state neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers and are available in a number of wavelengths (i.e. 810, 940, 941, 1,064, 1,320 and 1,470 nm) to target different absorbing molecules. Diode lasers are numerically the most common laser type.

The active material in a diode laser is a small semiconductor chip powered by injected electric current. Diode lasers have the advantage of being small in size, may be desktop- or trolley-mounted or stored in a cupboard, producing less heat than Nd:YAG and requiring minimal maintenance for reliable operation.

In a Nd:YAG laser, there are two main components. The active laser medium is a solid rod of the crystal YAG which has been “doped” or artificially contaminated by Nd. The laser medium is optically pumped with energy by a diode laser or flash tube, and the laser process amplifies the energy input by using the neodymium ion. The process causes significant heat production and therefore a cooling system is incorporated in the device. The laser is floor standing and so requires suitable storage space. Nd:YAG and diode lasers may also be used for other cosmetic, aesthetic or dermatological applications and cost-effectiveness will increase if they have multiple uses and if treatment is funded.
Diode lasers that produce infrared wavelengths are common as these wavelengths match an energy absorption peak in both oxyhaemoglobin and deoxyhaemoglobin. At these wavelengths, laser energy is preferentially absorbed by the blood, causing rapid heating and coagulation.

Laser energy at longer wavelengths is preferentially absorbed by water, so both water within the blood and the vein wall lining directly absorb the laser energy. The 1,470-nm diode laser has a reduced post-operative pain profile in one study [50], though previous studies have shown excellent results with the “old-fashioned” 810-nm laser [51].

EVLT delivers laser energy directly into the vein lumen, but the mechanism of action by which this brings about destruction of the vein wall is debated [52]. The laser energy causes the blood inside the vein to boil, and it may be the diffusion of the superheated steam bubbles to the vein wall that actually destroys the vein architecture [53]. Other authors argue that the heat generated by the steam bubbles is not sufficient to destroy the vein wall, and that this requires direct contact with the laser energy itself [54]. With either theory, the final common pathway is the same as the heating of the vein wall, resulting in collagen contraction and destruction of endothelium.

The use of lasers requires minor modifications to the room (fitting window blinds, warning notices), the wearing of safety glasses by all in the room, appointment of one of the team as laser protection supervisor, written safety procedures and safety training for all staff.

Radiofrequency ablation (RFA) uses electrical energy to heat the vein wall. The vein wall is exposed to high-frequency alternating current by direct contact of the catheter with the endothelium of the vein wall. Tissue destruction is precise with loss of vessel wall architecture and disintegration of the vessel. This technique also requires the injection of tumescent anaesthesia to minimise pain and reduce the risk of skin burns during the procedure.

Current RFA technology includes the VNUS ClosureFAST catheter and the Olympus Celon RFiTT catheter. Both require radiofrequency generators which are compact and portable.

- The VNUS ClosureFast catheter uses radiofrequency energy to achieve temperatures between 95 and 120 °C in a 7-cm-long heating element. The temperature is monitored by a thermocouple within the catheter tip.
- The Celon RFiTT catheter comprises two concentric bipolar electrodes, one at the tip and the other several millimetres down the catheter shaft. An electrical current at 470 kHz is conducted through the adjacent blood and vein wall. The generator monitors electrical impedance, which rises as the blood and the vein wall heat up to 85 °C. A continuous audible signal indicates that ablation is complete.

Extensive evidence is available to support the use of RFA, and indeed, direct comparisons between RFA and EVLA have resulted in the knowledge that RFA and EVLA have similar occlusion rates with RFA having a reduced side-effect profile [55–57].

Steam ablation is a new modality, currently in the early stages of development with few published studies. It utilises pressurised steam to thermally ablate the walls of the vein in a similar method to EVLA and RFA [41, 58].

Non-thermal techniques, such as mechanochemical ablation using the ClariVein device and pharmacological occlusion using the Sapheon device [40, 42], have recently come to prominence due to allowing treatment without tumescent anaesthesia. These devices are still in the early stages of clinical evaluation but show promising results and glimpses of the future.

Cost-effectiveness

Despite being one of the most commonly performed surgical procedures, few cost-effectiveness evaluations have been calculated.

Ratcliffe et al. conducted a randomised trial comparing open surgery with conservative management [59]. The surgical group was a heterogeneous collection of unilateral and bilateral procedures performed under general anaesthesia as a day case; the conservative group was treated with compression hosiery or bandaging. Not only did they demonstrate that open surgery was cost-effective using £20,000 QALY level, but a third of patients allocated to the conservative group dropped out to undergo surgery before the trial had finished.

This led to the development of the Randomised and Economic Assessment of Conservative and Therapeutic Interventions for Varicose Veins (REACTIV) study whose aim was to investigate the clinical and cost-effectiveness of varicose vein treatments [60].

Patients were split into three groups:

- **Group 1 (n = 34)** minor varicose veins below the knee without truncal reflux randomised to conservative or sclerotherapy treatment

- **Group 2 (n = 77)** moderate varicose veins below the knee with truncal reflux randomised to standard surgery or sclerotherapy treatment

- **Group 3 (n = 246)** significant varicose veins above and below the knee with truncal reflux randomised to conservative treatment or standard surgery

Once again, a significant number of patients allocated to a conservative management path became dissatisfied and dropped out of the study, so that they could undergo surgery.
Although numbers were small in some groups, this study further demonstrated the economic value in treating patients with symptomatic varicose veins.

Subramonia and Lees performed a study comparing surgery and RFA [61] which incorporated cost analysis into the design [62]. This study randomised 88 patients into RFA (VNUS ClosurePlus™) and conventional surgery (RFA 47, surgery 41) under general anaesthetic. RFA was found to be significantly more expensive (£1,276 vs. £559); however, the RFA group returned to work at an average of 1 week earlier (10 vs. 18.5 days), at a cost of £8.14 per additional working hour gained. However, this study utilised the VNUS ClosurePlus™ catheter, which is six times slower than the current VNUS ClosureFAST™ catheter (0.05 vs. 0.33 cm/s) and requires a constant pullback technique. The cost difference was due to increased theatre time (83.6 vs. 55.7 min, additional cost of £171.01) and catheter cost (£550).

Gohel et al. produced a Markov model to evaluate the cost-effectiveness of traditional and endovenous treatments for patients with unilateral primary great saphenous varicose veins [63]. Day-case open surgery under general anaesthetic or endovenous ablation using EVLA or RFA under local anaesthetic and foam sclerotherapy performed as an outpatient were shown to be the most likely cost-effective treatment strategies for patients with primary unilateral GSV reflux requiring treatment. This is supported by a study in the USA [64]. It should be expected that bilateral treatment and open surgery under local anaesthetic would also be cost-effective.

A recent work by Rasmussen et al. showed equivalence between all available modalities in a direct comparison trial of 580 legs [56]—125 patients were treated with open surgery, RFA, EVLA and UGFS. All procedures were under local anaesthetic, and treatment time was 19–32 min. RFA was shown to be associated with less post-operative pain leading to a faster return to work and therefore a better cost-effectiveness analysis compared to open surgery or laser ablation. Catheter costs were set at £307 for EVLA and £371 for RFA. Two separate lasers were used, 14 % 980 nm and 86 % 1,470 nm. Foam sclerotherapy remained the cheapest option but was associated with a significantly higher recurrence rate at 1 year (16 vs. 5–6 %).

Overall, this trial suggests that all modalities of venous intervention have comparable efficacy and cost-effectiveness. Importantly, the study allows a direct comparison of the 1,470-nm laser with VNUS ClosureFAST, as though there were two separate wavelengths used, the vast majority of laser patients were treated with the 1,470-nm laser. Similar efficacy profiles were demonstrated, but RFA had a reduced post-operative pain profile, allowing earlier return to work.

Conclusion

Endothermal ablation has enabled clinicians to provide easy access to treatment that improves quality of life and reduces the societal and personal burden of venous disease. Minimally invasive treatment with endothermal techniques results in high-quality treatment at low cost. Surely, this is the way of the future. Further studies using advancing technology will no doubt confirm this position.

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Management of chronic venous disease by primary care

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Abstract

Objective: To assess the patterns of referral for chronic venous disease (CVD).

Method: General practitioners (GPs) were invited by an email to complete a validated online survey evaluating the referral and community management of CVD.

Results: A total of 138 participants were recruited. Most GPs (85%) saw fewer than 50 patients with CVD a year. Thirty-one percent were aware of National Institute for Clinical Excellence referral guidelines for CVD and 36% were aware of and agreed with local referral guidelines. Eleven percent were aware of clinical venous scoring systems. Sixty-three percent believed mild CVD would progress and 84% believed treatment would improve the quality of life. Sixteen referred C3 disease, 43% C4, 37% C5 and 65% C6 disease. Forty-one percent would refer on request. Pain symptoms increased referral in C2 disease. Endothermal ablation was believed available to 33% and traditional stripping to 62% and 27% were unaware of the treatment options. Forty-five percent were happy to provide postoperative care.

Conclusions: Despite national guidelines, the management of CVD in the UK is variable.

Keywords: varicose veins; referral patterns; primary care; chronic venous disease

Introduction

Chronic venous disease (CVD) is extremely common, affecting 25–50% of the population.1–3 It is associated with a high level of morbidity and socioeconomic cost, and accounts for 2% of the National Health Service (NHS) budget per year.4 Ulceration is the endpoint of venous disease and alone consumes 1% of the NHS budget. Varicose vein intervention is common and over 37,000 treatments are performed each year in the NHS.5

Symptoms from varicose veins can vary widely; however, significant swelling, prominent varicocities, itching and pain are common.6 The treatment of varicose veins has advanced considerably in the past 15 years with the advent of endovenous ablation, regional or local anaesthetic for open surgery and an increased interest in foam sclerotherapy.7–10 Extensive work has shown the cost-effective nature of intervention11,12 and a poor compliance of patients with stockings, which ranges between 18% and 25%.13,14 Minimally invasive treatments now can provide large quality of life improvements at a low cost.7,11

General practitioners (GPs) are the gatekeepers to secondary care in the UK. Standard GP training, however, does not include any formal teaching on CVD and GPs have variable exposure to the surgical specialties during their medical training.15 GP trainees do though undergo an extensive apprenticeship with GP trainers and will cover such topics during this period. Interestingly, work by Chassany et al.16 demonstrated the disparity between patient-reported and GP-reported symptom severity with GPs routinely reporting lower levels of pain and quality-of-life impairment compared with patients.
Conway et al.\textsuperscript{17} have also shown that patient reported symptoms are unreliable compared with standardized questionnaires due to the subjectivity of symptoms.

In order to aid GPs in the management and referral of CVD, extensive guidelines have been developed in the UK by the National Institute for Clinical Excellence (NICE)\textsuperscript{18} and more recently by the Royal Society of Medicine’s Venous Forum.\textsuperscript{19} In the USA, guidelines on management of CVD patients have also been created.\textsuperscript{20} In order to stratify CVD, various clinical scoring systems have also been developed and validated, such as VCSS (Venous Clinical Severity Score).\textsuperscript{21,22} Despite the existence of guidelines and scoring systems, the treatment of varicose veins has been classified and is viewed of low clinical value,\textsuperscript{23} leading to the creation of disparate and confusing local guidelines and these are often in contention with national guidelines.

GPs are now also expected to perform routine postoperative follow-up for surgical procedures, such as varicose veins and hernia repairs,\textsuperscript{24} without appropriate remuneration or support. Previous work\textsuperscript{25} surveying patients, GPs and surgeons after postoperative outpatient attendance found that in the context of benign general surgical disease, 95\% of patients found follow-up specialist consultations useful, and only 49\% would prefer to see their GP. Importantly, management was changed by the specialist in 44\% of cases. Preference for specialty follow-up was mirrored in a similar study by Frew et al.\textsuperscript{26} in cancer patients.

The aim of this study was to assess patterns of referral and the management of CVD in primary care in the UK.

**Methods**

Following ethical review and categorization as service evaluation by the local ethical subcommittee, a 23-question electronic survey was created which assessed different aspects of CVD management and treatment pathways. The questionnaire was tested and validated for content and construct by GPs and vascular surgeons, with internal, external and independent assessors as previously described by other authors.\textsuperscript{27} In England there are approximately 34,101 GPs. Invitations to complete the survey were sent via email to an estimated 300 GPs throughout England (http://kwiksurveys.com?u=gpvaricoseveins), at random using local and national mailing lists. Please see Appendix 1 for the complete survey. Responses were collated by the survey server (KwikSurveys, Dover, UK) over a six-month period and results were analysed using Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA, USA) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA) software.

**Results**

A total of 138 completed responses were received, representing a response rate of 46\%. All received surveys were analysed and none were excluded.

**Cases seen**

The vast majority of GPs (85\%, $P < 0.001$) stated that they saw less than 50 patients with varicose veins per annum, which is an average of less than one per week. Seventy-eight percent managed CVD patients conservatively in the community, with one providing treatment with sclerotherapy. If specialist care was required most GPs (78\%, $P < 0.001$) referred to a vascular surgeon, 10\% to a general surgeon and 11\% to a vascular nurse specialist.

**Reasons for referral**

In all, 40\% of GPs would refer a patient at their request and 10\% for cosmesis, 43\% for venous skin changes and 58\% for pain (see Figure 1).

**Available treatments**

Figure 2 demonstrates which treatments GPs believe are available to their patients. Thirty-three percent believed that endovenous treatments were available in their locality, but a surprisingly low

![Figure 1 Reasons for referral from primary care (% of GPs). GP, general practitioner](http://kwiksurveys.com?u=gpvaricoseveins)
Guidelines and scoring systems

Only one-third of GPs (31% versus 69%, \( P < 0.001 \)) were aware of the NICE Referral Guidelines (published in 2001) for CVD. Sixty-one percent were aware of local Primary Care Trust (PCT) referral guidelines, but only 36% agreed with these guidelines. Twenty-six percent of GPs said that they were aware of NICE Treatment Guidelines; however, these guidelines do not actually exist. Local PCT guidelines do exist and 41% of GPs were aware of these, although again only 26% agreed with them. Eleven percent were aware of clinical scoring systems and 89% were not (\( P < 0.001 \)).

Role of intervention

Figure 3 illustrates how GPs determined whether there was a role for intervention using sample cases. Pain appeared to be the most important factor in this decision with 16% agreeing that CEAP class C2a (asymptomatic) warranted intervention but with pain (C2s) the referral rate increased to 71% (\( P < 0.001 \)). In patients with leg swelling and varicose veins (C3), 42% of GPs felt that pain-free patients should have treatment compared with 83% if patients also had pain (\( P < 0.001 \)). Interestingly, only 62% of GPs believed that venous skin changes warranted intervention. Moreover, only 78% believed venous ulceration required
intervention compared with 8% who did not and 14% were unsure ($P < 0.005$).

Progression, quality of life and cost-effectiveness

Sixty-four percent of GPs believed that mild CVD would progress to severe disease, compared with 36% who did not ($P < 0.001$). Eighty-four percent of GPs thought that treating varicose veins would improve a patient’s quality of life, and only 26% felt that it was not a cost-effective use of NHS resources. The majority (75%) believed that CVD for the purpose of improving quality of life could be managed conservatively.

Free of charge treatment

Figure 4 shows which treatments GPs felt should be provided free of charge on the NHS. Interestingly 11% of GPs believed that CEAP class C2a (visible but asymptomatic veins) should be treated free of charge and 8% were unsure. As CEAP class increased the proportion favouring free treatment also increased. Once again the onset of pain vastly increased the favour for free treatment.

Follow-up and ‘Me Too’?

Forty-five percent of GPs were happy to provide aftercare for varicose vein intervention, and 8% felt that no follow-up was required.

In the ‘Me Too’ question, 71% of GPs stated they would like invasive treatment if they have varicose veins, with none wanting traditional open surgery.

Discussion

The management of CVD is a common scenario encountered in general practice. The important aim of treatment is to avoid ulceration. From our results, it is evident that there is no clear consensus on the management of CVD in the community. While the majority of patients are no doubt treated appropriately, there is a reticence of primary care fund holders to allow referral for invasive treatment and consequently the burden of disease remains widespread. From our study, the treatment options also appear not to be universally available and in addition, there is patchy GP awareness of their availability.

What has become clear from this survey is that the CVD knowledge base of GPs is limited due to both a lack of exposure to the condition in their training and recent treatment progress. The number of GPs unaware of classification criteria, local and national guidelines, and the treatment options available demonstrates this. A substantial portion of GPs were also unsure of the benefits of treatment on a patient’s quality of life (11%), disease progression (23%) or on cost-effectiveness of treatment (34%), despite extensive literature published on these areas in the last two decades.

Our results would also suggest that follow-up should be with the treating physicians, and 92% of GPs felt that this was required, with only 45% were happy to provide postoperative care themselves.

National advice for referral for patients with CVD recommends referral to a specialist if there is quality-of-life detriment from prominent varicosities, not for cosmetic reasons or pain specifically. A key finding of the study is that pain is the main discriminator for patients being referred to second-stage treatment.
ary care. While this is unsurprising, as patients will not attend without symptoms, our study also demonstrates that only about one third of GPs were aware of the NICE Referral Guidelines and that among them only one third agreed with these guidelines. Crucially, 71% of GPs felt that C2 disease with pain (prominent varicose veins) should have intervention compared with 63% (NS) who thought that venous skin changes warranted treatment. This is concerning as the treatment of C4 disease is vital in the prevention of venous ulceration. Moreover, CVD intervention is far quicker and cheaper than ulcer treatment.

In an era of austerity and primary and secondary care commissioning, there must be improved discourse between venous specialists and primary care physicians. This must include mutual education sessions in order to disseminate recent advances. Surgical exposure in GP training is limited and topics such as venous disease are taught during an 18-month mentorship with GP trainers. It would therefore be prudent to encourage careful updating of these experienced GP trainers by the specialists to whom they refer.

This study is limited by two main factors – numbers and participants. There are approximately 34,101 GPs in England. It was not feasible to contact all GPs and therefore a representative sample of approximately 300 GPs was sought. The study additionally suffers from responder-bias, as those GPs willing to respond to the study are likely to be more engaged with local PCTs and commissioning services. They are also more likely to keep abreast of current treatments. Despite this the disparity between guidelines and practice was significant.

Conclusion

Despite clear national guidance and advice, referral and treatment patterns are extremely heterogeneous. This is the driving force behind the formulation of the various guidance documents available. CVD education is also lacking from GP training programmes despite CVD being a common condition, and venous specialists should aim to aid the lifelong learning needs for new and mature GP colleagues. For the benefit of our patients improved communication with GPs will lead to better patient care. We suggest that this should be sought at a local level with the development of clearer lines of feedback between primary and secondary care.

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Contributorship: TRAL, KS and AHD conceived the study. All authors drafted and finalized the survey questionnaire. TRAL collated and analysed the results. TRAL, KS and JRH drafted the manuscript. All authors reviewed, edited and finalized the study.

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Comparison of disease-specific quality of life tools in patients with chronic venous disease

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Abstract

Objectives: Quality of life (QoL) is an important outcome measure in the treatment for chronic venous disease. The Aberdeen Varicose Vein Questionnaire (AVVQ) and the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ-14) are two validated disease-specific QoL questionnaires in current use. The aim of this study is to evaluate the relationship between the AVVQ and the CIVIQ-14 to enable better comparison between studies and to compare these disease-specific QoL tools with generic QoL and clinician-driven tools.

Methods: Adults attending our institution for management of their varicose veins completed the AVVQ, CIVIQ-14 and EuroQol-5D (EQ-5D). Clinical data, CEAP classification and the Venous Clinical Severity Score (VCSS) were collected. The relationship between the AVVQ and CIVIQ-14 scores was analysed using Spearman’s correlation. The AVVQ and CIVIQ-14 scores were also analysed with a generic QoL tool (EQ-5D) and a clinician-driven tool, the VCSS.

Results: One hundred patients, mean age 57.5 (44 males; 56 females), participated in the study. The median AVVQ score was 21.9 (range 0–74) and the median CIVIQ-14 score was 30 (range 0–89). A strong correlation was demonstrated between the AVVQ and CIVIQ-14 scores ($r = 0.8; p < 0.0001$). Strong correlation was maintained for patients with C1-3 disease ($r = 0.7; p < 0.0001$) and C4-6 disease ($r = 0.8; p < 0.0001$). The VCSS correlated strongly with the AVVQ and CIVIQ-14 scores ($r = 0.7; p < 0.0001$ and $r = 0.7; p < 0.0001$, respectively). Both the AVVQ and CIVIQ-14 scores correlated well with the EQ-5D score ($r = 0.5; p < 0.0001$ and $r = 0.7; p < 0.0001$, respectively).

Conclusions: This study demonstrates that there is good correlation between two widely used varicose vein specific QoL tools (AVVQ and CIVIQ-14) across the whole spectrum of disease severity. Strong correlation exists between these disease-specific QoL tools and generic and clinician-driven tools. Our findings confirm valid comparisons between studies using either disease-specific QoL tool.

Keywords
Varicose veins, chronic venous disease, patient-reported outcome measures, quality of life, Aberdeen Varicose Vein Questionnaire, Chronic Venous Insufficiency Quality of life Questionnaire

Introduction

The introduction of endovenous treatments has heralded new advances in the management of chronic venous insufficiency over the past decade. Key to understanding the burden of venous disease and the long-term efficacy of newer endovascular approaches is the use of outcome measures relevant to the functional status of the patient.

Traditional objective measures of disease severity that focus on the morbidity and mortality of venous disease, whilst readily quantifiable, do not necessarily correlate with the functional status of the patient. To meaningfully capture outcomes in venous disease, the full biopsychosocial consequence of the disease must also be established. As the role for patient-centred care in venous disease increases, the assessment of quality of life (QoL) in venous disease is becoming

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increasingly important. Currently, there are a wide variety of validated outcome measures in use and these can be divided into generic and disease-specific QoL tools.

Generic QoL instruments permit a patient’s overall functional status to be measured regardless of their specific disease state and thus have the advantage of allowing comparison across different studies of different diseases. The EuroQoL 5 Domain score (EQ-5D) is a well-validated generic QoL score. Disease-specific QoL tools directly assess attributes related to a particular disease. They are increasingly becoming utilized in the study of varicose veins as they are more sensitive for assessing venous disease outcomes. The Aberdeen Varicose Vein Questionnaire (AVVQ) and the Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ) are two validated disease-specific QoL questionnaires most commonly used. Other examples of disease-specific QoL tools include the Charing Cross Venous Ulceration Questionnaire (CXVUQ), the Venous Insufficiency Epidemiological and Economic Study instrument (VEINES) and the Specific Quality of Life and Outcome Response Venous questionnaire (SQOR-V).

In a joint statement by the American Venous Forum and the Society of Interventional Radiology, the use of both disease-specific and generic QoL tools in conjunction with clinician-driven assessment is recommended in all clinical trials investigating venous insufficiency. There are significant differences in the choice of QoL tools amongst studies, making it challenging for the clinician to make direct comparisons between studies. Therefore, the correlation between different QoL tools is of huge significance if clinicians are to make valid comparisons between studies. However, at present the relationship between the various QoL tools has not been fully characterized. The aim of this study is to evaluate the relationship between two disease-specific QoL tools; the extensively validated AVVQ and more recently validated CIVIQ-14, to enable better comparison between studies and to compare these tools with generic QoL tools and clinician-driven tools.

Methods

Patient selection

Adult patients attending the vascular surgery outpatient clinic at our Institution for management of their varicose veins were prospectively invited to participate in this study. Patients were recruited over a four-month period, from August 2012 to December 2012 in a consecutive manner. Demographic data including patient age and gender were collected. All participants were asked to complete the two disease-specific QoL tools, the AVVQ and CIVIQ-14, prior to their outpatient appointment. The AVVQ consists of 13 questions addressing various biopsychosocial attributes of chronic venous disease, including specific signs and symptoms, use of compression stockings and daily functional impact. The overall score ranges from 0 to 100, with a higher score denoting greater burden of disease. The CIVIQ-14 is a revised version of the well-validated CIVIQ-20 instrument and has been shown to be valid in studies of patients across different countries. The CIVIQ-14 contains 14 questions covering three QoL dimensions: physical, pain and psychological and is scored from 0 to 100, with a higher score denoting a lower QoL.

Patients also completed the EuroQol-5D questionnaire (5-level version of the EQ-5D, EuroQol Group, Rotterdam, the Netherlands). The EQ-5D measures the biological, psychological and social aspects of a disease state to generate an overall score.

The clinical severity of venous disease for each patient was stratified by a single clinician using the following clinician-driven tools: the Clinical Etiologic Anatomic Pathophysiologic (CEAP) score and the revised Venous Clinical Severity Score (VCSS). The VCSS comprises nine characteristics of venous disease and each component is scored independently on a scale from 0 to 3.

Statistical analysis

Outcomes were scored for each patient. In cases of bilateral venous disease, scores were recorded for each leg and the score of the worst leg was used. Statistical analysis was performed using Prism 5.0a (GraphPad Software, Inc, La Jolla, CA). The relationship between the AVVQ and CIVIQ-14 scores was analysed using Spearman’s correlation for nonparametric data. Correlation was also analysed separately for patients with less severe (C1-3) disease and more severe (C4-6) disease.

The AVVQ and CIVIQ-14 scores were analysed against the EQ-5D and EQ-VAS. Both the AVVQ and CIVIQ-14 were analysed against the VCSS. Spearman’s correlation was used to assess the relationship for each analysis, and p values less than 0.05 were considered statistically significant.

Results

Patient demographics

Over a four-month period between August 2012 and December 2012, fully complete questionnaires were collected for 100 patients. There were 44 males (44%) and 56 females (56%). The mean age of participants was
57.5 years (range 22–84 years); 50% of patients were aged 65 years and over. The median AVVQ score was 21.9 (range 0–74; IQR 13.3–30.7) and the median CIVIQ-14 score was 30 (range 0–89; IQR 17.6–46).

**Relationship between disease-specific QoL tools (AVVQ and CIVIQ-14) and EQ-5D**

The EQ-5D score demonstrated a strong negative correlation with both the AVVQ (Figure 1(a)) and CIVIQ-14 scores (Figure 1(b)) (\(r = -0.5; p < 0.0001\) and \(r = -0.7; p < 0.0001\), respectively).

**Relationship between disease-specific QoL tools (AVVQ and CIVIQ-14) and VCSS**

There was a strong positive correlation between the VCSS and both the AVVQ (Figure 2(a)) and CIVIQ-14 scores (Figure 2(b)) (\(r = 0.7; p < 0.0001\) and \(r = 0.7; p < 0.0001\), respectively).

**Discussion**

Measurement of QoL is now common place in studies of chronic venous disease. Over the past decade, there has been increasing recognition amongst phlebologists that disease-specific QoL tools provide a more...
meaningful correlate of a patient’s functional status than objective anatomical or haemodynamic outcome measures.\textsuperscript{16,17} Reporting guidelines published by the American Venous Forum now recommend the use of disease-specific and generic QoL tools along with clinician-driven outcome measures in studies of chronic venous disease.\textsuperscript{9,10} In 2005, a review commissioned by the United Kingdom Department of Health recommended the routine use of patient-reported outcome measures after intervention for venous disease.\textsuperscript{18,19}

The choice of disease-specific QoL questionnaire is crucial to permit both the evaluation of the efficacy of current endovenous treatments and valid comparison of results from different trials. Currently, there are a number of different disease-specific and generic QoL tools and clinician-driven tools being utilized in studies of chronic venous disease.\textsuperscript{11,20} The AVVQ and CIVIQ-14 were chosen for evaluation in this study. The AVVQ is a commonly used validated disease-specific QoL tool that has been shown to be sensitive in assessing functional outcome after treatment for chronic venous disease.\textsuperscript{21} The CIVIQ-14 was recently developed as a more stable version of the CIVIQ-20 instrument, which itself has been commonly used and validated since 1996.\textsuperscript{2,5,22}

This study has established that a strong correlation exists between the two disease-specific QoL tools selected for evaluation, the AVVQ and CIVIQ-14, further demonstrating that these disease-specific questionnaires are useful tools in the assessment of QoL in chronic venous disease. The findings from this study show that the relationship between the AVVQ and CIVIQ-14 scores are predictable, thereby supporting the validity of making comparisons between studies regardless of whether the study has utilized the CIVIQ-14 or AVVQ QoL tool. The AVVQ differs in several aspects from the CIVIQ-14 questionnaire. In comparison with the CIVIQ-14, the AVVQ assigns a greater proportion of questions to the physical aspects of chronic venous disease. The CIVIQ-14 is validated for the entire spectrum of chronic venous disease,\textsuperscript{5} except venous ulcers, whilst the AVVQ specifically targets varicose veins and includes ulceration.\textsuperscript{4} Despite these differences, the current study shows that the two QoL tools closely correlate, and the correlation is maintained across the spectrum of disease severity, from less severe (C1-3) to more severe disease (C4-6).

Our findings have expanded on the findings of Shepherd et al.\textsuperscript{16} who found that the AVVQ correlated

\begin{figure}[h]
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\caption{Graphs demonstrating the relationship between AVVQ and CIVIQ-14 scores for: (a) CEAP 1-6 disease ($r = 0.8; p < 0.0001$); (b) CEAP 1-3 disease ($r = 0.7; p < 0.0001$) and (c) CEAP 4-6 disease ($r = 0.8; p < 0.0001$).\\AVVQ: Aberdeen varicose vein questionnaire; CIVIQ: chronic venous insufficiency quality of life questionnaire; CEAP: clinical etiologic anatomic pathophysiologic.}
\end{figure}
strongly with another disease-specific QoL tool, the SQOR-V questionnaire. The degree of correlation (Spearman coefficient 0.702) was similar to our findings (Spearman coefficient 0.8). Both the SQOR-V and CIVIQ-14 place a greater emphasis on patient-reported symptoms rather than physical signs and this may in part explain the comparable degree of correlation.

Other types of outcome measures utilized to assess chronic venous disease were also shown in this study to correlate with the AVVQ and CIVIQ-14 QoL tools. The study evaluated a generic QoL questionnaire, the EQ-5D, which was shown to correlate strongly with both of the disease-specific QoL tools. This is in contrast to findings from previous studies, which have compared different generic QoL questionnaires with disease-specific QoL questionnaires. Shepherd et al.\cite{Shepherd2016} found that the AVVQ only correlated weakly with a generic QoL tool, the Short Form-12 (SF-12) questionnaire. The reasons for the differences in our findings are not immediately clear, but may be attributed to the difference in construction of health profile-based questionnaires (Short Form series) and preference-based questionnaires (EQ-5D).\cite{Carradice2013}

This study also evaluated a clinician-completed assessment tool (VCSS) against the AVVQ and CIVIQ-14. A very strong correlation was found between the clinical scoring system and both of the disease-specific QoL tools. This relationship highlights the sensitivity of the AVVQ and CIVIQ-14 towards the physical aspects of QoL in chronic venous disease. Our results strongly reinforce the findings by Carradice et al.\cite{Carradice2013}, which also found that increasing venous disease severity was associated with poor disease-specific and generic QoL scores as measured by the AVVQ and EQ-5D, respectively.

The lack of consensus on which disease-specific QoL tool to use for measuring outcomes in chronic venous disease has contributed to an inconsistency in the choice of the QoL tool used in studies of venous disease.\cite{Launois2013, Shepherd2016} The need to make comparisons between studies using different outcome measures has highlighted the importance of understanding the relationship between these disease-specific QoL tools and clinician-driven tools. Our findings support the validity of comparisons of results between studies using either the CIVIQ-14 or AVVQ disease-specific QoL tool.

Conflict of interest

None declared.

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Cyanoacrylate glue for the treatment of great saphenous vein incompetence in the anticoagulated patient

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The Sapheon Venaseal Closure System (Sapheon Inc, Santa Rosa, Calif), using cyanoacrylate glue, has provided a new modality of treatment, with patients treated without both tumescent anesthesia and postoperative compression. We present the first case of great saphenous vein occlusion performed using glue while the patient was fully anticoagulated with warfarin. This was tolerated well, and the treated vein showed complete early occlusion at 8 weeks; however at 6 months, extensive recanalization was demonstrated on duplex imaging. (J Vasc Surg: Venous and Lym Dis 2013;1:298-300.)

Varicose vein treatments have advanced significantly during the past 10 years.1 With the development of endovenous ablation techniques, procedures to treat varicose veins have become available to most patients under local anesthesia. These techniques offer good technical and symptomatic benefit and reduce the risk of nerve and skin damage.2 Previously, patients with long-term anticoagulation presented a difficult scenario; however, endovenous thermal ablation and foam sclerotherapy offer minimally invasive treatment, which is not affected by anticoagulation.3-9

Recently, new techniques have been developed that do not require tumescent anesthesia.10,11 We present the first case of endovenous pharmacologic occlusion using cyanoacrylate glue via the Sapheon Venaseal Closure System (Sapheon Inc, Santa Rosa, Calif) while the patient was therapeutically anticoagulated using warfarin.

CASE REPORT

A 73-year-old man presented to the Charing Cross Varicose Vein clinic with complicated varicose vein disease of the right leg, with recurrent bleeding from extensive varicosities. He had a CEAP12 score of C4bE P A, an Aberdeen Varicose Vein Questionnaire (AVVQ)13 score of 15.44, and a Venous Clinical Severity Score (VCSS)14 of 14. His medical history included atrial fibrillation treated with warfarin and pre-existing use of compression hosiery for varicose vein symptom control. A venous duplex ultrasound scan revealed an incompetent deep venous system, saphenofemoral junction (SFJ), and great saphenous vein (GSV). The maximum diameter of the GSV was 15 mm just distal to the SFJ.

The patient underwent right leg GSV endovenous occlusion in March 2012 with the newly developed Sapheon Venaseal Closure System using standard procedure as follows: The patient was advised not to stop his warfarin anticoagulation. The international normalized ratio at treatment was 2.3. Under local anesthetic, the GSV was cannulated at the knee level and a guidewire passed into the vein. A standard 7F sheath was passed using the Seldinger technique into the vein.

The Sapheon outer catheter was fed into the vein and placed 5 cm distal to the SFJ. The inner glue catheter was primed, leaving a 3-cm air gap at the end of the catheter, and connected to the application gun. The catheter was fed into the outer catheter, and as the glue catheter reached 5 cm from the SFJ, the catheter was withdrawn to expose the glue catheter at 5 cm from the SFJ, and the catheters were locked together.

The proximal GSV was then occluded using transverse probe placement 2 cm distal to the SFJ. One full 3-second activation of the glue applicator was completed; then, the catheters were withdrawn 1 cm, and a further application was completed without moving the transverse probe occlusion. The catheter was withdrawn a further 3 cm, and light minimal compression was applied as the initial curing time of 3 minutes was completed using a stop-watch. The rest of the GSV was treated with one application, a 3-cm pullback, and a 30-second minimal compression time. This was repeated to treat 35 cm of GSV.

The wound was closed with a Steri-Strip dressing (3M, St. Paul, Minn) and a cannulation-site plaster (Mepore; Mölnlycke Health Care NHS Trust and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health.

Author conflict of interest: none.

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Care, Gothenburg, Sweden) without sutures. The total procedure took 20 minutes, from the first local anesthetic injection to the application of the wound plaster, and was well tolerated by the patient.

The patient was advised to continue with class II compression hosiery in the long term due to pre-existing mild deep venous incompetence. There was no perioperative bleeding. Completion duplex imaging showed GSV occlusion.

On postoperative clinical and duplex ultrasound review at 8 weeks, the GSV was occluded from the point of entry for treatment to the point of compression, 2 cm distal to the SFJ. The mild deep venous incompetence had resolved. His lower leg varicosities had shrunk in size, and he wanted no further treatment. Subjectively, he had experienced no postoperative pain and no inflammation. His VCSS was 7 and AVVQ was 4.64, a reduction of >10 points.

At the 6-month follow-up, his VCSS was 10 and AVVQ was 25.53. His varicosities had not returned; however, significant edema and symptoms had recurred. On repeat venous duplex imaging, the GSV was recanalized and incompetent (Supplemental Video, online only), with a maximal diameter of 7.2 mm at the SFJ (Figs 1-3). Two 2-cm sections of the GSV in the midthigh remained completely occluded. The deep venous incompetence remained absent. Repeat treatment of the GSV with foam sclerotherapy was arranged.

DISCUSSION

This report demonstrates the first case of cyanoacrylate glue GSV occlusion while a patient was formally anticoagulated with warfarin. Early technical success and symptom resolution, unfortunately, led to reopening of the treated vein. Despite an increase in venous symptoms and an incompetent GSV, this patient’s varicosities remained in remission.

Because the cyanoacrylate occlusion process is separate to the coagulation cascade, it is likely that this treatment failure was secondary to the large vein diameter and the learning curve associated with new procedures. Other techniques have shown early-to-midterm occlusion failures, despite experience, with previous studies highlighting the risks of track neovascularization.

CONCLUSIONS

This case report highlights the need for thorough follow-up for new technologies and an understanding that isolated cases of recanalization can occur after initial success.

We thank Sapheon Inc for providing the Sapheon Venaseal Closure Device for evaluation.

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Fig 1. Open saphenofemoral junction (SFJ) at 6 months after glue occlusion.

Fig 2. Duplex ultrasound imaging shows patent proximal great saphenous vein (GSV) with partial occlusion and reopening distally.

Fig 3. Occluded segment in midthigh, with open segment below.


Inferior vena cava filters: when, where, why?

Inferior vena cava (IVC) filters are believed by many to be an effective method of preventing clot from a lower extremity deep vein thrombosis (DVT) travelling centrally and causing a pulmonary embolism (PE). Prior to the development of percutaneous devices, open ligation/clip placement was utilized for PE prevention. The potential role of the IVC filter has been diminished by the effectiveness and low morbidity of systemic anticoagulation.

The complications of vena cava filter insertion can be significant with a mortality rate of 0.12% reported. The common complications include DVT, vena cava perforation, filter migration, total occlusion due to clot despite anticoagulation and PE despite filter placement. In the USA, IVC filters are placed in up to 15% of all DVTs, and indeed in 2008 over 65,000 filters were placed (20 per 100,000 population). In the UK, Hospital Episode Statistics reveal that 1173 IVC filters were placed in 2011 (2 per 100,000 population), an increase from 532 in 2006 (1 per 100,000 population).

It is estimated that there are 466,000 cases of DVT and 296,000 cases of PE per annum in the European Union, with 370,000 fatal cases (150, 95 and 120 per 100,000, respectively). In the USA, there are an estimated 900,000 venous thromboembolism cases, with 300,000 fatalities from PE alone (290 and 97 cases per 100,000, respectively).

Little evidence governs their insertion and even less for their effectiveness. This has led to extreme discordance between guidelines and practice. A disconcerting feature of the literature is the poor rate of randomized controlled trials – only two studies were methodologically sound enough to be included in Young et al.’s Cochrane review.

The only indications for insertion with guideline recommendation are for cases of DVT where anticoagulation is contra-indicated or where there is recurrent PE despite adequate anticoagulation. Most concerning of all is the poor rate of retrieval of so-called ‘temporary’ filters (also known as optional filters). This is despite the evidence that anticoagulation need not be stopped for safe retrieval, and the development of new filter designs which allow removal safely after some months. Importantly, technique of insertion to achieve accurate centre-lining is vital for removal and haemodynamic flow. The USA data show that only 1.5–2.1% of temporary filters were removed in 2008 with even prospective studies displaying disappointing removal figures of 10–70%.

In the UK, the retrieval rate has improved from 13% in 2006 to 26% in 2011, though this remains poor. The rate of IVC thrombosis ranges from 6–30%. The rate of IVC thrombosis without anticoagulation has been found to be as low as 0% in one study, with the large eight-year PREPIC study finding a rate of 13%, with only 35% of the IVC filter undergoing long-term anticoagulation. Those advocating placement must accept responsibility for removal.

Trauma is a field where there is great interest in the placement of IVC filters. Trauma patients are often immobile and often have contraindications to anticoagulation due to ongoing bleeding. This has led to the development of insertion under ultrasound guidance at the bedside. However, even here the evidence is conflicting at best: initial trials highlight the problems with retrieval, and further studies have shown the inconsistencies with US treatment. Indeed, a recent study of cost-effectiveness questioned the use of IVC filters even in this highly selected group.

IVC filter placement in the context of cancer patients has been advocated in some circles, especially when IVC manipulation is required; however, a recent review of patients with renal cell carcinoma undergoing resection recommended that filters should not be placed unless the conditions of contra-indicated anticoagulation or continued PE despite anticoagulation are met. IVC filters are also a hazard in this and similar groups of patients due to possibility of incorporation in tumour thrombus and technical difficulty in surgery secondary to the filter.

Prophylactic use of IVC filters during bariatric surgery has also gathered interest despite studies showing no reduction in rates of PE. Caution should be used in the interpretation of small scale studies in favour of the procedure. Thrombophilic patients remain a difficult group, with little evidence to guide decision-making, due to the complex nature of coagulation. There is a significantly increased risk of IVC filter thrombosis.
The recent implementation of the UK Inferior Vena Cava Filter Registry in conjunction with the British Society of Interventional Radiology\(^1\) has led to improved treatment and guideline adherence – in the latest report spanning 2008–2010, 1255 IVC filters were placed, with 25% overall retrieval rate (41% of temporary filters).\(^2\) This is mirrored by work on trauma patients in the USA.

Overall it is clear that IVC filters remain a favoured procedure despite limited evidence of its benefits and poor retrieval of the implanted filters. Further high-quality randomized studies are required to inform us of the benefits or detriments to placing filters. Currently, the practice is unguided despite decades of filter insertion, which it is vital to improve.

Conflicts of interest: None.

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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 management of varicose veins may be conservative (including lifestyle changes and compression hosiery) or surgical. Operative treatment aims to disconnect the superficial and deep venous systems at the sites of venous incompetence; traditionally saphenofemoral and saphenopopliteal junction ligation with or without stripping were the mainstay of treatment. In the last decade surgical treatment has been moving towards minimally invasive endovascular techniques, including thermal ablation (by means of radiofrequency, laser technology, steam), cyanoacrylation and mechanochemical ablation. These are less invasive than open surgery and may be done under local anaesthesia.

This article discusses the epidemiology, diagnosis and management of varicose veins, including the latest endovascular and targeted open surgical techniques such as haemodynamic surgery and varicose ablation.

Keywords Ablation; cyanoacrylate; endovenous; haemodynamic; laser; mechanochemical; radiofrequency; sclerotherapy; surgery; varicose veins

Definition
Varicose veins are a common condition affecting up to one in four patients; they cause significant morbidity, including depression, and have a negative impact on patients’ quality of life. They are a manifestation of chronic venous disease (CVD) and are characterized by tortuous, dilated superficial veins more than 3 mm in diameter. The condition can occur anywhere in the body where there is poor venous return; however, they are most often associated with the lower limb.

Epidemiology
Venous disease is extremely common, with similar incidences worldwide; spider veins (fine, dilated intradermal venules approximately 1 mm in diameter) affect up to 80% of the population and the reported incidence of varicose veins is variable, ranging from 20 to 64%.

Risk factors associated with venous disease include previous deep venous thrombosis (DVT), obesity, pregnancy, family history and posture (e.g. standing for long periods of time).

Although rarely life-threatening varicose veins are highly prevalent; their treatment accounts for approximately 2% of the total NHS budget and in 2001 an estimated £20–25 million (excluding non-hospital costs) was spent on varicose veins.

Varicose veins are a manifestation of CVD; in this condition venous return is impaired secondary to reflux, obstruction or calf muscle-pump failure. The exact aetiology is unclear. What is known is that there is an increase in the venous pressure distally, which leads to the cutaneous changes typical of the disease.

Primary varicocities 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. They most commonly occur in the great saphenous vein (GSV) and/or small saphenous vein (SSV) distribution (Figure 1), however surface examination can be misleading.

Secondary varicocities 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, pressure on the pelvic veins from an intra-abdominal mass, or simply obesity. 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. Symptoms include pain, heaviness, swelling, aching, restless legs, cramps and itching. These correlate well with the clinical severity of the disease, however varicose vein diameter does not correlate with symptoms and quality of life.

Symptoms are exacerbated by standing stationary or long periods sedentary 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 varicocities.

Skin changes consist of venous eczema, lipodermatosclerosis, haemosiderin deposition, ulceration and atrophic blanche.

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(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 treated with non-steroidal anti-inflammatory drugs.

Large, prominent varicosities may be prone to bleeding, either spontaneously or as a result of trauma. Rarely, this can result in fatal haemorrhage.

The patient should be assessed initially standing, allowing the veins to fill. A full neurovascular examination should be carried out, 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.

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. (Table 1).

The venous clinical severity score (VCSS) and Aberdeen varicose vein questionnaire are both assessment tools of venous disease. The VCSS is clinician-completed, scoring nine hallmarks of venous disease in order of severity from 0 to 3. The Aberdeen questionnaire is a patient-completed quality of life (QoL) assessment tool comprising 13 questions ranging from physical symptoms to social effect and cosmesis. Other assessment tools include the Chronic Venous Insufficiency Questionnaire-20 (CIVIQ-20), the Venous Insufficiency Epidemiological and Economic Study (VEINES) Symptom and QoL assessments, the Short Form Health Survey (SF-36, SF-12, SF-8) and the EuroQoL-5 domain survey.

**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,
The first-line of treatment for patients with symptomatic venous disease is compression hosiery; this 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 into a reduction in the symptoms of CVD and prevention of deterioration of the skin changes associated with venous hypertension.

In the UK, there are three grades of compression hosiery with general indications. European standard stockings utilize the RAL testing standard and therefore provide more reliable compression levels. 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 (Table 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 heterogeneous, 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.4 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 and cosmetically unsightly; non-adherence rates are as high as 33%. 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 long-term cost.

The advantage of compression hosiery is that it has few side effects. Risks include skin necrosis in poorly fitted stockings.

### CEAP (Clinical, Etiology, Anatomy, Pathophysiology) classification of lower venous disease

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>An: no venous location identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0: no visible or palpable signs of venous disease</td>
<td></td>
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<tr>
<td>C1: telangiectasia or reticular veins</td>
<td></td>
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<tr>
<td>C2: varicose veins</td>
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<tr>
<td>C3: oedema</td>
<td></td>
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<tr>
<td>C4a: pigmentation or eczema</td>
<td></td>
</tr>
<tr>
<td>C4b: lipodermatosclerosis or atrophie blanche</td>
<td></td>
</tr>
<tr>
<td>C5: healed venous ulcer</td>
<td></td>
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<tr>
<td>C6: active venous ulcer</td>
<td></td>
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<tr>
<td>S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps</td>
<td></td>
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<tr>
<td>A: asymptomatic</td>
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<thead>
<tr>
<th>Aetiological classification</th>
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<tr>
<td>E: congenital</td>
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<tr>
<td>P: primary</td>
<td></td>
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<tr>
<td>S: secondary (post thrombotic)</td>
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<tr>
<td>N: no venous cause identified</td>
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<table>
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<tr>
<th>Anatomical classification</th>
<th>A: asymptomatic</th>
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<tbody>
<tr>
<td>E: congenital</td>
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<td>P: primary</td>
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<td>S: secondary (post thrombotic)</td>
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<td>N: no venous cause identified</td>
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<table>
<thead>
<tr>
<th>Pathophysiological classification</th>
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<tr>
<td>F: reflux</td>
<td></td>
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<tr>
<td>O: obstruction</td>
<td></td>
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<tr>
<td>R: reflux and obstruction</td>
<td></td>
</tr>
<tr>
<td>N: no venous pathophysiology identifiable</td>
<td></td>
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</tbody>
</table>

### Treatment

The National Institute for Health and Clinical Excellence (NICE) guidelines for the diagnosis and management of varicose veins will be published in July 2013. Current guidelines recommend NHS treatment for patients with significant complications of varicose veins (progressive skin changes, bleeding, recurrent thrombophlebitis) or if the symptoms are significantly affecting their quality of life.

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.

### European classification of compression hosiery

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Class I</td>
<td>14–17 mmHg (light)</td>
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<tr>
<td>•</td>
<td>Indication: varicose veins; mild oedema</td>
</tr>
<tr>
<td>Class II</td>
<td>18–24 mmHg (medium)</td>
</tr>
<tr>
<td>•</td>
<td>Indication: severe varicose veins; mild oedema; prevention of ulcer recurrence</td>
</tr>
<tr>
<td>Class III</td>
<td>25–35 mmHg (strong)</td>
</tr>
<tr>
<td>•</td>
<td>Indication: severe varicose veins; post-phlebitic limb; prevention of ulcer recurrence; chronic venous insufficiency</td>
</tr>
</tbody>
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4. 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) less than 0.9.

Despite the lack of high-quality evidence on their role in varicose veins, these are non-invasive and cost-effective and are advised by the SVS and AVF as initial treatment options, but should not be used as a rationing tool.\(^3\)

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 (PD)).

In the UK STS (1–3%) and PD (0.5–3%) 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 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 PD 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).

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 randomized controlled trials suggesting it is just as effective as surgical therapy. FS still utilizes STS or PD but converts it from its liquid phase to foam by mixing it with air.

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.\(^4\) An alternative explanation is that the production of endothelin at the treatment point is the causative factor.\(^5\)

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 advise that ultrasound-guided FS (UGFS) is efficacious in the short term and should be performed under local (or no) anaesthetic. After the procedure compression bandaging should be used and the patient can have further treatment if, upon follow up, the varicosities have not resolved.

Contraindications are allergy to the sclerosant and DVT without recanalization.

Thermal ablation

Radiofrequency ablation (RFA)

RFA is a technique that employs radiofrequency waves to deliver thermal energy, reaching temperatures of 85–120°C. The heat generated damages the venous endothelium, sealing the incompetent vein. RFA of the GSV was described by Goldman in 2000 using the VNUS Closure Plus™ catheter (San Jose, CA, USA). 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). Tumescent 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 provides pain relief. Treatment without tumescence has shown poor technical outcomes.

Once adequate coverage is obtained and the temperature at the probe tip is reduced (25°C) the VNUS system can be activated and treatment started.

The patient should be placed in the 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 segment of vein over 20 seconds at temperatures of 120°C. 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 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.\(^6\) Prospective randomized studies also revealed that RFA has comparable results to high-tie and stripping with regards to recurrence both in the short, mid and long-term.\(^2\) RFA was better tolerated by patients and associated with a quicker recovery period and improved quality of life scores.\(^5\) RFA has been shown to be a minimally invasive, safe and effective procedure for the treatment of varicosities; 3-year data confirm 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™/C212) 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 pull-back 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 fibreoptic 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. 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 better 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 more than 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, fibreoptic catheters, micropuncture kit and a protected room. The catheters are very small (0.5–1 mm diameter) and can be difficult to navigate up a tortuous vein. The rate of postoperative DVT is 0.5%.

Steam therapy (Steam Varicose System™)

In steam ablation a catheter delivering pulsed 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. Large, long-term studies are required to further assess this method, with the first case-series in publication.

Cryoaablation

Cryoaablation combines open and endovascular techniques. The SFJ is divided via a groin incision and a cryoprobe is inserted into the GSV to the knee. The tip position is confirmed by ultrasound. Liquid nitrogen or carbon dioxide are released from the cryoprobe tip, reaching temperatures of −85°C for 10–15 seconds, freezing the GSV to the cryoprobe; the vein is then stripped by removal of the probe. Studies have shown that cryosurgery is as effective as conventional stripping and EVLA,11 in terms of recurrence, neovascularisation and quality of life measures.

Mechano-chemical endovenous ablation

ClariVein® (Vascular Insights, Madison, CT, USA), developed for saphenous incompetence, is a hybrid between endovenous ablation and sclerosant treatment. 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...

Figure 3 Ultrasound images of endovenous ablation. (a) Longitudinal view of endovenous catheter placement at the saphenofemoral junction (SFJ). Note the junction on the left side of the image. The GSV can be seen draining into the common femoral vein with the hyperechoic, linear catheter positioned 2 cm away from the junction. (b) Transverse view of the GSV after instillation of tumescent anaesthesia. The hyperechoic catheter is surrounded by hypoechoic fluid, collapsing the vein onto the catheter itself and separating away the surrounding structures.
principles are as for endovenous ablation, with venous cannulation via Seldinger technique and catheter insertion up to 2 cm from the SFJ.

The ClariVein\textsuperscript{TM} 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 PD) 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]

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. Larger studies with prolonged follow-up are needed to assess its efficacy.

\textbf{Sapheon\textsuperscript{TM} Venaseal Closure System}

The Sapheon\textsuperscript{TM} Venaseal Closure System (Sapheon Inc, Santa Rosa, CA, USA) uses the same principle as endovenous ablation, with ultrasound-guided catheterization. A proprietary glue and ongoing manual compression are used to occlude the vein, which fibroses. Initial first in-man studies and preliminary data from the ongoing European Sapheon Closure system Observational Prospective study (ESCOPE) have been presented but longer-term results are awaited.

\textbf{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 LSV in a patient with an incompetent SFJ. With recent advances in minimally invasive surgery, endovenous ablation is fast-becoming the treatment of choice, with the proportion of open surgery performed dropping from 83\% in 2006 to 44\% in 2012.[13]

Surgery for varicose veins can be performed under general, local or regional anaesthesia and should be a day-case procedure in all but special cases.

The basic principle is disconnection of the refluxing superficial venous system from the deep system.

\textbf{Saphenofemoral junction ligation (SFJL)}

SFJL for LSV incompetence 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 LSV 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 LSV. Winterborn et al\textsuperscript{14} recommended stripping the LSV in combination with SFJL, due to a 60\% reduction in re-intervention after 11 years.

The risks of open ligation +/- stripping include bleeding, infection, haematoma formation, recurrence and damage to the saphenous nerve. 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 open high-tie and stripping is 0.54\%.

\textbf{Saphenopopliteal junction ligation (SPIJ)}

SPIJ follows the same principles of SFJL. An incision is made in the popliteal fossa and dissection is performed to the junction, which is ligated or transfixed. SPIJ is less successful than SFJL, with high recurrence and complication rates, particularly regarding common peroneal nerve damage resulting in foot drop, which is a cause of litigation. Endovenous ablation is a suitable option for SSV treatment.

\textbf{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.

\textbf{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,\textsuperscript{15} multiple phlebectomies are performed on varices without intervening on the refluxing saphenous veins. 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.\textsuperscript{15} Isolated phlebectomies appear to improve venous haemodynamics by reducing LSV reflux duration, peak velocity and diameter.\textsuperscript{15}

\textbf{Conclusion}

The earliest Pubmed-indexed text titled “Observations on the treatment of Varicose Veins of the Legs” was published in 1816. Since then countless research has been performed on a common and troublesome condition. It is exciting that two centuries later new developments are still being presented. Open high-tie and stripping has truly become a procedure of the past, with the new generation of endovenous treatments offering effective, minimally invasive and safe treatment.
Interestingly, a 2009 survey revealed that only 14% of vascular surgeons offered endovenous treatment; this should be compared to the fact that in 2012 only 44% of procedures are open surgery. The paradigm shift in the treatment of varicose veins is on the way but the universal adoption of new techniques in everyday practice is yet to be achieved. With the current advances in minimally invasive treatment it is imperative that new vascular trainees are fully trained in these techniques.

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Short-term gain for long-term pain? Which patients should be treated and should we ration?

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Abstract
Objectives: Treatments of common conditions which do not affect mortality often become sidelined in the drive to improve efficiency and reduce costs. The rationing of patients is a divisive but crucial component to universal health care. How should this be accomplished?
Methods and Results: In this article we examine the outcomes of various rationing methods in varicose veins.
Conclusions: No method is perfect and treatment of symptoms and complications should remain the target for all physicians.

Keywords: varicose veins; rationing; treatment

Background
Varicose veins are currently the source of intense debate and is a common condition worldwide, with increasing prevalence with age. Despite extensive work on clinical and quality-of-life (QOL) outcomes after treatment, it has been classified as a ‘treatment of limited clinical value’. Indeed, the UK Audit Commission classifies varicose veins as ‘potentially cosmetic’, against the evidence. This reinforces the common misperception that varicose veins are not a significant condition.

This definition has not kept pace with epidemiological research progress and device development. By some it is used to enable the concept of rationing.

Treatment of all patients with varicose veins is unfeasible and indeed unnecessary, as not all patients experience symptoms or complications. As with many conditions, selecting the patients who would most benefit from intervention is extremely difficult and prone to socioeconomic bias. This article aims to review the evidence for different rationing methods employed.

In the UK, Primary Care Trusts (PCTs) are the current funding bodies for National Health Service (NHS) treatment, and they have applied criteria for funding, which limits treatment to those with permanent damage which may well lead to higher long-term costs – ‘short term gain for long term pain’. Only 68% of PCTs fund symptomatic varicose veins, compared with 90% of complicated cases. This is despite funding underspends and the complexities of such rationing. This setting is made even more difficult by the disparate management and training on chronic venous disease in the primary care setting, and leads to complex health disparities between public and private care.

In addition, with the ever-increasing centralization of care, rationing has become a crucial component, as it is becoming evident that far from improving care, mergers lead to worse financial and care outcomes.

Interestingly, patients with varicose veins are accepting waiting lists and delays in excess of the standard NHS 18-week pathway for diagnosis and treatment – while ideally they would like to be treated within 12 weeks of consultation and listing for the procedure, patients are willing to...
wait up to 26 weeks and this does not have an effect on their QOL.\textsuperscript{25–27} However, patients who wait longer show progression of disease,\textsuperscript{8} which in other fields leads to worse outcomes.\textsuperscript{28}

Many treatment criteria have been investigated to assess their suitability for treatment. Here we outline their impact.

**Rationing methods**

**Stocking treatment**

Treatment with conservative measures includes the use of compression hosiery, which has been shown to provide effective relief for subjective symptoms of aching and pain.\textsuperscript{29–31}

However, the stockings available take many forms and the evidence is extremely heterogenous in nature.\textsuperscript{32} Stockings are expensive, costing up to £200–300 per year per patient. In addition, compliance is moderate, with one-third of patients in a trial setting not wearing their stockings,\textsuperscript{33} increasing to two-thirds in a non-trial setting.\textsuperscript{34} This is partially due to difficulty in application.\textsuperscript{35,36}

Varicose veins lead to increased leg volume,\textsuperscript{37} and physiological assessment has shown a significant reduction in leg volume with compression hosiery, with varicose vein patients benefiting more with higher compression levels.\textsuperscript{38}

Post ulceration there is significant evidence that long-term use of compression hosiery reduces recurrence by half,\textsuperscript{39} in addition to aiding healing of those ulcers.\textsuperscript{40}

Intriguingly, while stockings do improve symptoms, they do not prevent the emergence of varicosities in pregnancy, which may be extrapolated to indicate long-term progression.\textsuperscript{41}

The additional cost of intervention has been shown to be modest (<£400 over 2 years), with a significant improvement in QOL for those undergoing open surgery.\textsuperscript{42}

**Waiting list**

Waiting lists have always been the simplest of rationing tools – with clinician input, the most urgent cases are performed earlier, and more elective procedures are done in due course. Patients are familiar and comfortable with such a process.\textsuperscript{23,25,43} However, there is evidence to show that long term the simplest cases continue to be pushed back without the aid of a waiting list limit, and in extremes never get performed at all.\textsuperscript{44} In addition, ‘wastage’ of cases occurs – patients pay to undergo private treatment, patients die and patients move, all of which remove the burden from the waiting list. It has also been shown that reducing waiting lists with increased resources does not lead to increased demand, indicating that extending waiting times will have a limited effect on reducing demand.\textsuperscript{45} However, the hospital load does not reduce, as it is replaced by alternative procedures.\textsuperscript{46}

**Vein diameter**

Vein diameter has been shown to be significantly positive correlated with venous haemodynamics\textsuperscript{47–49} and the clinical stage of disease\textsuperscript{48,50–52} using the clinical aetiological anatomical pathological (CEAP) scoring system.\textsuperscript{53} There is also evidence to show worsening clinical scores using the venous clinical severity score (VCSS)\textsuperscript{54} with increasing vein diameter.\textsuperscript{50,55}

Interestingly, despite this extensive work showing an anatomical and haemodynamic correlation, this does not apply to patient symptomatology. The presence of symptoms and their significance to the patient are independent of size or rate of reflux in the veins.\textsuperscript{50,55,56} This work indicates that as with pain,\textsuperscript{57,58} symptom thresholds vary from patient to patient.

**Complications**

Rationing by limiting treatment to those who already have complications of the disease is an attractive method in principle – those patients who never suffer significant long-term damage will not be treated unnecessarily. It can lead to a large reduction in the waiting list and load on treatment.\textsuperscript{59–61} However, this reactive process unfortunately does not prevent disease and allows permanent change to occur and is out of step with today’s evidence and practice of preventative medicine. Once patients have developed skin changes (CEAP C4) then lifelong compression hosiery is indicated at considerable cost.\textsuperscript{62} Indeed with the evidence now emerging from studies such as the Bonn Vein Study indicating that varicose veins do progress up the clinical scale at about 5% per year per class, suggesting such reactive action is flawed.\textsuperscript{5}

Waiting until the appearance of skin changes, or worse ulceration, leads to extensive QOL impairments and significant societal costs.\textsuperscript{63–65}

Recent work into superficial venous thrombosis has shown that it is a significant risk factor for deep vein thrombosis, and additionally, varicose
veins themselves are a four fold risk factor for deep vein thrombosis if present under the age of 45.66,67

Clinical stage (CEAP)

Rationing by CEAP53 criteria has been suggested with some areas only those patients with CEAP class 4 and above being treated – complicated varicose veins. The problems with this approach are detailed above, including the higher societal costs. However, crucially the CEAP classification is relatively insensitive to change, and does not correlate well with symptomatic problems.68 Patients with increasing CEAP do have worse QOL measures; however, improvement post-treatment is not significantly different between classes, leaving patients with higher CEAP classes worse off.56 This indicates that permanent damage has been done, leading to a longstanding QOL impairment.

Symptoms

Extensive work has been completed showing the QOL impairment caused by varicose vein symptomatology:56,69,70 Patients experience a constellation of symptoms, ranging from aching and heavy legs to restless legs.71 These can be difficult to unpick but extensive studies have shown improvements in QOL post-treatment,3,5,6,7,2, 7 which is now routinely performed under local anaesthetic.11

A crucial symptom is pain, which leads to a large number of referrals from primary to secondary care;71 however, this is extremely variable patient-to-patient 57,58 and can be difficult to quantify.71,74 Previous work in the 1990s showed significant dissatisfaction with varicose vein intervention,75 however, with treatment advances, satisfaction is currently high.76

There is no current literature utilizing QOL tools to ration treatment, and doing so would bias the questionnaires due to the possibility of gaming by patients to influence their desired outcome.

Conclusion

Rationing is not an ideal starting point, however, due to the prevalence of venous disease it is a necessity. No method is perfect, however the relief of symptoms and prevention of disease should always remain the main aim of any physician. Therefore, treatment on symptomatic grounds with QOL assessment for service evaluation purposes should be our rationing tool of choice. This allows the greatest benefit in the most cost-effective manner, before permanent chronic change is evident.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Review article

The European burden of primary varicose veins

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Abstract

Background: The treatment of varicose veins has been demonstrated to improve quality of life, alleviate symptoms of depression and treat the complications of venous disease. This study aims to show the studies which contain information regarding the prevalence and distribution of venous disease. Then using the population and prevalence data for venous disease, and considering the cost of treating varicose veins, this study aims to analyse the treatment of varicose veins and assess whether there is a disparity between European countries.

Methods: Relevant papers regarding the prevalence or incidence of venous disease were identified through searches of PubMed (1966 to October 2010). The search terms ‘prevalence OR incidence’ AND ‘varicose veins or venous disease’ were used. Population data, prevalence data and the number of varicose vein procedures performed in each country was obtained for 2010.

Results: Four studies were included. From calculated values comparing the predicted and actual number of patients requiring treatment for venous disease, the UK, Finland and Sweden are potentially not treating all patients with C2 disease. In contrast to this, all other European countries represented are treating more patients, suggesting that they may be treating additional patients. There was up to a four-fold difference in the numbers of procedures per million population that were performed for varicose veins in different European countries.

Conclusion: There is a marked disparity across Europe between the predicted number of patients with varicose veins requiring treatment and the actual care given. The factors influencing this need more detailed investigation.

Keywords: varicose veins; healthcare burden; treatment

Introduction

Venous disease is common in the UK.1 Although prevalence data are highly variable, other European cohorts report comparable prevalence data.2-4 The majority of patients with venous disease have superficial venous reflux alone with clinical manifestations including telangiectasia, varicose veins, oedema and venous ulceration. Superficial venous disease does not pose an immediate threat to life; however, the treatment of varicose veins has been demonstrated to improve quality of life,5 alleviate symptoms of depression,6 and treat the complications of venous disease.7 Patients with superficial venous reflux and varicose veins have benefitted from recent advances, particularly the use of endothermal technologies to ablate superficial veins.8 All treatment modalities have been shown to improve patients’ quality of life in national non-selected patient-reported outcome measures9 and in the UK, all treatment modalities have been shown to be cost-effective in terms of quality-adjusted life-years gained relative to conservative treatment.10

In the UK, the National Institute for Clinical Excellence referral advice document, published in 2001, recommends referral by the general practitioner for patients suffering from varicose veins, and clinical practice guidelines agree that patients should be referred if there is evidence of venous ulceration or significant clinical symptoms.11-14 However, there is limited evidence to support the efficacy of treatment for patients with varicose veins alone,15-17 and the optimal treatment strategy for varicose veins remains unknown.18-20

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practitioner (GP) for specialist advice if patients have ‘troublesome symptoms attributable to their varicose veins, and/or they and their GP feel that the extent, site and size of the varicosities are having a severe impact on quality of life’ as well as patients who have healed or active ulceration or bleeding varicosities. However, despite this, individual primary care trusts (National Health Service [NHS] funding bodies) are commonly recommending, and indeed will only reimburse treatment if patients have severe skin changes and have failed a six-month trial of compression, or if the patient has leg ulceration, chronic continuous pain or severe oedema. If patients are treated in the earlier clinical stages of disease, then progression, estimated to be approximately 2% per year from C2 to C3–C6 disease, may be halted. In the long term, to prevent the more costly severe clinical stages of venous disease, it may prove to be more cost-effective to treat early symptomatic disease, although larger studies are needed.

Is this management strategy reflected across the rest of Europe? How many procedures for varicose veins are performed and is there a difference between countries? Which clinical stages of disease are being treated and is there consistency? Importantly, what are the potential treatment costs of performing these procedures and can they be justified?

This study aims to show the studies which contain information regarding the prevalence and distribution of venous disease. Then using the population and prevalence data for venous disease, and considering the cost of treating varicose veins, aims to analyse the treatment of varicose veins and assess whether there is a disparity between European countries.

Methods

Relevant papers regarding the prevalence or incidence of venous disease were identified through searches of PubMed (1966 to October 2010). The search terms ‘prevalence OR incidence’ AND ‘varicose veins or venous disease’ were used. Article titles and abstracts were screened for inclusion. A manual reference list search was also carried out for further appropriate studies to be considered for inclusion. Articles regarding cardiac or coronary disease, cancer and thromboembolism were excluded. Relevant full-text articles were scrutinized and all studies reporting the distribution of venous disease in a representative sample population, that is not those seeking specific treatment for venous disease, were included. The relevant data including the prevalence of venous disease in the population and the distribution of clinical disease severity within that population were included.

For the subsequent calculations, prevalence data were obtained from the Bonn Vein Study (BVS). In this study 3072 people were selected at random from a population register and screened for venous disease. This included a full history, clinical assessment, completion of a quality-of-life questionnaire and venous duplex ultrasound examination. The severity of venous disease for each subject was given by the CEAP (clinical, aetiological, anatomical and pathological elements) classification.

Population data were obtained from the UK Office for National Statistics UKONS and Eurostat, the statistical office of the European Union, Luxembourg. The number of inhabitants aged between 15 and 79 years of age was obtained. This age range was selected as some of the data grouped patients from age 15 to 79 and also this represents the age range in which the majority of patients with venous disease would be offered a procedure in all countries. These data-sets were used to calculate the numbers within the population and the actual numbers that would fall into each of the clinical stages of disease.

The number of varicose vein procedures performed in each country was obtained from the Hospital Episode Statistics (HES) for the UK and from the Millennium Research Group for continental European countries for 2010. These data were compared with the predicted number of patients that were previously calculated that would require an intervention for varicose veins, that is, the predicted numbers of patients with C2–C6 disease.

Data regarding the cost of treating varicose veins were obtained from HES online in the UK and for continental European countries from health economic analyses. These data-sets were used to estimate the cost of treating these patients with superficial venous disease. Venous experts in each of the European countries were contacted if information regarding the cost of varicose vein interventions could not be found in the literature. In these cases the reimbursement fees for each of the procedures were used for each country if available.

Results

Epidemiology of venous disease

The initial search strategy yielded 4896 results. After title and abstract screening, 11 full-text articles were examined. Seven were excluded as either the
sampled populations consisted of patients presenting with venous disease so were not considered to be representative of the general population, or the population selected could not be classified by disease class as insufficient information was available, or if the selected population was restricted. The results from the four included studies regarding the prevalence and distribution of clinical disease class severity are shown in Table 1. Each study determined the prevalence of venous disease by a different consideration. Bihari et al.\textsuperscript{17} considered the presence of venous disease in any patient with a visible varicosity including reticular or spider veins. Evans et al.\textsuperscript{4} did not use the CEAP classification and considered patients with C1 disease in the ‘no disease’ category. Rabe et al.\textsuperscript{18} selected a large population; however, the results regarding clinical severity have not yet been correlated with the presence of reflux, so the number of patients with treatable disease is not known. Chiesa et al.\textsuperscript{19} and Evans et al.\textsuperscript{4} both assessed for the presence of reflux in the general population; however, there was selection bias in the study by Chiesa et al.\textsuperscript{19} as patients were selected by advertising, so it was not a representative of the general population. Rabe et al.\textsuperscript{14}, however, although they note a high prevalence of C1 disease and above, over 90\%, they also correlate this with reflux measurements, and therefore potentially treatable disease can be calculated. The prevalence data from all of these studies are shown in Table 1.

**Prevalence of venous disease across Europe**

Population data were obtained from the UK Office for National Statistics, the statistical office of the European Union, Luxembourg. The number of inhabitants aged between 15 and 79 years of age was obtained for each country. According to the BVS, the prevalence of venous disease in the population was 20\%; therefore, the number of patients with potentially treatable venous disease between these age ranges was calculated. Subsequently, using data from the BVS regarding the percentage distribution of patients for each stage of clinical severity by CEAP classification, the estimated number of population with C0, C1, C2, C3, C4, C5 and C6 diseases were calculated. This is shown in Table 2.

**A comparison of the calculated and actual number of varicose vein procedures performed**

In order to calculate the estimated number of varicose vein procedures per year that would be required to treat all patients at each stage of clinical severity, the absolute numbers (Table 1), were divided by 64 (the number of years in the age range 15–79 years). The estimated number of treatments that would be performed per year in each European country if all patients with C2–C6, C3–C6 and C4–C6 diseases were treated was calculated. These are shown in Table 3.

Patients with C2 and more severe venous disease are likely to be the population who would seek treatment as visible varicosities and other symptoms may have an impact on their quality of life. Patients with C1 disease generally do not require treatment, apart from cosmesis. Therefore, a treatment threshold of C2 disease and above was assumed. The actual number of treatments carried out in each country was compared with the

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**Table 1** The prevalence and distribution of varicose veins from epidemiological studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Prevalence of venous disease (%)</th>
<th>Clinical disease class severity distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabe et al. (2003)\textsuperscript{14}</td>
<td>Germany</td>
<td>90.4</td>
<td>9.6 59 14.3 13.5 2.9 0.6 0.1</td>
<td></td>
</tr>
<tr>
<td>Chiesa et al. (2005)\textsuperscript{19}</td>
<td>Italy</td>
<td>62.9</td>
<td>22.7 64.8 29.4 13.6 13.6 3.4 8.6</td>
<td></td>
</tr>
<tr>
<td>Bihari et al. (2011)\textsuperscript{17}</td>
<td>Hungary</td>
<td>5713</td>
<td>42.0 31.1 10.1 7.1 6.9 1.8 1.0</td>
<td></td>
</tr>
<tr>
<td>Rabe et al. (2012)\textsuperscript{18}</td>
<td>Worldwide</td>
<td>83.6</td>
<td>36.1 21.7 17.9 14.7 7.5 1.4 0.7</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2** The calculated number population in each European country with each stage of severity of venous disease

<table>
<thead>
<tr>
<th>Number of population \times 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
</tr>
<tr>
<td>C1</td>
</tr>
<tr>
<td>C2</td>
</tr>
<tr>
<td>C3</td>
</tr>
<tr>
<td>C4</td>
</tr>
<tr>
<td>C5–C6</td>
</tr>
</tbody>
</table>
calculated figure of all patients with C2–C6 disease were offered treatment. This is represented graphically in Figure 1. The line running through ‘0’ represents the level at which the calculated number of required treatments is equal to the actual number of procedures carried out, that is if all patients with C2–C6 disease were treated. Above the line is additional actual number of procedures performed, and below the line is the shortfall, representing the predicted number of patients with C2 disease and above who are not receiving treatment. This is represented as a percentage relative to the predicted number of patients with C2 disease.

As shown on the graph, the UK, Finland and Sweden, according to the calculated values are not treating all patients predicted to have C2–C6 disease. In contrast to this, all other European countries represented are treating more patients, suggesting that they may be treating additional patients, which may represent the treatment of recurrent disease, multiple procedures on individual patients or that the calculated predicted numbers of patients with C2–6 disease were under-estimated.

The cost of performing varicose vein procedures

The number of additional procedures or the number of patients with C2 disease not treated was compared with the actual number of procedures carried out in each country. The costs of performing varicose vein procedures in each of the European countries were obtained from recent health-economic analyses, insurance reimbursement costs and from European venous experts. The potential additional costs for the countries performing more varicose vein procedures than patients with C2–C6 disease were calculated and are shown in Table 4. The potential cost-savings by the countries not treating all patients with C2–C6 disease are shown in Table 5.

The term ‘potential’ is emphasized as these calculations are based on the predicted numbers of patients with C2–C6 disease and they do not take into account the long-term costs of disease.

<table>
<thead>
<tr>
<th>CEAP range</th>
<th>UK</th>
<th>Denmark</th>
<th>Germany</th>
<th>Spain</th>
<th>France</th>
<th>Italy</th>
<th>Finland</th>
<th>Sweden</th>
<th>Netherlands</th>
<th>Austria</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2–C6</td>
<td>47,509</td>
<td>4225</td>
<td>65,350</td>
<td>36,188</td>
<td>48,393</td>
<td>47,477</td>
<td>4137</td>
<td>7160</td>
<td>12,770</td>
<td>6604</td>
</tr>
<tr>
<td>C3–C6</td>
<td>25,873</td>
<td>2301</td>
<td>35,589</td>
<td>19,708</td>
<td>26,354</td>
<td>25,856</td>
<td>2253</td>
<td>3899</td>
<td>6954</td>
<td>3597</td>
</tr>
<tr>
<td>C4–C6</td>
<td>5447</td>
<td>484</td>
<td>7492</td>
<td>4149</td>
<td>5548</td>
<td>5443</td>
<td>474</td>
<td>821</td>
<td>1464</td>
<td>757</td>
</tr>
</tbody>
</table>

CEAP, clinical, aetiological, anatomical and pathological elements

Figure 1 A comparison of the actual number of procedures performed with the calculated number that should be carried out if all patients with C2–C6 disease were treated
progression, compression hosiery and societal costs of not treating this group of patients.

Comparison of the actual number of varicose vein procedures performed in different European countries

The number of varicose vein procedures carried out in each country in 2010 was compared with the number of population, and the number of procedures per million population was calculated to see if there was a disparity across Europe. The numbers of procedures per million ranged from a low of 685 in the UK to a high of 2853 in Germany. The values for each of the other European countries is shown in Figure 2.

Discussion

From this study, there is currently a marked disparity in the way in which varicose veins are treated throughout Europe. This is shown by both the wide variation in the numbers of procedures per million persons as well as the calculated values of the different numbers of patients with different disease severity being treated. The UK is performing the lowest number of varicose vein procedures per million persons and from the calculated data it is assumed that all patients with higher disease class severities are being treated, the majority of patients with uncomplicated varicose veins are not undergoing intervention. Current trends indicate that the number of varicose vein procedures performed each year in the UK is decreasing (Figure 3). This may increase costs overall, and leave patients with worsening but potentially treatable venous disease.

In the UK, patients with C2 disease, are often not offered treatment on the NHS. Conversely, in other European countries, notably Germany, the Netherlands and Austria, many more procedures are being carried out per million population, up to

Table 4  Potential additional costs of treating more patients than those with C2–C6 disease

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost of all C2–C6 (€millions)</th>
<th>Additional procedures carried out</th>
<th>Potential costs saving (€millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>8</td>
<td>1775</td>
<td>4</td>
</tr>
<tr>
<td>Germany</td>
<td>105</td>
<td>124,650</td>
<td>199</td>
</tr>
<tr>
<td>Spain</td>
<td>58</td>
<td>30,812</td>
<td>49</td>
</tr>
<tr>
<td>France</td>
<td>77</td>
<td>31,607</td>
<td>50</td>
</tr>
<tr>
<td>Italy</td>
<td>76</td>
<td>22,523</td>
<td>36</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>20</td>
<td>22,230</td>
<td>36</td>
</tr>
<tr>
<td>Austria</td>
<td>11</td>
<td>11,187</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 5  Potential cost-saving of not treating all patients with C2–C6 disease

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost of all C2–C6 (€millions)</th>
<th>Potential patients with C2 not treated</th>
<th>Potential costs saving (€millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>67</td>
<td>14,327</td>
<td>23</td>
</tr>
<tr>
<td>Finland</td>
<td>6</td>
<td>1152</td>
<td>2</td>
</tr>
<tr>
<td>Sweden</td>
<td>10</td>
<td>697</td>
<td>1</td>
</tr>
</tbody>
</table>

![Figure 2](image-url) The number of varicose vein procedures carried out per million population in each European country
four times more than that in the UK, and from the calculated data, patients with disease class severity of less than C2 disease are even being treated. The differences between countries may occur for many reasons, including primary health-care service availability, patient and physician perceptions of the importance of venous disease and the demand for cosmetic treatment. Different procedures for reimbursement may contribute, as in some countries procedures are carried out in stages as each modality of treatment is separately reimbursed.

There is currently a paucity of accurate longitudinal evidence to support this supposition, as there are currently no studies that exist assessing whether endovenous or open varicose vein procedures performed early in clinical disease have an impact on progression. However, there is evidence to suggest that the number of patients with venous ulcers can be reduced by half if patients with mild-to-moderate venous disease are offered surgery. In the long-term, this may prove to be more cost-effective, although larger studies are needed. The calculated potential additional shown in Tables 3 and 4 are only for the treatment of one leg and not for recurrent varicose veins, so these may be underestimated. In the UK, the procedures performed in private practice are not included in these calculations. However, estimates from independent private health-care providers in the UK suggest that these figures are not increasing as the number of procedures performed within the NHS are decreasing.

This study has limitations. The data from the BVS on the distribution of clinical venous disease severity by CEAP classification was applied to the 20% of patients with reflux in at least one superficial vein, which represents those that would be suitable for treatment, rather than the whole population. This is likely to have resulted in an underestimation of the number of patients that may be eligible for treatment, as patients with radiological reflux are probably more likely to have signs of venous disease than a selection of the population as a whole. The costs of ongoing treatments including compression stockings, treating higher classes of disease severity and recurrence were not included. It was assumed that each treatment was carried out on one limb of one patient and costs of treating recurrence were not included. This resulted in an underestimation of the cost of treating venous disease. The costs used were taken as either the reimbursement tariffs for a procedure or the average costs of the different procedures from the literature, but as some procedures, for example sclerotherapy, are less expensive than open surgery, this will alter the results. Data regarding whether the procedures were carried out under local or general anaesthetic were not available and so could not be taken into consideration.

In the current time of economic austerity, where public spending is under considerable inspection, treatment provision is an area of growing interest. Across Europe, there is a wide disparity in the number of procedures for varicose veins between countries. Different clinical stages of disease are being treated and there is little consistency. Importantly, the potential treatment costs of performing these procedures need to be considered and the
question asked: can they be justified? If the costs of treating higher classes of disease severity and the impact on patients' quality of life are taken into consideration, it may be that treating more patients with varicose veins is more cost-effective in the long term.

Conclusions

There is a marked disparity across Europe between the predicted number of patients with varicose veins requiring treatment and the actual care given, with the UK, Finland and Sweden possibly under-treating varicose veins. However, it may prove more cost-effective in the long term to treat all patients with varicose veins to prevent disease progression which may prove more expensive to treat. The factors influencing this need more detailed investigation.

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Patterns of short saphenous vein incompetence

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Abstract
The significance of short saphenous vein (SSV) reflux is an under-explored territory in chronic venous disease (CVD). We have examined the origin and significance of SSV reflux in primary and secondary CVD. While the natural history of SSV incompetence remains uncertain, its prevalence has been shown to approximate 3.5%, rising with progressing clinical venous insufficiency, and bears an association with lateral malleolar venous ulceration. The most common pattern of reflux extends throughout the SSV. Patterns of incompetence in recurrent disease are highly variable, but SSV reflux may itself pose a risk for recurrence, in part due to the complex anatomy of the saphenopopliteal system. Further studies are required to delineate the impact of SSV reflux in secondary venous disease and deep venous incompetence.

Keywords: anatomy; venous; pattern; varicose vein

Introduction
Chronic venous disease (CVD) is the most prevalent vascular disorder, and can result in a spectrum of disorders ranging from mild pain and oedema through to frank ulceration. The advent of duplex ultrasonography has permitted direct and accurate visualization of incompetent venous segments relating to reported symptomatology and clinical findings. The most commonly documented site of reflux is the great saphenous vein (GSV). While the association between small saphenous vein (SSV) incompetence and venous disease was established as early as 1959, the significance of SSV reflux is an under-explored territory in CVD.

Tributaries from the dorsal aspect of the foot combine with those from the dorsal venous arch to form the SSV, which drains the heel and subcutaneous tissues of the posterior aspect of the leg. Also termed the lesser or short saphenous vein, the SSV runs posterior to the lateral malleolus, within the saphenous fascia, and ascends to drain into the popliteal vein via the saphenopopliteal junction (SPJ). The latter is an entity of varying anatomical position, with both ultrasound and cadaveric studies showing little predictability in its localization. This anatomical variation, together with the proximity of the SPJ to important neurovascular structures such as the common peroneal nerve, may complicate the invasive management of SSV disease.

Origin of SSV reflux
There remains no clear consensus on how superficial primary CVD commences and progresses, thus its natural history remains uncertain. Traditionally, superficial venous incompetence was attributed to a primary valvular insufficiency that commenced at the saphenous junction and progressed distally—the ‘descending theory’. This posed a significant problem for SSV reflux, as without deep venous incompetence or an incompetent Giacomini vein, there could not be a continuous blood column.

More recently, the advent of duplex ultrasonography has rendered support to an alternative ‘ascending theory’, that hypothesizes the proximal progression of distal venous incompetence. This is supported by the observation that superficial venous incompetence often occurs with...
a competent saphenous junction. Moreover, varicose veins can occur with no evidence of truncal incompetence (particularly in young patients), suggesting that varicose disease can extend in an antegrade manner, from saphenous tributaries to saphenous veins.

Duplex imaging has also shown vein dilation occurring distal to an incompetent valve, as opposed to proximal dilation that would be expected as a consequence of descending incompetence. Studies have demonstrated that tributary incompetence predominates in younger patients suggesting that saphenous trunk or junction reflux may be a secondary occurrence.

In fact, primary venous reflux can occur in any superficial or deep vein of the lower limb. The below-knee veins may well be affected in asymptomatic individuals and in those who have prominent or varicose veins. These data suggest that reflux appears to be a local or multifocal process in addition to or separate from a retrograde process.

### Prevalence of SSV incompetence

The Edinburgh Vein Study assessed subjects with both clinical and duplex ultrasonographic examination, leading to a true estimate of the prevalence of CVD among the population. Of the 1092 subjects with complete scans, 43 had duplex evidence of SSV incompetence (3.9%). The prevalence of SSV reflux increased with progression of chronic venous insufficiency ($P < 0.001$). The Bonn Vein Study echoed these findings with a prevalence of 3.5% and furthermore showed that SSV reflux (as well as GSV and deep venous incompetence) increased with age, obesity and CEAP (clinical, aetiological, anatomical and pathological elements) classification of disease.

### SSV incompetence in primary CVD

Duplex ultrasonography studies have shown marked variation in the prevalence of SSV reflux in patients with symptoms and/or signs of primary CVD.

In a small study of 32 patients with symptomatic venous disease, only 2% of limbs were shown to have SSV incompetence. Kurt et al. found that 5.8% of limbs from 178 patients with symptoms/signs of primary CVD had evidence of isolated SSV reflux; of note, there was no significant difference between the age, BMI, and gender of those with and without SSV disease. Labropoulos et al. found a similar prevalence of isolated SSV incompetence at 6.6% in their large duplex ultrasonographic study of 2254 limbs. The most common pattern of reflux in the short saphenous system extended throughout the length of SSV (57%) without involvement of Giacomini or gastrocnemial veins. These patients were most likely to present at stage C2–C4. Nuehardt et al. found a SSV reflux prevalence of 13% in a study of 410 symptomatic legs.

When considering patients with primary superficial incompetence only (and competent deep and perforating veins), the presence of isolated SSV reflux rose to 33%, with 19% of limbs showing evidence of both GSV and SSV incompetence. While the presence of ache or pain was not related to the extent of reflux, the presence of extensive reflux in both GSV and SSV was associated with a higher incidence of ulceration. This association is not clear-cut, as early duplex ultrasonography studies related ulceration to SPJ incompetence, as opposed to reflux of the SSV.

The influence of SPJ reflux on lateral leg ulceration was emphasized in a study of 20 legs with isolated lateral malleolar ulceration. Ligation and division of the refluxing SPJ in association with conservative management resulted in all ulcers healing within 12 weeks. However, 15 of these limbs had been previously treated as a non-venous aetiology, and there was no control group. A larger study compared patterns of venous incompetence in 776 limbs with primary uncomplicated varicose veins with those in 166 limbs with the complications of lipodermatosclerosis or past venous ulceration (C4–C5). Limbs with complications more frequently showed SSV reflux ($P < 0.05$).

Despite the suggested association between SSV incompetence and high CEAP classifications of disease, short saphenous reflux has also been demonstrated in patients with primary varicose veins but no clinical suspicion of SSV incompetence. Jutley et al. reported 42 of 223 scanned limbs (19%) to demonstrate SSV reflux, of which 67% had not been clinically suspected. This highlights the importance of preoperative duplex assessment.

### SSV incompetence in recurrent venous disease

The recurrence of venous reflux following treatment is highly variable and, like primary venous disease, often multifocal.

Studies have highlighted the increased likelihood of recurrence in the presence of SSV reflux,
following surgical treatment. This may be due to anatomical variation in the position of the SPJ.

Labropoulos et al. studied patterns of recurrent venous incompetence following surgical intervention in patients with CVD. One hundred and thirty-four limbs from 123 patients with recurrent varicose veins underwent duplex ultrasonography assessment of GSV and SSV systems to determine extent of reflux. Following SPJ ligation, the more common pattern of incompetence observed was SSV reflux (75%), whereas after SSV stripping was performed, SSV tributary reflux predominated (64%).

**Treatment of SSV incompetence**

The pattern of venous reflux is often unpredictable, and with specific regard to the short saphenous system, the position of the SPJ is inconsistent. Invasive management may be further complicated by the proximity of the SPJ with important neurovascular structures, such as the common peroneal nerve, and the added anaesthetic risk of intervention with the patient placed in the prone position. Traditional open surgery – ligation of the PSJ with or without vein stripping is effective, but has a high recurrence rate, likely due to anatomical complexity.

However, with the advent of endovenous techniques using ultrasound guidance, standardized treatment of the SPJ and SSV is now far easier to replicate with few side-effects.

The degree of heterogeneity of patterns of SSV incompetence and their clinical sequelae imply that individualized treatment is necessary to achieve the optimum outcome. Few studies have investigated the effect of SSV treatment in the context of deep venous incompetence, though previous work has shown improvement in haemodynamics with superficial vein ablation.

**Conclusion**

SSV incompetence is a significant contributor to the global burden of CVD but due to anatomical variability it remains a complex variable. Endovenous treatments offer a reproducible answer to this variability. Further work is needed to delineate the impact of SSV disease in secondary venous disease and in deep venous incompetence.

**Funding**

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**Conflict of interest**

The authors have no conflicts of interest to declare.

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Short Report
Management of Uncomplicated Varicose Veins — A Case Vignette for a Clinical Decision Proposal

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Abstract

Venous disorder is common in the general population. Uncomplicated varicose veins represent a significant proportion of the disease burden, and can impact considerably on quality of life, producing a wide spectrum of symptoms. Little is known about the natural course of the disease at this stage and the treatment strategy employed is often not based on robust scientific evidence.

The aim of this article is to elucidate the options to manage uncomplicated varicose veins. There are likely to be significant geographic differences in the treatment strategy employed, and it is hoped that we will arouse discussion among physicians regarding the management of this very common medical condition. The reader will be asked for their preferred treatment choice for a given clinical case vignette.

Background

Venous disorders affect a large proportion of the adult population, and are both commonly encountered in primary care and frequently referred to hospital services. It encompasses a spectrum of diseases, and there are a number of treatment options available, which are likely to be variably practised. The aim of this article is to evaluate current strategies in the management of uncomplicated varicose veins, which represents a significant portion of this condition, in the context of the available evidence.

Recommendations for the treatment of patients with varicose veins should be based on an understanding of the natural history of the condition at this stage, taking into account the likely consequences of leaving the disease untreated and the benefits and risks of any treatments. Conservative and invasive treatment options are available and should be applied taking into account the impact of disease progression, quality of life and health-care resources. In the early disease stages Clear scientific evidence is lacking for one or another management option. Therefore, differences in disease awareness and treatment approaches are subject to an animated discussion amongst specialists.

Following reading the clinical vignette, you will be asked to select your preferred management option from a list of three choices.

Case Vignette

A 48-year-old woman was seen by her general practitioner (primary care physician) for a routine examination. He refers the patient to you for your specialist opinion on ‘some varicosity’ on the left leg. The patient has a past medical history of hypothyroidism for which she takes thyroxin 50 mcg daily. She drinks alcohol rarely and does not smoke.

She is overweight, with a body mass index of 28. Her blood pressure is 130/85 mmHg, and heart rate is 84 beats per minute. Cardiovascular examination is normal. Examination of the legs demonstrates left leg varicosities along the distribution of the great saphenous vein. There are no associated skin changes and no oedema can be detected at this time of the day (10 am).

On questioning, the patient does not report any history of leg trauma, deep vein thrombosis or superficial thrombophlebitis. Her mother suffered from varicose veins without progression to severe skin changes or venous ulceration. She first noticed her left leg varicose veins after her first pregnancy. They increased in prominence during her second pregnancy at the age of 39, but subsequently have remained unchanged. When asked specifically, she confirms that she experiences symptoms of heaviness in the left leg, which is worse in the evening and during hot summer days. She also
reports mild swelling of the left calf and ankle. She has not been previously investigated or received treatment for her varicose veins.

The patient following referral to you undergoes a duplex scan, which reveals primary varicose veins with incompetence of the left sapheno-femoral junction and long saphenous vein down to the proximal calf region and two tributaries. The deep venous system is normal and competent.

Which one of the following management strategies, any of which would be considered correct, would you employ for this patient? Please base your choice on your routine clinical practice.

a) No further diagnostic work-up or treatment. Follow-up at routine visits with the GP once a year. No special treatment recommendations.

b) Recommend the use of compression stockings (e.g., 20–30 mmHg) during work and periods of prolonged standing.

c) Ask the patient for her preferences, explain the evidence for the natural course of the disease and for the various treatment options and decide according to patient’s preference.

d) Consider ablative treatment for varicose veins, only if there is secured funding.

e) Clear statement for varicose vein ablation. Treatment is indicated to prevent further evolution of venous disorder in this relatively young and otherwise healthy subject.

**Comment on Case Vignette**

In the case presented, the patient has clinical stage C2 according to the clinical classification of the Clinical Etiology Anatomical Pathological (CEAP) system. Duplex scan reveals a primary varicosity with complete incompetence of the long saphenous vein down to the proximal calf level giving rise to two tributaries. The deep venous system is normal and competent.

This is a commonly encountered situation and any interventional treatment, given the above, might be considered to be fairly controversial in this patient, as there are no significant skin changes and apparently no substantial reduction of quality of life. Conservative and invasive treatment options will be briefly presented below. However, according to the latest recommendation of the Venous Forum of the Royal Society of Medicine, ablative treatment at this stage of disease should be considered, but is not compulsory. A slightly more aggressive stance is advocated in the recent Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum. Based on grade B evidence (best estimates of the critical benefits and risks outcome from randomised, controlled trials with important limitations), they advise against compression therapy as a first line approach, and recommend endothermal saphenous vein ablation as the primary treatment of symptomatic varicose veins in those patients who are suitable for therapy.

**Treatment Options for Varicose Veins**

**Conservative treatment**

Compression therapy forms the cornerstone of conservative treatment for venous disorders independent of the underlying cause. If no invasive or ablative treatment is being contemplated, it can be suggested even without diagnostic work-up, in the absence of significant peripheral vascular disease. A calf-long medical compression stocking with a defined ankle pressure of 20–30 mmHg, that is, class II compression hosiery is usually adequate. However, the data available suggest that compliance to compression therapy is generally poor. Moreover, given the relatively young age of the patient, who is also likely to be in good health, lifelong medical compression therapy is unlikely to be considered to be an acceptable option by the patient and indeed is unlikely to be cost effective. Anti-oedema drugs, for example, horse-chestnut seed extracts, hydroxethylrutosides, (Daflon) and red-vine-leaf extract AS195 (Antistax), have been shown to be efficacious in the treatment of venous symptoms in previous trials and should be considered. However, their long-term impact on disease progression and skin changes is unknown. Other conservative measures, such as lifestyle changes, have not been shown to offer any long-term preventative or beneficial effect in the presented case vignette.

**Invasive treatment**

Nowadays, there are a number of treatment options available for ablation of varicose veins. Surgery was previously considered to be the gold standard, but is now sidelined by less invasive techniques, such as, endothermal procedures, for example, laser or radiofrequency ablation and ultrasound guided foam sclerotherapy. These treatments can be performed in an outpatient setting under local anaesthesia, and their use is guided and dependent on the anatomic/physiological findings on duplex.

Patient co-morbidities, skill of the treating specialist, local health-care system proprieties and patient preference are all factors that will influence the therapeutic modality applied. Short- and mid-term results for endothermal ablation are promising and have led to their routine use in many centres. Severe adverse events appear to be very rare with both endothermal ablation and foam sclerotherapy.

**Conclusion**

This case vignette presents a commonly encountered situation for the venous specialist. Different treatment options, any of which can be considered correct, can be applied. More long-term data of randomised controlled trials are needed to tailor the management of uncomplicated varicose veins.

**Conflict of Interest/Funding**

None.

**References**


The Burden of Depression in Patients with Symptomatic Varicose Veins

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WHAT THIS PAPER ADDS

• This article highlights the need to regard venous disease as a chronic illness, and evaluates its impact on quality of life and importantly on depression an area which has not been tackled previously. The article emphasises the need for vascular surgeons to look beyond the disease process and take a more holistic approach to patient care.

INTRODUCTION

Depression is a common mental health disorder, and affects more than 120 million people worldwide.¹ It is characterised by symptoms of sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration (WHO). These symptoms can become chronic or recurrent impairing an individual’s ability to cope with daily life. Depression costs the UK economy over £9 billion in lost working days, and although it can be both reliably diagnosed and treated in a primary care setting only a quarter of patients with depression seek medical advice or are receiving treatment.²

Overall, 1 in 10 adults in Britain suffer from depression at any one time and depression is approximately 2–3 times more common in patients with chronic physical health problems, compared to those who have good physical health.³ This observation led to the development in 2009 of NICE guidelines in the UK,³ recommending that all adults, aged 18 years and older, with chronic physical illness be screened for depression.

Varicose veins have been shown to impact on quality of life (QoL),⁴ with increasing severity of disease having a proportionately

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ABSTRACT

Objective: To evaluate the burden and impact of depression in patients with symptomatic varicose veins.

Methods: Patients with varicose veins referred to the vascular surgeons for further management, were invited to complete a validated questionnaire relating to quality of life, using the Aberdeen Varicose Veins Questionnaire (AVVQ), EuroQol-5D questionnaire (EQ-5D) and the EuroQol-Visual Analogue Score (EQ-VAS); and depressive symptoms, using the Centre of Epidemiological Studies Depression Scale (CES-D). Social, demographic, clinical (CEAP classification, venous clinical severity score (VCSS)) and venous disability score (VDS) data was also collected.

Results: One hundred patients, mean age 52.7 years (63 females; 37 males) were recruited. Twenty-nine per cent of patients with varicose veins had depression scores suggestive of depression; no patient had previously been diagnosed or was on treatment. Depression scores were not influenced by age (p = 0.30) or gender (p = 0.60); and there was no correlation between depression scores and VCSS (p = 0.07, r² = 0.034), or between VDS groups 1, 2 or 3 (p = 0.75). There was a weak correlation between depression scores and AVVQ (p = 0.0009, r² = 0.12) and depression scores and EQ-5D (p < 0.0001, r² = 0.32) and EQ-VAS (p < 0.0001, r² = 0.25).

Conclusion: Depression is prevalent in patients with symptomatic varicose veins, where it is commonly undiagnosed and untreated. A more holistic approach to patients with venous disease is therefore advocated.

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greater impact. Depression has also been shown to adversely affect QoL. The effect of symptomatic varicose veins on mental health outcomes and on depression specifically is less well defined. The aim of this study was to evaluate the burden of depression in patients with symptomatic uncomplicated and complicated (associated with skin changes which include eczema, lipodermatosclerosis and ulcers) varicose veins presenting to tertiary care for treatment.

Methods

Patient selection

All patients referred by their General Practitioner (GP) to the vascular surgery outpatients clinic at Charing Cross Hospital, London, for management of their varicose veins, over a 6 month period from January to June 2011, were invited to complete a validated questionnaire relating to disease-specific quality of life, using the Aberdeen Varicose Veins Questionnaire (AVVQ) and health-related QoL, using the EuroQol-5D questionnaire (EQ-5D, EuroQol Group, Rotterdam, The Netherlands) and EuroQol-Visual Analogue Score (EQ-VAS). The presence of depressive symptoms was determined using the Centre for Epidemiological Studies Depression Scale (CES-D Scale) (see Table 1). A 20 item self-reporting scale which has been shown to be both a sensitive and valid screening tool for detecting depressive symptoms across different populations.

No patients were excluded from the study. Ethics approval was obtained from the Local Research Ethics Committee (LREC). Questionnaires were administered in a clinic setting following the consultation and prior to any intervention. Questionnaires typically took 30 min to complete. Patients did not receive any direction regarding how they should be filled, but were provided standardised guidance notes and given the opportunity to ask questions.

Generic QoL measurement tools, such as the EuroQol (EQ-5D), are divided into domains of interest. They thereby allow mental, physical and social aspects of QoL to be evaluated independently. Disease-specific QoL measurement tools, such as the AVVQ, attempt to quantify the change in QoL due to an individual disease state. In combination, these two types of tool provide a powerful and robust method for assessing both the baseline QoL and disease-specific QoL and were therefore both utilised in this study.

Patient age, occupation, gender, medical co-morbidity and history of previous intervention for varicose veins were also determined. The clinical severity of venous disease was established by the treating physician using the Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification, Venous Clinical Severity Score (VCSS) and Venous Disability Score (VDS).

Once completed, all questionnaires were collated and analysed. The number of eligible patients who did not complete the questionnaire was also recorded. Patients with CES-D scores of >16 were referred to their GP for further management.

Statistical analysis

Univariate linear correlation analysis was used to assess the relationship between two independent variables. Mann-Whitney-U test was used to assess the difference between two independent groups. Statistical significance was expressed as both p values and 95% confidence intervals. A p value <0.05 was considered statistically significant.

Results

Demographic data

A hundred patients were recruited from a total of 125 eligible patients (80% uptake) over the 6 months study period. There were 37 men (37%) and 63 women (63%). All questionnaires were fully completed and included in the analysis. The mean age of patients was 52.7 years (range, 24–91 years), 72% of patients were under the age of 65 and 28% were aged 65 years or more. There was no significant correlation between CES-D score and patient age (p = 0.30, r² = 0.011). There was no difference in depression scores

Table 1

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Number of items</th>
<th>Parameters evaluated</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberdeen Varicose Vein Questionnaire (AVVQ)</td>
<td>13</td>
<td>- Physical symptoms</td>
<td>0 (no effect) to 100 (severe effect)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Compression therapy use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Limitations of disease on daily and social activities</td>
<td></td>
</tr>
<tr>
<td>EuroQol-5D (EQ-5D)</td>
<td>5</td>
<td>- Mobility</td>
<td>n/a</td>
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<tr>
<td></td>
<td></td>
<td>- Self-care</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pain/Discomfort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anxiety/Depression</td>
<td></td>
</tr>
<tr>
<td>EuroQol-Visual Analogue Score (EQ-VAS)</td>
<td>n/a</td>
<td>This is a 20 cm subjective visual analogue scale relating to health-related quality of life</td>
<td>100-0</td>
</tr>
<tr>
<td>Centre of Epidemiological Studies Depression Score (CES-D)</td>
<td>20</td>
<td>This is a sensitive and validated self-reporting depression-symptom scale</td>
<td>0–60</td>
</tr>
<tr>
<td>Clinical Stage of the Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification</td>
<td>6</td>
<td>CD  – no visible varicose veins</td>
<td>0–6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C1  – spider or reticular veins</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  – Varicose veins</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  – Oedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4  – Skin changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5  – Healed ulcer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6  – Active ulcer</td>
<td></td>
</tr>
<tr>
<td>Venous Clinical Severity Score (VCSS)</td>
<td>9</td>
<td>Evaluates for presence of skin changes and pigmentation, inflammation and induration, presence of ulcers and use of compression hosiery</td>
<td>Maximum score of 27</td>
</tr>
<tr>
<td>Venous Disability Score (VDS)</td>
<td>1</td>
<td>Based on the ability to work an 8-h day with or without the requirement for external compression hosiery support</td>
<td>0–3</td>
</tr>
</tbody>
</table>
between those patients aged over 65 years and those aged less than 65 years old \( (p = 0.60) \).

Twenty-nine per cent of all patients had CES-D scores greater than 16 and 5% of patients had CES-D scores greater than 26. No patient had previously been diagnosed or treated, or were on current treatment for depression.

In terms of past medical history, no patient had co-existing peripheral vascular disease. Thirty-three patients (33%) had previously undergone intervention for their varicose veins. There was no significant difference in CES-D scores in patients who had previously undergone treatment for their varicose veins, compared to those who had not \( (p = 0.94) \).

**Depression and quality of life**

A weak positive correlation was seen between CES-D score and disease-specific QoL as evaluated using the AVVQ \( (p = 0.0009, r^2 = 0.11) \) (see Fig. 1). A significant negative correlation was seen between CES-D score and health-related QoL as indicated by EQ-5D \( (p < 0.0009, r^2 = 0.32) \) and EQ-VAS scores \( (p < 0.0009, r^2 = 0.25) \) (see Figs. 2 and 3). Higher EQ-5D and EQ-VAS, unlike the AVVQ score, indicate better QoL and lower EQ-5D and EQ-VAS scores worse QoL.

**Depression and clinical severity of venous disease**

Patients with severe depression \( (n = 5) \) were observed to have venous disease of clinical stage 4–6, as defined by the CEAP classification. However, overall there was no difference in CES-D scores with varying clinical stage \( (p = 0.30) \). CES-D score did not correlate with the VCSS \( (p = 0.07, r^2 = 0.03) \) or VDS \( (p = 0.75) \) (see Figs. 4 and 5).

**Discussion**

The presence of depression in patients with varicose veins has undergone only limited investigation previously. In contrast, QoL status in patients with varicose veins has been extensively investigated, and is an accepted outcome measure used both in clinical practice and in clinical trials investigating varicose vein treatment. QoL measures are also shown to be better correlated with symptomatology and patient satisfaction than anatomical or technical measures.

Varicose veins are common with a reported incidence of 20–25% in women, and 10–15% in men. A number of studies have shown an increased incidence of depression and anxiety in patients with venous ulcers, with reported incidences ranging from 40 to 60%. Our study reports an incidence of depression in patients with symptomatic varicose veins of 29% and this falls to

![Figure 1](image1.png) **Figure 1.** Graph demonstrating a positive correlation between CES-D and disease specific quality of life as indicated by the AVVQ score \( (p = 0.0009, r^2 = 0.11) \).

![Figure 2](image2.png) **Figure 2.** Graph demonstrating a correlation between CES-D and health-related quality of life as indicated by the EQ-5D \( (p < 0.0001, r^2 = 0.32) \) and EQ-VAS scores \( (p = 0.0009, r^2 = 0.25) \).

26% when patients with healed or active venous ulcers are excluded. This is twice the reported prevalence of depression within the general population, but is similar to that reported in patients with chronic physical health problems.

Esteban et al, in a Spanish study of 7341 subjects aged >15 years with a variety of chronic medical diseases, found that depression had a significant impact on health-related QoL. When looking specifically at the impact of venous disease on mental health, Smith et al in their study found no significant difference in the mental health domain of the SF-36 in patients with varicose veins compared to those without, but following treatment with open surgery there was a significant improvement in the mental health domain. In our study, depressive symptoms correlated with disease-specific and health-related QoL outcomes, however, we failed to demonstrate any correlation with clinical disease severity. A possible explanation is that depression may alter a patient’s perception of the severity of venous disease. Chronic physical health problems are also seen to precipitate and exacerbate depression and this may be true for varicose veins.

In our study similar depression scores were reported amongst men and women. This is in contrast to the incidence within the general population, where women are twice as likely to suffer from depression compared to men. The reasons for this are unclear. In addition, there was no correlation with depression and age as documented in other studies of depression in the general population. However, there were few patients in our study over the age of 65 years.

Both depression and varicose veins are treatable once diagnosed. Work by Chassany et al showed that general practitioners...
routinely under-estimate the quality of life impairment due to venous disease whilst over-estimating that from peripheral arterial occlusive disease. Notably, no patients in our study had previously been diagnosed or were on treatment for their depression.

The aim of this study was to assess the burden of disease in ambulatory patients with symptomatic varicose veins, who have presented to their GP and subsequently to a vascular surgeon for treatment. However, this group of patients may not reflect the burden of depression in varicose veins patients within the general population. Moreover, the influence of socioeconomic factors and ethnicity on depression scores was not ascertained in this study. Further information regarding depression scores following venous intervention will be useful in establishing whether the symptoms of depression are reversible following intervention and hence would enhance our understanding of the problems these patients face. This is part of on-going work by our group.

Conclusion

Patients with symptomatic varicose veins are at increased risk of depression compared to the general population. This study reports a high incidence of previously unreported and undiagnosed depression in this group of patients. Further investigation of a patient’s wellbeing and a more holistic approach in the management of patients with venous disease is therefore recommended.

Conflict of Interest

None.

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Varicose veins are a common disease, with a reported prevalence of 20–40%.\textsuperscript{1–3} Their treatment represents one of the most common elective surgical procedures in vascular surgery. Numerous advances have been made in this field, moving away from surgical ligation of the saphenofemoral junction and stripping, towards less invasive options, including ultrasound-guided foam sclerotherapy, radiofrequency ablation (RFA) and endovenous laser ablation (EVLA).

Although these methods all address the truncal incompetence with similar technical success rates,\textsuperscript{4} residual superficial varicosities may remain postoperatively and their treatment is still a matter of debate.

There are two schools of thought with regard to treating varicosities in those patients undergoing truncal vein ablation. The first suggests simultaneous truncal treatment and phlebectomy as a single procedure.\textsuperscript{5} The second advises delayed phlebectomy after monitoring for varicosity regression. If still present, these can be addressed with ambulatory phlebectomies or foam sclerotherapy.\textsuperscript{6}

Advocates of the first option suggest that immediate treatment of surface varicosities is advantageous in that it ensures patients are treated in a single session and reduces the varicosity reservoir. However, this may increase operative time,\textsuperscript{7} and could be over-treating patients whose varicosities may regress.

Those in favour of delayed phlebectomies claim that this treatment is shorter, saving operative time. However, a variable number of patients do come back with troublesome residual varicosities, which require secondary procedures.

The evidence of the timing for phlebectomy is at best confusing. Carradice\textit{et al.}\textsuperscript{7}’s 2009 study showed that while there was no sustained difference in quality-of-life measures between delayed and simultaneous phlebectomy in the context of EVLA treatment, 66% of patients in the truncal ablation only group required secondary interventions. Monahan\textit{et al.}\textsuperscript{8} suggested that after RFA, 13% of patients had spontaneous varicosity regression and 41% of patients did not require further treatment, suggesting that monitoring for regression is the best option.

This appears confusing and contradictory, but both EVLA and RFA truncal ablation have been shown to save 30–40% of patients from having needless phlebectomies. However, Doganci\textit{et al.}\textsuperscript{9}'s comparison of laser wavelengths utilized a delayed approach but 100% of subjects required further intervention.

Part of the issue is that the literature is very heterogeneous, making comparisons between studies challenging.\textsuperscript{9} Variations exist in the reporting standards for surgical vs. EVLA/RFA or foam sclerotherapy both in terms of vein classification, as well as length to follow-up, objective assessments and questionnaires. Studies looking at specifically immediate vs. delayed phlebectomies are few in number.\textsuperscript{7,10,11} Most randomized studies into catheter type or modality to date have used standardized delayed or simultaneous phlebectomies across their study groups, with no clear definition of the trigger to varicosity treatment. This makes comparison difficult.

Furthermore, there are a number variables that confound the picture. Patient factors such as age, body habits and mobility will influence the result of any intervention on the venous system. Patient preference and expectations, as well as operator experience, may have an effect on patient and operator satisfaction. Pain levels experienced have been assessed in only one study, which showed no statistical difference in pain or return to normal activities.\textsuperscript{7} Finally the anatomy of the venous system and its preoperative haemodynamic state\textsuperscript{12,13} will also influence the outcome of any intervention, as will the condition of the patient and the venous calf pump. These factors need to be considered when considering treatment options, with the appreciation that any alteration in the venous tree will lead to haemodynamic changes.\textsuperscript{14}

Ultimately, the aim of procedures for residual venous disease are to provide the maximum symptomatic relief for as long as possible. An ideal treatment would be minimally invasive, safe, effective from a functional and cosmetic point of view, have low recurrence rates and be cost-effective. However, the goal of ambulatory minimally invasive treatment should not preclude the full management of the disease.

Venous disease affects a large proportion of our population. Despite advances in the field, the evidence behind treatment is still unclear; this is particularly true of tributary vein treatment at the
time of truncal ablation. Further studies, in terms of randomized controlled trials targeting the questions above, are required to provide evidence to best lead our practice.

Conflict of interest: None.

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Treatment options, clinical outcome (quality of life) and cost benefit (quality-adjusted life year) in varicose vein treatment

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Abstract
Varicose veins are an extremely common condition causing morbidity; however, with current financial pressures, treatment of such benign diseases is controversial. Many procedures allow the treatment of varicose veins with minimal cost and extensive literature supporting differing approaches. Here we explore the underlying evidence base for treatment options, the effect on clinical outcome and the cost-benefit economics associated with varicose vein treatment. The method of defining clinical outcome with quality-of-life assessment tools is also investigated to explain concepts of treatment success beyond abolition of reflux.

Keywords: QALY; varicose veins; cost-effectiveness

Background
With the onset of the global economic crisis and the threat of world recession, health economics has become increasingly important in health-care decision-making. Discussions on the health economic benefits or burdens of new endovascular techniques are common.

Health-care costs are spiralling; in the UK they have doubled over the last decade to £126 billion annually,1 and a similar picture is seen in the USA with spending now at $1.2 trillion/year,2 equivalent to over 8% GDP, a value seen throughout Europe as well.3 In the National Health Service (NHS), austerity measures require a saving of £20 billion on this budget of £126 billion (16%), whilst caring for an ever more elderly and frail population.4

Although costs and value for money have always had a role in the decision-making processes, these increasing financial pressures at the hospital, regional and national level have caused hospital managers to look at ways to cut costs at all levels. Varicose veins have been labelled as a ‘Procedure of Low Clinical Value’ due to the low mortality rates associated with this benign disease, leading to a reduced rate of referral for treatment.5,6

With the majority of patients with varicose veins being young and otherwise systemically well and with varicose veins rarely having a significant effect on mortality, they are afforded low priority. Therefore, by reporting crude outcomes through serious morbidity (or complications) and mortality, the object of treatment is missed and it allows questions to be raised over the necessity for intervention.

In benign diseases quality-of-life (QOL) assessments are invaluable in revealing the true clinical benefit of intervention.7,8 Varicose veins are extremely common (approx. 25% of the population),9 and so even moderate improvements in patient outcome generate large overall population improvements.10

QOL assessment
QOL instruments include both generic and disease-specific surveys. Generic surveys assess global

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states of wellbeing and provide a subjective measure of treatment efficacy, while disease-specific surveys focus on elements associated with particular disease processes and treatment effects.11–14

In the UK, the National Institute for Health and Clinical Excellence (NICE) was founded in 1999. NICE is an independent government-funded organization that advises the National Health Service and has become a role model for the development of clinical guidelines and attempts to evaluate the cost and cost-effectiveness of potential new treatments and technologies within the NHS. It has set a cost-effectiveness threshold of £20–£30,000 per QALY (quality-adjusted life year) gain for appraisal of surgical procedures.

Vascular surgery is a specialty where there has been an ever-expanding introduction of new and often expensive technologies, some of which have not been fully evaluated.

Varicose veins

Varicose veins affect approximately 25–50% of the adult population,15 and complications arising from them are a significant cause of patient morbidity and health service expense.16

Symptoms are often vague and non-specific but include aching, discomfort, pruritus and muscle cramps; however, there are more obvious and objective symptoms which include varicose eczema, pigmentation, bleeding and ulceration.17 Extensive previous work has shown that venous disease significantly impairs QOL.18–20

There are widespread misconceptions held by both the general public and primary care physicians with regard to varicose veins. The public fear that there is an increased likelihood of deep vein thrombosis (DVT) and that chronic venous changes are a common cause of limb amputation. However, primary care physicians are often mistaken in believing varicose veins are merely a cosmetic concern and even the skin changes of chronic venous insufficiency (a precursor to ulceration) are inconsequential. Extensive evidence exists to show the outcome of treatment of venous disease, but this requires the use of QOL measures. All forms of venous treatment have been shown to improve QOL.10,21–26

Varicose vein assessment

CEAP classification

Varicose veins have often been inadequately defined and have variously been described as being visible subcutaneous veins, to dilated palpable subcutaneous veins generally larger than 3 mm in the upright position. Due to this lack of consensus in the reporting and classification in the published literature, the CEAP (Clinical severity, AEtiology, Anatomy, Pathophysiology) classification for chronic venous disorders was developed in 1994 by an international ad hoc committee of the American Venous Forum, endorsed by the Society for Vascular Surgery, and this classification became incorporated into ‘Reporting Standards in Venous Disease’ in 1995, with further refinements made to it in 2004.27 This classification has been ubiquitously adopted and so allows more a direct comparison between studied modalities.

This is a clinician-implemented categorization tool. The clinical component indicates disease severity, ranging from zero points, for completely asymptomatic patients, up to six points for active ulcers. The aetiological component denotes the venous disease as congenital, primary or secondary in nature. The anatomic classification pinpoint the veins involved as superficial, deep or perforating. The pathophysiological classification identifies the presence of reflux in the superficial, communicating, or deep systems, as well as the existence of outflow obstruction. The CEAP classification is doctor driven, and highlights the cause of the underlying venous abnormality; however, it is not sensitive enough to track progressive changes.

Venous clinical severity score

The venous clinical severity score (VCSS) is a clinician-completed tool, which includes nine hallmarks of venous disease, each scored on a severity scale from 0 to 3. In order to generate a dynamic score, VCSS categories are scored individually. These include skin changes and pigmentation, inflammation and induration, and ulcers (including number, size and duration). In 2007, an international ad hoc working group was created to revise the VCSS to update the terminology, simplify the application and clarify ambiguities, which was completed in 2010.28

The value of the VCSS is its ease of use along with an emphasis on the most severe manifestations of venous disease which are likely to show the greatest response to therapy allowing tracking and quantification of improvement (or deterioration).

Aberdeen varicose vein questionnaire

The Aberdeen varicose vein questionnaire is a 13-question patient-completed survey addressing multiple elements of varicose vein disease, first
Compression

Compression stockings may be employed as a primary treatment for patients with symptomatic varicose veins. They act by providing graduated radial pressure between ankle and knee/thigh, and this along with the calf muscle pump returns venous blood cranially. Stockings are extremely attractive for the cost-conscious initially; however, the need for replacements (4 times per year) and poor compliance greatly reduce their effectiveness. Additionally some patients (37%) still complain of persistent venous symptoms despite stockings.

Conventional surgery

Standard surgery for varicose veins was first described over 100 years ago, and is still considered the gold standard against which other treatment modalities are tested. The results of surgery are good and patients are generally satisfied. Surgery is associated with an improvement in QOL in most patients. However, there is a significant rate of minor complications. Rates of morbidity vary from series to series.

New techniques that have arisen interrupt the reflux haemodynamics while preserving the long saphenous vein and include the ASVAL and CHIVA techniques. These provide minimally invasive treatments performed under tumescent local anaesthesia, and have produced good results. One single-centre series has shown that while CHIVA offers improved recurrence rates compared with open stripping in experienced hands, it has a steep learning curve and can lead to worse outcomes.

Endovenous ablation

In the last decade the introduction of minimally invasive endovenous ablation therapy has revolutionized the treatment of varicose veins.

Three endovenous modalities offer thermal ablation – RFA, EVLA and steam (SVS). RFA and EVLA have 10 years of evidential data, though with rapid advances in technology many series have now been superseded.

Current RFA technology includes the VNUS ClosureFAST catheter and the Olympus CELON RFITT catheter. These offer effective reproducible treatments under local anaesthetic in the outpatient setting. Direct comparisons with laser ablation have shown an equivalent efficacy with a reduced side-effect profile.
Laser treatment has expanded from the original 810 nm wavelength laser to a wealth of different wavelengths, with different treatment profiles. These different wavelengths offer a flexibility of treatment not found in other endovenous modalities.

Steam is a new technology of thermal ablation, with only limited evidence of proof of concept at present. Puffs of steam provide the energy for thermal denaturing of the long saphenous vein. New developments include Clarivein mechanochemical ablation and Sapheon cyanoacrylate glue closure. Clarivein has shown encouraging early results of 96.7% closure at six months. This technique of mechanical scarifying of the vein and instillation of liquid sclerotherapy needs no tumescent and so offers a less invasive alternative to thermal ablation. A further option is the Sapheon Venaseal Closure System, which utilizes proprietary glue to seal the vein; however, this has only been described at conference presentations so far.

Ultrasound-guided foam sclerotherapy
UGFS is an effective and cheap method of chemically ablating incompetent varicosities. It is truly minimally invasive, requiring only a single needle puncture and no catheterization and has been shown to be more effective than conservative therapy with compression. The literature on foam sclerotherapy is extensive and it can provide similar closure rates and significant improvements in QOL outcomes at one year. It appears to be more user-dependent than other modalities, though in experienced hands can provide excellent treatment at an unbeatable price. Recurrence, however, can be a problem in some series.

Cost-effectiveness
Despite being one of the most commonly performed surgical procedures, very few cost-effectiveness evaluations have been calculated. Ratcliffe et al. conducted a randomized trial comparing open surgery with conservative management. The surgical group was a heterogeneous collection of unilateral and bilateral procedures performed under general anaesthesia as a day case, and the conservative group was treated with compression hosiery or bandaging. Not only did they demonstrate that open surgery was cost-effective using £20,000 QALY level, but a third of patients allocated to the conservative group dropped out to undergo surgery before the trial had finished.

The main aim of the REACTIV (Randomized and Economic Assessment of Conservative and Therapeutic Interventions for Varicose Veins) study was to investigate the clinical and cost-effectiveness of varicose vein treatments. Patients were split into three groups:

- **Group 1** – minor below knee varicose veins without truncal reflux, randomized to conservative or sclerotherapy treatment, \( n = 34 \);
- **Group 2** – moderate below knee varicose veins with truncal reflux, randomized to standard surgery or sclerotherapy treatment, \( n = 77 \);
- **Group 3** – significant varicose veins above and below the knee with truncal reflux, randomized to conservative treatment or standard surgery, \( n = 246 \).

Once again, a significant number of patients allocated to a conservative management path became dissatisfied and dropped out of the study so that they could undergo surgery. Although numbers were small in some groups, this study demonstrated the economic value in treating patients with symptomatic varicose veins.

Subramonia and Lees performed a study comparing surgery and RFA which incorporated cost analysis into the design. This study randomized 88 patients into RFA (VNUS ClosurePlusTM) and conventional surgery (RFA 47, surgery 41) under general anaesthetic. RFA was found to be significantly more expensive (£1276 versus £559); however, the RFA group returned to work an average of one week earlier (10 days versus 18.5 days), at a cost of £6.14 per additional working hour gained. However, this study utilized the VNUS ClosurePlusTM catheter, which is six times slower than the current VNUS ClosureFASTTM catheter (0.05 cm/second versus 0.33 cm/second). The cost difference was due to increased theatre time (£171.01) and catheter cost (£550).

Gohel et al. produced a Markov model to evaluate the cost-effectiveness of traditional and endovenous treatments for patients with primary great saphenous varicose veins. Day-case surgery or endovenous ablation using EVLA or RFA performed as an outpatient were shown to be the most likely cost-effective treatment strategies for patients with primary unilateral great saphenous vein reflux requiring treatment. However day-case traditional surgery was also shown to be below the conventional threshold of the cost-per-QALY in the UK and therefore cost-effective.
Recent work by Rasmussen et al.\textsuperscript{22} showed equivalence between all available modalities, in a direct comparison trial of 580 legs. All procedures were under local anaesthetic and treatment time was 19–32 minutes. RFA was shown to be associated with less postoperative pain leading to a faster return to work and therefore a better cost-effectiveness analysis compared with open surgery or laser ablation. Catheter costs were EVLA £307 and RFA £371. Foam sclerotherapy remained the cheapest option, but was associated with a significantly higher recurrence rate at one year (16\% versus 5–6\%).\textsuperscript{22}

With a wide range of available treatments and few comparative studies, treatment choices are currently made on the basis of local availability and clinician preference, rather than clinical evidence. All procedures have been shown to be effective at both abolishing reflux and improving QOL.\textsuperscript{22,24,52,55,58,59} Additionally, day-case surgery, RFA, EVLA and UGFS have been demonstrated to be cost-effective at the limit of £20,000 per QALY.\textsuperscript{57}

### Patient preference

With the evolution of a patient-centred model of health care, the preferences of the patient must be one of the major contributors to the treatment plan. Varicose veins have many options and these should all be offered to patients with appropriate guidance before a definitive plan is agreed. Recent studies show that while patients felt unable to access modalities formally, they had significant preferences for local anaesthetic and one sitting treatment,\textsuperscript{60} though expectations need to be managed prospectively to avoid patient disappointment.\textsuperscript{61}

### Conclusion

Varicose veins have a multitude of treatment options, all of which provide excellent improvements in QOL at a cost-effective level. Overall costs have fallen dramatically despite material requirements, and no patient should be without a treatment option. The treatment of varicose veins is one of the few treatments that offer low morbidity for large improvements in QOL. Importantly, despite the higher incidence of varicose veins in older patients, a high percentage of patients are of working age when health improvements are most cost-effective.

### Conflicts of interest

None declared.

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Total preservation of patency and valve function after percutaneous pharmacomechanical thrombolysis using the Trellis®-8 system for an acute, extensive deep venous thrombosis

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ABSTRACT
Pharmacomechanical thrombolysis is being used increasingly for the treatment of deep vein thrombosis (DVT) and aims to reduce the severity of post-thrombotic syndrome. We report the case of a 60-year-old woman with extensive lower limb DVT that was treated using pharmacomechanical thrombolysis leading to complete recovery of her deep venous system. The prompt use of pharmacomechanical thrombolysis for the acute management of extensive DVT should be considered when treating patients with extensive DVT in order to facilitate return of normal function.

KEYWORDS
Deep vein thrombosis – Pharmacomechanical – Thrombolysis – Thrombosis

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Pharmacomechanical thrombolysis is being used increasingly for the treatment of deep vein thrombosis (DVT). It provides a more aggressive treatment of DVT than catheter directed thrombolysis and improves thrombolysis time and recanalisation rate. The Trellis®-8 system (Bacchus Vascular, Santa Clara, CA, US) isolates the thrombus between two balloons and breaks down the clot by rotating a guidewire in the isolated thrombosed segment in combination with thrombolytic agent. Previous studies have provided early clinical results demonstrating the efficacy of the Trellis®-8 system.

Case history
A 60-year-old woman was admitted with an acutely painful and swollen left lower limb. There was no associated chest pain or shortness of breath at presentation. She had several risk factors for DVT: recent long haul travel by aeroplane and train in addition to a recent subtotal colectomy and ileostomy formation for an exacerbation of Crohn’s disease from which she had made a good recovery. There was no underlying malignancy, nor was she taking any regular medication.

At presentation the left leg was markedly swollen and comparatively cooler with impalpable left popliteal and posterior tibial pulses. However, ankle brachial pressure indices were normal (>1.0) with triphasic signals.

Initial investigation with duplex ultrasonography established DVT and complete occlusion extending from the left posterior tibial vein to the common iliac vein. Computed tomography venography was carried out, confirming acute DVT of the left lower limb vessels (Fig 1). No abnormality was seen in the pelvic viscera.

An intravenous heparin infusion was commenced immediately for anticoagulation and the patient was given full length thromboembolic deterrent stockings. Four days after presentation, she attended the interventional radiology department for pharmacochrombolysis. Initially, a retrievable inferior vena cava (IVC) filter (OptEase™; Cordis, Bridgewater, NJ, US) was placed via the right common femoral vein. This was followed by ultrasonography guided insertion of a 4Fr thrombolysis catheter into the posterior tibial vein to treat the below-knee DVT. Via a 10Fr sheath inserted under ultrasonography guidance into the thrombosed popliteal vein, the Trellis®-8 procedure was performed from the IVC to the popliteal vein (Fig 2). Subsequent clearance of the clot revealed a severe stenosis at the left common iliac vein origin (May–Thurner syndrome), across which a bare metal self-expanding stent (Luminexx™; Bard, Covington, GA, US) was placed with a satisfactory result.

Due to some residual clots below the knee in the region not amenable to Trellis®-8, thrombolysis was continued for...
TOTAL PRESERVATION OF PATENCY AND VALVE FUNCTION AFTER PERCUTANEOUS PHARMACOMECHANICAL THROMBOLYSIS USING THE TRELLIS®-8 SYSTEM FOR AN ACUTE, EXTENSIVE DEEP VENOUS THROMBOSIS

16 hours via the posterior tibial vein catheter from the ankle and the popliteal vein. Post-thrombolysis venography demonstrated excellent thrombus resolution. The deep venous system was free of thrombus from the IVC to the calf except for a minor residual clot in a small deep venous branch vessel of the posterior tibial vein (Fig 5). There was good flow throughout the deep venous system and thrombolysis was stopped. The IVC filter was removed two days later. All intervention including filter removal was completed within four days.

Prior to discharge, warfarin was commenced for six months. This was felt to be an appropriate duration given the multiple risk factors for DVT.

At the follow-up appointments at three and six months, the patient's lower limb venous system duplex scan revealed no evidence of DVT or scarring throughout the left deep venous system. Furthermore, all deep vein valves were competent. The patient is now symptom free, off anticoagulation and has fully returned to her usual quality of life with no evidence of post-thrombotic syndrome.

Discussion

Prompt treatment of extensive DVT using the Trellis®-8 system in combination with catheter directed thrombolysis and venous stenting can be used successfully to treat extensive lower limb DVT. More importantly, it can achieve complete return of normal valve function. Our patient had treatment and complete thrombus resolution within five days of the onset of symptoms. This led to a vastly improved outcome. Previous Trellis®-8 cases in our department have not had
such complete resolution due to longer symptom duration. Consequently, we believe early treatment provides better results.

**Conclusions**

Results from large scale trials (eg ATTRACT)$^5$ are awaited but this case supports the need for consideration of more aggressive DVT management.

**References**

Complications of radiofrequency ablation of varicose veins

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Abstract
Radiofrequency ablation (RFA) has become a valued weapon in the phlebologist’s armoury. It offers ease of use and reproducibility with good outcomes. However, as with all interventions, complications arise. In this review we examine the complications inherent with RFA and their relative risk, with their avoidance measures if available. Overall, we find that RFA offers a very safe procedure with rare severe complications.

Keywords: complications; endovenous; ablation; radiofrequency

Introduction
Varicose vein treatment is one of the most common vascular operations performed in the National Health Service1 with the aim of reducing symptoms and the burden of skin ulceration.2 The management of varicose veins has changed rapidly in recent years. Saphenofemoral ligation and stripping of the great saphenous vein (GSV) once used to be the standard treatment for GSV reflux but has been challenged and in some areas replaced by endovenous therapies.3,4 Evidence has favoured endovenous modalities in terms of reduced post-operative hospital stay, early return to work and low complication rates.3,5–7

The following endovenous therapies have emerged in practice:

- Thermal ablation:
  - Laser,
  - Radiofrequency,
  - Steam,
  - Cryotherapy.

- Non-thermal ablation:
  - Foam sclerotherapy,
  - Sapheon™ (glue),
  - Clarivein™ (mechanical scarification and liquid sclerosant).

The authors have reviewed the potential complications and possible risks associated with radiofrequency ablation (RFA) of varicose veins.

Radiofrequency ablation
RFA of varicose veins was first described by Goldman in 20008 utilizing the VNUS ClosurePlus™ catheter (Covidien, Dublin, Ireland). Since then, two further catheters have been introduced – VNUS ClosureFast™9 and Olympus Celon RFITT™ (Olympus, Tetlow, Germany).10

Radiofrequency energy thermally denatures vein wall collagen, leading first to vein wall inflammation, then fibrosis and finally to occlusion. Surrounding tissues are protected by tumescent local anaesthesia, which acts as both a heat sink and anaesthetic.11 The vein lumen is compressed by the tumescent solution around the tip of the catheter, improving energy transfer and reducing power requirements.

The original ClosurePlus™ catheter required a constant pullback technique of 3 cm/minute (0.05 cm/second), whereas the ClosureFAST™ catheter treats a 7 cm segment of vein for 20 seconds (0.33 cm/second). An electronic feedback mechanism...
with varying power maintains a constant catheter temperature of 120°C in the ClosureFAST™ and 85°C in the ClosurePlus™ system. The Olympus Celon RFITT™ provides bipolar electrode treatment and utilizes a pullback technique with an optimal speed of 1–1.4 cm/second.12 ClosureFAST™ and RFITT™ have similar treatment profiles versus laser ablation but have not been directly compared.12

The ability of RFA to treat varicose veins under local anaesthetic has aided the transformation from inpatient operation to outpatient or office-based procedure. The ease of use and high patient satisfaction have led to a surge of interest.13,14

Complications with RFA

All treatments for venous disease involve the risk of adverse events. It is important that the risk of a treatment is small compared with the likely benefits.

Early complications

Closure success

Short-term technical success is defined as the successful occlusion of the vein lumen. Immediate failure of the technique should be identified at the time of the procedure by the completion of a duplex ultrasound scan. Immediate technical success rates of more than 95% with RFA have been reported.3,12,15 A multicentre trial using the ClosureFAST™ catheter has achieved an occlusion rate of 99.6% at six months.9

Pain

RFA has been found to be associated with less postoperative pain, a lower requirement for analgesia and a reduced impact on daily activities than other treatment modalities.3,5 Rasmussen et al.3 reported a mean pain score of 1.21/10 during the first 10 days and the time to return to normal activity was only one day. In the VAlVV randomized trial comparing RFA with laser ablation, RFA patients reported a mean pain score of 2.2/10 and an analgesia requirement of 10.9 tablets over 10 postoperative days. In all, 60% of patients returned to normal activities within three days.5 The EVOLVeS study compared RFA with surgery and found that RFA patients returned to normal activities in 1.15 days and had a persistently improved pain score (compared with both baseline and surgery) throughout two years of follow-up.15 Results from other studies also suggest low pain and analgesic requirements following RFA treatment.16

Phlebitis

Thrombophlebitis is the presence of inflammation at the site of the treated GSV associated with localized inflammatory changes such as hyperaemia, oedema and tenderness. It can also occur in varicosities and has an association with deep vein thrombosis (DVT).17 A recent meta-analysis reported an early phlebitis rate of 8% with RFA (by combining the results of three large trials).7 Recent studies have reported rates of 7–9.6%.3,5 However, Shepherd et al.5 also had one case of pulmonary embolism following RFA but with no evidence of deep vein thrombosis.

Endovenous heat-induced thrombosis

Thrombus can protrude into the common femoral vein (CFV) as well, an entity called endovenous heat-induced thrombosis (EHIT).18–20 For safety, the manufacturers recommend the tip of the ablation catheter should be at least 2 cm from the saphenofemoral junction.

In EHIT, thrombus can be seen either:

1. At the level of the deep vein without protruding into CFV;
2. Projecting into the deep system with <50% luminal occlusion of CFV;
3. Protruding into the deep system with more than 50% luminal occlusion;
4. Causing complete occlusion of the deep system – in other words, a full DVT.

A recent small-scale study into GSV patency and EHIT after RFA showed a 2.7% (2/73) rate of class II EHIT with no DVT,20 which corresponds to earlier work by Mozes et al.19 of 2.1% and Lawrence et al.,21 however, Proebstle et al.9 found a rate of 0% from 252 patients with ClosureFAST and Marsh et al.22 found a rate of 0.4% from 2470 limbs. Cases of EHIT class II have been successfully treated with two weeks of low-molecular-weight heparin (LMWH) with complete resolution in all cases.20 For classes III–IV full DVT treatment is recommended.18

Deep vein thrombosis

DVT can develop in the calf deep veins or a thrombus can circulate from the treated superficial veins...
(as described above) following RFA. DVT after endovenous ablation is extremely rare and indeed most case series and trials show no evidence of DVT at all.\textsuperscript{3,7,23,24} This makes quoting advice and risks difficult – the 2011 Venous Forum meeting at the Royal Society of Medicine had a dedicated session for debate on this issue, due to limited evidence.

Most clinics quote risks of approximately 1:1000 and provide perioperative prophylaxis.\textsuperscript{22} Concomitant small saphenous vein surgery or transluminal occlusion of perforator with RFA have been considered risk factors for high calf DVT.\textsuperscript{22}

Risks are reduced by the postprocedural use of compression stockings, the use of local anaesthetic and patients walking in and out. However, once again there are no detailed data for guidance.

Pharmacological prophylaxis may be used for all patients undergoing treatment or only in selected cases. Universal coverage prevents missed cases but is probably unnecessary in many patients. Selective treatment provided on the basis of risk assessment will miss some cases in need of prophylaxis and increase clinical load.

Patients at high risk of DVT (active malignancy, age over 60, known coagulation disorders, one or more significant medical co-morbidities, use of oestrogen-containing oral contraceptive pills or hormonal replacement therapy, and previous history of phlebitis or DVT) should have an injection of LMWH before the endovenous treatment. There is no evidence for prolonged anticoagulation as a prophylactic measure (beyond the day of treatment), but in the high-risk group, self-administration of LMWH can be suggested until the patient is fully mobile. Some surgeons request that female patients stop oestrogen-containing oral contraceptive pills or hormone replacement therapy a month before treatment. There is no evidence in support of this practice, and there is a risk of unwanted pregnancy.

During ultrasound-guided endovenous therapy, the presence of any thrombus in deep veins is easy to recognize and should be treated with appropriate anticoagulation. For total deep vein occlusion, full DVT treatment should be instigated while for partial occlusion of a deep vein, a short course of it may be sufficient.

Air travel of more than four hours duration (especially in high-risk group patients) is generally discouraged for two weeks following RFA treatment, but again evidence is lacking due to the rarity of DVT after ablation. Some surgeons extend this delay to 4–6 weeks. Patients should be advised to reduce their risk by keeping well-hydrated, wearing compression stockings and exercising their calf muscles.

Wound problems and skin burns
Other early complications including wound problems (6–8\%) and skin burns (8\%) have been reported following RFA.\textsuperscript{3,7} The incidence of skin burns has reduced since the advent of tumescent anaesthesia from 1.8\% to 0.5\%.\textsuperscript{25} The treated vein may be palpable as a cord; however, this rarely causes significant discomfort, and is poorly reported in studies.

Lignocaine toxicity
The routine use of tumescent anaesthesia in a clinic room setting has now become an established way to treat varicose veins. Tumescent anaesthesia consists of lactated Ringer’s or normal saline fluid combined with lidocaine, epinephrine and optionally bicarbonate to form a 0.1\% anaesthetic solution (or 1 mg per mL).\textsuperscript{11} Tumescent anaesthesia has been found to be very safe in large series,\textsuperscript{26} and previous work on tumescent local anaesthetic has shown that used subcutaneously a dose of 35 mg/kg is safe and extremely effective in vein surgery.

In an average 70 kg man this equates to 2450 mL – a substantial safety margin for most endothermal procedures (35mg/kg for 70 kg person = 2450 mg = 2450 mL of 0.1% solution). Despite this, surgeons and phlebologists should be aware of the potential for adverse events due to lidocaine injection. Complications of early or mild toxicity of lidocaine may cause light-headedness, dizziness, tinnitus, confusion and drowsiness. It is important to talk to the patient throughout the procedure and to discontinue injection if suspicious of any of these symptoms arising. Tonic–clonic convulsions leading to progressive loss of consciousness, coma, respiratory depression and arrest are the signs of serious toxicity.

Management of lidocaine toxicity involves standard resuscitation techniques, however patients may require extended resuscitation.\textsuperscript{27} Hypoxia needs to be prevented and hypotension and arrhythmias treated. Grand mal convulsions may require treatment with intravenous diazepam. Lipid emulsion therapy has recently emerged as a significant aid in managing toxicity.

Late complications
Skin pigmentation
Skin discolouration or hyperpigmentation may occur following endovenous treatment due to the
residual blood trapped within the veins. This normally resolves over a few months. The pooled rate of bruising and skin pigmentation of 19% following RFA has been reported in a meta-analysis. Other studies have reported lower rates of skin staining, between 6% and 9%. RFA (both VNUS and RFiTT) has been shown to cause less pain and ecchymosis than laser ablation. The risk of this complication can be lessened by careful application of tumescence and avoiding treating very superficial veins with RFA.

Nerve damage (paraesthesia)

Nerve damage is one of the most common causes of litigation after varicose veins surgery. Paraesthesia or numbness may arise following RFA but in most cases improves over the course of a few weeks. In a review of case series of patients who underwent RFA, the median rate of paraesthesia has been reported as high as 13%, with other studies reporting it as 4.8–12%. In the meta-analysis reported by Nesbitt et al., the pooled rate of paraesthesia from three large studies was 20% at three months. Significant reduction in the incidence of paraesthesia has been shown after the introduction of tumescence local anaesthesia to the RFA procedure — from 14.5% to 9.1%. For treatment of the short saphenous vein, a study of laser ablation has shown that mid-calf cannulation may avoid thermal damage to the sural nerve (3% versus 20%, P < 0.05).

Recurrence

Patients with late failure of RFA may remain asymptomatic or present with recurrent varicose veins (REVAS). REVAS is a clinical definition that represents true recurrences in addition to residual varicosities and the progression of venous disease. Therefore, the presence or absence of REVAS is dependent not only on efficacy of the treatment to the saphenous trunk but also the management plan for the varicosities. It certainly has an influence on patients and therefore the concept of REVAS and asymptomatic recurrence should be carefully explained. The management of patient expectations plays a large role in treatment satisfaction.

The long-term outcome for RFA has also been assessed in a number of studies. In a meta-analysis, van den Bos et al. have looked into 64 eligible studies comparing laser, RFA, surgery and foam sclerotherapy. They identified that estimated pooled success rates at three years for RFA was 84%. Recent separate one- and three-year follow-up data have shown an absence of reflux in 95.2% at 12 months and 92.6% at 36 months postprocedure.

Recanalization of a vein could be due to either reflux from a tributary or an incompetent perforator. Similarly, if the main lumen is patent reflux from the groin due to an accessory vein can also lead to failure and recurrence. Technical problems such as difficult access, problems in advancing the catheter or a tortuous GSV can all play a role in failure of the procedure or incomplete occlusion of the vein ultimately causing recurrence. Neovascularization, though less frequent with RFA than surgery, is also considered a cause for REVAS and has been seen in 2.8–7% of cases. Insufficient energy delivery and too-rapid pullback have been adjudged causes for incomplete obliteration of the vein lumen. RFA for recurrence has been shown to cause less pain and bruising than surgery as well as taking less time.

Discussion

In summary, RFA is associated with up to a 92% occlusion rate at three years. The common risks are of paraesthesia (4–20%), phlebitis (7–9%) and bruising or skin pigmentation (6–19%). The risk of DVT is low (<0.1%) but its consequences ensure that it is a major risk that must be mentioned (see Table 1). Technical failure and recurrence rates are equivalent to the gold standard of open surgery while neovascularization is significantly less frequent after RFA.

The routine use of tumescent anaesthesia in a clinic room setting has now become an established and viable way to treat varicose veins.

There are certain points, which need to be carefully addressed during the RFA technique to avoid complications:

- Adequate vein emptying by leg elevation;

Table 1  Complication rates associated with radiofrequency ablation of varicose veins

<table>
<thead>
<tr>
<th>Complications</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlebitis</td>
<td>7–9</td>
</tr>
<tr>
<td>EHIT–DVT</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Skin burns</td>
<td>0.5</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>6–19</td>
</tr>
<tr>
<td>Wounds problems</td>
<td>6–8</td>
</tr>
<tr>
<td>Nerve injury/paraesthesia</td>
<td>4–20</td>
</tr>
</tbody>
</table>

EHIT, endovenous heat-induced thrombosis; DVT, deep vein thrombosis
- Tumescent anaesthesia should be instilled below the saphenous fascia and above the deep muscular fascia surrounding the vein using ultrasound guidance;
- The GSV should be compressed to separate it from the inflow tributaries;
- Appropriate use of tumescent anaesthesia and maintenance of an adequate probe temperature are vital to the RFA technique.

The advantages of RFA are far greater than its associated risks. A full explanation of the procedure along with its relevant risks is important in managing patient expectations. With the increased use of endovenous therapy it is likely that the incidence of varicose vein litigation will decrease in step.

Conflicts of interest: None declared.

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The natural progression of chronic venous disorders: An overview of available information from longitudinal studies

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ABSTRACT

Chronic venous disorders remain a common problem worldwide; however, despite increasing research into novel endovenous therapies for the treatment of superficial venous disease, the natural history of primary venous disorders remains poorly understood. The following article provides a review of the longitudinal studies evaluating the progression of chronic venous disorders in the published literature. This includes a summary of the rate of development of venous disease in asymptomatic limbs and the rate of progression of venous disease in terms of hemodynamic, anatomical, and clinical progression including the development of skin changes and venous ulceration.

Venous disorders, including varicose veins and superficial venous insufficiency, are a common pathology, thought to affect between 15% and 40% of the adult population.1-2 They have plagued mankind for thousands of years and there is documentation of their existence from as early as 3500 BC.3 In the last decade, the development of endovenous techniques has led to a rapid increase in the popularity of many novel therapies including thermal and chemical ablation techniques.4-7 Yet, despite the large number of research studies supporting the use of new devices, the etiology and natural history of the progression of venous disease remains poorly understood. Evidence from clinical ultrasonographic and histological studies supports a multicentric theory for the development of venous disorders due to abnormalities in the composition of the vein wall leading to functional changes.8-9 However, the investigation of the progression of venous disease is complex and can be measured in a number of different ways. In recent years, there has been a move away from the use of surrogate end points to grade disease severity, such as the presence or absence of reflux, or the use of hemodynamic parameters such as venous refill times. A greater emphasis is now placed on the clinical assessment of disease severity and its functional impact on the individual patient. The association between the presence of superficial reflux and venous hemodynamic measurements with clinical and functional outcomes has been shown to be weak,2,10,11 and the relationship between these parameters remains poorly understood.

Keywords:
CEAP classification; natural history; varicose veins

To date, there have been few studies that have investigated the natural history of the progression of primary venous disease. Much of the current information is based on patients self-reporting their symptoms, many of whom subsequently undergo treatment, and the natural history of the condition is infrequently documented. In the current financial climate, the natural history of patients presenting with mild or moderate venous disease becomes increasingly important in order to justify the allocation of scarce resources. The overall societal burden of venous disease is unknown; however, chronic venous ulceration is debilitating for patients and costly for society and therefore preventative treatments are likely to be cost effective.\(^{12,13}\) This article includes a review of the available information from longitudinal studies to date.

**LONGITUDINAL STUDIES EVALUATING CLINICAL DISEASE PROGRESSION**

**The Framingham study (1988)\(^{14}\)**

One of the earliest longitudinal epidemiological studies of varicose veins was the Framingham study, which followed 5209 male and female subjects for 16 years at 2-yearly intervals starting in 1966. Subjects were examined for the presence of varicose veins—defined as dilated tortuous veins on the lower limbs—and potential risk factors were recorded. At the beginning of the study, 1720 men and 2102 women had no clinical evidence of varicose veins. Over the 16-year period, 396 men and 639 women developed varicose veins. The development of varicose veins was significantly greater in obese women. Significant differences were also noted in those with a higher systolic blood pressure, and those who were less physically active. The data suggested an incidence of varicose veins of 39.4 per 1000 men and 51.9 per 1000 women with no significant increase with age; however, there was an increase in prevalence with age due to accumulation. The study provided useful information regarding the incidence and potential risk factors associated with the development of varicose veins; however, it did not provide details of the progression of venous disease.

**Brewster et al (1991)\(^{15}\)**

Brewster et al published one of the earliest longitudinal studies documenting the details of venous disease progression in 304 patients on an NHS waiting list for superficial venous surgery. The median waiting time for patients on the waiting list was 4 years (range, 6 months to 13 years) and the median reported length of symptom duration was 28 years (range, 2-47 years). Primary varicose veins were observed in 85.5% of patients while 64% of patients reported that they felt that their venous disease had progressed since their initial presentation, and 5.2% suffered an episode of thrombophlebitis. In the time since their initial presentation, 68 patients (22%) had developed skin changes and 12 patients (3.9%) had developed venous ulceration, although the degree of clinical severity at baseline in those who developed ulceration was not reported.\(^{15}\) As with previous published studies, the development of further varicosities did not necessarily correlate with worsening of symptoms.

**Sarin et al (1993)\(^{16}\)**

In a small study of 56 limbs in 36 patients on an NHS waiting list for treatment of uncomplicated varicose veins (43 primary and 13 recurrent), patients underwent noninvasive imaging and clinical examination at initial presentation and again prior to surgery. Superficial venous surgery was delayed by a median of 20 months (range, 15-27 months). An additional 3 patients had developed varicosities along the distribution of the great saphenous vein (GSV), and 11 had developed new varicosities in the small saphenous vein (SSV) distribution prior to treatment. There were no new cases of venous ulceration; however, 1 patient developed lipodermatosclerosis.\(^{16}\) Of the 16 previously clinically normal contralateral limbs, 5 (31%) developed varicosities. Duplex ultrasonography demonstrated that an additional 14 patients developed superficial reflux at new sites (27%) and 18% were shown to have progressive reflux compared to initial duplex scans. New reflux developed in 25% of normal contralateral limbs. No significant deterioration in venous refill times was observed.

**Labropoulos et al (2005)\(^{17}\)**

Labropoulos et al carried out a longitudinal study comprising 116 limbs from 90 patients presenting with symptomatic chronic venous disease, who—for various reasons—did not undergo immediate treatment for their venous disorder and underwent treatment at a later date.\(^{17}\) All patients underwent two duplex ultrasound scans prior to intervention and reflux was classified as retrograde flow >0.5 s in truncal veins and >350 ms for perforator veins. All changes were documented and the time in between scans was specified. At the time of the
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initial duplex scan, 3.4% of patient had C1 disease, 43.8% had C2 disease, 23.3% had C3 disease, 13.8% had C4 disease, and 6.9% and 4.3% had C5 and C6 disease, respectively. Over a total of 43 months, 27 of 116 limbs (23.3%) had changes on duplex ultrasonography and patients reported worsening symptoms at some point in 13 of 116 limbs (14.4%), although patients underwent scans at different time intervals. In patients who underwent a second duplex between 1 and 3 months, 1 of 15 limbs exhibited noticeable changes on duplex ultrasonography and 5 of 28 limbs showed duplex changes when scanned after 4-6 months, although none of these patients had worsening clinical symptoms. In the patients who underwent their second scan at 7-9 months, 6 of 18 limbs showed duplex changes and worsening symptoms were reported in 1 of 18 limbs. In the patients scanned after 10-12 months, 3 of 15 limbs exhibited duplex changes, and worsening symptoms were reported for 1 of 15 limbs. When scanned after 13-18 months, 3 of 12 limbs showed duplex changes and worsening symptoms were reported for 3 of 12 limbs. At 19-24 months and 25-30 months, scans showed duplex changes in 3 of 10 limbs and 2 of 8 limbs, respectively, while worsening symptoms were reported in 3 of 10 limbs and 2 of 8 limbs, respectively. Between 31 and 36 months, 3 of 7 limbs exhibited duplex changes and worsening symptoms were reported in 2 of 7 limbs, while between 37 and 43 months, 1 of 3 limbs had duplex changes and worsening symptoms were reported in 1 of 3 limbs. New reflux was documented at 14 new sites including the GSV (n=2), SSV (n=1), tributaries (n=4), nonsaphenous vein (n=1), perforator veins (n=4), and deep veins (n=2). Extension of reflux in existing refluxing veins was documented in 17 limbs including at the saphenofemoral junction (SFJ) (n=1), GSV (n=7), SSV (n=4), tributaries (n=7), nonsaphenous veins (n=3), perforator veins (n=6), and deep veins (n=3). Overall when compared separately with other veins, saphenous veins and their tributaries were significantly more likely to have undergone change (P<0.01, Fisher exact test). Extension was antegrade in 7 limbs, retrograde in 7 limbs, and in both directions in 3 limbs. Worsening swelling (C2 to C3 change) was reported in 7 cases, worsening skin changes (C3 to C4) in 4 cases, and there were 2 cases of venous ulceration (C4 to C6). Overall 73% of limbs did not undergo any change; in those that did, this was usually after 6 months from the original scan. Approximately half of the patients who had significant changes on duplex ultrasonography reported a change in symptoms that occurred after 1 year. In addition, a number of patients who did not have noticeable changes on duplex ultrasonography were observed to have progressive clinical disease.

The Bonn Vein Study – Rabe et al18, Pannier et al19
The aim of the Bonn Vein study was to investigate the prevalence of deep and superficial reflux in the general population. The most recent evidence from the Bonn Vein Study—which surveyed over 1978 patients in Germany—showed that over 6.6 years, progression of C2 disease to higher C classes was 31.8% in patients with saphenous reflux and 19.8% in patients with nonsaphenous reflux. The prevalence of varicose veins rose from 22.7% to 25.1%, and the prevalence of CVI increased from 14.6% to 16%. Risk factors for disease progression were identified using a multivariate analysis and included increasing age, obesity, and arterial hypertension.19

73 patients with primary superficial venous disease who underwent unilateral varicose vein surgery were followed up after 5 years with regard to the contralateral limb, which was either asymptomatic or minimally symptomatic at the time of initial treatment. Patients underwent clinical examination and were graded according to the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification. Duplex ultrasonography was performed to establish the presence of retrograde flow >0.5 s in either deep or superficial veins. At initial recruitment, 5 of 73 patients had mild symptoms in the contralateral limb and 56 patients (77%) had no evidence of venous disease, 21% of patients were graded as C1, and 4 patients (5%) were graded as C2. A total of 12 limbs had isolated superficial reflux, and 6 limbs had deep reflux on duplex ultrasonography. At 5 years, 48 new sites of reflux were found in 38 limbs, most frequently in the superficial veins; however, 6 limbs developed deep venous reflux. In the limbs where reflux had propagated, this was antegrade in 10 limbs and retrograde in 8. In the majority of patients, changes in detectable reflux were associated with clinical changes, with 5 limbs progressing from C0 to C1, 5 from C0 to C2, 2 from C0 to C3, and 5 from C0 to C2/3. Progression from C1 to C2 was observed in 6 limbs, while 3 limbs progressed from C1 to C3, and 2 from C2 to C3. There were 2 patients who were initially classified as C2 who developed C4 skin changes. The study found that the progression of CVD...
was significantly affected by orthostatism and obesity, and that progression was reduced to some extent with the use of elastic compression stockings. Conversely, parity and estrogen treatments were not associated with progression of CVD. Overall, approximately a third of limbs with mild or asymptomatic reflux developed clinical signs over 5 years. This is similar to the 27% reported by Labropoulos.17

Labropoulos et al (2009)22
The progressions of primary and secondary venous disorders are noticeably different. A prospective comparison of the rate of progression of primary and secondary venous disease was performed over a 5 year period in 41 patients with a proximal DVT (group A), compared with a cohort of 41 patients with primary venous disease (group B) and followed up at 5 years with duplex ultrasonography. These were also compared with 15 control cases with no evidence of venous disease (group C). At 5 years, CEAP scores for the 3 groups were as follows: group A, C0 n=6, C1 n=0, C2 n=0, C3 n=29, C4 n=8 C5 n=1, C6 n=2; group B, C0/C1 n=0, C2 n=29, C3 n=18, C4 n=3, C5/C6 n=0; group C, C0 n=25, C1 n=3, C2 n=2 C3/C4/C5/C6 n=0. All patients were encouraged to wear compression stockings with 30 to 40mm Hg of graduated compression. Results confirmed that patients with a previous history of DVT developed significantly more skin changes compared with those with primary venous disease (P=0.019), and those with no venous disease (P<0.01) and that the progression was more rapid in patients with a previous history of DVT. Skin changes also occurred significantly more frequently in patients with combined reflux and venous obstruction (P=0.12).22

Data from this cohort study included 1566 randomly selected adults between 18 and 64 years of age who were examined at baseline and then at 13 years as part of the Edinburgh Vein Study. Recorded measurements included a questionnaire of lifestyle factors, CEAP grade, and duplex ultrasonography. Of the 1566 patients, 880 were followed up at 13 years. A total of 325 patients had truncal varicosities at baseline, and at 13 years, 154 patients had deterioration in their varicosities (47.4%) while 62 had stayed the same (19.1%). Of the 555 patients with no truncal varices at baseline, 101 developed C2 varices during the 13-year follow-up. The annual incidence of developing trunk varices was 1.35%, the rate of disease progression was 3.54% per annum, and the number of patients with unilateral disease who developed bilateral disease was 25.3%. A total of 109 patients showed improvement (33.5%), of which 16.6% had undergone surgery or sclerotherapy. Patients who had not undergone treatment were all reported to have mild disease and differences in grade may be attributable to interobserver variability.

LONGITUDINAL STUDIES EVALUATING VENOUS HEMODYNAMICS

The Bochum study surveyed 73 pupils over a period of 9 years at the beginning, middle, and end of their schooling. A fourth survey was also performed at 11 years. Pupils underwent clinical examination, duplex ultrasonography, and digital PPG and were classified according to the CEAP classification. Overall venous refill times appeared to lengthen from childhood to adulthood; this was thought to be due to maturation of the venous calf pump during adolescence. Interestingly, no clinical deterioration was observed in this cohort.24

LONGITUDINAL STUDIES EVALUATING THE EFFECTS OF INTERVENTION ON DISEASE PROGRESSION

This study evaluated 195 limbs in 183 patients with primary chronic venous insufficiency and reflux affecting the femoral vein, the SFJ, and the GSV.25 Venous ulceration lasting for more than 6 months but less than 3 years was reported in 99 limbs. Patients underwent ascending and descending venograms and duplex scanning, and were randomized to receive one of three treatment options including elastic compression hosiery (n=68), surgical treatment of venous insufficiency/saphenectomy (n=75), or deep vein reconstruction/valvuloplasty with saphenectomy (n=52). Clinical results were recorded based on the clinical severity scoring system recommended by the subcommittee on the reporting standards for venous disease.26 Over a mean follow-up period of 6.2 years, no significant difference was observed between the results of the three interventions in patients who had a disease duration of less than 5 years. However, in patients with a disease history of greater than 5 years, the results of valvuloplasty were significantly better, and the incidence of recurrent
varicosities was significantly lower after valvuloplasty in comparison with superficial vein repair alone. Recurrent varicosities were observed in 18 patients (14.2%). The authors concluded that valvuloplasty significantly improved the results of superficial venous surgery and that successful treatment was associated with an improvement in valvular function.25

LONGITUDINAL STUDIES EVALUATING RISK FACTORS AND THE DEVELOPMENT OF VENOUS ULCERATION

It is known that disease progression is related to the severity of venous reflux and duration of disease.27 The sensation of leg swelling in otherwise mild disease was found to be an indicator of likely disease progression and poorer prognosis.28 The number of patients with superficial reflux who are likely to progress to edema, skin changes, lipodermatosclerosis, and venous ulceration is unknown; however, the overall incidence of edema and skin changes in the general UK population is thought to be approximately 1% per year.27 The incidence of venous ulceration is 1% in the UK and the majority of those presenting with venous ulceration have had venous disease for more than 20 years.15 29

Heit et al (2001)30
A retrospective population cohort study was conducted in 1131 patients, including 263 patients who had venous ulceration over a 25-year period, to evaluate the incidence of venous stasis syndrome and venous ulceration. The incidence of venous stasis was 76.1 per 100 000 person-years and the incidence of venous ulceration was 18 per 100 000 person-years. Of the 945 patients who had venous reflux alone and no previous history of ulceration, 60 (6.3%) developed venous ulceration and the mean (±SD) time from the diagnosis of venous stasis to the development of a venous ulcer was 5 (±5) years with a range of 14 days to 24 years.30 Venous ulceration increased with age in linear fashion and was higher in women than men.

A SUMMARY OF THE ANATOMICAL AND HEMODYNAMIC EVIDENCE FOR THE PROGRESSION OF VENOUS DISEASE

Although the presence of superficial venous reflux and abnormal venous hemodynamics are associated with symptoms, the degree of symptoms reported and the severity of venous disease frequently correlate poorly with quantitative anatomical or hemodynamic findings. Therefore, it is difficult to interpret the relevance of the observed anatomical progression of venous reflux demonstrated on duplex ultrasonography or the deterioration in hemodynamic function. Nevertheless, the evidence is summarized below.

Sarin et al reported that 27% of patients developed sites of new reflux in limbs where venous reflux previously existed and 25% of normal contralateral limbs had developed new reflux over this time, although no significant deterioration in venous refill times were observed. Labropoulos et al observed that over a total of 43 months, 23.3% of limbs had changes on duplex...
The natural progression of chronic venous disorders

A SUMMARY OF THE FACTORS AFFECTING THE PROGRESSION OF VENOUS DISEASE

Although the etiology of venous disease is incompletely understood, a number of factors appear to be related to the progression of venous disease. There is good evidence that obesity and arterial hypertension significantly affect disease progression. In addition, there is evidence that prolonged standing increases the rate of disease progression, and that the use of elastic compression hosiery may reduce disease progression.

The presence of deep venous reflux, a past history of venous thromboembolism, and the presence of lipodermatosclerosis, corona phlebectatica, or varicose eczema are associated with an increased risk of developing venous ulceration. In patients with secondary venous disease following acute deep venous thrombosis, the natural history of the disease is better understood. Studies suggest that approximately 30% of patients will go on to develop postthrombotic syndrome, with 3% to 6% developing venous ulceration, and that disease progression occurs more rapidly than in those with primary venous disorders.

Improving the diagnosis and treatment of patients with venous ulceration has been shown to significantly improve patient outcomes. Evidence from a Swedish study confirmed that through education and a coordinated multidisciplinary approach—including early diagnosis, thorough investigation, and early use of superficial venous surgery—venous ulceration was reduced by 46% between 2002 and 2005.

PRACTICAL GUIDANCE

Based on the available evidence, the Society of Vascular Surgery and the American Venous Forum have produced practical guidance regarding the management of primary venous disorders. According to this guidance, there is weak evidence for compression hosiery for patients with symptomatic varicose veins and it is not recommended as the primary treatment if a patient is a candidate for saphenous vein ablation. Compression treatment is recommended for patients with primary venous ulceration, with ablation of superficial reflux to reduce the risk of ulcer recurrence. Thermal ablation (radiofrequency or laser) is recommended for the treatment of great saphenous vein reflux in preference to high ligation and stripping, although foam sclerotherapy is also suggested as a treatment option. The treatment of tributaries with phlebectomy or foam sclerotherapy is also recommended. The routine treatment of perforating veins in C2 patients is not supported, although the selective treatment of perforators in patients with ulceration is suggested.

CONCLUSION

Chronic venous insufficiency is a complex disorder with an incompletely understood multifactorial etiology. The majority of patients presenting with venous disorders request treatment, so the natural history of the disorder is difficult to evaluate. At present there is a lack of published evidence from longitudinal studies that have evaluated the natural history of disease progression. Combining data from different studies is difficult due to the heterogeneity of the outcome measures reported in different studies and a lack of understanding of the relationship between them. However, there is promising data from large long-term studies, including the Bonn Vein and Edinburgh Vein studies, which are likely to allow a better understanding of disease progression in the future. Nevertheless, based on the data currently available in the published literature, it could be suggested that in patients with uncomplicated varicose veins, disease progression to higher C stages is likely to be somewhere between 3.5% and 7% per annum and is subject to a number of patient and environmental factors. The development of venous ulceration usually occurs in patients who have had venous disease for over 20 years, and skin changes and deep venous incompetence are associated with a significantly higher risk of venous ulceration. The rate of progression from C4 disease in patients with skin changes to venous ulceration is unknown, but based on the available evidence, it is estimated to be in the in the region of 1% to 2% per annum. These figures become highly important when considering the prevalence of venous disease. A recent study evaluating the societal cost of C4-C6 disease in European countries and the USA confirms
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of publication</th>
<th>No. of study participants</th>
<th>No. of limbs</th>
<th>Brief study description</th>
<th>Duration of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand14 (Framingham study)</td>
<td>1988</td>
<td>5209</td>
<td>-</td>
<td>Epidemiological study of the incidence prevalence and risk factors for the development of varicose veins</td>
<td>16 years, patients reviewed at 2-yearly intervals</td>
</tr>
<tr>
<td>Brewster15</td>
<td>1991</td>
<td>304</td>
<td>-</td>
<td>Patients on an NHS waiting list for varicose vein surgery</td>
<td>Median (range) waiting time of patients was 4 (6-13) years.</td>
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<tr>
<td>Sarin16</td>
<td>1993</td>
<td>36</td>
<td>56</td>
<td>Patients on an NHS waiting list for varicose vein surgery</td>
<td>Median (range) waiting time 20 (15-27) months</td>
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<td>Labropoulos17</td>
<td>2005</td>
<td>90</td>
<td>116</td>
<td>Longitudinal study of patients presenting with venous disease who did not undergo immediate treatment</td>
<td>43 months</td>
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<tr>
<td>Rabe20,19 (Bonn Vein Study II)</td>
<td>2008-ongoing</td>
<td>1978</td>
<td>-</td>
<td>Longitudinal study of the development and progression of venous disease in the general population</td>
<td>6.6 years</td>
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<td>Kostas21</td>
<td>2010</td>
<td>73</td>
<td>73</td>
<td>Patients undergoing superficial venous surgery for 5 years were followed with regard to the contralateral limb, which was asymptomatic or minimally symptomatic at the time of surgery</td>
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<td>Labropoulos22</td>
<td>2009</td>
<td>97</td>
<td>126</td>
<td>Longitudinal study comparing the progression of primary and secondary venous disease</td>
<td>5 years</td>
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<td>Robertson23 (Edinburgh Vein Study)</td>
<td>2011</td>
<td>880</td>
<td>-</td>
<td>Longitudinal study of the prevalence of venous disease in the general population</td>
<td>13 years</td>
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<td>Stucker24 (Bochum study)</td>
<td>2005</td>
<td>73</td>
<td>-</td>
<td>Study of venous refill times and duplex findings in school pupils</td>
<td>9 years</td>
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<tr>
<td>Lurie25</td>
<td>1998</td>
<td>183</td>
<td>195</td>
<td>Randomized clinical trial comparing results following treatment with compression hosiery (n=68), valvuloplasty plus saphenectomy (n=52) or saphenectomy (n=75) in patients with reflux of the SFV and superficial reflux.</td>
<td>Mean duration of follow-up 6.2 years</td>
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<tr>
<td>Heit26</td>
<td>2001</td>
<td>1131</td>
<td>-</td>
<td>A retrospective cohort study of patients to estimate the incidence of venous stasis syndrome and venous ulceration.</td>
<td>25 years</td>
</tr>
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</table>
The natural progression of chronic venous disorders

<table>
<thead>
<tr>
<th>Incidence/ Rate of development of venous disease according to CEAP</th>
<th>Rate of progression of C2 disease to higher disease stages</th>
<th>Rate of development of venous ulceration</th>
<th>Duplex findings</th>
<th>Additional outcomes</th>
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<tr>
<td>Incidence of the development of varicose veins-CEAP unspecified 39.4/1000 in males, 51.9/1000 in females</td>
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<td>Not specified</td>
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<td>Not specified</td>
<td>22% developed skin changes/C4 disease from initial presentation</td>
<td>3.9% developed venous ulceration, baseline CEAP unspecified.</td>
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</tr>
<tr>
<td>25% of contralateral limbs had developed new reflux and 31% developed new varicosities in the contralateral limb</td>
<td>1 patient (2.7%) developed lipodermatosclerosis</td>
<td>No cases of venous ulceration</td>
<td>27% had developed reflux at new sites and 18% of patients had progressive reflux compared to baseline studies</td>
<td>3 patients developed additional varices of the GSV, 11 patients developed new varices of the SSV</td>
</tr>
<tr>
<td>A change in either duplex findings or symptoms occurred in 38 limbs at 6 months or later</td>
<td>11.6% progressed from C2 to C3 and 14.8% from C3 to C4</td>
<td>2 patients with C4 disease developed ulceration (12.5%)</td>
<td>31 limbs (26.7) of limbs had progression on venous duplex, of these 29 were symptomatic.</td>
<td>14.4% of patients reported worsening of symptoms</td>
</tr>
<tr>
<td>Prevalence of VVS rose from 22.7% to 25.1% over the study duration</td>
<td>31.8% of patients with saphenous reflux and 19.8% of patients with nonsaphenous reflux progressed from C2 disease to higher C stages.</td>
<td>Not specified</td>
<td>Details unpublished</td>
<td></td>
</tr>
<tr>
<td>16 (23.1%) of patients with C0 or C1 disease at baseline developed C2 disease by 5 years.</td>
<td>2 patients with C2 disease developed C3 disease and 2 developed C4 disease</td>
<td>No patients developed C5/C6 disease</td>
<td>48 new sites of reflux were found in 38 limbs, including 6 limbs that showed development of deep reflux.</td>
<td>13 patients with C0 disease at baseline progressed to C3 disease at 5 years.</td>
</tr>
<tr>
<td>2 patients in group C developed varicose veins at 5 years (13%)</td>
<td>In group A, the incidence of skin changes at 1 year was 4% (2/46 limbs) and at 5 years was 24%(11/46) In group B, skin changes occurred in 3 patients (6%)</td>
<td>In group A, 9 limbs progressed from C3 to C4 and C6 and 2 limbs from C4 to C5 and C6.</td>
<td>47.4% had deterioration in their varicosities. A change in CEAP clinical class occurred in 14 limbs in group A (30%), of these 11 limbs had progression of reflux or recurrence of DVT.</td>
<td></td>
</tr>
<tr>
<td>101/ 555 participants with no varices at baseline developed C2 disease. The annual incidence of developing trunk varices was 1.31%</td>
<td>The rate of disease progression was 3.54% per annum</td>
<td>Not specified</td>
<td>-</td>
<td>25% of those with unilateral disease developed bilateral disease</td>
</tr>
<tr>
<td>Not specified</td>
<td>No clinical deterioration was observed.</td>
<td>Not specified</td>
<td>-</td>
<td>Venous refill times lengthened from childhood to adulthood, thought to be due to the maturation of the venous calf pump.</td>
</tr>
<tr>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>73% of patients had decreased leakage of the femoral vein after valvuloplasty. This did not occur in the saphenectomy or compression hosiery groups.</td>
<td>No significant difference in outcomes was observed between treatment groups in patients with disease duration of greater than 5 years. Results after valvuloplasty were significantly better than saphenectomy or compression. Recurrent varicosis occurred in 7.7% of cases following valvuloplasty compared to 17.3% following saphenectomy alone (P&lt;0.01).</td>
</tr>
<tr>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>The incidence of venous ulceration was 18.0/100 000 persons per year. The incidence of venous stasis was 76.1/ 100 000 person-years.</td>
<td></td>
</tr>
</tbody>
</table>

that the costs run to hundreds of millions of euros each year for the treatment of superficial reflux, the treatment of venous ulcers, and the cost of days lost from work due to venous disorders. A better understanding of the rate of progression of venous disease, and the ability to identify patients at risk of venous ulceration will help with the allocation of healthcare resources and ensure the appropriate management of patients with moderate venous disorders, and, therefore, further data from ongoing longitudinal studies is awaited.

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The natural progression of chronic venous disorders

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Superficial Venous Disease Treatment – Is There Still a Role for Open Surgery in 2011?

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Abstract. The treatment of superficial venous disease (commonly described as varicose veins by the general public) has remained relatively constant over the past 100 years until the refinements of endovenous treatments such as sclerotherapy and more recently, the development of endovenous ablation. This has radically changed the treatment profile of this disease with treatments easily administered and well tolerated even in those patients who would not be considered fit for open surgery previously. With the advent of day surgery and improved general and local anaesthetic techniques, venous surgery has forged a path towards the end goal of outpatient treatment with no requirement for inpatient stay. The end goal of all superficial venous surgery is an improvement in quality of life, and with such new treatments reducing the impact of the actual intervention, such gains are easier to make.

This review assesses and presents the current literature describing superficial venous disease treatments covering all treatment modalities.

With endovenous treatment, true ambulatory treatment is available, providing high quality treatment at speed and convenience for patients.

Introduction

Superficial venous disease affects up to 1 in 4 of the UK population (1) and has been estimated to cost €600-900 million per year in Western European countries (2), with over 37,000 varicose vein procedures performed each year in the UK, the majority of which as day cases (3). The recent Bonn Vein Study found less than 10% of the Bonn general population had no evidence of venous disease (CEAP class 0) (4).

The treatment of superficial venous disease has been standard for hundreds of years until the recent development of sclerotherapy in the mid 20th century and then ultrasound guided endovenous ablation. These recent advances have greatly changed the patient experience, the logistics of intervention and have provided the opportunity for ambulatory treatment. Treatment has previously been assessed by merely technical means – occlusion and recurrence rates, however patient preference and quality of life assessments are also vital components of treatment analysis. Quality of life assessment pre and post intervention allows a vital stratification of treatment methods.

Due to the lack of a perfect ‘one-size-fits-all’ solution to superficial venous disease many treatments are available. This can make it extremely difficult for the clinician to make a fully informed choice between modalities let alone between equipment. With the huge patient population optimum treatment can lead to vast improvements in both individual and population health and well-being, in excess of that offered by optimal treatment of arterial disease.

Compression Therapy

Compression therapy using either graduated elastic hosiery or compressive bandaging has become the standard conservative treatment for patients with uncomplicated varicose vein disease. It has also become a screening method for patients with aspecific symptoms, with a trial of compression hosiery allowing symptom improvement assessment and risk stratification for treatment. Such stratification is becoming especially important in the current age of austerity.

The evidence base for compressive hosiery is sparse, and a recent systematic review (5) showed a sparse and heterogeneous evidence base, but stockings were shown to improve symptoms, but not to effect progression or recurrence of varicose veins.

Compressive hosiery is not without its own morbidity, leading to poor compliance. This led over half of those patients randomised to conservative treatment in the large REACTIV randomised controlled trial to chose to withdraw and undergo surgery within 3 years (6).

Surgical intervention has been shown to provide significant quality of life improvement for minimal additional healthcare cost when compared to conservative management (7).
In a recent cost effectiveness study, conservative management was considered to have a cost of zero for comparison with intervention (8). However this does not take into account the significant expenditure in time and materials associated with symptomatic venous disease requiring compression hosiery or bandaging. Ulcer disease increases the cost of chronic venous insufficiency enormously (2). The benefits of intervention to prevent such complications are clear, with 2 million working days lost to venous disease in 2002.

Sclerotherapy

The technique of liquid sclerotherapy with direct injection was described by Chassaignac in 1855 (9). This was refined into foam sclerotherapy during the 20th century with the Tessari method being most practised (10) and this has lead to improved occlusion and patient satisfaction rates. Foam sclerotherapy is thought to improve occlusion rates with smaller quantities of sclerosant by displacing more blood and improving wall contact. It allows the treatment of varicose veins in a true clinic environment, with no assistance required once skilled at the technique (11). Due to the simple cannulation nature of the technique, minimal post-procedure morbidity is encountered, leading to high patient acceptance.

The major failing of foam sclerotherapy has previously been occlusion and recurrence rates. However, with the advent of foam, it has been shown that ultrasound guided foam sclerotherapy (UGFS) has equivalent success and recurrence rates to open surgery, as shown by a recent meta-analysis (10), a recent systematic review (12) and a recent Cochrane review (13). However, sclerotherapy was found to be less effective than endovenous ablation, although long-term data are lacking.

There is sparse evidence in the literature to guide the actual application of sclerotherapy, with disparate sclerosant volumes, foaming techniques and concentrations used, however Coleridge Smith has published recommendations for clinic requirements and suggested technique (11).

Overall complications after sclerotherapy are rare, however this much be weighed against the relatively benign nature of varicose veins, and the availability of effective conservative management. Major complications include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and transient embolic events. The event rate of these complications is very low, with an event rate of 0.6% for DVT, 2.1% for cerebral events and one previously reported PE (10). Air embolism is the most feared complication, which can be fatal when associated with gas volumes of > 1 ml/kg injected into the venous system, with 50 ml able to cause significant complications. Most procedures utilise up to 10 ml of foam, though some report use of up to 30 ml (14).

One case report has been published of stroke following UGFS (14). The risk of debilitating complications is extremely rare. It further requires a patent foramen ovale.

Overall the risk profile of sclerotherapy is not significantly altered in comparison to surgery and therefore is gives a reasonable alternative for those patients for whom surgery or endovenous ablation is deemed inappropriate or too strenuous.

Endovenous Ablation

The principles of endovenous ablation are the same – minimally invasive destruction of the incompetent veins using either thermal energy or sclerosant and mechanical disruption. This leads to fibrosis of the vein wall and ablation of vessel lumen, thus removing the incompetent vein from the circulation. The advantages of endovenous treatment are faster procedure times, reduced post-operative pain, optional general anaesthesia, patient preference and the possibility of truly ambulant treatment. The various endovenous methods are detailed below. The qualities of endovenous treatment have been reviewed in depth with a meta-analysis of 64 studies, covering over 12,000 treated limbs, with a mean 2.5 year follow-up period (12). Whilst such analyses are hindered by non-standardised reporting (15), it has produced significant positive data for endovenous treatment. Endovenous procedures have been shown to be at least equivalent to open surgery for technical success. Coupled with ease of use and patient acceptability, this has led to a huge, increasing practice and success of the procedure.

Endovenous Laser Ablation (EVLA)

The technique of endovenous laser ablation (EVLA) has advanced greatly since its description in 2001 by Navarro et al. (16). Following Food and Drug Administration approval, the technique has grown enormously. The major drawback of laser technology is the requirement for a specially shielded, secure treatment room and the requirement for laser goggles for all in that room.

The advancement of technology has lead to a proliferation of different laser wavelengths, with the wavelengths offering different treatment profiles. The wavelengths used are based on the absorptive properties of blood (17). The technical success rate is highly dependent on energy delivered by unit length (J/cm) with the target for occlusion being > 70 J/cm, but no ill effects of increased energy delivery are seen until 160 J/cm (18, 19). A recent meta-analysis found that EVLA showed significantly better technical success characteristics, compared to open surgery, sclerotherapy and radiofrequency ablation (12). However the studies analysed did
produce a surprising improvement in occlusion rates over successive years despite no further intervention, which is difficult to explain. Differing wavelengths are available for use, with 810, 940, 980, 1064, 1320 and 1470 nm lasers available. Shorter wavelength lasers were initially chosen due to the correspondent absorption by deoxygenated haemoglobin, however it has been found that longer wavelength lasers produce less post-operative complications, such as pain (20-22). This has lead to a proliferation of longer wavelength lasers, focused on water absorption wavelengths as opposed to haemoglobin absorption wavelengths. This targets the vein wall, as opposed to the blood in the vein, leading to reduced energy requirements for fibrosis (23).

Long-term outcomes are obviously lacking, due to the young nature of the technique and the constantly changing laser wavelengths available. However, in series reporting follow-up beyond one year, occlusion rates remain high, ranging from 86% at 6.7 years in more than 2400 limbs (24) to 97.1% at 4 years in 511 limbs (25).

A recent study has showed that EVLA with concomitant phlebectomies significantly improved quality of life and reduced risk of delayed procedures. 66% of the delayed phlebectomy group required secondary intervention, compared with 4% (p = < 0.001) in the concomitant group (26).

Overall EVLA offers a reliable, technically successful technique for endovenous ablation, which can be done in the day surgery or clinic setting. Current advances in longer wavelength lasers are allowing stepwise progression to the ultimate aim of technical success without post-operative complication.

Endovenous Radio-Frequency Ablation (RFA)

Endovenous Radiofrequency ablation (RFA) was first described by Goldman et al. in 2000 (27). A systematic review in 2009 outlined the literature and status of the two competing radiofrequency catheters currently licensed for use in the UK and Europe – VNUS ClosureFAST™ and Olympus Celo RFITT™ (28). In the USA, only the VNUS™ brand is licensed for endovenous ablation.

The technique is the same as utilised for endovenous laser ablation – ultrasound guided, under tumescent local anaesthesia and Seldinger cannulation technique. General anaesthesia is optional in most cases and the procedures can be done in a clean clinic room environment. The VNUS™ system requires the use of tumescent anaesthesia to ensure adequate pain relief and adequate compression of the vein to allow secure ablation. The RFITT™ system due to its induction heating technique does not require tumescent anaesthesia, resulting in fewer needle punctures for the anaesthetic.

The VNUS ClosureFAST™ system utilises a segmental treatment approach, ensuring that all sections of the vein are treated equally. The RFITT™ system uses the same continuous pullback mechanism as EVLA, which can lead to areas of over and under treatment.

Several studies have been published showing significantly improved quality of life scores and improved venous clinical severity scores after RFA when compared to laser (29) as well as reduced post-operative pain (30-32). The recent meta-analysis of endovenous treatment found that RFA offered at least equivalent technical success as sclerotherapy and open surgery (12).

Overall RFA offers a safe, reliable, fast technique for the treatment of varicose veins. With the recent launch of the RFITT™ system, and its differing catheter profile many more patients are now suitable for radiofrequency ablation.

Conventional Surgery

Open surgery for varicose veins has been practiced in varying forms since 500 BC (33) with saphenofemoral junction ligation being the gold standard of care for varicose veins since 1907 when the saphenofemoral junction and ligation with vein stripping technique was first described by Babcock (34). It has undergone refinements since then, but the basic procedure has not altered. Despite its venerable history it remains the gold standard against which all new methods must be judged, and the most widely offered treatment (35).

Furthermore, it remains a cost-effective procedure when performed as a day case (8), can be performed under local anaesthesia (36) and achieves good improvements in Quality of Life (QoL) scores such as the Aberdeen Varicose Vein Questionnaire (AVVQ) and clinical scores such as the Venous Clinical Severity Score (VCSS). Ligation without stripping of the truncal vein runs the significant risk of recurrence due to neovascularisation (6).

Recent studies with 2 year follow-up (37, 38) and a meta-analysis (12) showed that open surgery is as effective as both RFA endovenous treatment and sclerotherapy. EVLA showed higher rates of technical success, but no significant difference in clinical outcomes.

Saphenofemoral junction ligation with stripping is often, but not exclusively, paired with multiple phlebectomies at the same sitting. There is evidence to show that delayed procedures reduce the rate of eventual intervention, with both phlebectomy first and ligation first providing complete relief in some patients (39). Carradice et al. however showed a significant increase in AVVQ scores at 6 weeks, with a significant drop in VCSS scores when patients received multiple phlebectomies and endovenous ablation in one sitting. Follow-up data at one
year showed normalisation of both generic and disease specific quality of life measures with no significant difference between delayed and concurrent multiple phlebectomies (26).

Future Advances

The advent of steam producing devices as shown by the recent pilot study (40) which suggests steam catheters offer a further modality for endovenous treatment, based on thermal ablation. The principle behind this technique is to ‘cut out the middle man’ and use discrete bursts of steam to transfer energy to the vein wall, as opposed to utilising laser or radio-frequency energy to heat the blood at the catheter tip to create steam. In the pilot study of 20 limbs, an occlusion rate of 65% was obtained at 6 months, with significant improvements in disease severity at 3 months. One major benefit of the steam system is a much finer and more flexible catheter than comparable endovenous treatments. Large-scale efficacy trials comparing energy modalities are required.

The Clarivein™ treatment is now also available, offering endovenous ablation without thermal energy. This alternative technology uses a battery-powered rotating catheter tip, which both macerates the vein and can infuse sclerosant. No clinical trials have been published in peer reviewed literature, however initial trial data (2010) available from the company website claims a 97% truncal vein closure rate at six months, in the doctor’s office setting. The procedure utilises no tumescence and requires no generator for ablative energy. Long-term data is unavailable currently.

Cost Effectiveness

A cost analysis of chronic venous insufficiency was performed as part of the REACTIV trial (7), which assessed conservative treatment, sclerotherapy and open surgery (6). A further cost-effectiveness study also included endovenous ablation techniques which were not available for formal comparison in the first analysis (8). Both studies have found that intervention is cost effective, when performed as a day case or in clinic.

Conclusion

The treatment of chronic venous disease has entered a new and exciting era. With the multitude of options available, very few patients should be left without a treatment pathway that alleviates their symptoms and ideally cures the source of those symptoms. Endovenous treatments have allowed ambulatory and day case management of venous insufficiency reducing costs and increasing acceptability.

In an era of austerity, the treatment of chronic venous insufficiency at an early stage is of paramount importance to reduce the long-term healthcare burden. Despite the initial high cost of endovenous ablation techniques, this is more than offset by increased throughput.

Open ‘traditional’ surgery remains the gold standard treatment with no studies yet showing significant superiority for endovenous modalities.

Local anaesthetic treatment, whether open surgery or endovenous ablation, is highly acceptable to patients and provides an appropriate and cost-effective pathway for most cases. The vast majority can now be treated with a combination of endovenous ablation and foam sclerotherapy, with the associated reduced post-operative morbidity. With rapid developments in laser technologies and long-term data available for radiofrequency ablation, a patient and physician choice can be made between energy modalities. Radiofrequency ablation offers treatment with a reduced burden of morbidity with slightly reduced technical success rates, and can be performed without additional safety requirements. Laser ablation offers the best technical success rate but has worse post-operative side effects and limited long-term data due to the proliferation of new devices. Further long-term randomised trials and data collection registries are both in progress and are required to provide a definitive answer for the appropriate energy source.

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